Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial

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Summary

Background Definitive chemoradiotherapy (CRT) is an alternative to surgery for the curative treatment of oesophageal carcinoma. The SCOPE1 trial aimed to investigate the addition of cetuximab to cisplatin and fluoropyrimidine-based definitive CRT in patients with localised oesophageal squamous-cell cancer and adenocarcinomas to assess activity, safety, and feasibility of use.

Methods In this multicentre, randomised, open-label, phase 2/3 trial, we recruited patients aged 18 years and older from UK radiotherapy centres who had non-metastatic, histologically confirmed carcinoma of the oesophagus (adenocarcinoma, squamous-cell, or undifferentiated; WHO status 0–1; stage I–III disease) and been selected to receive definitive CRT. Patients were randomly assigned (1:1) via a central computerised system using stratified minimisation (with an 80:20 random element) to receive CRT alone or CRT with cetuximab (400 mg/m² on day 1 followed by 250 mg/m² weekly), stratified by recruiting hospital, primary reason for not having surgery, tumour histology, and tumour stage. CRT consisted of cisplatin 60 mg/m² (day 1) and capecitabine 625 mg/m² twice daily (days 1–21) for four cycles; cycles three and four were given concurrently with 50 Gy in 25 fractions of radiotherapy. The primary endpoint was the proportion of patients who were treatment failure free at week 24 for the phase 2 trial and overall survival for the phase 3 trial, both measured from randomisation. We analysed data by intention to treat. This trial is an International Standard Randomised Controlled Trial, number 47718479.

Findings 258 patients (129 assigned to each treatment group) from 36 UK centres were recruited between Feb 7, 2008, and Feb 22, 2012. Recruitment was stopped without continuation to phase 3 because the trial met criteria for futility, but we continued to follow-up recruited patients until all had reached at least 24-week follow-up (median follow-up of patients who survived was 16·8 months [IQR 11·2–24·5]). Fewer patients were treatment failure free at 24 weeks in the CRT plus cetuximab group (79 of 119 patients [66·4%, 90% CI 58·6–73·6]) than in the CRT only group (93 of 121 patients [76·9%, 69·7–83·0]). The CRT plus cetuximab group also had shorter median overall survival (22·1 months [95% CI 15·1–24·5] *vs* 25·4 months [20·5–37·9]; adjusted HR 1·53 [95% CI 1·03–2·27]; p=0·035). Patients who received CRT plus cetuximab had more non-haematological grade 3 or 4 toxicities (102 [79%] of 129 patients *vs* 81 [63%] of 129 patients; p=0·004). The most common grade 3 or 4 toxicities were low white blood cell count (14 [11%] in the CRT plus cetuximab group *vs* 21 [16%] in the CRT only group), low absolute neutrophil count (15 [12%] *vs* 24 [19%]), fatigue (26 [20%] *vs* 25 [19%]), and dysphagia (35 [27%] *vs* 37 [29%]).

Interpretation The addition of cetuximab to standard chemotherapy and radiotherapy cannot be recommended for patients with oesophageal cancer suitable for definitive CRT.

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Introduction

In the UK, oesophageal cancer is the sixth most common cause of cancer death, accounting for around 5% of all cancer deaths.[1] Worldwide, oesophageal cancer is the eighth most common cancer—an estimated 482 300 new cases and 406 800 deaths occurred in 2008—and it has the fifth highest mortality rate of all tumour sites.[2] The incidence of oesophageal adenocarcinomas predominantly affecting the lower oesophagus and gastro-oesophageal junction has increased substantially in recent decades, especially in Europe and the USA.[2] The incidence of squamous-cell carcinoma is stable or falling in the UK, but is much more prevalent in southern and east Africa and east Asia.

Surgery has been the cornerstone of curative treatment for this disease for the past 50 years, but is only appropriate for 10–20% of the patient population, and despite improvements in patient selection, perioperative care, and adjuvant treatment, less than 25% will survive 5 years after treatment[3,4] and those who relapse within 2 years of surgery never regain their former quality of life.[5]

Chemoradiotherapy when given as definitive treatment is more effective than radiotherapy[6] or chemotherapy alone.[7] In the UK, this treatment is usually offered to patients who are unsuitable for surgery.

Unsuitability for surgery might be due to the extent of disease precluding the likelihood of a curative resection, or because the patient is physiologically not fit for surgery because of comorbidities or poor performance status. Less often, patients or clinicians will opt for this strategy.[8] Increasingly, definitive chemoradiotherapy is being considered as a standard of care in patients with oesophageal squamous-cell carcinoma, because evidence suggests that outcomes are similar to those of surgical treatment.[3,6,9] By contrast, for adenocarcinomas, evidence to support the use of definitive chemoradiotherapy is less strong and is restricted to studies of chemoradiotherapy in patients who are unsuitable for surgery.

See Online for appendix

Concurrent chemoradiotherapy regimens have been based on cisplatin and fluorouracil. Both drugs have good single-agent activity in oesophageal malignant disease and are two of the best radiosensitisers in tumour models.[10,11] The regimen used most frequently in the UK consists of conformal external beam radiotherapy (50 Gy in 25 fractions for 5 weeks) with two cycles of cisplatin and fluorouracil given concurrently, with or without a further two cycles of the same chemotherapy, given in a neoadjuvant phase. This neoadjuvant phase, as well as delivering additional systemic therapy, allows time for careful radiotherapy planning, frequently improves patients' dysphagia, and debulks the tumour before radiotherapy. Capecitabine has been shown to be as effective as fluorouracil in locally advanced and metastatic oesophagogastric cancer.[7] Encouraging outcomes with definitive chemoradiotherapy regimens were reported in single-centre series,[8,12] but whether the findings could be replicated in a prospective, multicentre trial was unclear.

Although definitive chemoradiotherapy in patients with a poor outlook can lead to useful long-term disease control, most patients still succumb to the disease. The pattern of treatment failure differs from that after surgery, with a higher rate of locoregional recurrence.[6,8,9,12] Improvements to both the systemic and locoregional components of this treatment strategy are therefore urgently needed.

EGFR is overexpressed in up to 55% of oesophagogastric cancers and is associated with poor prognosis.[13] Cetuximab, a monoclonal EGFR antagonist, improved outcomes when given in combination with chemotherapy in other tumours—eg, advanced colorectal adenocarcinomas[14] and squamous-cell head and neck cancer.[15] More importantly, preclinical studies have shown that cetuximab can overcome an important mechanism of radioresistance,[16] and results of a phase 3 trial by Bonner and colleagues[17] in squamous-cell carcinoma of the head and neck showed that cetuximab in combination with radiotherapy can improve local control and overall survival compared with radiotherapy alone. We therefore postulated that cetuximab in combination with conventional definitive chemoradiotherapy might improve local control, quality of life, and overall survival in patients with localised oesophageal squamous-cell cancer and adenocarcinomas. On behalf of the UK National Cancer Research Institute (NCRI) Upper GI Clinical Studies Group we designed the SCOPE1 trial (Study of Chemoradiotherapy in OesoPhageal cancer with Erbitux) to test this hypothesis.

