Clinical Oncology

# SCOPE 2 – still answering the unanswered questions in oesophageal radiotherapy? SCOPE2: A randomised Phase II/III trial to study radiotherapy dose escalation in patients with oesophageal cancer treated with definitive chemo-radiation with an embedded Phase II trial for patients with a poor early response using positron emission tomography/computed tomography (PET-CT)

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| **Manuscript Region of Origin:** | UNITED KINGDOM |
| **Abstract:** | The SCOPE 2 trial of definitive chemo-radiotherapy (dCRT) in oesophageal cancer investigates the benefits of radiotherapy (RT) dose escalation and systemic therapy optimisation. The trial opened in 2016. The landscape of oesophageal cancer treatment over the lifetime of this trial has changed significantly and the protocol has evolved to reflect this. However, with the recent results of the Dutch phase III ART DECO study showing no improvement in local control (LC) or overall survival (OS) with RT dose escalation in a similar patient group we seek to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal RT. Here we discuss the rationale behind the SCOPE 2 trial, outline the trial schema and review current data on dose escalation and outline recommendations for future areas of research. |

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**11.10.2021**

Dr. A. Choudhury, MA (Cantab), PhD, MRCP, FRCR
Editor
*Clinical Oncology*

Dear Dr. Choudhury

We wish to submit an original research article entitled 'SCOPE 2 – still answering the unanswered questions in oesophageal radiotherapy?' for consideration by *Clinical Oncology* journal.
We confirm this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

In this paper we present the SCOPE 2 trial schema which is investigating the benefits of radiotherapy dose escalation and systemic therapy optimisation in oesophageal cancer. The recent Dutch phase III ART DECO study showed no improvement in local control or overall survival with radiotherapy dose escalation in a similar patient group therefore we seek to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal RT. We discuss the rationale behind the SCOPE 2 trial and review current data on dose escalation and outline recommendations for future areas of research.

We believe it is important that your readers see this work, both as the SCOPE 2 trial remains open and recruiting in the UK and as there needs to be a more personalised adaptive treatment paradigm for this patient group to achieve better outcomes.

Thank you for your consideration of this manuscript

Sincerely,

Dr. Betsan Thomas

Consultant Clinical Oncologist Velindre University NHS Trust

**Summary of revisions**

Dear Editor in Chief, Assistant Editor and reviewers

Many thanks for your comments regarding our paper

CLINONC-2021-655: SCOPE 2 – still answering the unanswered questions in oesophageal radiotherapy? SCOPE2: A randomised Phase II/III trial to study radiotherapy dose escalation in patients with oesophageal cancer treated with definitive chemo-radiation with an embedded Phase II trial for patients with a poor early response using positron emission tomography/computed tomography (PET-CT)

We appreciate all of your thoughts and comments on our work and thank you for your time.

Here I will present a summary of our revisions in response to your comments.

Editor: Thank you for a well written contribution. As per Reviewer #1's suggestion a 'lessons learnt' figure/box would be a useful addition

Reply: This has been done, as below. Thank you for your comments.

Reviewer #1: This is a well written overview of outlining the SCOPE 2 trial schema and illustrating the clinical need of carrying out this trial to address the key unanswered questions for oesophageal chemoradiotherapy in terms of dose escalation strategies. I would definitely recommend Clinical Oncology to accept this manuscript for publication and it would be much appreciated if the authors could try to address the below minor points in their final published version.

- It would be extremely useful for the readers of Clinical Oncology to have an individual section detailing the lessons learnt from the SCOPE 2 trial in terms of both bottlenecks of running the trial and the success achieved. The authors have already included the amendments to the eligibility criteria made through the screening logs of the trial. With the fact that the trial is currently open in 31 UK centres with an accrual of 278 patients, this "lessons learnt" session can be expanded to include the journey of implementing advanced radiotherapy technologies (such as motion management, image guided adaptive radiotherapy) through the RTTQA.

Reply: We have added a table detailing the lessons learnt from the SCOPE 2 trial and thank you for suggesting this valuable addition to the paper

Reviewer #2: This is a very clearly written, succinct article that reviews the relevant current literature and puts into perspective the potential role of the SCOPE2 trial with respects to current treatment/research. It may have been beneficial to have some comments about the role of

induction chemotherapy for gastro-oesophageal junction tumours or distal oesophageal cancers vs chemoradiotherapy (e.g. TOPGEAR trial has recently closed recruitment and MAGIC trial treated distal oesophageal cancers with FLOT having better outcomes than ECX) however that is probably not a major issue and goes beyond the remit of this paper.

Reply: Thank you for your comment. We agree that the role of chemotherapy versus CRT for distal oesophageal and junctional cancer is very interesting and very topical. However, we also agree that discussing this complex topic to a high standard but also honouring the word count allowable would be very difficult, and would be beyond the remit of this paper. We apologies for this but hope you understand our reasoning.

**Title page**

**SCOPE 2 – still answering the unanswered questions in oesophageal radiotherapy?**

SCOPE2: A randomised Phase II/III trial to study radiotherapy dose escalation in patients with oesophageal cancer treated with definitive chemo-radiation with an embedded Phase II trial for patients with a poor early response using positron emission tomography/computed tomography (PET-CT)

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**Trial Registration**

ClinicalTrials.Gov NCT027 41856,

EudraCT 2015-001740-11

**Ethics approval and consent**

SCOPE2 has full ethical approval from Wales Research Ethics Committee 3 (dated 22nd January 2016, with subsequent approval of each amendment; REC reference 15/WA/0395), and is conducted in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments, and the Declaration of Helsinki 1996. Written informed consent has been obtained from all study participants.

