MASTERCLASS

When the appendix plays nasty: intraoperative surprises, immediate solutions and long-term treatment options
Justin Davies, Cambridge, UK

All you need to know about stomas but never dared to ask
Willem Bemelman, Amsterdam, NL

The colorectal anastomosis: time-proven wisdom, innovative configurations, and salvage techniques
André d’Hoore, Leuven, BE

Extended lymph node dissection: indications, surgical anatomy and technical approaches
Peter Sagar, Leeds, UK

taTME in 2020 – when does the dust settle: current and innovative indications, implementation and practical advice
Roel Hompes, Amsterdam, NL

To ostomize or to fear a leak – purpose and function of a diversion and clinical experience with virtual ileostomy
Gabriela Möslein, Wuppertal, DE

Is the longer the new better – how to safely extend the interval after neoadjuvant chemoradiotherapy prior to surgery for locally advanced rectal cancer
Ronan O’Connell, Dublin, IE

Complete mesocolic excision: indications, surgical approaches, pitfalls and an appraisal of the literature
Paris Tekkis, London, UK

All the secrets of the pelvic floor – common disorders and proven solutions
Julie Cornish, Cardiff, UK

The views of an Editor and the wisdom of an Expert: contemporary publications with the potential and improve practice
Neil Mortensen, Oxford, UK

The EBSO Coloproctology Elimination
Michel Adamina, Winterthur, CH

SCIENTIFIC PROGRAMME

Pathophysiology and non-operative management of symptomatic uncomplicated diverticular disease
Robin Spiller, Nottingham, UK

Surgery of acute diverticulitis – evidence, eminence and real life
Willem Bemelman, Amsterdam, NL

Management of atypical diverticulitis
Dieter Hahnloser, Lausanne, CH

Hartmann reversal: open, laparoscopic or transanal?
Roel Hompes, Amsterdam, NL

The surgeon personality – influence on decision making, risk taking and outcomes
Desmond Winter, Dublin, IE

Clinical applications of image-guided cancer surgery
Cornelis van de Velde, Leiden, NL

Volvulus of the colon – a treatment algorithm
Peter Sagar, Leeds, UK

Hereditary colorectal cancer syndromes: tailored surgical treatment
Gabriela Möslein, Wuppertal, DE

Lars Pålman and Herand Abcarian (2015)
Herand Abcarian, Chicago, US

Lars Pålman Lecture
Steven Wexner
Weston, US

Iterative cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases
Vic Verwaal, Aarhus, DK

Is anastomotic leak an infectious disease
Ronan O’Connell, Dublin, IE

Neoadjuvant chemotherapy for advanced colon cancer: clinical and pathological Results
Dion Morton, Birmingham, UK
Philip Quirke, Leeds, UK

Mechanical bowel obstruction: rush to the OR or stent and dine
Neil Mortensen, Oxford, UK

Controversies in IBD surgery
André d’Hoore, Leuven, BE

How to deal with IBD and dysplasia
Janandra Warusavittane
London, UK

Perianal Crohn – avoiding delay and best surgical practice
Justin Davies, Cambridge, UK

Perianal Crohn – stem cells therapy and current medical approach
Gerhard Rogler, Zürich, CH

Is it time to invest in robotic surgery?
Antonino Spinelli, Milan, IT

New developments in robotic systems
Alberto Arezzo, Torino, IT

Robotic multivisceral resection
Paris Tekkis, London, UK

Posterior compartment separation for abdominal wall reconstruction: evolution from open to minimal invasive using the robotic platform
Filip Muysems, Gent, BE

Coloproctology 4.0 – the networked surgeon
Richard Brady
Newcastle upon Tyne, UK

The elderly colorectal patient – functional outcomes and patient reported outcomes
Isacco Montironi, Faenza, IT

The microbiome and colorectal cancer
Philip Quirke, Leeds, UK

Surgical management of rectal endometriosis
Eric Rullier, Bordeaux, FR

EAES Presidential Lecture 3D printing for the general surgeon
Andrea Pietrabissa, Pavia, IT

ROUNDTABLE

Herand Abcarian, Chicago, US
Bill Heald, Basingstoke, UK

Management of locoregionally advanced colon cancer
Torbjörn Holm, Stockholm, SE

Artificial intelligence in colorectal surgery
Michele Dianz, Strasbourg, FR

The mesentery in colonic diseases
Calvin Coffey, Luton, IE

Technical pearls and typical mistakes in minimal invasive colectomy
Antonio Lacy, Barcelona, ES

Choosing the right anastomotic technique in colon surgery
Roberto Persiani, Rom, IT

Precision surgery: past, present and future
Brendan Moran, Basingstoke, UK

Poster award
Michel Adamina, Winterthur, CH

Information & Registration

www.colorectalsurgery.eu

The publication of this advertisement does not constitute endorsement by the society, publisher, or Editors, and is unrelated to the content that follows.
Quality assurance of surgery in the randomized ST03 trial of perioperative chemotherapy in carcinoma of the stomach and gastro-oesophageal junction

W. H. Allum1, E. C. Smyth1, J. M. Blazeby3, H. I. Grabsch5,6, S. M. Griffin4, S. Rowley2, F. H. Cafferty2, R. E. Langley2 and D. Cunningham1

1Gastrointestinal Unit, Royal Marsden NHS Foundation Trust, and 2Medical Research Council Clinical Trials Unit at University College London, London, 3Bristol Centre for Surgical Research, Bristol Medical School, University of Bristol, Bristol, 4Department of Gastrointestinal Surgery, Royal Victoria Infirmary, Newcastle upon Tyne, and 5Pathology and Data Analytics, Leeds Institute of Medical Research at St James's, School of Medicine, University of Leeds, Leeds, UK, and 6Department of Pathology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands

Correspondence to: Mr W. H. Allum, Gastrointestinal Unit, Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK (e-mail: william.allum@rmh.nhs.uk)

Background: The UK Medical Research Council ST03 trial compared perioperative epirubicin, cisplatin and capecitabine (ECX) chemotherapy with or without bevacizumab (B) in gastric and oesophagogastric junctional cancer. No difference in survival was noted between the arms of the trial. The present study reviewed the standards and performance of surgery in the context of the protocol-specified surgical criteria.