Methods

Study design and patients

In this multicentre, randomised, open-label, parallel, two-arm, phase 2/3 trial, we recruited patients from radiotherapy centres in the UK who had the following key eligibility criteria (for full inclusion and exclusion criteria see appendix): non-metastatic, histologically confirmed carcinoma of the oesophagus (adenocarcinoma, squamous-cell, or undifferentiated carcinoma) or gastro-oesophageal junction (Siewert type 1 or 2 with <2 cm extension into the stomach); selected for definitive chemoradiotherapy by a designated multidisciplinary team; aged 18 years or older; WHO performance status 0 or 1; stage I–III disease (TNM stage 6); and disease length of less than 10 cm defined by endoscopic ultrasound. Patients with M1a or M1b were not eligible for this study. The protocol for the study has been published elsewhere[18] and the trial was coordinated by the Wales Cancer Trials Unit (WCTU).

Patients were required to have staging investigations that consisted of endoscopic ultrasound and contrast-enhanced spiral CT scan of the thorax and abdomen. ^{18}F-fluorodeoxyglucose CT-PET scan was optional. In patients in whom endoscopic ultrasound was not possible because of advanced malignant oesophageal stricturing, patients were staged with CT with or without CT-PET. Patients were physiologically assessed to identify those with eligible lung function (forced expiratory volume in 1 s >1·0), cardiac function (left ventricular ejection fraction >40% on echocardiogram or multigated acquisition scan), renal function (EDTA glomerular filtration rate [GFR] >40 mL/min, or estimated by Cockcroft-Gault formula to be >60 mL/min), liver function (serum bilirubin ≤1·5×upper limit of normal [ULN], aspartate aminotransferase to alanine aminotransferase ratio ≤2·5×ULN, alkaline phosphatase ≤3×ULN) and haematological assessment (haemoglobin >100 g/L, white blood cells >3×10^9/L, absolute neutrophil count [ANC] >1·5×10^9/L, platelet count >100×10^9/L). All treatment and assessments were done in UK radiotherapy centres.

All patients had to provide written informed consent before registration and the trial protocol was approved by the UK Medicines and Healthcare products Regulatory Agency and a multicentre research ethics committee. The SCOPE1 trial was sponsored by Velindre NHS Trust and coordinated by the WCTU at Cardiff University. Cancer Research UK's Clinical Trials Awards and Advisory Committee (CTAAC) approved the trial design.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to chemoradiotherapy with cetuximab (CRT plus cetuximab) or chemoradiotherapy without cetuximab (CRT only) by stratified minimisation with a random element (80:20). Randomisation was stratified by recruiting hospital, primary reason for not having surgery, tumour histology, and tumour stage. To conceal the sequence until interventions were assigned, research nurses (who recruited the patients) telephoned the WCTU where the random allocation sequence was generated by a trial or data manager interacting with a computerised system. The study had an open-label design. Participants, those administering the interventions, and those assessing the outcomes were aware of which treatment had been allocated.

Procedures

Both study groups received the same chemotherapy, which consisted of four 3-weekly cycles of cisplatin (60 mg/m² intravenously on day 1) and capecitabine (625 mg/m² orally twice daily from day 1 to day 21); cycles one and two were given as neoadjuvant treatment. Cycles three and four were given concurrently with radiotherapy. This regimen is the most frequently used regimen in the UK. Patients randomly assigned to the CRT plus cetuximab group also received intravenous cetuximab 400 mg/m² on day 1 of chemotherapy and 250 mg/m² weekly for the 12 weeks of treatment. If patients were unable to swallow capecitabine, investigators could use a protracted intravenous infusion of fluorouracil at a rate of 225 mg/m² per day from day 1 to day 21 of each cycle. Full details of protocol treatment and dose reductions are detailed in the trial protocol.

Dose modification for haematological toxicity was based on a full blood counts taken within the 3 days before the start of each cycle of chemotherapy. Full-dose chemotherapy was given if ANC was 1×10^9/L or higher and platelet count was 75×10^9/L or higher. For ANC $0\cdot5\times10^9$/L to less than 1×10^9/L or a platelet count 50×10^9/L to less than 75×10^9/L, chemotherapy was stopped until recovery of counts and restarted with a 25% dose reduction of cisplatin and capecitabine. For ANC below $0\cdot5\times10^9$/L or platelet count below 50×10^9/L, chemotherapy was restarted with a 50% dose reduction. Renal modification was based on GFR at baseline and before day 1 of chemotherapy. Patients received full-dose chemotherapy if their GFR was 50 mL/min or higher. Cisplatin was given at a 75% dose reduction to patients with GFR of 40–50 mL/min, and replaced by carboplatin (at a concentration to achieve an area under the concentration–time curve of 5) if GFR was below 40 mL/min. Capecitabine was given at a 75% dose reduction if GFR was below 50 mL/min, a 50% dose reduction if GFR was below 40 mL/min, and omitted if GFR was below 30 mL/min. For other non-haematological toxicities of grade 2 or higher, chemotherapy was withheld until resolution to grade 0–1. Further chemotherapy was omitted for grade 4 toxicity, and given at 75% and 50% dose reductions after the first and second occurrences of grade 3 toxicity. For grade 2 toxicity, subsequent chemotherapy was given at 100%, 75%, and 50% dose reductions after the first, second, and third occurrences of toxicity. For cetuximab-induced skin toxicity, cetuximab was continued along with topical emollient and antibiotics if the patient had a grade 1 acneiform rash. Oral antibiotics were mandated for grade 3 rash and recommended for grade 2 rash. Sequential dose reduction of cetuximab to 200 mg/m² and 150 mg/m² was advised for second and third occurrences of grade 3 skin rash, respectively; it was permanently discontinued after a fourth appearance.

The radiotherapy protocol and planning guidance document mandated the use of intravenous contrast CT simulation with minimum 3-mm CT slices. 50 Gy in 25 fractions, prescribed according to recommendations by the International Commission on Radiation Units and Measurements (ICRU-50/62), was delivered Monday to Friday as a three-dimensional (3D) conformally planned single-phase treatment, usually with four radiotherapy fields to achieve the following normal organ dose constraints: less than 30% of the heart volume to receive at least 40 Gy, less than 25% of the lung volume to receive at least 20 Gy, and a maximum dose in the spinal cord of less than 40 Gy. Gross tumour volume was defined by diagnostic CT scan, endoscopy and endoscopic ultrasound, and PET scan information (when available). The clinical target volume was calculated by adding 2 cm manually along the oesophagus superiorly–inferiorly and 1 cm radially. The final planning target volume was then created by adding 1 cm superiorly–inferiorly and 0·5 cm radially to the clinical target volume. Elective nodal irradiation was not done.