**Acknowledgements**

The authors would like to thank Velindre University NHS Trust as Sponsor and the Trial Steering Committee (Chair: Prof Barry Hancock), the Independent Data Monitoring Committee (Chair: Prof Peter Hoskin), the Trial Management Group and the Investigators for their valued involvement in this study.

SCOPE 2 remains open to new recruitment sites and interested investigators are invited to contact the trials unit (SCOPE2@cardiff.ac.uk) for further discussion.

**Abstract**

The SCOPE 2 trial of definitive chemo-radiotherapy (dCRT) in oesophageal cancer investigates the benefits of radiotherapy (RT) dose escalation and systemic therapy optimisation. The trial opened in 2016. The landscape of oesophageal cancer treatment over the lifetime of this trial has changed significantly and the protocol has evolved to reflect this. However, with the recent results of the Dutch phase III ART DECO study showing no improvement in local control (LC) or overall survival (OS) with RT dose escalation in a similar patient group we seek to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal RT. Here we discuss the rationale behind the SCOPE 2 trial, outline the trial schema and review current data on dose escalation and outline recommendations for future areas of research.

**Trial Registration**

ClinicalTrials.Gov NCT027 41856,

EudraCT 2015-001740-11

**Keywords**

Oesophagus, radiotherapy, dose escalation

## Introduction

The SCOPE 2 trial, the 2nd UK multi-centre trial of definitive chemo-radiotherapy (dCRT) in oesophageal cancer (OC), investigates the benefits of radiotherapy (RT) dose escalation and systemic therapy optimisation through assessment of positron emission tomography /computed tomography (PET-CT) response. It is building on the SCOPE series of trials [1,2] which have shaped the developments of oesophageal RT in UK centres [3]. The trial opened in 2016 and is currently open in 31 UK centres and to date has recruited 278 patients. The landscape of OC treatment over the lifetime of this trial has changed significantly, and the protocol has evolved to reflect this. However, with the recent results of the Dutch phase III ART DECO study showing no improvement in local control (LC) or overall survival (OS) with RT dose escalation in a similar patient group [4], we seek to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal RT.

## Materials and methods

### Methods/Design

The SCOPE 2 trial schema is shown in figure 1.

The study objectives are:

In squamous cell carcinoma (SCC):

1. Does high dose RT (60Gy/25 fractions) improve OS when compared to standard dose RT (50Gy/25 fractions)?
2. In patients who do not respond (as defined by PET) to cisplatin and capecitabine chemotherapy does switching to carboplatin + paclitaxel chemotherapy backbone show activity and toxicity profiles that warrant a Phase III trial? *

In adenocarcinoma (ACA):

1. Does high dose RT (60Gy/25 fractions) show activity and toxicity profiles which warrant taking this strategy forward to a Phase III trial when compared to standard dose RT (50Gy/25 fractions)?
2. In patients who do not respond (as defined by PET) to cisplatin and capecitabine chemotherapy does switching to carboplatin + paclitaxel chemotherapy backbone show activity and toxicity profiles which warrant a later phase trial? *

*Patients undergoing up-front induction carboplatin+ paclitaxel will not participate in PET randomisation

**Amendments made through life of the SCOPE 2 trial**

All recruiting centres are encouraged to send in screening logs to help identify reasons for ineligibility. In response to this feedback, several amendments to the eligibility criteria have taken place. The key amendments are detailed in table 1.

Table 1: key amendments to the SCOPE 2 trial protocol

| | Original protocol | Protocol amendments |
|---|---|---|
| Patient selection | Primary tumour ≤8cm and total disease length ≤10cm | Eligible tumour length extended (primary tumour ≤10cm and total disease length ≤13cm) |
| | GFR ≥ 50 mls/min (by either Cockcroft-Gault or EDTA). Participants whose GFR is 50-<60 ml/min by Cockcroft-Gault should have a formal GFR estimation (EDTA or 24 hour clearance) | GFR eligibility updated to provide clarity to sites and allow local institutional equivalent of EDTA, DTPA renal scan or 24 hour clearance |
| | Haemoglobin (Hb) ≥ 100g/L | Haemoglobin can be corrected to (Hb) ≥ 100g/L (if necessary through blood transfusion) in patients with low haemoglobin before start of treatment |

| | | |
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| Treatment | Patients with known DPD deficiency excluded | DPD testing strongly recommended. If DPD deficiency detected carboplatin and paclitaxel should be given from outset |
| | All participants will receive cisplatin and capecitabine for the first cycle | Carboplatin (AUC 5) allowed in patients either with a contra-indication to cisplatin or by choice of local investigator<br><br>Carboplatin and paclitaxel based chemotherapy allowed as the upfront treatment of choice** |
| Investigations | EUS required as screening assessment | Increased flexibility with screening EUS requirement (COVID concession due to pressures on endoscopy capacity) |
| Follow up | Face to face appointments | Allowance of telephone assessments |

Abbreviations

GFR: Glomerular filtration rate

EDTA: Ethylenediaminetetraacetic acid

DTPA: Diethylenetriamine pentaccetate

DPD: Dihydropyrimidine dehydrogenase

EUS: Endoscopic ultrasound

** The comparable survival data for this regimen [5] means a change in the baseline parameters of the sample size calculations is not necessary, however patients undergoing up-front induction carboplatin and paclitaxel will not undergo PET response randomisation as we predict the number of patients in this arm will be low.