Methods: Surgical and pathological clinical report forms were reviewed to determine adherence to the surgical protocols, perioperative morbidity and mortality, and final histopathological stage for all patients treated in the study.

Results: Of 1063 patients randomized, 895 (84.2 per cent) underwent resection; surgical details were available for 880 (98.3 per cent). Postoperative assessment data were available for 873 patients; complications occurred in 458 (52.5 per cent) overall, of whom 71 (8.1 per cent) developed complications deemed to be life-threatening by the responsible clinician. The most common complications were respiratory (211 patients, 24.2 per cent). The anastomotic leak rate was 118 of 873 (13.5 per cent) overall; among those who underwent oesophagogastrectomy, the rate was higher in the group receiving ECX-B (23.6 per cent versus 9.9 per cent in the ECX group). Pathological assessment data were available for 845 patients. At least 15 nodes were removed in 82.5 per cent of resections and the median lymph node harvest was 24 (i.q.r. 17–34). Twenty-five or more nodes were removed in 49.0 per cent of patients. Histopathologically, the R1 rate was 24.9 per cent (208 of 834 patients). An R1 resection was more common for proximal tumours.

Conclusion: In the ST03 trial, the performance of surgery met the protocol-stipulated criteria. Registration number: NCT00450203 (http://www.clinicaltrials.gov).

Paper accepted 26 February 2019
Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.11184

Introduction

Surgeons in East Asia established the extent of resection of the stomach and the philosophy of extended lymphadenectomy1. However, whether this converts to a survival benefit in all patients has been controversial. Surgical resection for gastric and oesophagogastric junctional (OGJ) cancer in non-Asian countries has also been variable in extent. Most European studies have demonstrated limited benefit for extended lymphadenectomy2,3, with the exception of data from the long-term follow-up in the Dutch trial4 which confirmed fewer cancer deaths in the group treated by D2 dissection. Surgery for OGJ cancers has evolved based on the classification described by Siewert and colleagues5, in which patterns of lymph node spread were defined according to tumour origin in relation to the OGJ. Although some have promoted abdominal,
mediastinal and cervical nodal dissection, particularly for squamous cell carcinoma, most surgeons combine abdominal and posterior mediastinal nodal dissection into a so-called two-field lymphadenectomy.

This lack of consistency has led to global variability in surgical approach and individual surgeon practice. National guidelines, based on evidence and expert opinion, have been designed to promote consistency of surgical practice and have recommended D2 dissection and two-field lymphadenectomy in appropriately selected patients with gastric and OGJ cancer respectively. Another approach to assess and implement consistency of surgery is to conduct multicentre trials where the type and extent of surgery is prespecified in the trial protocol. In the MAGIC (Medical Research Council (MRC) Adjuvant Gastric Infusional Chemotherapy) trial, surgeons were recommended to resect local and regional perigastric lymph nodes, and at least sample more distant lymph nodes for staging. Based on this recommendation, the D2 resection rate in MAGIC was 41 per cent.

The MRC ST03 trial was designed to evaluate the addition of bevacizumab, which targets vascular endothelial growth factor, to the combination chemotherapy regimen used in the MAGIC trial. The primary outcome was overall survival, with secondary outcomes of macroscopic disease-free survival, progression-free survival, response rates to preoperative chemotherapy and curative (R0) resection rates. The study protocol described recommended surgical procedures and stipulated resection of a minimum of 15 lymph nodes from specified lymph node stations in order to meet the pathological staging requirements of the UICC TNM classification seventh edition, with further nodal dissection according to the individual surgeon’s discretion.

The aim of this report was to examine compliance with the surgical protocol in the ST03 trial, and to review whether surgical procedure influenced outcome, irrespective of perioperative treatment group. This is particularly important in view of the overall similar outcomes between the trial arms, as differences in surgical procedures could have confounded any treatment effect in the trial.

Methods

The MRC ST03 trial was a randomized phase II–III open-label comparison of perioperative epirubicin, cisplatin and capecitabine (ECX) with ECX and bevacizumab (ECX-B) in patients with operable oesophagogastric adenocarcinoma. The trial began in 2007, completed recruitment in 2014 and recruited 1063 patients; no significant difference in overall survival was demonstrated between the two arms of the trial.

Surgery

At trial entry, all patients were considered operable and fit for surgical resection. Eligibility criteria have been detailed previously. Patients entered into the trial included those with adenocarcinoma of the stomach, OGJ (Siewert types I, II and III) and lower oesophagus. Staging at diagnosis required spiral or multislice CT with laparoscopy for all patients with gastric tumours and Siewert II and III OGJ cancers, as well as for patients with Siewert type I and lower oesophageal cancers if indicated clinically. Endoscopic ultrasound examination was recommended for all lower oesophageal and Siewert type I, II or III cancers, and performed according to local practice for all other cancers. PET–CT and MRI were recommended where clinically indicated according to local practice. Eligible stages were based on the sixth edition of the TNM classification (stomach, Siewert type III OGJ: stage Ib, II, III and IV with no evidence of distant metastases; oesophagus (lower third, Siewert types II and III): stage II to IVa), including those with positive coeliac axis nodes if the surgeon believed that R0 resection could be achieved. The trial protocol stipulated pathological staging according to the TNM sixth edition initially, but this was changed to the seventh edition during the trial with appropriate protocol amendment. For patients treated with ECX, surgery was planned for 5–6 weeks after the completion of preoperative chemotherapy; for those who had ECX-B, surgery was scheduled 8 weeks after the last dose of bevacizumab.

Recommended surgical procedures

At the time of trial initiation, oesophageal and gastric cancer surgery had been centralized in specialist centres across the UK, with experienced surgeons working in multidisciplinary teams that specialized in the management of patients with upper gastrointestinal cancer. Many surgeons and oncologists had taken part in the previous ST01, ST02 (MAGIC) and OE02 trials. In view of this experience, the protocol did not mandate any further quality assessment other than the following procedure descriptions.