For the **trial protocol** see http://www.wctu.org.uk/trial.php?trial=scope1

All potential principal investigators and radiotherapy centres received a CD-ROM containing the detailed radiotherapy protocol, a radiotherapy planning guidance document, and example planning cases. All principal investigators had to outline a benchmark case

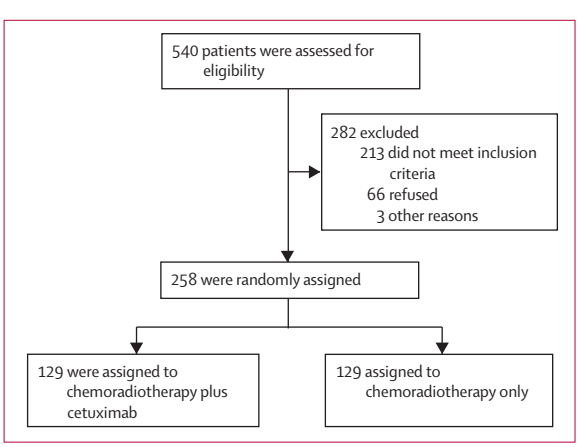

Figure 1: **Trial profile**

and radiotherapy centres then planned the same case, which had to pass central review before patient recruitment.[19] On-trial radiotherapy trials quality assurance (RTTQA) consisted of all principal investigators' first plans, 10% of all subsequent plans, and trial-specific planning assessment forms for each patient submitted for central review that outlined and assessed the 3D dose distribution before treatment. SCOPE1 RTTQA was coordinated by the NCRI RTTQA centre in Cardiff, UK.

	CRT plus cetuximab (n=129)	CRT only (n=129)
Age (years)		
Median	66·9	66·6
Range (IQR)	44·9–84·1 (61·3–73·7)	35·7–81·9 (60·2–72·3)
Aged ≥70 years	50 (39%)	48 (37%)
Sex		
Male	71 (55%)	74 (57%)
Female	58 (45%)	55 (43%)
WHO performance status		
0	61 (47%)	70 (54%)
1	68 (53%)	59 (46%)
Reason for no surgery		
Local extent of disease	60 (47%)	62 (48%)
Patient choice	48 (37%)	49 (38%)
Comorbidity/poor performance status	21 (16%)	18 (14%)
PET used in staging		
Yes	109 (84%)	112 (87%)
No	17 (13%)	16 (12%)
Missing data	3 (2%)	1 (<1%)
Site of predominant tumour		
Upper	15 (12%)	12 (9%)
Middle	56 (43%)	58 (45%)
Lower	54 (42%)	58 (45%)
Missing data	4 (3%)	1 (<1%)
Tumour type		
Adenocarcinoma	33 (26%)	32 (25%)
Squamous cell	92 (71%)	96 (74%)
Undifferentiated	4 (3%)	1 (<1%)
Stage		
I	4 (3%)	4 (3%)
IIa	36 (28%)	36 (28%)
IIb	12 (9%)	11 (9%)
III	77 (60%)	78 (60%)
Total EUS disease length (cm)		
Mean (SD)	5·6 (2·7)	5·6 (2·4)
Missing data	37 (29%)	28 (22%)
Time of start of treatment from randomisation (days)		
Median	5	4
Range (IQR)	0–34 (2–7)	0–22 (2–7)

Data are number (%) unless otherwise specified. CRT=chemoradiotherapy. EUS=endoscopic ultrasound.

Table 1: **Baseline characteristics of randomly assigned patients**

During treatment, patients were reviewed within the 3 days before day 1 of each cycle of chemotherapy during the neoadjuvant phase and weekly during the definitive chemoradiotherapy phase. Assessment at each review consisted of medical examination and assessment of WHO performance status, dysphagia score, and toxicity according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Capecitabine compliance was assessed by counting the number of tablets at each visit. Blood tests including full blood count and biochemical profile were done at each clinic visit. Blood and biopsy samples were obtained at both baseline and week 24, but the processing of these samples is still in progress, and correlations with treatment response will be the subject of a future paper.

Follow-up was at 24 weeks, then every 3 months after that during the first year, every 4 months during the second year, and yearly thereafter for a minimum of 5 years from randomisation. All patients had an endoscopic assessment, biopsy, and CT scan 12 weeks after completion of definitive chemoradiotherapy (at week 24). No further CT scan was mandated, and further investigations (endoscopy or CT scan) were done according to patient symptoms. The choice of second-line treatment, including salvage surgery in the case of locoregional recurrence, was left to the discretion of the treating clinician. Patients completed validated quality-of-life questionnaires (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30[20] and QLQ-OES18,[21] dermatology life-quality index, and EQ-5D) and a health-care resource utilisation log at baseline and weeks 7, 13, 24, and 52, and yearly thereafter (to 5 years after randomisation). We postulated that scores for physical and role function, fatigue, dysphagia, and eating restrictions would be better over time in the CRT plus cetuximab group than in the CRT only group. Missing data were managed according to the standard guidelines associated with each questionnaire.

The primary endpoint of the phase 2 trial was the proportion of patients who were treatment failure free at 24 weeks (12 weeks after completion of treatment). A patient was deemed treatment failure free if they were still alive with no evidence of residual malignancy in the endoscopic biopsy sample, and no evidence of disease progression outside the radiotherapy field on CT scan. Secondary endpoints were toxicity, quality of life, health economics, progression-free survival (overall, local, and distant), treatment compliance, and feasibility of recruitment. Local progression-free survival was defined as the time to progression within the radiotherapy field (with or without metastatic disease) or death by any cause. Distant progression-free survival was defined as time to progression with metastases or death by any cause.

Statistical analysis

With the addition of cetuximab to the intervention group, we felt that a treatment-failure-free rate of less than 60%

at week 24 would not be sufficiently large enough to warrant further investigation in a phase 3 setting, but that a rate of 75% or higher would warrant further investigation. Using a Fleming's single-stage design (p1=0·60; p2=0·75; α=0·05; 90% power; 10% loss to follow up), we needed to recruit 90 patients in the CRT plus cetuximab group (180 patients overall). Subject to the independent data monitoring committee's review of the phase 2 analysis, the study would proceed to phase 3 with a primary endpoint of overall survival from date of randomisation. However, we were to continue recruiting patients until the phase 2 trial was analysed. For the phase 3 trial, we needed to recruit 420 patients (269 events) to detect an improvement in 2-year overall survival from 35% to 47·5% (hazard ratio [HR] 0·71) in patients assigned to CRT plus cetuximab, with 80% power at 5% significance.

Data were analysed with the Stata 11 statistical package according to intention to treat. We used the Clopper-Pearson exact binomial method to calculate 90% CIs for the phase 2 primary endpoint. Analyses of the proportion of patients who were treatment failure free were done using the number of patients who died or progressed before 24 weeks, or those with a valid 24-week assessment, as the denominator. A valid 24-week assessment was defined as a follow-up visit between 20 and 28 weeks after randomisation at which a CT scan or endoscopic biopsy was done. We calculated survival from date of randomisation to when an event occurred (ie, progression

	CRT plus cetuximab (n=129)	CRT only (n=129)
Cisplatin		
Completed cycles 1–4 at full dose	73 (57%)	69 (53%)
Completed cycles 1–4 at full or reduced dose	99 (77%)	116 (90%)
Stopped before cycle 4 due to patient choice	4 (13%)*	1 (8%)†
Stopped before cycle 4 due to toxicity/illness	26 (87%)*	12 (92%)†
Capecitabine		
Completed cycles 1–4 at full dose	32 (25%)	44 (34%)
Completed cycles 1–4 at full or reduced dose	89 (69%)	110 (85%)
Stopped before cycle 4 due to patient choice	4 (10%)‡	0§
Stopped before cycle 4 due to toxicity/illness	36 (90%)‡	19 (100%)§
Switched to fluorouracil before cycle 4	7 (5%)	7 (5%)
Number of cycles of cetuximab completed at full or reduced dose		
0	1 (<1%)	NA
1	9 (7%)	NA
2	16 (12%)	NA
3	14 (11%)	NA
4	89 (69%)	NA
Radiotherapy		
Full protocol dose	100 (78%)	116 (90%)
Dose reduction	4 (3%)	3 (2%)
No radiotherapy given	25 (19%)	10 (8%)

CRT=chemoradiotherapy. NA=not applicable. *Out of 30 patients who stopped cisplatin before cycle 4. †Out of 13 patients who stopped cisplatin before cycle 4. ‡Out of 40 patients who stopped capecitabine before cycle 4. §Out of 19 patients who stopped capecitabine before cycle 4.