**Rationale for the SCOPE 2 trial**

The SCOPE1 trial reported unprecedented outcomes in the standard dCRT arm with a median OS (mOS) of 25.4 months and 2-yr OS of 56% [1], rising to 34.5 months in the long term follow up [6], with low rates of long-term toxicity. Despite this study demonstrating that with a detailed protocol and robust RT trials quality assurance (RTTQA) programme, high quality dCRT can be delivered throughout the UK and lead to outcomes equivalent to that seen in published surgical series, outcomes remain poor. In line with priorities for future direction of oesophageal RT research [7], in the era of intensity modulated RT (IMRT), volumetric intensity-modulated arc therapy (VMAT) and enhanced image guided RT (IGRT) we felt it was time to revisit the role and safety of RT dose escalation in OC. The PET-CT sub study will also investigate optimisation and personalisation of systemic treatment by adapting the chemotherapy regimen depending on metabolic response.

Building on an established network of UK centres who participated in the SCOPE series of trials, we have shown that we continue to have an engaged and collaborative oesophagogastric community and can recruit and deliver high quality clinical trials in this area. However there have been a broad range of challenges in the development and running of this trial and we have included a 'lessons learnt' section (table 2) highlighting not only the difficulties we have encountered during this unprecedented time but also lessons we have learnt along the way.

Table 2

| Theme | Topic | Issues | Positive | Recommended practice/successful implementation |
|---|---|---|---|---|
| Early collaboration | Building on established network of UK centres/principle investigators (SCOPE1, NeoSCOPE trial) | | Engaged and very collaborative community | |
| | Investigator meetings to inform design | | Meeting post SCOPE1 to seek feedback on design/ideas for future trials<br>Consensus meeting re SCOPE 2 soon after grant awarded<br>Radiotherapy workshop between grant approvals and opening at sites | Enabled focus<br>Helped inform grant<br>Helped inform protocol to be in line with current standard of care |
| Educational provision | Radiotherapy (RT) | | Many centres adopted SCOPE 1 protocol as their standard for oesophageal RT. Made development of SCOPE 2 protocol easier<br>Provided educational events such as workshops and webinars to support | SCOPE1 standardised and modernised RT techniques so was key to build on for SCOPE2<br>Developments in RT techniques at sites driven by the developments in trial protocols e.g. 4DCT, IMRT/VMAT with simultaneous integrated boost |

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| | | | implementation of new technical advances in RT | |
| Radiotherapy Trials Quality Assurance Team (RTTQA) | Radiotherapy (RT) | QA requirements can add to workload and timescales | Streamlining of RTTQA: Outlining from NeoSCOPE acceptable for SCOPE2<br><br>RT guidance document amended through learning from RTTQA process | Relationships built between trial team, RTTQA team and participating centres<br><br>Focus on being an iterative and collaborative process, guiding and supporting implementation and ensuring consistency with individualised feedback<br><br>Targets for turnaround time to avoid delays to the treatment pathway |
| Ongoing collaboration | Principal Investigator feedback<br><br>Investigator meetings | Ensure the trial maintains its academic / scientific integrity and remains relevant and applicable to clinical practice<br><br>Time/personnel required to produce the trial amendments | Pragmatically respond to issues at sites | Responsive Trial Management Group (TMG) to discuss the adaptation of the trial protocol<br><br>Enables alignment of the protocol with standard clinical care<br><br>Ongoing prioritisation in workload to balance amendments and support sites |
| Co-ordination | Site set up | Set up times significantly delayed by resource at sites | Consistent Trial Management Group (TMG) members and Trials Unit staff helped with | Previous SCOPE trials have allowed us to build relationship with sites and provide support to set-up |

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| | | Overcoming challenges of prioritisation of complex trials at individual centres | building relationships with sites | Provide a supportive environment and deal with queries promptly<br><br>NHS research resource in all departments remains an ongoing problem across all trials |
| | Low recruitment | Lack of eligibility following the initial protocol design lead to low recruitment | Changes to eligibility following conversations with sites | Improvement of recruitment |
| | Slow recruitment | Time pressures in clinic are barrier to complex consent process<br><br>Increasing elderly population and complexities of decision making in this context<br><br>Pathways not in line with best practice | | Adapting protocol to fit the patient population based on review of queries, screening logs and deviations. |
| Changing environment | COVID-19 | Access to diagnostics/staging tests reduced<br><br>Need to reduce physical face to face consultations | Aligned trial risk with national guidelines as they were released<br><br>Flexibility to eligibility criteria and allowed virtual consultations | Challenge for all trials<br><br>Importance of listening to feedback and supporting sites |

| | | | | |
|---|---|---|---|---|
| | | Recruitment was slow to recover to pre-COVID levels | | |