For gastric and Siewert type III cancers, acceptable resection methods included proximal gastrectomy for Siewert type III cancers and cancers of the cardia; total gastrectomy for Siewert type III cancers and cancers of the cardia, fundus or body; and distal subtotal gastrectomy for cancers of the antrum. Combined resection of other organs was permitted if required to achieve complete macroscopic tumour resection. In both total and distal gastrectomy, the greater omentum was removed. For Siewert type II cancers, either extended gastrectomy or two-phase oesophagogastrectomy...
was recommended at the surgeon’s discretion. For lower oesophageal and Siewert type I OGJ tumours, oesophagogastrectomy, either as a two-phase right thoracoabdominal approach or a left thoracoabdominal approach, was recommended. Removal of sufficient crural fibres and a cuff of diaphragm, together with the pericardial fat pad and adjacent strips of parietal pleura, was recommended to minimize the risk of a positive radial resection margin.

Acceptable methods of reconstruction according to the surgeon’s preference included oesophagogastrostomy, oesophagojejunostomy (Roux-en-Y), oesophagojejuno-gastrostomy (jejunal interposition), gastrojejunostomy (Roux-en-Y or Billroth II) and gastrojejunoduodenostomy (jejunal interposition). Anastomotic techniques included handsewn, stapled or combined approaches.

The recommended extent of lymphadenectomy was determined by the location of the primary tumour and the type of resection. The protocol mandated the removal of additional lymph nodes from other lymph node stations to ensure that the total number of lymph nodes excised exceeded 15. A formal D2 dissection was the preferred option for gastric and Siewert type III cancers. This included removal of lymph node stations 1, 2, 3, 7, 8 and 11 via the abdomen. In the thoracic phase, paraoesophageal and diaphragmatic lymph node stations (stations 108, 110 and 111) should ideally be removed en bloc in continuity with the lower oesophagus and lymph nodes at the tracheal bifurcation and along the right and left main bronchi to the pulmonary hilus (stations 107 and 109). The surgical clinical report form required recording of the extent of lymph node dissection as one group of lymph node stations and did not allow for dissection of multiple stations (Table S2, supporting information).

The option of a minimally invasive approach was included if specific eligibility criteria for this type of procedure were met. The Trial Management Group (TMG) determined that, for totally minimally invasive procedures, surgeons should provide summary evidence of their previous 20 minimally invasive operations, including total gastrectomy and oesophagogastrectomy, with details of lymph node yields in both the abdomen and the mediastinum and postoperative complication rates. A hybrid approach of an open chest procedure combined with a laparoscopic abdominal procedure was permitted for lower oesophageal, and Siewert type I and II OGJ cancers, without review of previous cases.

Pathology

The ST03 trial protocol included a detailed briefing document for local pathologists to ensure standardized local pathology procedures and high-quality pathology in all centres. Pathological staging was initially done according to the sixth edition of the TNM classification13, but changed to the seventh edition12 once this had been published, with appropriate trial protocol modification. Pathological reporting of pretreatment biopsy and resection specimens was based largely on the WHO classification of digestive tumours (4th edition)16, the Royal College of Pathologists data sets for oesophageal and gastric cancer17,18 and other relevant literature. As a result, the trial pathology reporting pro forma required details of T category (including macroscopic and histological detail), N status (based on number of nodes examined and number positive) and histologically confirmed distant metastases. In addition, assessment of tumour response using the Mandard system19 and resection margin involvement (longitudinal and circumferential, defined as viable tumour within 1 mm of the margin) was required. Following full reporting of the pathology of the resected specimen and review at the local multidisciplinary team meeting, centres were asked to send all haematoxylin and eosin-stained histological slides of pretreatment biopsies and the resected specimens, together with the respective reports and photographic documentation, for central pathological review.

Analysis

Details of surgery and the postoperative clinical course were recorded prospectively on case report forms, which were analysed at the MRC Clinical Trials Unit at University College London.

All toxicity in the trial was reported according to Common Terminology Criteria for Adverse Events (CTC-AE) version 3.020, then grouped by organ system. Specific surgery-related postoperative complications in the data set included intraoperative events, anastomotic leak (clinical versus radiological), return to surgery, intestinal obstruction, pancreatic fistula and intra-abdominal sepsis. Anastomotic leaks were recorded as clinical, radiological/endooscopic or both clinical and radiological/endooscopic. General postoperative complications included cardiorespiratory and thromboembolic events, sepsis and renal dysfunction. Pathology-related outcomes were measured using lymph node yield and resection margin involvement.

All data were tabulated and summarized (with either percentages or median (i.q.r.), as appropriate) according to treatment group and in the trial as a whole. No comparative
Results

Of 895 patients who underwent resectional surgery in the ST03 trial (84.2 per cent of 1063 randomized), surgical details were available for 880 (98.3 per cent) (Fig. 1 and Table 1). There was no difference in surgical approaches across the arms of the trial. Open surgery was performed in 547 patients (62.2 per cent), and a minimally invasive approach in 222 (25.2 per cent), which was either a totally minimally invasive procedure (49, 5.6 per cent), a hybrid approach (laparoscopic abdomen and open thoracotomy: 110, 12.5 per cent) or a laparoscopically assisted procedure (63, 7.2 per cent). Data on surgical approach were missing for 77 patients (8.8 per cent). Extended lymphadenectomy including perigastric, left gastric, hepatic and splenic artery lymph nodes was performed according to the surgeon’s discretion in 46.6 per cent of patients, which was similar in both trial arms (Table S2, supporting information).

Sites undertaking total minimally invasive laparoscopic operations routinely within the trial were required to provide information on their previous experience with these techniques. Evidence was submitted for 67 of 112 operations at 14 sites. Of the remaining 45 operations, five were performed just once by centres and noted as a protocol deviation. The surgical requirements were followed by sites in 95.5 per cent of resection procedures.