Table 2: **Treatment compliance in randomly assigned patients**

	CRT plus cetuximab (n=129)	CRT only (n=129)
Haematological	27 (21%)	36 (28%)
Haemoglobin	3 (2%)	3 (2%)
WBC	14 (11%)	21 (16%)
ANC	15 (12%)	24 (19%)
Platelets	11 (9%)	6 (5%)
Lymphocytes	5 (4%)	3 (2%)
Non-haematological	102 (79%)	81 (63%)
Cardiac disorders	8 (6%)	2 (2%)
Cardiac ischaemia/infarction	3 (2%)	1 (<1%)
Other	5 (4%)	1 (<1%)
Dermatological	28 (22%)	5 (4%)
Acne	9 (7%)	0
Hand-foot syndrome	7 (5%)	4 (3%)
Rash	14 (11%)	0
Other	9 (7%)	1 (<1%)
Metabolic/laboratory	31 (24%)	14 (11%)
Hypomagnesia	9 (7%)	2 (2%)
Hypokalaemia	9 (7%)	7 (5%)
Hypophosphataemia	6 (5%)	1 (<1%)
Hyponatraemia	2 (2%)	1 (<1%)
Bilirubin	2 (2%)	0
Hyperuricaemia	2 (2%)	0
Other	13 (10%)	6 (5%)
Pulmonary	8 (6%)	4 (3%)
Dyspnoea	8 (6%)	3 (2%)
Other	2 (2%)	1 (<1%)
Constitutional symptoms	27 (21%)	26 (20%)
Fatigue	26 (20%)	25 (19%)
Weight loss	3 (2%)	3 (2%)
Gastrointestinal	55 (43%)	57 (44%)
Diarrhoea	12 (9%)	8 (6%)
Dysphagia	35 (27%)	37 (29%)
Stomatitis	4 (3%)	2 (2%)
Nausea	6 (5%)	11 (9%)
Oesophagitis	3 (2%)	7 (5%)
Vomiting	7 (5%)	11 (9%)
Anorexia	12 (9%)	13 (10%)
Other	7 (5%)	9 (7%)
Infection	8 (6%)	9 (7%)
Febrile neutropenia	3 (2%)	3 (2%)
Infection with normal ANC	5 (4%)	6 (5%)
Neurological	5 (4%)	5 (4%)
Vascular	14 (11%)	13 (10%)
Thrombosis/thrombus/embolism	14 (11%)	12 (9%)
Other	2 (2%)	1 (<1%)
Other	12 (9%)	10 (8%)

All randomly assigned patients received at least one dose of treatment. CRT=chemoradiotherapy. WBC=white blood cell. ANC=absolute neutrophil count. CTCAE=Common Terminology Criteria for Adverse Events.

Table 3: **CTCAE grade 3 or 4 toxicity in patients during treatment (weeks 1 to 12)**

or any death for progression-free survival, and any death for overall survival). Patients who were event free were censored at the time they were last assessed. We estimated event time distributions with the Kaplan-Meier method and compared overall survival and progression-free survival with an unadjusted log-rank test and HRs from Cox regression, both unadjusted and adjusted for randomisation stratification factors (we tested the proportional hazards assumption with Cox-Snell residuals and Schoenfeld's global test). We included all randomly assigned patients who met the eligibility criteria in the analysis of their allocated group. We assessed toxicity by comparing proportions of haematological and non-haematological toxicities during chemoradiotherapy with Pearson's χ^2 tests in all patients who received at least one dose of treatment. We compared quality-of-life score differences with Wilcoxon rank sum tests. We prespecified all the analyses that we have presented below. Detailed quality-of-life analyses, health economic analyses, and correlation of outcomes with radiotherapy treatment delivery will be presented in future reports.

This trial is an International Standard Randomised Controlled Trial, number 47718479.

	CRT plus cetuximab (n=129)	CRT only (n=129)
Lost to follow-up before 24 weeks	10 (8%)	8 (6%)
Too ill for assessments/withdrew/moved away	8 (80%)	6 (75%)
Invalid 24 week assessment (too early/late)	2 (20%)	2 (25%)
Died before 24 weeks	17 (13%)	8 (6%)
Oesophageal cancer	11 (65%)	4 (50%)
Treatment related	3 (18%)	0
Other	3 (18%)	4 (50%)
Valid 24-week assessment	102 (79%)	113 (88%)
Failure at 24-week assessment	23 (23%)	20 (18%)
By biopsy	20 (87%)	10 (50%)
By endoscopy	0	3 (15%)
By CT scan	3 (13%)	7 (35%)
Failure free at 24 weeks	79 (66%)	93 (77%)
Alive and without progression at last follow-up	49 (62%)	58 (62%)
Progressed at last follow-up	17 (22%)	23 (25%)
Local	7 (41%)	10 (43%)
Metastatic	2 (12%)	6 (26%)
Both	8 (47%)	7 (30%)
Died of any cause before progression	13 (16%)	12 (13%)
Oesophageal cancer	13 (100%)	8 (67%)
Pulmonary embolism	0	1 (8%)
Stroke	0	1 (8%)
Cardiac failure/heart disease	0	1 (8%)
Liver disease	0	1 (8%)
Post-trial treatments up to 12 months after randomisation*		
Patients with completed treatment follow-up data	88 (68%)	97 (75%)
Surgery	0	3 (3%)
Palliative chemotherapy	7 (8%)	2 (2%)
Radiotherapy	1 (1%)	2 (2%)
Endoscopic intervention		
Oesophageal stent	2 (2%)	2 (2%)
Oesophageal dilatation	1 (1%)	6 (6%)
Oesophageal laser therapy	1 (1%)	0
Stent plus dilation	1 (1%)	1 (1%)

CRT=chemoradiotherapy. *No patients started more than one of the treatments listed here.

Table 4: **Failure-free rate at 24 weeks, and subsequent pattern of treatment failure and treatments given**

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The statistician (CH) had full access to all the data and the corresponding author (TC) and statistician (CH) had final responsibility for the decision to submit for publication. Merck Serono provided the cetuximab free of charge but had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Results

258 patients were recruited from 36 of the 56 radiotherapy centres in the UK between Feb 7, 2008, and Feb 22, 2012 (figure 1). In February, 2012, the independent data monitoring committee undertook a preplanned analysis of the first 180 patients recruited who had completed 24 weeks of follow up, and recommended stopping recruitment because the trial had met predetermined criteria for futility. When making this decision, they also took into account toxicity, treatment compliance, and overall survival, and recommended completion of treatment and follow-up of all recruited patients. The data presented here are those from all 258 patients (129 patients allocated to each treatment group) who were recruited up until the independent data monitoring committee's decision, analysed after the last patient had undergone assessment at week 24. The median length of follow-up for patients who had survived by the time of analysis was 16·8 months (IQR 11·2–24·5).

Patient and tumour baseline characteristics were well balanced between groups (table 1). Patients who were assigned to receive CRT plus cetuximab were less likely to complete standard protocol treatment than were those assigned to the CRT only group (table 2). The compliance difference between groups was significant for completion (at full or reduced dose) of four planned cycles of cisplatin (p=0·005), completion of four cycles of capecitabine (p=0·002), and delivery of any radiotherapy (104 [81%] of 129 patients in the CRT plus cetuximab group *vs* 119 [92%] of 129 patients in the CRT only group; p=0·006; table 2). The number of patients whose cisplatin dose was reduced (or stopped) was similar in each group (56 [43%] in the CRT plus cetuximab group *vs* 60 (47%) in the CRT only group). The number of patients whose capecitabine dose was reduced was higher in the CRT plus cetuximab group than in the CRT only group (97 [75%] *vs* 85 [66%]). More patients in the CRT plus cetuximab group stopped both cisplatin and capecitabine treatment early because

of toxicity or illness than did those in the CRT only group (cisplatin stopped, 26 [20%] *vs* 12 [9%]; capecitabine stopped, 36 [28%] *vs* 19 [15%]).

All CTCAE grade 3 or 4 toxicities (including serious adverse reactions and suspected unexpected serious adverse reactions) reported during treatment are shown in table 3. Patients who received CRT plus cetuximab had more non-haematological toxicity (p=0·004). These toxicities were mainly dermatological, biochemical (metabolic or laboratory tests), and cardiac disorders (table 3).

The proportion of patients who were treatment failure free at 24 weeks was lower in the CRT plus cetuximab group than in the CRT only group (79 of 119 patients [66·4%, 90% CI 58·6–73·6] *vs* 93 of 121 patients [76·9%, 69·7–83·0]). Patients who were failure free at 24 weeks had significantly better median overall survival than did those who were not failure free (8·3 months [95% CI 6·7–12·5] *vs* 26·7 months [24·5–42·7]). Of those patients who were failure free at 24 weeks, 107 (62%) of 172 were still alive without progression at the end of the study follow-up, whereas 40 (23%) were alive with progression and 25 (15%) had died. Of patients who died before 24 weeks, more were recorded as having oesophageal cancer as the cause of death in the CRT plus cetuximab group than in the CRT only group (table 4). Three treatment-related deaths occurred in the CRT plus cetuximab group (one stroke, one multiorgan failure, one pulmonary embolism). 29 patients are known to have had further treatment during the 12 months after randomisation (table 4).

Overall survival was significantly worse in the CRT plus cetuximab group than in the CRT only group (unadjusted HR 1·45 [95% CI 1·01–2·09], log-rank p=0·043; adjusted HR 1·53 [1·03–2·27], p=0·035; figure 2). Median overall survival was 22·1 months (95% CI 15·1–24·5) in the CRT plus cetuximab group and 25·4 months (20·5–37·9) in the CRT only group. This pattern was consistent across randomisation stratification characteristics (figure 3). 2-year overall survival was also lower in the CRT plus cetuximab group than in the CRT only group (41·3% [95% CI 30·9–51·4] *vs* 56·0% [45·1–65·6]), as well as median progression-free survival, but not significantly so (15·9 months [95% CI 11·0–21·1] *vs* 21·6 months [16·2–27·8]; unadjusted HR 1·26 [95% CI 0·90–1·77], log-rank p=0·17; adjusted HR 1·29 [0·89–1·85], p=0·18), median distant progression-free survival (18·4 months [13·3–23·2] *vs* 25·4 months [18·4–29·3]), and local progression-free survival (15·9 months [11·0–21·1] *vs* 21·6 [16·2–27·8]).

Figures 4 and 5 show the results of the quality-of-life analysis. At baseline, 246 (95%) patients completed the QLQ-C30 and 240 (93%) patients completed QLQ-OES18. A completion rate of 69% or above was maintained at week 13 (184 [71%] completed QLQ-C30 and 178 [69%] completed QLQ-OES18); the major reason for loss to follow-up was attrition. The change in the following scores from baseline to week 13 did not differ significantly between groups: physical function (z=–1·139, p=0·25; n=177), role function (z=–1·207,p=0·23; n=177), fatigue (z=0·520, p=0·60; n=177), dysphagia (z=1·395, p=0·16; n=167), and eating restrictions (z=0·031, p=0·98; n=167). In each case, n represents the number of patients who had completed questionnaires at both baseline and week 13. Full quality-of-life data will be reported elsewhere.

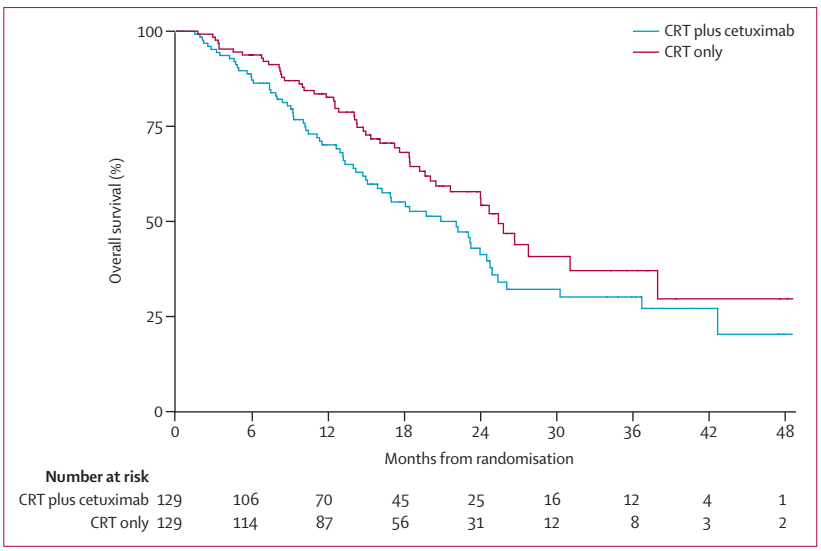

Figure 2: **Kaplan-Meier curves of overall survival by treatment group**
CRT=chemoradiotherapy.

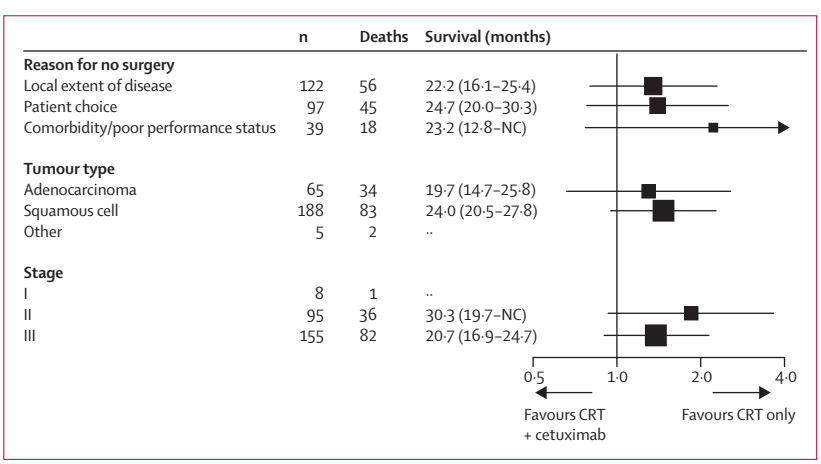

Figure 3: **Hazard ratio plots for overall survival, by baseline characteristics**
Survival data are median number of months (95% CI) in all patients. Positions of squares show hazard ratio of death in the CRT plus cetuximab group compared with death in the CRT only group; the area of each square represents the amount of information (ie, the number of patients) in each category. Lines show 95% CIs. CRT=chemoradiotherapy. NC=not calculable because of small numbers of patients.

Discussion

As the result of a preplanned assessment, the independent data monitoring committee reported that the primary endpoint of the phase 2 stage of the SCOPE1 trial had not been met and recommended closing the

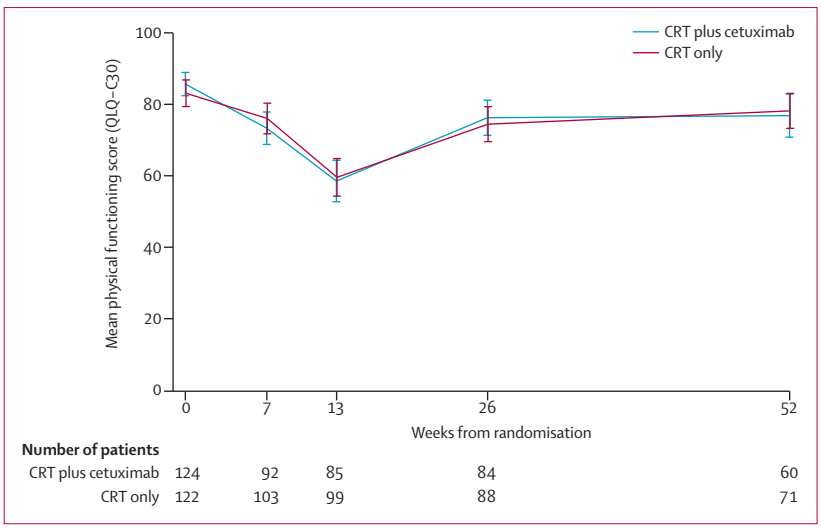

Figure 4: **Physical functioning score from QLQ-C30 in each treatment group at five timepoints over 52 weeks**
The number of patients shows the amount who completed QLQ-C30 at each timepoint. A higher score indicates better function. Bars show 95% CI. QLQ-C30=European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire C30.

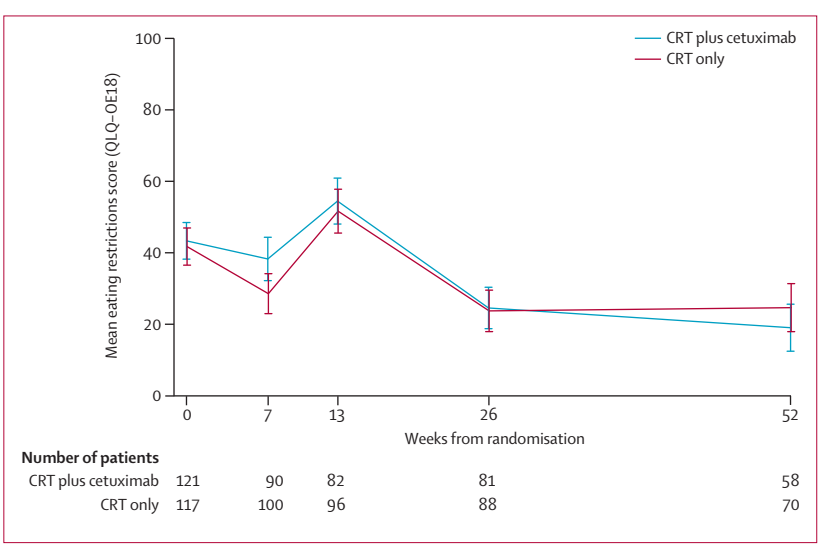

Figure 5: **Eating restrictions score from QLQ-OES18 in each treatment group at five timepoints over 52 weeks**
The number of patients shows the amount who completed QLQ-OES18 at each timepoint. A higher score indicates a greater number of problems. Bars show 95% CI. QLQ-OES18=European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire OES18.

trial to further recruitment and not proceeding to phase 3. The addition of cetuximab to chemoradiotherapy resulted in more toxicity, less protocol treatment being delivered, and worse overall survival than with chemoradiotherapy alone, although quality of life was not reduced compared with chemoradiotherapy alone. This effect on overall survival was consistent across predetermined subgroups—ie, histological subtype, tumour stage, and the reason for not undergoing surgery. Therefore, the addition of cetuximab to standard definitive chemoradiotherapy cannot be recommended.

The outcome of SCOPE1 is consistent with recent results from other randomised trials comparing the addition of anti-EGFR therapy to standard treatment across several tumour sites (panel). In the REAL3 study,[23] patients with advanced oesophagogastric cancer received epirubicin, oxaliplatin, and capecitabine with or without panitumumab. Patients who received the monoclonal antibody received a lower protocol dose of capecitabine and oxaliplatin. Despite this prespecified dose modification, patients in the chemotherapy plus panitumumab group received a lower median number of cycles than did the control group (five *vs* six), a lower median dose intensity of capecitabine, and had worse overall survival (8·8 months *vs* 11·3 months; HR 1·37; p=0·01). The Radiation Therapy Oncology Group (RTOG) 0522 trial[24] sought to build on the results of Bonner and colleagues' study[17] by adding cetuximab to cisplatin or fluoropyrimidine-based chemoradiation in a similar patient population with squamous-cell head and neck cancer. Once again, no benefit was reported in terms of progression-free survival or overall survival, although an increased rate of mucositis was noted in the patients treated with cetuximab.[24] In the COIN trial,[25] which randomly assigned 2445 patients with metastatic colorectal cancer to oxaliplatin–fluoropyrimidine (fluorouracil or capecitabine) chemotherapy with or without cetuximab, a higher than anticipated incidence of grade 3 or 4 diarrhoea (30%) in the experimental group resulted in a dose modification of capecitabine during the course of the trial. No overall improvement in survival was reported in patients randomly assigned to receive cetuximab. The EXPAND study[26] also showed no benefit from adding cetuximab to first-line chemotherapy in advanced gastric cancer. In the SCOPE1 trial, the REAL3 trial,[23] and for most patients in the COIN trial,[25] a capecitabine backbone was used and the resultant reduction in doses of standard therapy might have contributed to the worse outcome in the cetuximab groups of these trials. As seen in the REAL3 study,[23] patients receiving cetuximab had a lower rate of haematological toxicity, possibly as a result of the lower chemotherapy dose intensity delivered.

Perhaps more importantly—with respect to this study of an investigational drug in definitive treatment of oesophageal cancer—was the effect on the dose of radiotherapy delivered. More than twice the number of patients in the CRT plus cetuximab group than in the CRT only group did not receive any radiotherapy (25 *vs* 10). As systemic therapies move from palliative, through to adjuvant, to definitive treatment protocols, evidence-based treatment regimens should be vigilantly protected, especially if such treatments are intensified.

Another explanation for these results, independent of dose intensity, is the possible occurrence of a negative interaction between cetuximab and chemoradiotherapy. The proinflammatory and antitumour proliferative effects of cetuximab have been proposed as the cause of

reduced efficacy in combination with chemoradiation in rectal cancer.[27] A similar interaction between oxaliplatin and cetuximab has been proposed, specifically that cetuximab might protect against free-radical damage by platinum drugs,[28] and again could explain the negative outcome in this and other studies.[25,29] Despite this reduction in survival, however, and increased toxicity, we did not record an effect on quality of life according to standard EORTC generic and disease-specific measures.

The EGFR pathway seems to be important in the carcinogenesis of oesophagogastric malignancy[30] and a benefit of anti-EGFR therapy has been shown in head and neck cancer in combination with radiotherapy[17] and in advanced disease.[15] The negative outcome in this study therefore seems to be a result of tumour-specific interactions and biology that are not fully understood, or overlapping toxicities that preclude the delivery of effective standard treatment.

An understanding of why the overall survival in this trial was better than anticipated will be important; 2-year overall survival was predicted to be 35% in the CRT only group in the phase 3 design. Despite the fact that most patients had stage III disease, 38% of patients were older than 70 years, and 15% of patients had comorbidities that precluded surgery, the 2-year overall survival in all patients was 49%, and was 56% in those receiving CRT only. Indeed, the overall survival in the CRT only group exceeded that which was hoped to be seen by the addition of cetuximab and was better than that seen in the US and UK studies exploring the role of the addition of neoadjuvant chemotherapy to surgery.[3] Although one of the lead authors in our investigation (TC) has previously published encouraging outcomes of single centre, retrospective series,[8,12] whether these outcomes could be reproduced in a multicentre, prospective study was unclear. Before this trial, concerns had been raised about the quality of radiotherapy delivered in multicentre UK studies of radiotherapy in upper gastrointestinal cancers.[31] Such studies did not have detailed radiotherapy treatment protocols and had near-absent radiotherapy quality assurance. Standard practice throughout the UK varied substantially before this study;[32] therefore, we made RTTQA an important aspect of the study design. We developed a detailed protocol mandating the use of endoscopic ultrasound and intravenous contrast to aid localisation of target volume and used a single-phase conformal treatment plan.[33] This plan, together with a comprehensive radiotherapy planning protocol and test cases, was sent to all principal investigators and radiotherapy centres before patients were recruited.[19] We propose that this protocol, together with the on-trial quality assurance programme providing a positive dialogue between recruiting units and the RTTQA central team, was a crucial component to the successful outcomes seen in the CRT only group. The benefit of RTTQA has been reported in other studies.[34] To the best of our knowledge, this trial is the largest prospective study with a comprehensive assessment of quality of life with disease and cancer-specific questionnaires in patients undergoing definitive chemoradiotherapy. Scores achieved in patients surviving for 2 years in our study are compatible with that achieved by surgical-based treatments.[5]

Other factors that could have contributed to improved outcomes in this study are patient selection and organisation of cancer services throughout the UK. Although not mandated, 86% of patients had a PET scan before starting radiotherapy. PET has been shown to both exclude patients with metastatic disease not otherwise seen with endoscopic ultrasound and CT scan[35] and be useful in radiotherapy planning.[36] Substantial reconfiguration of oesophagogastric cancer treatment services in the UK has also taken place in the past decade.[37,38] Although the changes have mainly been in centralisation of surgical services, they have led to the development of regional specialist multidisciplinary teams, which has

***Panel:* Research in context**

Systematic review

We identified a systematic review[22] on combined modality radiotherapy and chemotherapy in non-surgical management of localised carcinoma of the oesophagus that searched Medline (1996–2001), Cancerlit (1983–2001), Cochrane Library databases (2001), and abstracts published in the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology (1999–2001) for articles published in any language. Search terms included "esophageal neoplasms" with the subheadings "drug therapy", "radiotherapy", or "therapy". The review reported the benefits of chemoradiotherapy (CRT) compared with radiotherapy alone; however, it also showed that most patients still relapse with locoregional or metastatic disease. We also identified studies that reported that cetuximab, a monoclonal EGFR antagonist, improved outcomes when given in combination with: chemotherapy in advanced colorectal adenocarcinomas and squamous-cell head and neck cancer; and radiotherapy in squamous-cell head and neck cancer.

Interpretation

Cetuximab should not be given in addition to chemoradiation in an unselected patient population. The results of our study do, however, support the use of chemoradiation alone as a standard of care in patients with non-metastatic squamous-cell carcinoma of the oesophagus and in patients with non-metastatic adenocarcinoma who are not suitable for surgery. Indeed, the outcomes of this study would support the increased use of this treatment in patients who have a higher risk of failure of surgical treatment, either due to the existence of comorbidities or where surgical excision is likely to be incomplete. A randomised trial to compare surgical and radiotherapy-based treatments in patients with oesophageal cancer with a better outlook is warranted.

undoubtedly added rigour to treatment decisions and patient selection. The 2012 annual report of the UK National Oesophago-gastric Cancer Audit[38] has showed an improvement in outcomes for patients undergoing surgery, with 45% of patients surviving for 3 years. Both of these areas have scope for further development, namely the incorporation of CT-PET more directly into radiotherapy planning and assessment of caseload, with outcomes in specialist non-surgical services.

How can we build further on the encouraging clinical outcomes reported in the CRT only group of this study? Clearly, as patients continue to relapse with both metastatic and locoregional disease, systemic and local components of this treatment strategy need to be improved and intensified. Systemic treatments should either have independent activity in oesophageal cancer or have synergistic effects with radiotherapy in the form of radiosensitisation or overcoming mechanisms of radioresistance. However, newer therapies need to be carefully integrated so as not to compromise the dose intensity of standard chemoradiotherapy. High concentrations of tumoral ERCC1 might predict platinum resistance,[39] which might be overcome with alternative chemotherapy such as taxane-containing regimens. The overexpression of HER2 (also known as ERBB2) predicts whether the addition of trastuzumab will benefit patients with advanced oesophagogastric cancer.[40] The safety and efficacy of anti-HER2 therapy should be tested as part of chemoradiotherapy treatment in this patient population.

A radiotherapy dose–response effect in patients with oesophageal cancer has been known for some time.[41] However, a study designed to test the benefit of a higher radiation dose given concurrently with cisplatin and fluoropyrimidine chemotherapy was prematurely stopped for futility as a result of an excess of treatment-related deaths occurring in the high-dose treatment group.[9] We believe, however, that by using newer radiotherapy techniques, such as intensity-modulated and image-guided radiotherapy, we can now safely deliver a higher dose of radiation to a highly conformal target volume within the context of a high-quality RTTQA programme.

This trial was a phase 2/3 study that ended on completion of phase 2. The study did not reach the full sample size needed for the comparison of overall survival powered for under the phase 3 design. However, we do plan to follow-up patients for 5 years. Additionally, although the study stratified patients according to tumour histology, it was not powered to assess with certainty the benefit of cetuximab in each of the two main histological variants of this disease.

This trial has not shown that the addition of cetuximab to standard definitive chemoradiotherapy benefits patients with locally advanced oesophageal cancer. In fact, the addition of cetuximab increased toxicity, reduced delivery of all components of standard chemoradiotherapy, and was associated with a significant reduction in overall survival. The use of cetuximab in combination with cisplatin and capecitabine-based definitive chemoradiotherapy in patients with localised oesophageal cancer cannot be recommended. However, the very encouraging outcomes seen with definitive chemoradiotherapy alone should provide an excellent platform to test more targeted therapeutic approaches, incorporating biomarker-driven systemic therapies and newer radiotherapy technologies to safely intensify treatment, including increases to radiotherapy doses.

Contributors

TC, CNH, SF, SG, JS, JAB, JIG, JB, TM, and GG were involved in the design and development of the trial and the writing and review of the protocol. CNH, NB, and RRa were involved in the day-to-day running of the trial. CNH was responsible for the statistical analysis. TC, CNH, SM, JB, and GG were responsible for preparing the manuscript. All authors have contributed to, seen, and approved the final draft. TC, SF, SG, RRo, JIG, and DC were principal investigators at centres recruiting more than 5% of patients. A full list of all SCOPE1 study investigators is listed in the appendix.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Cancer Research UK. Oesophageal cancer: statistical information on gullet cancer. http://publications.cancerresearchuk.org/cancerstats/statsoesophapgeal (accessed Feb 28, 2013).

2 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011, **61:** 69–90.

3 Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359:** 1727–33.

4 Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29:** 1715–21.

5 Blazeby J, Farndon J, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. *Cancer* 2000; **88:** 1781–87.

6 Cooper JS, Guo MD, Herskovic A, et al. Chemotherapy of locally advanced esophageal cancer: long term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA* 1999; **281:** 1623–27.

7 Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358:** 36–46.

8 Crosby TD, Brewster AE, Borley A, et al. Definitive chemoradiation in patients with inoperable oesophageal carcinoma. *Br J Cancer* 2004; **90:** 70–75.

9 Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20:** 1167–74.

10 Tsutsumi K, Yasuda M, Nishioka T. X-ray irradiation altered chemosensitivity of a p53-null non-small cell lung cancer cell line. *Cell Struct Funct* 2006; **31:** 47–52.

11 Byfield JE, Calabro-Jones P, Klisak I, Kulhanian F. Pharmacologic requirements for obtaining sensitization of human tumor cells in vitro to combined 5-Fluorouracil or ftorafur and X rays. *Int J Radiat Oncol Biol Phys* 1982; **8:** 1923–33.

12 Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer—a standard of care in patients with non-metastatic oesophageal cancer. *Clin Oncol (R Coll Radiol)* 2011; **23:** 182–88.

13 Wang KL, Wu TT, Choi IS, et al. Expression of epidermal growth factor receptor in esophageal and esophagogastric junction adenocarcinomas: association with poor outcome. *Cancer* 2007; **109:** 658–67.

14 Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastic colorectal cancer. *N Engl J Med* 2004; **351:** 337–45.

15 Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; **359:** 1116–27.

16 Baumann M, Krause M. Targeting the epidermal growth factor receptor in radiotherapy: radiological mechanisms, preclinical and clinical results. *Radiother Oncol* 2004; **72:** 257–66.

17 Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; **354:** 567–78.

18 Hurt CN, Nixon LS, Griffiths GO, et al. SCOPE1: a randomised phase II/III multicentre clinical trial of definitive chemoradiation, with or without cetuximab, in carcinoma of the oesophagus. *BMC Cancer* 2011; **11:** 466.

19 Gwynne S, Spezi E, Wills L, et al. Toward semi-automated assessment of target volume delineation in radiotherapy trials: the SCOPE 1 pretrial test case. *Int J Radiat Oncol Biol Phys* 2012; **84:** 1037–42.

20 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

21 Blazeby JM, Conroy T, Hammerlid E, et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. *Eur J Cancer* 2003; **39:** 1384–94.

22 Wong RK, Malthaner RA, Zuraw L, Rumble BR, for the Cancer Care Ontario Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group. Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. *Int J Radiat Oncol Biol Phys* 2003; **55:** 930–42.

23 Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14:** 481–89.

24 Ang KK, Zhang QE, Rosenthal DI, et al. A randomized phase III trial (RTOG 0522) of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III-IV head and neck squamous cell carcinomas (HNC). *Proc Am Soc Clin Oncol* 2011; **29** (suppl): abstr 5500.

25 Maughan TS, Adams RA, Smith CG, et al, on behalf of the MRC COIN Trial Investigators. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; **377:** 2103–14.

26 Lordick F, Kang Y-K, Chung H-C, on behalf of the Arbeitsgemeinschaft Internistische Onkologie (AIO) and EXPAND Investigators. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14:** 490–99.

27 Glynne-Jones R, Mawdsley S, Harrison M. Cetuximab and chemoradiation for rectal cancer—is the water getting muddy? *Acta Oncol* 2010; **49:** 278–86.

28 Dahan L, Sadok A, Formento J-L, Seitz JF, Kovacic H. Modulation of cellular redox state underlies antagonism between oxaliplatin and cetuximab in human colorectal cancer cell lines. *Br J Pharmacol* 2009; **158:** 610–20.

29 Tveit KM, Guren T, Glimelius B, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J Clin Oncol* 2012; **30:** 1755–62.

30 Paterson AL, O'Donovan M, Provenzano E, et al. Characterisation of the timing and prevalence of receptor tyrosine kinase expression changes in esophageal carcinogenesis. *J Pathol* 2012; **230:** 118–28.

31 Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350:** 1200–10.

32 Button M, Staffurth J, Crosby T. National variations in the treatment of oesophageal carcinoma with chemo-radiotherapy. *Clin Oncol (R Coll Radiol)* 2007; **19:** S25.

33 Nixon L, Wills L, Staffurth J, Crosby T, Casbard A, Griffiths G. Implementation of a QA RT substudy for SCOPE 1: preliminary results for test cases. *Clin Oncol* 2009; **21:** 255.

34 Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J Clin Oncol* 2010; **28:** 2996–3001.

35 Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 2000; **18:** 3202.

36 Leong T, Everitt C, Yuen K, et al. A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. *Radiother Oncol* 2006; **78:** 254–61.

37 NHS Executive. Guidance on commissioning cancer services: improving outcomes in upper gastro-intestinal cancers. NHS Executive Catalogue Number 23943. London: NHS Executive, 2001.

38 Groene O, Cromwell DA, Hardwick R, Riley S, Crosby T, Greenaway K. The National Oesophageal-Gastric Cancer Audit: 2012 annual report. London: The Royal College of Surgeons of England, 2012.

39 Leichman LP, Goldman BH, Bohanes PO, et al. S0356: a phase II clinical and prospective molecular trial with oxaliplatin, fluorouracil, and external-beam radiation therapy before surgery for patients with esophageal adenocarcinoma. *J Clin Oncol* 2011; **29:** 4555–60.

40 Bang Y-J, Van Cutsem E, Feyereislova A, et al, for the ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376:** 687–97.

41 Geh JI, Bond SJ, Bentzen SM, Glynne-Jones R. Systematic overview of preoperative (neoadjuvant) chemoradiotherapy trials in oesophageal cancer: evidence of a radiation and chemotherapy dose response. *Radiother Oncol* 2006; **78:** 236–44.