**PET-CT sub-study: PET scanning in response assessment**

The optimal role of PET in detecting 'non-responders' to systemic treatment is still uncertain [7]. Gillies et al [8], in a single centre phase two trial of 48 patients, demonstrated a relationship between metabolic response seen on fluorodeoxyglucose (FDG) PET and histopathological response and survival. Meanwhile, the MUNICON [9] and MUNICON II [10] studies have demonstrated the feasibility of using PET-CT response to guide neo-adjuvant (NA) therapy. Patients in the MUNICON study underwent a PET scan on day 14 of platinum/fluorouracil chemotherapy with median OS and major histopathological response favouring metabolic responders. The MUNICON II study confirmed an early PET-CT response may select out patients with a better outcome but also suggested that the addition of standard dose RT to a "failing" chemotherapy backbone may not be able to reverse treatment resistance, and a change in concurrent chemotherapy should be simultaneously investigated. The CALGB 80803 trial showed using PET imaging as a biomarker to individualize therapy for patients with resectable oesophageal ACA was an effective way of improving pathological complete response (pCR) rates in PET non-responders [11]. SCOPE 2 has adopted the PET sensitivity sub-study to adapt the systemic therapy backbone during treatment based on assessment of early response to cisplatin/fluoropyrimidine therapy.

**PET-CT sub-study: Alternative chemotherapy regimen**

In both NA CRT and dCRT studies, distant failure remains an issue even in the presence of LC, suggesting the need to refine systemic treatment in addition to local treatment intensification [6,12,13,14,15]. Toxicities associated with systemic treatment can lead to lower doses of standard therapy (both chemotherapy and RT) and has been implied as a potential cause of inferior survival in the experimental arms in the REAL3 and the SCOPE1 trials [16],[1]. It is therefore imperative that the systemic therapy used in dCRT is effective and tolerable.

Cisplatin and fluorouracil (5FU) became the standard of care in dCRT following the publication of the RTOG 85-01 trial [17], albeit at the cost of increased toxicity, and was used in the standard arm of the SCOPE 1 trial where survival was amongst the best in published literature on dCRT [1, 6]. However, as only 40-50% of OC patients respond to platinum-5FU based chemotherapy [18] work is needed to identify patients who may be more appropriately treated with an alternative regimen. Historically, in the UK, patients were only offered carboplatin and paclitaxel if had contraindications to cisplatin and/or 5FU but it is now considered standard in many parts of North America and Europe, as exemplified by its inclusion within the ART DECO trial [4]. Several phase II studies have shown that carboplatin and paclitaxel given concurrently with RT in OC is both tolerable and active [19] [20]. The largest study using carboplatin/paclitaxel based CRT was the CROSS trial of NA CRT vs surgery alone [21]. The pCR rate was 23% (18/121) in the ACA group and 49% (18/37) in the SCC group, comparing favourably with trials using cisplatin and fluoropyrimidine regimens, and with a favourable toxicity profile. In addition, long-term results of the NeoSCOPE trial demonstrated that in patients with resectable disease OS and progression free survival favoured NA carboplatin and paclitaxel over platinum and 5FU concurrent with RT [22]. Retrospective UK data also suggests that OS is comparable to those undergoing cisplatin and 5FU chemotherapy [5]. Similarly, Chen et al. [23] randomised to either cisplatin 5FU or paclitaxel 5FU in their study of dose-escalated oesophageal RT and found no difference between the two arms.

**Dose escalation**

The optimal dose/fractionation for oesophageal dCRT remains uncertain, with patterns of relapse often being loco-regional and in most instances this occurs within the irradiated field [13,14,15]. Cancers in other regions of the aero-digestive tract are treated safely with higher doses of RT [24, 25]. This has led to the hypothesis that RT dose escalation may improve outcomes in OC, which has been tested in both modelling studies and clinical trials. A systematic overview of preoperative CRT by Geh et al. [26] found that increasing the RT

dose increased the probability of a pathological complete response (pCR) (p=0.006), whereas increasing duration of treatment was found to be detrimental (p=0.035). This suggests that RT dose escalation could improve outcome if the overall treatment time is not increased as a consequence.

A planning study using data on 10% of UK SCOPE 1 [1] patients found that by using a simultaneous integrated boost (SIB) technique, a dose of 60Gy in 25 fractions could be delivered to gross tumour volume (GTV) whilst maintaining lung and heart constraints in most patients [28]. Using the radiobiological model described by Geh at al [26] it was predicted that the higher dose of radiotherapy increased tumour control probability by an estimated 18.6% (from 38.2% to 56.3%) [28].

## Results

### Current clinical evidence for dose escalation

INT 0123 trial (RTOG 94-05) [27], was opened in 1995 in the era of two-dimensional (2D) RT planning and randomised patients to a sequential boost of 64.8Gy/36 fractions. The trial was discontinued prematurely for futility after recruiting 236 patients and showed an excess of treatment related deaths in the high dose arm. However, most of the deaths (7/11) occurred before a cumulative dose of 50Gy was delivered and only one death could be directly attributable to high dose radiation. The reason for lack of benefit in the high dose arm was not clear, but it is postulated that the early deaths and significant prolongation of treatment time due to toxicity may have contributed to this outcome.

Subsequent studies of dose escalation have focused on attempting to reduce toxicity by escalating dose to smaller volume, taking advantage of the progress in RT techniques.

### Prospective Phase I-II studies

A US single-institution phase I study conducted between 2007 and 2013 by Vlacich et al was recently published in abstract form [30]. Gross disease received 60Gy with SIB. The primary objective was to assess feasibility as determined by a <15% rate of grade 4 or 5 toxicity. While the feasibility threshold for the study was achieved, toxicity to therapy was still

significant and treatment compliance was relatively poor, with outcomes otherwise comparable to historical controls.

Another US single institution phase I-II single-arm trial recruited 46 patients from 2010-2015 [31]. 63Gy was delivered to the gross tumour and involved nodes with SIB and concurrent docetaxel and fluoropyrimidine. No patients experienced grade 4 or 5 toxicities. Comparison with 97 contemporaneous controls who received a standard dose of RT showed superior LC and OS in the high dose arm.

Long-term outcomes of a single arm phase II study from China of dCRT with SIB in oesophageal SCC was presented in abstract form in ESTRO 2020 [32]. Between 2012 and 2015, 87 patients received 66Gy to the primary tumour concurrent with cisplatin and 5FU. 1, 3 and 5 year loco-regional control rates and survival were high at 78%, 72.4% and 72.4% and 82.8%, 60.8% and 58.3 % but there were 16 cases (18.4%) of severe late toxicities, including 4 cases (4.6%) of grade 5 oesophageal ulceration, 7 cases (8.0%) of Grade 3 oesophageal ulceration and 3 cases (3.4%) of Grade 3 oesophageal stricture.

A single institution phase I study from Japan published in 2021 [33] aimed to estimate the maximum tolerated CRT dose for locally advanced oesophageal SCC using SIB IMRT via the standard 3+3 radiation dose-escalation trial design. Dose to the primary tumour was escalated from 66Gy to a planned maximum dose of 72Gy in 3Gy increments with an elective nodal irradiation (ENI) dose of 48Gy. Nine patients were recruited. Two of the three patients allocated to the II dose level (69Gy) experienced pre-defined dose limiting toxicities and no patients were able to progress to dose level III. The authors recognise that the size of their ENI field, which encompassed large areas of the mediastinum and thus increased the volume of irradiated oesophagus contributed to being unable to proceed with a higher than 66Gy dose to the primary tumour.

**Prospective Phase II-III studies**

In the era of modern RT, there are two main studies to consider in addition to SCOPE 2. These are detailed in table 3.

The phase II-III French CONCORDE study (PRODIGE 26) [34] has been published in abstract form only and has shown no improvement in loco-regional progression free survival with dose escalated chemoradiotherapy. The phase III Dutch ART DECO trial has recently been published in full [4] and disappointingly showed no improvement in 3 year loco-regional control or OS in the experimental arm. There was evidence of (non-statistically significant) higher toxicity in the experimental arm with 61% grade 3 toxicity (versus 55%) and 8 deaths (versus 4 deaths) secondary to haemorrhage, perforation, respiratory failure and sepsis. The authors acknowledge that toxicities make studying the effect of higher radiation doses more challenging.

**Table 3**

Table comparing trial protocol for ART DECO, CONCORDE (PRODIGE 26) and SCOPE 2, all looking at dose escalation in oesophageal radiotherapy.

| | ART DECO | CONCORDE (PRODIGE 26) | SCOPE 2 |
|---|---|---|---|
| Phase | III | II-III | II-III |
| Histology | SCC and ACA stratified | SCC and ACA stratified | SCC (III) and ACA (II) separated out |
| Chemotherapy | Carboplatin and paclitaxel<br>Concurrent with RT weekly (x6) | Platinum/5FU<br>3 cycles concurrent with RT followed by 3 cycles adjuvant | Platinum/5FU or<br>Carboplatin and paclitaxel<br>2 cycles of induction chemotherapy followed by concurrent CRT<br>(PET sensitivity sub-study with change of |

| | | | |
|---|---|---|---|
| | | | chemotherapy based on response) |
| RT dose in standard arm | 50.4Gy in 1.8Gy fractions | 40Gy in 2Gy fractions ENI and sequential boost 10Gy in 2Gy fractions to primary and involved nodes | 50Gy in 2Gy fractions |
| RT dose in experimental arm | 50.4Gy ENI in 1.8Gy fractions<br>61.6Gy SIB to primary in 2.2Gy fractions | 40Gy in 2Gy fractions ENI and sequential boost 26Gy in 2Gy fractions to the primary and involved nodes | 50Gy ENI in 2Gy fractions<br>60Gy SIB to primary in 2.4Gy fractions |
| Maximum length of tumour (if known) | Maximum length of primary tumour 10cm | Not defined | Maximum length of primary tumour ≤10cm and total tumour length ≤13cm |