Some 159 patients completed preoperative chemotherapy but did not undergo resection. Fifty-four of these patients had surgery, which comprised a laparotomy only (51 patients) or a laparotomy and bypass procedure (3 patients). The remaining patients did not undergo surgery...
Table 1 Surgical procedures and techniques

| Surgical procedure              | ECX (n = 450) | ECX-B (n = 430) | Total (n = 880) |
|--------------------------------|---------------|----------------|----------------|
| Oesophagogastrectomy           | 235 (52.2)    | 224 (52.1)     | 459 (52.2)     |
| Total gastrectomy              | 142 (31.6)    | 130 (30.2)     | 272 (30.9)     |
| Subtotal gastrectomy           | 16 (3.6)      | 17 (4.0)       | 33 (3.8)       |
| Proximal gastrectomy           | 1 (0.2)       | 1 (0.2)        | 2 (0.2)        |
| Distal gastrectomy             | 44 (9.8)      | 44 (10.2)      | 88 (10.0)      |
| Other                          | 12 (2.7)      | 14 (3.3)       | 26 (3.0)       |
| Surgical technique             |               |                |                |
| Open surgery                   | 275 (61.1)    | 272 (63.3)     | 547 (62.2)     |
| Laparoscopically assisted surgery | 36 (8.0) | 27 (6.3)       | 63 (7.2)       |
| Laparoscopic abdomen and open chest | 59 (13.1) | 51 (11.9)      | 110 (12.5)     |
| Laparoscopic abdomen and thoracoscopic chest | 26 (5.8) | 23 (5.3)       | 49 (5.6)       |
| Other                          | 12 (2.7)      | 22 (5.1)       | 34 (3.9)       |
| Missing                        | 42 (9.3)      | 35 (8.1)       | 77 (8.8)       |

Values in parentheses are percentages. ECX, epirubicin, cisplatin and capecitabine; B, bevacizumab.

Table 2 Summary of postoperative complications

| All postoperative complications (maximum severity) | ECX (n = 446) | ECX-B (n = 427) | Total (n = 873) |
|--------------------------------------------------|---------------|----------------|----------------|
| None                                             | 231 (51.8)    | 184 (43.1)     | 415 (47.5)     |
| Non-life-threatening                              | 178 (39.9)    | 209 (48.9)     | 387 (44.3)     |
| Life-threatening                                 | 37 (8.3)      | 34 (8.0)       | 71 (8.1)       |
| Notable events (maximum severity)                |               |                |                |
| None                                             | 369 (82.7)    | 330 (77.3)     | 699 (80.1)     |
| Non-life-threatening                              | 62 (13.9)     | 81 (19.0)      | 143 (16.4)     |
| Life-threatening                                 | 15 (3.4)      | 16 (3.7)       | 31 (3.6)       |
| Other complications, not notable events (maximum severity) | | | |
| None                                             | 245 (54.9)    | 213 (49.9)     | 458 (52.5)     |
| Non-life-threatening                              | 172 (38.6)    | 187 (43.8)     | 359 (41.1)     |
| Life-threatening                                 | 29 (6.5)      | 27 (6.3)       | 56 (6.4)       |
| Revisional operations                            |               |                |                |
| No                                               | 406 (91.0)    | 390 (91.3)     | 796 (91.2)     |
| Yes                                              | 39 (8.7)      | 37 (8.7)       | 76 (8.7)       |
| Unknown                                         | 1 (0.2)       | 0 (0)          | 1 (0.1)        |
| Death before discharge from hospital             |               |                |                |
| No                                               | 432 (96.9)    | 414 (97.0)     | 846 (96.9)     |
| Yes                                              | 12 (2.7)      | 11 (2.6)       | 23 (2.6)       |
| Unknown                                         | 2 (0.4)       | 2 (0.5)        | 4 (0.5)        |

Values in parentheses are percentage of patients with postoperative assessment details available; this information was missing for 11 patients who underwent surgery in each group. ECX, epirubicin, cisplatin and capecitabine; B, bevacizumab.

because of disease progression, patient preference or for a number of other reasons.

Postoperative complications

Postoperative morbidity and mortality after resection are summarized in Table 2. Postoperative assessment details were available for 97.5 per cent of operated patients (873 of 895). There were 24 deaths (2.7 per cent) within 30 days of surgery and 33 (3.7 per cent) within 90 days. There were no deaths within 30 days among those who underwent laparotomy alone and were found to be inoperable (Table S3, supporting information).

Complications were recorded as wound-related, including wound healing, wound infection, intra-abdominal sepsis and haemorrhage, or respiratory, including pleural
| Complication                                | ECX (n = 446) | ECX-B (n = 427) | Total (n = 873) |
|--------------------------------------------|---------------|-----------------|---------------|
| **Wound healing complications**            |               |                 |               |
| No                                         | 413 (92.6%)   | 374 (87.6%)     | 787 (90.1%)   |
| Present but not life-threatening            | 30 (6.7%)     | 48 (11.2%)      | 78 (8.9%)     |
| Life-threatening                            | 3 (0.7%)      | 5 (1.2%)        | 8 (0.9%)      |
| **Superficial wound infection**            |               |                 |               |
| No                                         | 409 (91.7%)   | 389 (91.1%)     | 798 (91.4%)   |
| Present but not life-threatening            | 35 (7.8%)     | 37 (8.7%)       | 72 (8.2%)     |
| Life-threatening                            | 2 (0.4%)      | 1 (0.2%)        | 3 (0.3%)      |
| **Deep wound infection**                   |               |                 |               |
| No                                         | 431 (96.6%)   | 415 (97.2%)     | 846 (96.9%)   |
| Present but not life-threatening            | 12 (2.7%)     | 8 (1.9%)        | 20 (2.3%)     |
| Life-threatening                            | 3 (0.7%)      | 4 (0.9%)        | 7 (0.8%)      |
| **Intra-abdominal sepsis**                 |               |                 |               |
| No                                         | 428 (96.0%)   | 410 (96.0%)     | 838 (96.0%)   |
| Present but not life-threatening            | 11 (2.5%)     | 10 (2.3%)       | 21 (2.4%)     |
| Life-threatening                            | 7 (1.6%)      | 7 (1.6%)        | 14 (1.6%)     |
| **Haemorrhage requiring transfusion or intervention** |               |                 |               |
| No                                         | 433 (97.1%)   | 414 (97.0%)     | 847 (97.0%)   |
| Present but not life-threatening            | 9 (2.0%)      | 6 (1.4%)        | 15 (1.7%)     |
| Life-threatening                            | 4 (0.9%)      | 7 (1.6%)        | 11 (1.3%)     |
| **Pleural effusion requiring treatment**   |               |                 |               |
| No                                         | 396 (88.8%)   | 386 (90.4%)     | 782 (89.6%)   |
| Present but not life-threatening            | 45 (10.1%)    | 35 (8.2%)       | 80 (9.2%)     |
| Life-threatening                            | 5 (1.1%)      | 6 (1.4%)        | 11 (1.3%)     |
| **Empyema**                                |               |                 |               |
| No                                         | 437 (98.0%)   | 409 (95.8%)     | 846 (96.9%)   |
| Present but not life-threatening            | 8 (1.8%)      | 14 (3.3%)       | 22 (2.5%)     |
| Life-threatening                            | 1 (0.2%)      | 4 (0.9%)        | 5 (0.6%)      |
| **Respiratory failure**                    |               |                 |               |
| No                                         | 419 (93.9%)   | 404 (94.6%)     | 823 (94.3%)   |
| Present but not life-threatening            | 14 (3.1%)     | 10 (2.3%)       | 24 (2.7%)     |
| Life-threatening                            | 13 (2.9%)     | 13 (3.0%)       | 26 (3.0%)     |
| **Respiratory tract infection**            |               |                 |               |
| No                                         | 374 (83.9%)   | 356 (83.4%)     | 730 (83.6%)   |
| Present but not life-threatening            | 66 (14.8%)    | 64 (15.0%)      | 130 (14.9%)   |
| Life-threatening                            | 6 (1.3%)      | 7 (1.6%)        | 13 (1.5%)     |
| **Pulmonary embolism**                     |               |                 |               |
| No                                         | 439 (98.4%)   | 418 (97.9%)     | 857 (98.2%)   |
| Present but not life-threatening            | 5 (1.1%)      | 8 (1.9%)        | 13 (1.5%)     |
| Life-threatening                            | 2 (0.4%)      | 1 (0.2%)        | 3 (0.3%)      |
| **Deep vein thrombosis**                   |               |                 |               |
| No                                         | 443 (99.3%)   | 420 (98.4%)     | 863 (98.9%)   |
| Present but not life-threatening            | 3 (0.7%)      | 6 (1.4%)        | 9 (1.0%)      |
| Life-threatening                            | 0 (0)         | 1 (0.2%)        | 1 (0.1%)      |
| **Cardiac complications**                  |               |                 |               |
| No                                         | 423 (94.8%)   | 397 (93.0%)     | 820 (93.9%)   |
| Present but not life-threatening            | 15 (3.4%)     | 24 (5.6%)       | 39 (4.5%)     |
| Life-threatening                            | 8 (1.8%)      | 6 (1.4%)        | 14 (1.6%)     |
Values in parentheses are percentage of patients with postoperative assessment details available; this information was missing for 11 patients who underwent surgery in each group. ECX, epirubicin, cisplatin and capecitabine; B, bevacizumab; MRSA, methicillin-resistant *Staphylococcus aureus*.

**Table 3 Continued**

| MRSA                                      | ECX (n = 446) | ECX-B (n = 427) | Total (n = 873) |
|-------------------------------------------|---------------|-----------------|-----------------|
| No                                        | 437 (98.0)    | 421 (98.6)      | 858 (98.3)      |
| Present but not life-threatening           | 9 (2.0)       | 6 (1.4)         | 15 (1.7)        |
| Other                                     |               |                 |                 |
| No                                        | 337 (75.6)    | 309 (72.4)      | 646 (74.0)      |
| Present but not life-threatening           | 95 (21.3)     | 100 (23.4)      | 195 (22.3)      |
| Life-threatening                           | 14 (3.1)      | 18 (4.2)        | 32 (3.7)        |

Values in parentheses are percentages. *Includes subtotal, distal and proximal gastrectomies. †Requiring transfusion or intervention.

**Table 4 Postoperative complications by procedure**

|                  | Oesophagogastrectomy (n = 453) | Total gastrectomy (n = 272) | Subtotal gastrectomy* (n = 123) | Other (n = 25) |
|------------------|---------------------------------|-----------------------------|---------------------------------|----------------|
| Sepsis           | 80 (17.7)                       | 51 (18.8)                   | 20 (16.3)                       | 7 (28)         |
| Respiratory      | 145 (32.0)                      | 45 (16.5)                   | 12 (9.8)                        | 9 (36)         |
| Bleeding†        | 17 (3.8)                        | 6 (2.2)                     | 2 (1.6)                         | 1 (4)          |
| Thromboembolic   | 15 (3.3)                        | 4 (1.5)                     | 5 (4.1)                         | 1 (4)          |
| Cardiovascular   | 38 (8.4)                        | 9 (3.3)                     | 4 (3.3)                         | 2 (8)          |
| Other            | 137 (30.2)                      | 57 (21.0)                   | 21 (17.1)                       | 12 (48)        |

Surgical complications

Two specific indicators of technical complications were evaluated: anastomotic leaks and return to theatre. Combining both trial arms, the anastomotic leak rate was 13.5 per cent (118 of 873 patients with postoperative data available) (Table 5). Twenty-six patients had clinical leaks, 25 leaks were identified radiologically or endoscopically, and 65 were diagnosed clinically and confirmed radiologically or endoscopically; in two patients the evidence for a leak was unclear. After oesophagogastrectomy, the anastomotic leak rate was higher in those randomized to ECX-B than in the ECX group: 52 of 220 (23.6 per cent) versus 23 of 233 (9.9 per cent) respectively. There was no difference between groups in leak rates after any type of gastrectomy. The anastomotic leak rate was 10.2 per cent (43 of 420) in patients undergoing a procedure other than oesophagogastrectomy. The majority of leaks (80 of 118, 67.8 per cent) occurred within the first 10 days after surgery.

Seventy-six patients (8.7 per cent) had to return to the operating theatre in the initial postoperative period; this occurred in the first week in 38 patients (50 per cent) and in the second week in a further 20 (26 per cent). The commonest reasons for reoperation were anastomotic leak (18 patients, 24 per cent), and laparotomy (17, 22 per cent) or thoracotomy (12, 16 per cent) for lavage to treat sepsis.
Table 5: Anastomotic leak rates

| By tumour site at randomization | ECX (n = 446) | ECX-B (n = 427) | Total (n = 873) |
|--------------------------------|--------------|----------------|----------------|
| Lower oesophageal               | 7 of 65 (11) | 16 of 59 (27)  | 23 of 124 (18.5)|
| OGJ, type I                     | 5 of 57 (9)  | 10 of 53 (19)  | 15 of 110 (13.6)|
| OGJ, type II                    | 11 of 87 (13)| 12 of 71 (17)  | 23 of 158 (14.6)|
| OGJ, type III                   | 6 of 75 (8)  | 19 of 88 (22)  | 25 of 163 (15.3)|
| Stomach                         | 14 of 162 (8.6)| 18 of 156 (11.5)| 32 of 318 (10.1)|
| By surgical procedure           |              |                |                |
| Oesophagogastrectomy            | 23 of 233 (9.9)| 52 of 220 (23.6)| 75 of 453 (16.6)|
| Total gastrectomy               | 18 of 139 (13.0)| 19 of 129 (14.7)| 37 of 268 (13.8)|
| Subtotal gastrectomy            | 0 of 16 (0)   | 1 of 17 (6)    | 1 of 33 (3)    |
| Distal gastrectomy              | 1 of 43 (2)   | 2 of 43 (5)    | 3 of 86 (3)    |
| Other                           | 1 of 15 (7)   | 1 of 18 (6)    | 2 of 33 (6)    |
| By surgical procedure (combined)|              |                |                |
| Oesophagogastrectomy            | 23 of 233 (9.9)| 52 of 220 (23.6)| 75 of 453 (16.6)|
| All other procedures            | 20 of 213 (9.4)| 23 of 207 (11.1)| 43 of 420 (10.2)|
| Overall                         | 43 of 446 (9.6)| 75 of 427 (17.6)| 118 of 873 (13.5)|

Values in parentheses are percentages. ECX, epirubicin, cisplatin and capecitabine; B, bevacizumab; OGJ, oesophagogastric junctional.

Table 6: Total number of lymph nodes retrieved from the resected specimen according to local pathologists

| Total no. of lymph nodes | ECX (n = 436) | ECX-B (n = 409) | Total (n = 845) |
|--------------------------|--------------|----------------|----------------|
| Median (i.q.r.)          | 24 (17–33)   | 25 (18–34)     | 24 (17–34)     |
| Range                    | 0–96         | 0–89           | 0–96           |
| 0                        | 5 (1·1)      | 5 (1·2)        | 10 (1·2)       |
| < 15                     | 74 (17·0)    | 57 (13·9)      | 131 (15·5)     |
| 15–24                    | 146 (33·5)   | 137 (33·5)     | 283 (33·5)     |
| 25–34                    | 109 (25·0)   | 110 (26·9)     | 219 (25·9)     |
| 35–44                    | 56 (12·8)    | 60 (14·7)      | 116 (13·7)     |
| ≥ 45                     | 42 (9·6)     | 37 (9·0)       | 79 (9·3)       |
| Unknown                  | 4 (9·9)      | 3 (0·7)        | 7 (0·8)        |

Values in parentheses are percentages unless indicated otherwise. ECX, epirubicin, cisplatin and capecitabine; B, bevacizumab.

Surgical pathology

Details of pathological staging and response to chemotherapy have been described previously. Pathology results were available for 845 patients (94.4 per cent of those who underwent tumour resection). The median number of lymph nodes dissected from the resection specimen by the local pathologist was 24 (i.q.r. 17–34); this was similar in both arms of the trial. At least 15 lymph nodes were retrieved in 82.5 per cent of resection specimens, and 25 or more lymph nodes in 49.0 per cent of specimens (Table 6).

Information on pathological resection margin status was available for 834 patients; 626 of these patients (75.1 per cent) had an R0 resection and 208 (24.9 per cent) had a pathologically positive resection margin (R1) (Table S4, supporting information). The majority with an R1 margin (146 patients) had an oesophagogastrectomy, and 132 of these patients had a positive circumferential (radial) margin. This equated to an R1 resection rate of 31.8 per cent for all of the oesophagogastric resections. The remaining R1 resections included proximal resection margin involvement in 42 patients (20.2 per cent of all R1 resections) and distal margin involvement in 33 (15.9 per cent).

Discussion

The ST03 trial was a national multicentre trial that recruited patients at almost 100 hospitals in the UK between 2007 and 2013. Its primary outcome was overall survival between the two treatment arms. The trial had a pragmatic design, with R0 resection as the only secondary outcome measure with a surgical theme. As a result, specific details of surgical procedures were not recorded as in
a trial comparing surgical procedures. This trial therefore delivers a snapshot of UK contemporary surgical practice. The ST03 surgical protocol was designed to prespecify the surgical approaches and extent of resection to minimize performance bias related to individual surgeon preference, which may be influenced by tumour response to perioperative chemotherapy. The study included prospective data collection on case report forms to record the type of surgical procedure actually undertaken. Development of the ST03 trial protocol was informed by best current evidence. However, it was also pragmatic, thus allowing flexibility in several components of the intervention (such as minimal access or open surgery, extent of lymph node dissection). High-quality pathological data were available to relate surgical procedures to outcome measures, such as lymph node yield and resection margin status, owing to use of a prespecified histopathology protocol, which included detailed guidance for local pathologists as well as a comprehensive prospective data collection. This analysis showed that surgical procedures and outcomes were similar in both arms of the trial. Therefore, heterogeneity of surgical approach was unlikely to be responsible for the lack of benefit observed in the experimental arm of the trial.

The inclusion of minimally invasive surgery required a protocol modification as such techniques were not commonplace at the inception of the trial. The TMG required surgeons undertaking these procedures in patients entered into the trial to provide evidence of their qualitative outcomes. Despite this requirement, formal review by the TMG was completed for only 28.1 per cent of the minimally invasive procedures undertaken. Retrospective review of the remaining patients showed no excess complication rates and equivalent lymph node yields, suggesting consistency of the quality of the surgery. However, this does highlight one of the challenges in a randomized trial where protocol modifications may be required that could affect outcome.

Despite comprehensive staging assessments at the time of diagnosis and randomization into the trial, 15.8 per cent of the trial population did not undergo resection, with 5.1 per cent found to be inoperable at laparotomy. The outcome for this group was not complicated by excess postoperative morbidity. These levels of inoperability and unresectability are important findings, which should be explained to patients when entering into a trial21.

Surgeons performing operations and pathologists dissecting resection specimens within the context of the ST03 trial were highly compliant with respect to the protocol requirement of resecting and retrieving a minimum of 15 lymph nodes; this goal was achieved in 82.5 per cent of resections. Furthermore 25 or more lymph nodes were retrieved by the pathologist in 49.0 per cent of resections. Although pathological examination of the resected specimens in the trial was based on Royal College of Pathologists guidance, there are limitations in this data as lymph node stations were not examined individually in the majority of patients. Nevertheless, these lymph node harvest figures show a definite increase compared with those in the MAGIC trial10, in which 53 per cent of patients had more than 15 nodes removed and 19 per cent had more than 25 excised. Notably, in the MAGIC trial, surgeons undertook procedures at their discretion; the extent of lymphadenectomy was not specified in the MAGIC trial protocol. Moreover, these lymph node yield figures are higher than those reported in the Dutch CRITICS22 trial, in which 72.8 per cent of resections were compliant with the protocol stipulation of sampling a minimum of 15 nodes and 87.5 per cent of patients had at least a D1+ resection. Furthermore, the median number of nodes examined in CRITICS was 20 (range 0–72) contrasting with 24 (0–96) in ST03.

Surgery in the ST03 study was associated with a low rate of postoperative mortality which, at 3.7 per cent at 90 days, is a further improvement in comparison with both the MAGIC trial (ST02), in which the 90-day mortality rate was 6 per cent, and the MRC ST01 study, with hospital mortality rates of 9 and 16 per cent after D1 and D2 total gastrectomy respectively. The postoperative mortality rate in ST03 was similar to that reported for oesophagectomy and gastrectomy in the UK National Oesophago-Gastric Cancer Audit (NOGCA)23, which records approximately 98 per cent of cases resected annually in the UK.

Despite these improvements in postoperative mortality compared with earlier trials, there was a relatively high rate of postoperative complications in ST03 (52.5 per cent of all patients). However, this figure describes all levels of the spectrum of complications, including many that did not require clinical intervention. This represents a limitation of the present study and is a reflection of the protocol, which was developed before more specific definition of complications was standardized. The authors therefore advocate use of a systematic classification such as the Clavien–Dindo classification24 in future trials as well as consensus guidance on recording complications25,26. In addition, patients undergoing oesophageal and gastric cancer resection have established comorbidity, and optimization of pulmonary function should be standard practice in the context of rehabilitation and enhanced recovery approaches to minimize predictable postoperative complications.

Overall compliance with the protocol in ST03 represents a definite improvement in surgical and pathology practice compared with previous studies. However, it is important
to recognize that surgery within the ST03 trial was subject to a number of other significant changes in practice. The trial was undertaken during the time of reconfiguration of surgical services for oesophageal and gastric cancer in the UK, which included greater prominence of multidisciplinary team management for all patients. In addition, there was enhanced surgical and pathology specialization as well as advances in critical and intensive care treatments. The inclusion of minimally invasive techniques required a careful review of practice and outcomes for those wishing to use these procedures in the context of their established expertise. The majority of surgeons had contributed to previous multicentre studies (ST01, ST02 and OE05). It was acknowledged that their adherence to the protocol would not be problematic, and specific evidence of their practice and outcomes was not considered necessary. Data from audits have clearly shown improvements and consistency in overall outcome with the emphasis on quality assurance and publication of individual-surgeon outcomes. The pragmatic nature of this trial has shown how large multicentre trials can be undertaken effectively with consistent outcomes.

Two challenges are highlighted by the ST03 results. The first of these, the high rate of anastomotic leak in patients who underwent oesophagogastrectomy after treatment with bevacizumab (23.6 per cent), is unique to the present trial. This inflated the overall rate of anastomotic leakage to 13.5 per cent, which compares unfavourably with 7 per cent in the NOGCA data set. However, the overall reoperation rate of 8.7 per cent is comparable to rates of 9-8 per cent for oesophagectomy and 8-1 per cent for gastrectomy recorded in the NOGCA. Despite careful evaluation of all potential variables, it was not possible to explain the difference in leak rate between patients who received bevacizumab and those who did not, and it is currently considered to represent a potential adverse effect on local healing secondary to microvascular insufficiency related to treatment with bevacizumab. Consideration of other data and sensitivity analyses did not provide any indication that this excess rate of anastomotic leakage had a substantial effect on the overall primary outcome of the trial; the Independent Data Monitoring Committee had reviewed the data when this rate was identified and stopped recruitment of patients scheduled for oesophagogastrectomy.

The second challenge is the relatively high rate of R1 resections (25.1 per cent) in the trial (gastrectomy 15.7 per cent and oesophagogastrectomy 31.8 per cent). The majority of positive margins (90.4 per cent for oesophagogastrectomies) were circumferential. Similar results have been reported in the contemporaneous OE05 study, in which the R1 rate was 34 per cent. The OE05 protocol specified the extent of dissection at the diaphragmatic hiatus to include resection of a cuff of diaphragm and both parietal pleura adjacent to the OGj. Compliance with this aspect of the protocol has not been determined in the present trial. However, lower rates of circumferential resection margins have been described in surgical series with more radical procedures. In CROSS (Chemoradiotherapy for Oesophageal cancer followed by Surgery Study), the R1 rate in the chemoradiotherapy arm was 8 per cent compared with 30 per cent in the control surgery-only arm. There is thus a challenge to determine whether more standardized surgery can achieve R0 rates similar to those achieved after neoadjuvant chemoradiotherapy. However, the high R0 rate in the treatment arm of the CROSS trial may reflect the effect of chemoradiotherapy as well as the fact that patients with adenocarcinoma and those with squamous cell carcinoma were included in the trial. Furthermore, more contemporary taxane-containing preoperative chemotherapy regimens such as FLOT (5-fluorouracil, oxaliplatin and docetaxel) seem to be associated with improved R0 resection rates compared with the anthracycline-based regimens used in ST03 and OE05. This is of particular relevance, as the survival benefit of chemoradiotherapy over perioperative chemotherapy is still unclear. Ongoing clinical trials are currently addressing this issue. The results of these studies and assessment of response to neoadjuvant therapy are likely to affect selection of patients who have the greatest chance of benefit from operative intervention.

The present analysis has shown that surgery in the ST03 trial was performed to a higher standard than in previous similar UK trials, in terms of postoperative mortality and lymphadenectomy, which also reflects a higher standard of pathology reporting. This was consistent across both treatment arms, indicating that surgery had no effect on the overall outcome of the trial. The rates of postoperative complications were high, partly reflecting the inclusion of all grades of morbidity, although few patients developed life-threatening complications. There remains the challenge of achieving a higher rate of R0 resection to complement the benefits of perioperative strategies.

**Acknowledgements**

The trial was sponsored and coordinated by the UK Medical Research Council (MRC) Clinical Trials Unit at University College London (MC_UU_12023/28), with funding from Cancer Research UK (C1504/A6410). F. Hoffmann-La Roche provided free bevacizumab and an educational grant. D.C. and E.C.S. were funded by the
National Institute for Health Research (NIHR) Biomedical Research Centre based at the Royal Marsden and Institute of Cancer Research. J.M.B was supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust, and the MRC ConDuCT-II (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures) Hub for Trials Methodology Research (MR/K025643/1). J.M.B. is an NIHR Senior Investigator. H.I.G was funded by Cancer Research UK for slide collection and central pathology review.

D.C. reports research funding from Amgen, AstraZeneca, Bayer, Celgene, MedImmune, Merck Serono, Merrimack and Sanofi. E.C.S. declares honoraria for an advisory role from BMS, Celgene, Gritstone Oncology, Five Prime Therapeutics and Servier.

Disclosure: The authors declare no other conflict of interest.

References

1 Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017; 20: 1–19.
2 Cuschieri A, Weeden S, Fielding J, Banciewicz J, Craven J, Joypaul V et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. *Surgical Co-operative Group*. *Br J Cancer* 1999; 79: 1522–1530.
3 Bonenkamp JJ, Songun I, Hermans J, Sasaki M, Welvaart K, Plukker JT et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995; 345: 745–748.
4 Songun I, Putter H, Kranevanger EM, Sasaki M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; 11: 439–449.
5 Rüdiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastroduodenal junction: results of surgical therapy based on anatomical/topographic classification in 1002 consecutive patients. *Ann Surg* 2000; 232: 353–361.
6 Lerut T, Nafeux P, Moons J, Coosemans W, Decker G, De Leyn P et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg* 2004; 240: 965–974.
7 Griffin SM. Surgery for cancer of the oesophagus. In *A Companion to Specialist Surgical Training: Upper Gastrointestinal Surgery*, Griffin SM, Raines SA (eds). WB Saunders: London, 1998; 111–144.
8 Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland. The British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011; 60: 1449–1472.
9 Moehler M, Al-Batran SE, Andus T, Anthuber M, Arends J, Arnold D et al.; AWMF. [German S3-guideline ‘Diagnosis and treatment of esophagogastric cancer’.] *Z Gastroenterol* 2011; 49: 461–531.
10 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M et al.; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11–20.
11 Cunningham D, Stenning SP, Smyth EC, Okines AF, Allum WH, Rowley S et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. *Lancet Oncol* 2017; 18: 357–370.
12 AJCC. AJCC Cancer Staging Manual (7th edn). Springer International Publishing: New York, 2010.
13 Sobin LH, Wittekind C (eds). *TNM Classification of Malignant Tumours* (6th edn). John Wiley: New York, 2002.
14 Allum WH, Stenning SP, Banciewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; 27: 5062–5067.
15 MRC Clinical Trials Unit. *ST03 Trial Protocol*. https://www.cru.mrc.ac.uk/1298/st03-protocol.pdf [accessed 13 February 2019].
16 Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). *WHO Classification of Tumours of the Digestive System* (4th edn). IARC: Lyon, 2010.
17 Mapstone NP. *Standards and Datasets for Reporting Cancers – Dataset for the Histopathological Reporting of Oesophageal Carcinoma* (2nd edn). Royal College of Pathologists: London, 2006.
18 Novelli M. *Standards and Datasets for Reporting Cancers – Dataset for the Histopathological Reporting of Gastric Carcinoma* (2nd edn). Royal College of Pathologists: London, 2006.
19 Mandard AM, Dalilhard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: clinicopathologic correlations. *Cancer* 1994; 73: 2680–2686.
20 National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. *Common Terminology Criteria for Adverse events (CTCAE). Version 3*. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services: Washington DC, 2003.
21 Blencowe NS, Chana P, Whistance RN, Stevens D, Wong NA, Falk SJ et al. Outcome reporting in neoadjuvant surgical trials: a systematic review of the literature and proposals for new standards. *J Natl Cancer Inst* 2014; 106: dju217.
Surgical quality assurance in the ST03 trial

22 Claassen YHM, de Steur WO, Hartgrink HH, Dikken JL, van Sandick JW, van Grieken NCT et al. Surgicopathological quality control and protocol adherence to lymphadenectomy in the CRITICS gastric cancer trial. Ann Surg 2018; 268: 1008–1013.

23 Healthcare Quality Improvement Partnership. National Oesophago-gastric Cancer Audit 2017. Healthcare Quality Improvement Partnership: London, 2017.

24 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205–213.

25 Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D’Journo XB et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015; 262: 286–294.

26 Baiocchi GL, Giacopuzzi S, Marrelli D, Reim D, Piessen G, Matos da Costa P et al. International consensus on a complications list after gastrectomy for cancer. Gastric Cancer 2019; 22: 172–189.

27 Alderson D, Cunningham D, Nankivell M, Blazeby JM, Griffin SM, Crellin A et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol 2017; 18: 1249–1260.

28 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP et al.; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074–2084.

29 Al-Batran SE, Homann N, Schmalenberg H, Kopp HG, Haag GM, Luley KB et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol 2017; 35(Suppl): Abstract 4004.