Cancer of Oesophagus or Gastricus – New Assessment of Technology of Endosonography (COGNATE): report of pragmatic randomised trial

IT Russell,[1,2]* RT Edwards,[3] AE Gliddon,[1] DK Ingledew,[4] D Russell,[1,2] R Whitaker,[1] ST Yeo,[3] SE Attwood,[5] H Barr,[6] S Nanthakumaran[7] and KGM Park[7]

[1]North Wales Organisation for Randomised Trials in Health (NWORTH), Bangor University, Bangor, UK
[2]College of Medicine, Swansea University, Swansea, UK
[3]Centre for Economics and Policy in Health, Bangor University, Bangor, UK
[4]School of Psychology, Bangor University, Bangor, UK
[5]North Tyneside General Hospital, North Shields, UK
[6]Gloucestershire Royal Hospital, Gloucester, UK
[7]Aberdeen Royal Infirmary, Aberdeen, UK

*Corresponding author

Scientific summary

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Scientific summary

Background

Each year in the UK, 13,000 patients are diagnosed with gastro-oesophageal cancer. It is the fourth most common cause of cancer death. The general prognosis of patients with gastro-oesophageal cancer is poor: fewer than 10% survive 5 years. However there have been many advances in the treatment of these tumours, so it is important to select the most appropriate management plan for each patient. Endoscopic ultrasonography, introduced in the early 1980s, became common practice in the early 2000s. Mounting an ultrasonic probe on an endoscope can improve staging, and guide management, of gastro-oesophageal tumours. Endoscopic ultrasound (EUS) itself is safe and does not impose greater risks on patients than endoscopy.

However there has been no published or current randomised trial to evaluate whether EUS is effective and cost-effective in the management of gastro-oesophageal cancer. So the National Institute of Health Research Health Technology Assessment (NIHR HTA) programme commissioned the COGNATE (Cancer of Oesophagus or Gastricus – New Assessment of Technology of Endosonography) team to evaluate this. Our philosophy was pragmatic in the sense that, after randomising patients to EUS or not, participating centres followed best practice in staging and managing gastro-oesophageal cancer, but without the constraints of a rigid clinical protocol.

Objectives

As the link between staging and managing gastro-oesophageal cancer was not clear, we did not know whether EUS improved management decisions. To monitor the long-term sequelae of EUS, we collected data on participants' treatment plans, changes to them, subsequent progress and use of health care. Evidence that EUS improves choice of treatment and patient outcome would benefit individual patients and the population of patients with gastro-oesophageal cancer by targeting resources better.

Thus COGNATE evaluated, not the accuracy of EUS, but the effect it has on patient management and subsequent survival and quality of life. Most previous assessments of EUS staging neglected patients with non-surgical treatment but COGNATE adopted a broader approach because, if EUS leads to less surgery, it is as important to measure effects on patients who do not receive surgery as on patients who do. In short, COGNATE assessed whether the addition of EUS to usual staging tests changes treatment, improves survival and quality of life, and uses resources cost-effectively. The COGNATE team also developed a quality assurance process for EUS scans.

Methods

Design and interventions

COGNATE was a pragmatic, eight-centred, two-arm randomised controlled trial. All patients with gastro-oesophageal cancer received standard staging algorithms, after which the relevant multidisciplinary team (MDT) chose a provisional management plan from: endoscopic mucosal resection (EMR); immediate surgery; surgery after neo-adjuvant chemotherapy; and chemotherapy and radiotherapy. In principle patients randomised to the intervention group then received EUS, while those randomised to the control group continued with their agreed management plan.

Setting
The trial took place in eight British hospitals, two of which – Aberdeen Royal Infirmary, a teaching hospital, and Gloucestershire Royal Hospital, a district general hospital – contributed most participants.

Participants
Participants were eligible for the trial if they had cancer of the oesophagus, stomach or gastro-oesophageal junction and had not started treatment. To be randomised, patients had to be free of metastatic disease, fit for surgery (even if not planned) and graded less than 3 on both ASA (American Society of Anesthesiologists) and WHO (World Health Organization) criteria. Clinicians could exclude from the trial any patient for whom they were not in equipoise about the value of EUS. The trial co-ordinating centre monitored all exclusions and reasons given.

We invited eligible patients to participate in the trial, gave them the patient information sheet approved by the Multi-centre Research Ethics Committee for Scotland, and allowed them time to study it and ask questions. We stressed that the choice of treatment after EUS was the same in both groups. We then asked consenting patients to sign the approved consent form.

Randomisation
We stratified consented patients by centre and tumour location, and randomised them in equal proportions between EUS and not – by telephone call to the co-ordinating centre, which used dynamic software to prevent subversion.

Sample size
Our original application proposed survival as the primary outcome and a target of 700 patients. Difficulty in recruiting centres led us to change the primary outcome to 'quality-adjusted survival' and the target to a maximum of 400 and a minimum of 220. The latter would yield 80% power to detect a hazard ratio of 0.5, or a 'small' effect size of 0.4 in quality of life, or some combination of these.

Follow up
We followed participants until death or the end of data collection, which was between 12 and 54 months after recruitment. We collected data at discharge from hospital after initial treatment and at follow-up clinics after 1, 3, 6, 12, 18, 24 and 36 months.

Outcome measures
To compare the two randomised groups we used:

(a) quality-adjusted survival (primary outcome)
(b) survival censored at between 12 months (for those last recruited) and 54 months
(c) participant-reported quality of life using three questionnaires: European Quality of Life – 5 Dimensions (EQ-5D) (generic), Functional Assessment of Cancer Therapy – General (FACT-G) scale (cancer related) and FACT Additional Concerns (FACT-AC) scale (gastro-oesophageal cancer specific)
(d) process of care:
    - changes in management plans agreed by MDTs
    - complete resection rate, and
    - adverse events related to EUS
(e) use of health-care resources.

Psychometric methods to refine quality-of-life measurement
We asked participants to assess their quality of life through EQ-5D and FACT, specifically the general module (FACT-G), the oesophageal module [Functional Assessment of Cancer Therapy – Oesophageal (FACT-E)] and the gastric module [Functional Assessment of Cancer Therapy – Gastric (FACT-Ga)]. As FACT-E and FACT-Ga have many similar questions, the FACT team encouraged us to combine them into a single 'Additional Concerns' module. We used factor analysis to examine the structure of FACT and thereby

assess whether to aggregate these two modules into one. We used structural equation modelling to examine the relationships between EQ-5D and FACT scores, and thereby assess whether EQ-5D reflected all aspects of quality of life experienced by these patients.

Statistical methods

Primary analysis was by allocated group, whether or not participants received EUS. This reflects the pragmatic nature of the trial and our aim of evaluating EUS in informing decisions in the real world. We used baseline characteristics, including quality-of life scores, as covariates to improve the precision and generalisability of the model. Although blinding participants to their allocation was neither possible nor desirable, those responsible for analysis remained blind until the Trial Steering Committee and Data Monitoring and Ethics Committee had reviewed the definitive analysis.

Economic methods

We assessed the cost-effectiveness of EUS in the diagnosis and treatment of gastro-oesophageal cancer by estimating differences between the cost of patients' care including EUS, and the cost when limited to conventional staging; and corresponding differences in effectiveness as estimated by quality-adjusted life-years (QALYs). We used 'bootstrapping' to overcome the skewed data and cost-effectiveness acceptability curves to quantify uncertainty.

In accordance with National Institute for Health and Care Excellence (NICE) guidance we analysed COGNATE from the perspective of the NHS, focusing on health-care resources used by participants after randomisation. These included investigation, treatment and palliation, and other elements of secondary and pharmaceutical care. The local co-ordinator at each trial site used an electronic database to record the use of NHS resources by participants throughout the period of the trial. To cost these resources, we refined and used published national unit costs.

We used sensitivity analysis to explore whether or not the estimated benefits and costs of endoscopic ultrasonic staging relative to conventional staging were sensitive to key features of our analysis, notably the cost of EUS scans.

Quality assurance of endoscopic ultrasound scans

The COGNATE team asked trial sites to record EUS scans as videos and their interpretations on a proforma. A panel of six COGNATE investigators reviewed 20 anonymised scans (21% of 97 performed within COGNATE trial), both individually before, and together during, five web-based conferences. Each conference reached a blinded consensus on the staging of four tumours. We compared the original report with the staging decisions of individual reviewers, their consensus and that of an external reviewer.

Results

We randomised 223 patients, of whom 213 (96%) yielded enough data for primary analysis. Over three-quarters of participants were male, and nearly half were over 65 years. The most common tumour site was the oesophagus and the most common tumour type was adenocarcinoma. The most common tumour stage was T3, and slightly more participants had nodal stage N1 than N0. At the end of the trial 44% of EUS participants and 32% of control participants were alive.

Our psychometric analyses confirmed that it was appropriate to aggregate the FACT-E and FACT-Ga modules into a single Additional Concerns module. The structural equation modelling suggested that EQ-5D scores captured individuals' physical and functional well-being but not their social and emotional well-being as measured by FACT. There are two possible explanations for this: either EQ-5D items do not cover these domains; or the general public in weighting the health states defined by EQ-5D chose to give

little weight to social and emotional issues. However EQ-5D utility scores correlated well with EQ-5D visual analogue scores. This is consistent with patients and the public agreeing that physical and functional well-being deserve more weight, possibly because of the extreme nature of gastro-oesophageal cancer. Thus our preparatory analysis supported our use of EQ-5D as a generic measure of quality of life, and persuaded us to adjust survival using not only EQ-5D, but also FACT-G and FACT-AC.

Endoscopic ultrasound significantly improved participant survival, with a hazard ratio of 0.706 [95% confidence interval (CI) from 0.501 to 0.996] and an increase of 121 days in estimated median survival – from 1.63 years in the control group to 1.96 years in the intervention group. Participants reported consistent, although non-significant, improvements in mean outcomes at 12 months, notably a difference of 0.061 (95% CI from –0.043 to 0.164) in mean EQ-5D scores between 0.449 in the control group and 0.509 in the intervention group; and a difference of 0.12 (95% CI from –0.27 to 0.51) in mean FACT-G between 2.15 in the control group and 2.27 in the intervention group. Combining survival and quality of life, EUS improved survival adjusted for generic quality of life with a hazard ratio of 0.705 (95% CI from 0.499 to 0.995) and an increase of 66 days in estimated median quality-adjusted survival – from 0.94 QALYs in the control group to 1.12 QALYs in the intervention group.

Trial sites reported consistent, although non-significant, reductions in total resource use in secondary and pharmaceutical care (including EUS scans when undertaken), generating mean savings of about £2860 (95% 'bootstrapped' CI from –£2200 to £8000) from an average of £32,000 [with a standard deviation (SD) of £22,000] in the control group to £29,200 (SD £14,900) in the intervention group. Combining these estimated benefits and savings yields probability of 96.6% that EUS is cost-effective in the sense of achieving the NICE criterion of costing less than £20,000 to gain a QALY.

The benefits of EUS were significantly greater for those with poor initial quality of life, but did not differ between centres. Similarly there was a significant interaction between initial quality of life and the effect of EUS on all the FACT scales; again, sicker patients benefitted more from EUS. However there was no significant difference between intervention and control groups in mean FACT scores adjusted for covariates. There were no serious adverse reactions attributable to EUS.

Both management plans and final treatment varied between centres. EUS increased the proportion of tumours completely resected from 80% (44 out of 55) to 91% (48 out of 53). Furthermore participants allocated to EUS who then transferred to a 'therapeutic' treatment, namely EMR or surgery in some form, survived much better than control subjects who made this change, and better than intervention participants confirmed for one of these 'therapeutic' treatments. The few intervention participants who transferred to 'conservative' treatment, namely chemotherapy, radiotherapy or both, survived worse than both the control subjects who made this change and intervention participants confirmed for 'conservative' treatment. In contrast, control subjects who changed plans in either direction experienced intermediate survival, arguably because they lacked the discriminatory power of EUS. In short, changes are consistently more appropriate in the intervention group than in the control group. Although all of these analyses have low power, and are therefore not statistically significant, they underpin the significant differences in outcomes, and help to explain them.

The quality assurance panel achieved excellent agreement on the tumour node metastasis (TNM) staging of the 20 endoscopic ultrasonic films. Their web-based conferences failed to agree staging for only one T stage and only one N stage, and reached consensus agreeing with the original investigator on 19 T stages and 17 N stages. There was excellent agreement between the original investigator and the consensus on T stage (weighted kappa = 0.866; $p < 0.001$) and moderate agreement on N stage (kappa = 0.562; $p = 0.012$). In short, we developed an effective quality assurance process for EUS scans. It provides a useful model for future NIHR-funded assessments of diagnostic technologies and has the potential to improve routine clinical practice.

Conclusions

Although EUS was common practice by the time COGNATE began recruiting in 2005 we achieved the first rigorous evaluation of EUS. The COGNATE team ameliorated many problems of recruiting centres and participants, mainly through two centres – Aberdeen and Gloucester. EUS achieved a surprising combination of significant improvements in survival (121 days) and quality-adjusted survival (66 days); a substantial, although non-significant, net saving of £2800 per trial participant; and, combining these statistical and economic findings, 96.6% probability of being cost-effective by NICE criteria. We judge that these impressive findings provide strong evidence in favour of EUS scans for all patients with gastro-oesophageal cancer who have the potential to benefit.

As the COGNATE team 'caught the EUS horse just as it was leaving the stable', we make no recommendation for future research into EUS. Instead we recommend:

1. policy-orientated research into the best time to evaluate new technologies
2. methodological research to streamline the collection of data to evaluate complex technologies such as EUS, notably on the costs of the extensive care for conditions such as gastro-oesophageal cancer, and
3. psychometric research to refine the integrated Functional Assessment of Cancer Therapy – Oesophageal and Gastric (FACT-EG) module as a valid measure of the outcome of gastro-oesophageal cancer.

Trial registration

This trial is registered as ISRCTN1444215.

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Editorial contact: nihredit@southampton.ac.uk

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