| | | | |
|---|---|---|---|
| TVD | *CTV:*GTV + **3cm** superior-inferior<br><br>Inclusion of periesophageal fatty tissue, aorta pulmonary window, sub carinal area, bilateral supraclavicular area and fatty tissue along the left gastric artery in the hepatogastric ligament (if these regions within the 3 cm superior-inferior extension).<br>If positive cervical nodes all jugular nodes included (II, III, IV and VI)<br><br>*PTV*<br><br>CTV +1cm all directions. | *CTV:*<br><br>CTV 1: GTV **+ 5cm** superior-inferior<br><br>Inclusion of lymph node stations with ≥ 20% risk of involvement as defined by RTOG atlas<br><br>CTV 2: GTV +**3cm** superior-inferior<br><br>*PTV*<br><br>CTV1 + 1cm all directions | *CTV*: GTV + **2cm** superior-inferior, 10mm radially<br><br>Inclusion of fatty perioesophageal tissue, edited for normal structures,<br>minimum GTV-to-CTV margin of 5mm<br><br>Bilateral SCF region if positive SCF node. Below diaphragm ELNI along lesser curve of stomach, left gastric artery and coeliac region (within 2cm inferior of GTV)<br><br>ITV: (4DCT only): composite of CTV volumes from all phases of respiratory cycle<br><br>*PTV*<br><br>3DCT: CTV +1cm superior, 1-1.5cm inferior, 0.5cm radially |

| | | | |
|---|---|---|---|
| | <u>Boost</u><br><br>primary tumour GTV + 1cm in all directions | <u>Boost</u><br><br>CTV2 +1cm all directions | 4DCT – ITV plus 0.5cm in all directions<br><br><u>Boost</u><br>GTV primary + 5mm in all directions |
| RTTQA | No | Pre-accrual benchmark case | Pre accrual benchmark case<br><br>Real time review of outline and planning of first cases from all centres and all high dose cases during the initial toxicity assessment stage.<br><br>Timely retrospective review of a 10% sample of cases<br><br>All planning scans and dose cubes collected centrally for retrospective analysis. |

Abbreviations

SCC - Squamous cell carcinoma

ACA - Adenocarcinoma

ENI - Elective nodal irradiation

SIB - Simultaneous integrated boost

RTOG – Radiation Therapy Oncology Group

TVD – Tumour volume delineation

GTV - Gross tumour volume

CTV - Clinical tumour volume

PTV – Planning tumour volume

ITV – Internal target volume

TVD – Tumour volume delineation

RTTQA - Radiotherapy trials quality assurance

4DCT – Four-dimensional Computed Tomography

SCF – Supraclavicular fossa

## Discussion

### Where now for dose escalation?

The results of the ART DECO trial have raised questions as to the continued relevance of the SCOPE 2 trial. The latter is overseen by a Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC). The IDMC have reviewed the SCOPE 2 data regularly and at its most recent review was in August 2021, where the full ART DECO data was discussed and the decision has been to continue the dose escalation component of the trial.

The ART DECO authors have postulated the reasons for the lack of effect in the high dose arm, which include toxicity [4]. Taking all of the available data on dose escalation into account [4, 23, 26-33] it is possible that increased toxicity seems to be a major obstacle in attempts to dose escalate and could be hypothesised to be the main limitation to date. It is worth noting that grade 5 toxicity in the standard dose arm of the ART DECO trial was 5%, whereas no grade 5 toxicities were seen in the dCRT SCOPE 1 trial using the same dose [5]. Methods to further reduce toxicity, some of which are incorporated into the SCOPE 2 trial, will be important in seeking to minimise this as a cofounder, in fact the lack of significant toxicity in the SCOPE 2 dose earlier in the study were given as reasons for approving the continuation of the trial.

## Methods to minimise toxicity from dose escalation

### Minimising volumes

Theoretically, treatment-related toxicities should decline with smaller irradiated volumes. As summarised in table 1 there are differences in the RT volumes (both the ENI field and boost margins) of the CONCORDE, ART DECO and SCOPE 2 trials. The role of ENI remains uncertain and a survival advantage has not yet been conclusively shown [35]. An analysis of recurrence patterns by Button et al [14] showed only 3/85 (3%) developed isolated out-of-field regional failure without distant metastases, and it was felt that larger field margins would not have been clinically acceptable or effective in these cases; supporting the SCOPE 2 approach of boosting the primary GTV alone with smaller margins.

Ward et al. [36] demonstrated that local recurrences occurred predominantly in the region of high SUV uptake on the diagnostic pre-treatment FDG PET. A recent feasibility study of dose escalation to a PET-defined GTV by Fan et al. [29] showed that selective boosting of sub-volumes appears more feasible than boosting the whole of the GTV due to limitations of failing dose constraints to surrounding organs at risk, but there remains a modest increase in the risk of cardiac and lung toxicities.

### Motion management

Motion of the lower oesophagus, GOJ and the associated regional nodal areas can be marked during respiration because of swallowing, gastric filling and vascular pulsations [7]. Four-dimensional CT (4DCT) planning has the potential to reduce the resulting risk of geographical miss by taking into account internal motion allowing the creation of individualised margins [37]. In addition, it has been shown to result in a smaller median absolute PTV volume and a reduction of dose to surrounding OARs [38]. The SCOPE 2 trial strongly encourages the use of 4DCT for lower oesophageal tumours providing a detailed 4D planning protocol.

### Adaptive radiotherapy

Cone beam CT (CBCT) has significantly enhanced on-set image guided radiotherapy compared to electronic portal imaging [39]. The use of CBCT matched to the planning CT scan is mandated in the SCOPE 2 trial and the minimum protocol for verification is on-line imaging of the initial five fractions and then a minimum of weekly imaging thereafter. The trial team are capturing data on re-planning decisions based on changes identified on-set during treatment introducing an element of real-time adaptive RT. Integration of a linear accelerator with MRI functionality enables high contrast soft-tissue imaging directly at the time of treatment, capturing anatomical changes through inter and intra-fraction motion [40]. Early studies comparing MRI and conventional linear accelerator delivered treatment led to clinically acceptable dose distributions [41]. On-going work in the UK through the RadNet group is currently looking at incorporating MRI-guided RT for oesophageal cancer enabling real time adaptation of treatment, but limitations include longer treatment times at a time when service delivery is already under significant pressure. Another potential effect of utilising MRI would be the integration of functional sequences, which may indicate early or poor responders to potentially allow escalation/de-escalation. Equally important would be the utility of identifying potential predictors of late toxicity, for instance cardiac biomarkers to adapt treatment dose escalation safely for each individual case.

**Radiotherapy Trials Quality Assurance (RTTQA)**

It is well documented that protocol deviations in clinical trials can affect outcome and that non-adherence to protocol-specific RT requirements is associated with reduced LC, survival and can potentially increase toxicity [42] and lead to the benefits of the interventions discussed not being realised. To ensure a high quality of RT is delivered as part of the SCOPE 2 trial we provide a detailed RT planning protocol for upper, mid and lower oesophageal tumours and an associated rigorous RTTQA programme, including a pre-accrual outlining and planning exercise as well as a real time review case. The PRODIGE 26/CONCORDE trial also mandated a pre-accrual benchmark case procedure for each centre with a detailed tumour volume delineation (TVD) protocol. Overall 25% of the pre-accrual test case plans for this trial were rejected based on unacceptable protocol deviations [43]. The main reason for major protocol deviations were under-dosage of the planning tumour volume (PTV) and unacceptable dose to organs at risk.

**Protons**

Due to its unique dose distribution, proton beam therapy (PBT) has the potential to improve outcomes from oesophageal cancer and further systematic evaluation in prospective studies is warranted [44]. PBT exhibits a Bragg peak resulting in a sharp dose fall-off at the distal edge of the beam thereby reducing RT dose to distal organs at risk [45]. Several studies from Japan report outcomes using a dose-escalated schedule with PBT in combination with photon RT with acceptable levels of pulmonary and cardiac toxicity [46-51]. Ono et al. [50] retrospectively evaluated the safety and efficacy of PBT for the treatment of oesophageal cancer using multicentre data in Japan. Over 200 hundred patients were recruited and a median dose of 87.2Gy was delivered. 4% developed grade 3 oesophageal ulceration, 1 patient developed grade 3 pneumonitis and 2 patients developed grade 3 pericarditis however; these patients had also received extensive photon ENI. No grade 4 or 5 toxicities were recorded.

**Where next after dose escalation?**

The results of the ART DECO trial are clearly disappointing and as discussed by the authors, the small excess in toxicity-related deaths in the high dose arm of the trial does not fully explain the lack of improvement in local tumour control [3] and there is a need to explore other areas of research that may form a part of, or all, treatment strategies in the future.

Alongside the optimisation of RT technique, there remains work to be done on optimising systemic therapy as well as stratification of patients based on GTV size [52] and comorbidity alongside a greater focus on prehabilitation to optimise patients for treatment.

The role of molecular biomarkers in predicting response to systemic treatment, thus enabling the development of more personalised treatment strategies, needs to be further explored. For example, the nucleotide excision repair and inter-strand cross-link pathways seem to be key in cellular responses to platinum-induced DNA damage [53]. Further research in this area is essential as only three molecular biomarkers have thus far been demonstrated to predict a response to targeted therapies in this group of patients: HER2

positivity [54], microsatellite instability (MSI) status and PD- L1 expression [55, 56]. Despite this lack of clinically relevant biomarkers, distinct molecular subtypes of oesophageal cancers have been identified and targeted biological therapy and immunotherapy are tested in clinical trials.

The recently published Checkmate 577 study [57] was a global phase III study looking at the role of adjuvant nivolumab following neo-adjuvant CRT and surgical resection in those with residual pathological disease. There was a 31% reduction in the risk of recurrence or death and a doubling in median progression free survival (PFS) in the experimental arm, with an acceptable safety profile. The KEYNOTE-975 phase III trial [58] is currently open to recruitment and is assessing the efficacy and safety of adjuvant pembroluzimab following dCRT in OC.

## Conclusion

Personalised medicine is the future of cancer treatment. Despite the negative results of the ART DECO trial and the CONCORDE study (PRODIGE 26), we believe the SCOPE 2 trial continues to ask important questions for the oesophageal RT community. In addition, it is hoped that the sub studies within SCOPE 2 exploring the systemic therapy backbone and PET response will also add to the future data in this area to inform future studies. Further work is needed to characterise molecular differences between tumours and integrate better imaging and treatment technology allowing us to stratify patients for treatment and deliver a more personalised adaptive treatment paradigm resulting in better outcomes for this patient group.

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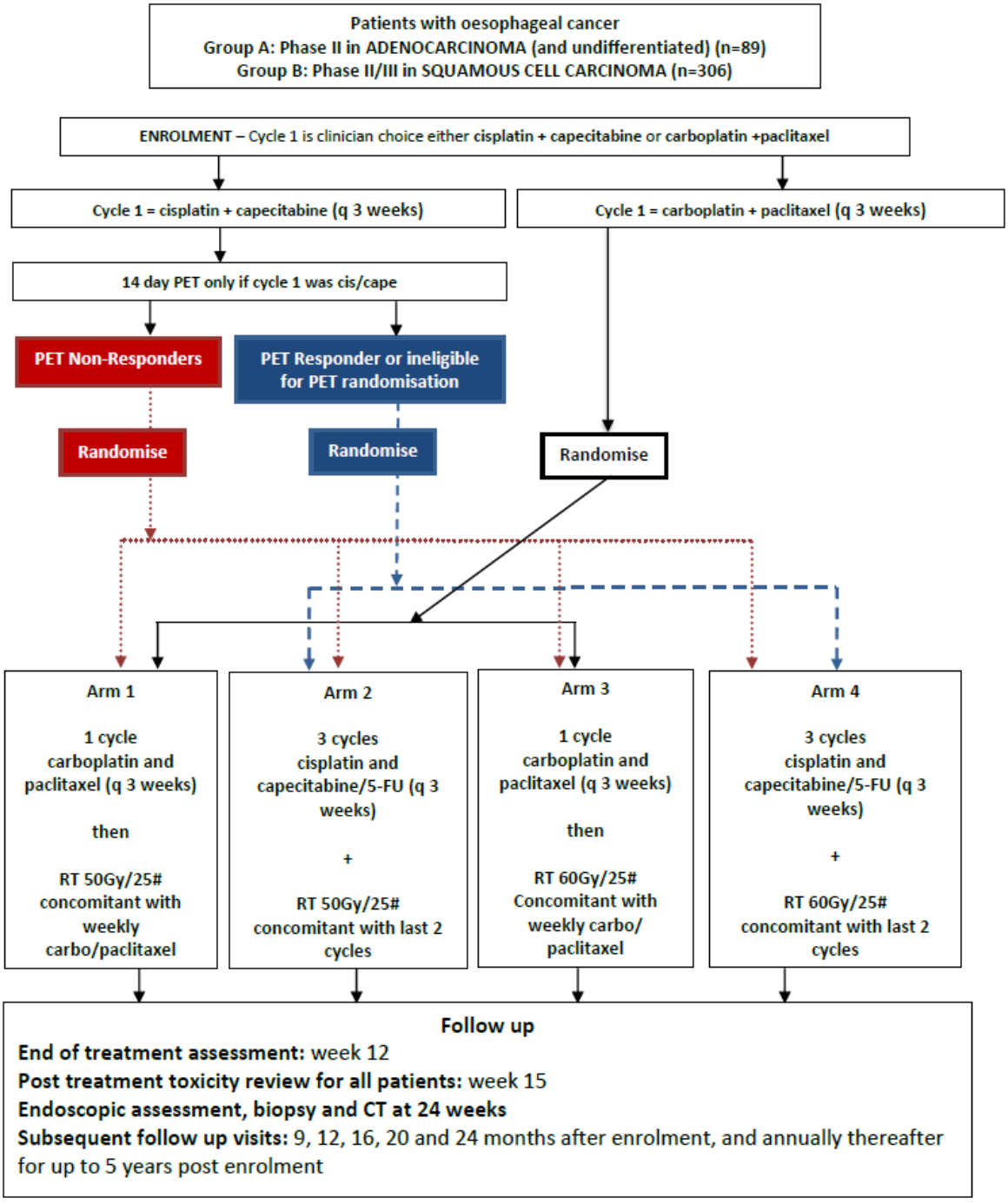
**Figure 1** SCOPE 2-trial schema.



**Abstract**

The SCOPE 2 trial of definitive chemo-radiotherapy (dCRT) in oesophageal cancer investigates the benefits of radiotherapy (RT) dose escalation and systemic therapy optimisation. The trial opened in 2016. The landscape of oesophageal cancer treatment over the lifetime of this trial has changed significantly and the protocol has evolved to reflect this. However, with the recent results of the Dutch phase III ART DECO study showing no improvement in local control (LC) or overall survival (OS) with RT dose escalation in a similar patient group we seek to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal RT. Here we discuss the rationale behind the SCOPE 2 trial, outline the trial schema and review current data on dose escalation and outline recommendations for future areas of research.

**Trial Registration**

ClinicalTrials.Gov NCT027 41856,

EudraCT 2015-001740-11

**Keywords**

Oesophagus, radiotherapy, dose escalation

## Introduction

The SCOPE 2 trial, the 2nd UK multi-centre trial of definitive chemo-radiotherapy (dCRT) in oesophageal cancer (OC), investigates the benefits of radiotherapy (RT) dose escalation and systemic therapy optimisation through assessment of positron emission tomography /computed tomography (PET-CT) response. It is building on the SCOPE series of trials [1,2] which have shaped the developments of oesophageal RT in UK centres [3]. The trial opened in 2016 and is currently open in 31 UK centres and to date has recruited 278 patients. The landscape of OC treatment over the lifetime of this trial has changed significantly, and the protocol has evolved to reflect this. However, with the recent results of the Dutch phase III ART DECO study showing no improvement in local control (LC) or overall survival (OS) with RT dose escalation in a similar patient group [4], we seek to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal RT.

## Materials and methods

### