Comparing open and minimally invasive surgical procedures for oesophagectomy in the treatment of cancer: the ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) feasibility study and pilot trial

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Scientific summary

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Scientific summary

Background

Localised oesophageal cancer can be curatively treated with surgery (oesophagectomy). The national audit of patients in England and Wales (2011–20) undergoing oesophagectomy collected details of 1220 operations. Oesophagectomy had a 3% risk of in-hospital mortality, a 9% risk of reoperation and a 16% risk of respiratory complications. Health-related quality of life is significantly worsened after oesophagectomy, with patients reporting major impacts in terms of physical and social function, fatigue, breathlessness and pain for at least 3 months. Recovery takes about 6–9 months after open surgery.

There is therefore a need to improve outcomes of patients undergoing oesophagectomy. Minimal-access surgical techniques may cause less tissue damage and allow a more rapid recovery. Whether or not this is a cost-effective approach, however, is unknown, as high-quality comparative evidence is limited.

Two previous trials had methodological flaws that preclude firm conclusions being drawn from their results. In particular, the sample sizes were small and, therefore, the studies made only a modest contribution to the evidence of equivalent survival benefits with the different approaches to oesophagectomy. The primary end points reflected surgical interest and did not incorporate meaningful benefits for minimal-access surgery from the patients' perspective. Both trials were at risk of biased outcome assessment as assessors were not blinded and one trial used sealed envelopes for randomisation, bringing the concealment of allocation into question.

A UK trial is needed to provide definitive evidence on the relative cost-effectiveness of minimally invasive and open surgery for oesophagectomy. However, there are many challenges to conducting high-quality randomised trials of surgery. The particular hurdles that may affect a full trial of open oesophagectomy and minimally invasive oesophagectomy (MIO) are (1) strong preferences held by surgeons about the two procedures, which may mean that it is difficult to recruit centres to the main trial, and (2) preferences of patients that do not permit randomisation. The feasibility of the main trial would also be in doubt if (3) the number of eligible patients was lower than a mean of 2.5 patients per month per centre. These and further methodological issues were addressed in the feasibility study reported here.

Objectives

The ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open) feasibility study aimed to establish the methodology and infrastructure for a definitive trial comparing the cost-effectiveness of minimally invasive and open surgical techniques for oesophagectomy in the treatment of cancer. The core of this preliminary work was an assessment of the feasibility of comparing surgical procedures for oesophagectomy in a pilot two-centre randomised trial. Specific objectives were:

- To pilot the randomisation process and investigate reasons for any difficulties that affect recruitment so that these can be tackled before the main trial.
- To establish the proportion of potentially eligible patients who can be approached about the trial, who are confirmed as eligible, who are successfully recruited and randomised and who are able and willing to undergo research assessments. This addresses the feasibility of the main trial by indicating the achievable sample size and the number of centres required.

- To document in detail, using IDEAL (Innovation, Development, Exploration, Assessment, Long-term study) recommendations, the technical developments of the totally minimally invasive approach for oesophagectomy, to inform the design and choice of interventions in the main trial. This work developed manuals for the different surgical procedures, and methods of monitoring adherence to them, which will then be available for the main trial. It also informed the development of a competency assessment tool for objective evaluation of technical performance to be used to evaluate surgeons' skills before participating in the main trial.
- To develop a manual for the cutting up of specimens, specimen fixing and pathology to optimise the quality of lymph node counts and ascertainment of positive resection margins.
- To consider the appropriate statistical model for estimating treatment effectiveness while allowing for 'clustering' in the data because of between-surgeon variation.
- To develop and evaluate feasible, acceptable and effective methods of keeping patients blind to their treatment for the first week after surgery.
- To establish outcome measures for the main trial that are recognised as a comprehensive, valid and reliable assessment of oesophagectomy outcome by patients and the clinical community.

Methods

The ROMIO feasibility study was based around a pilot parallel three-arm randomised controlled trial (RCT) nested within feasibility work. This was conducted in two centres, University Hospitals Bristol NHS Foundation Trust and Plymouth Hospitals NHS Trust, which each have a team of upper gastrointestinal cancer surgeons.

Patients were eligible for the pilot trial if they were aged $\geq$ 18 years with confirmed histopathological evidence of oesophageal or oesophagogastric junctional adenocarcinoma, squamous cell cancer or high-grade dysplasia that was referred for oesophagectomy or oesophagectomy following neoadjuvant chemo(radio)therapy. The technology was oesophagectomy, with patients randomised to open surgery, a hybrid open chest and minimally invasive abdomen [laparoscopically assisted oesophagectomy (LAO)] or totally MIO.

The primary outcome measure for the pilot trial was the number of patients recruited per month, with the main trial being considered feasible if at least 2.5 patients per month were recruited. The primary outcome measure for the main trial was to be confirmed during the feasibility study based on expert input from the Trial Steering Committee and the consensus meetings held to inform the core outcome set. At the outset of the feasibility study the initial candidate for the primary outcome of the main trial was a patient report of fatigue.

Participants completed baseline measurements prior to random allocation. On the second day post surgery, patients completed assessments of pain and blinding, followed by completion of the full assessment 6 days, 6 weeks and 3 and 6 months after surgery. During the first year of the feasibility study, permission was obtained to continue follow-up for 3 years post randomisation. Patient-reported outcomes were subsequently administered at 9, 12, 18, 24 and 36 months.

Allocation of patients to surgical procedure was at random, the allocation being conducted separately for the two centres and further stratified by whether or not patients had undergone neoadjuvant treatment. Patients were randomly allocated to one of the three procedures at Bristol and to the open procedure or the two-phase laparoscopically assisted procedure at Plymouth. Allocation was concealed through centralised randomisation.

Recruitment to the pilot RCT was planned for a 12-month period, with 72 potentially eligible patients being expected during that time. This would allow a true 50% recruitment rate to be estimated with a 95% confidence interval of approximately 38% to 62%.

Summary statistics that inform plans for the main trial are presented including the number of potentially eligible patients per month per centre, the percentage of these patients confirmed as eligible, the percentage of patients agreeing to be randomly allocated to a study procedure in the pilot trial and the percentage of randomised patients completing outcome measurements.

Key aspects of the associated methodological work included the qualitative recruitment intervention, the documentation of the different surgical procedures and the production of materials to allow quality assurance of surgery and pathology, determination of outcome measures that are important to patients undergoing oesophagectomy and their clinicians, identification of the key cost differences between the surgical approaches and methods to capture these and establishing a method to keep patients blind to their treatment allocation while pain levels were assessed in the first week post surgery.

Results

In the first 21 months of recruitment (until the end of December 2014) 263 patients have been assessed for eligibility, of whom 135 (51%) were found to be eligible and 104 (77%) were randomised across the two centres. Of the recruited patients, 46 were from Plymouth ($n = 22$ open surgery, $n = 24$ LAO) and 58 were from Bristol ($n = 19$ open surgery, $n = 19$ LAO, $n = 20$ MIO). To allow continuation into the definitive trial, recruitment was continued beyond the planned 12-month period and was ongoing at the time of writing. In this report we focus on those patients randomised on or before 31 August 2014 for whom 6-week follow-up data were expected to be available for analysis.

The majority of participants were male and the mean age at randomisation was approximately 66 years for each treatment group (standard deviation approximately 7 years). A lower proportion of patients had undergone neoadjuvant treatment before surgery in Plymouth than in Bristol, although the proportion in each treatment arm was well balanced within each centre. Considering disease stage at diagnosis, most participants had a tumour that was growing through the wall of the oesophagus but involving one to two lymph nodes at most (stages 2a and 2b) or a cancer that had just started to spread to the tissues surrounding the oesophagus (stage 3a). There was no convincing evidence of imbalance between the randomised intervention arms in terms of disease staging.

The large majority of patients underwent their allocated surgical approach (69/79, 87%). The three patients for whom the allocation to open surgery could not be followed were found to be inoperable. Of the patients allocated to LAO, one converted to open surgery to stop a bleed, one requested MIO having spoken to a patient who had undergone this procedure previously and one underwent a gastrectomy for more extensive disease. Four patients allocated to MIO underwent LAO, two because of the position of the tumour and two because a surgeon was not available to undertake the MIO procedure.

The median length of postsurgical stay across the two centres was 10 days, with stays typically lasting between 8 and 16 days (interquartile range). Among the first 76 patients recruited there was one death occurring within 30 days of surgery, with a further death occurring on the 31st postsurgical day. Four anastomotic leaks occurred, all of which resulted in a return to theatre. A further nine patients returned to theatre one or more times. Eight patients returned to the intensive care unit, six because of respiratory problems and two because of renal failure. Eight patients were readmitted within 30 days of surgery.

Completion of the pain scale at day 2 post surgery was low (39/73, 53%), the reasons for non-completion being illness or insufficient recovery (9/73, 12%), lack of cover to administer the scale at the weekend (16/73, 22%) and administrative error (9/73, 12%). Completion of the pain scale was considerably better at day 6 (64/73, 88%). The primary outcome measure for the planned definitive trial is likely to be a patient-reported outcome at 6 weeks post randomisation; the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) was available for 74% (54/73) of participants at that time point.

Dressing patients with large bandages, covering all possible incisions, was successful in keeping patients blind while pain was assessed during the first week post surgery. On both day 2 and day 6, the majority of responders believed that they had undergone the LAO procedure, irrespective of their allocation.

Hierarchical task analysis has allowed the documentation of the steps of oesophagectomy and the differences between the open approach and the minimally invasive approach. Assessment tools have been produced for quality assurance of surgery, recorded on video or with photographs. This will be supplemented with an 'op note' allowing the recording of each step of the operation. The study pathologists at the two centres and the study's independent advisor have reached consensus on a standard approach to pathological processing and recording and have planned quality assurance procedures for the proposed main trial.

In conducting the qualitative recruitment intervention, the patient eligibility and recruitment pathway at each centre has been mapped. In-depth interviews with nine clinical investigators and staff undertaking recruitment have been conducted and analysed to explore views about the evidence on which the trial is based, perceptions of levels of equipoise in relation to the trial arms, how the arms are or can be delivered in their clinical centre and methods for identifying eligible patients. Audio recordings of > 100 consultations have also been conducted and analysed to scrutinise recruiters' ability to summarise the details of the trial design and protocol and provide information about the trial and to identify examples of actual recruitment successes and challenges. This has informed feedback and training meetings with recruiters. Furthermore, the patient information provided at recruitment has been updated and a 'recruitment tips' guidance document has been developed.

In developing a core outcome set to evaluate the clinical effectiveness of oesophageal cancer surgery, a literature review identified 901 measures, which were synthesised into 67 outcome domains and operationalised into 68 questions. Delphi methodology was used to reduce the initial list of outcome domains to a final core set according to prespecified criteria, by surveying key stakeholders (consultant surgeons, clinical nurse specialists and patients). Analyses of responses led to 41 and 19 outcomes being retained as important after the first and second surveys, respectively. The retained outcomes from the second survey were presented at a face-to-face patient consensus meeting at which patients were asked to anonymously rate their importance. The final core outcome set consists of 10 outcomes.

One area in which cost differences will exist between the approaches to oesophagectomy is in relation to the actual operation. Piloting of a Clinical Report Form was ongoing at the time of writing, which aimed to capture use of equipment and consumables in terms of brand and quantity and use of operation staff in terms of role and time. This level of detail of the operation itself is unlikely to be available from patients' medical records. Readmissions to the treating hospital will be captured in a review of medical records and it seems reasonable to rely on Healthcare Resource Group codes to indicate the cost of these. Secondary care visits and inpatient stays at other hospitals will not be captured in this way and neither will community-based NHS resource use. These aspects require the patients to provide information and a patient diary with a nurse-led telephone interview has been piloted. Early experience suggests that patients would prefer a narrower NHS and Personal Social Services perspective to reduce the burden of this aspect of the study and that patients vary in whether they prefer to provide their resource use diary to the study team or take part in the telephone interview while referring to the diary.

Conclusions

This feasibility study has demonstrated that different approaches to oesophagectomy can be compared in an unbiased fashion in a RCT and we are now planning the definitive trial.

At the time of writing we are proposing to focus on a comparison between LAO and open oesophagectomy as MIO continues to be subject to refinement. We plan to recruit 406 patients, allowing a clinically important benefit for postsurgical recovery of physical function to be detected with 90% power, and making a major contribution to an individual patient meta-analysis of survival. A seven-centre study is planned; the new centres have varying experience of recruiting to surgical trials and so the qualitative recruitment intervention will be continued. Currently, the plan is for two centres to randomly allocate patients to three interventions, the third being MIO, allowing further unbiased data to be collected on that approach.

Trial registration

This trial is registered as ISRCTN59036820.

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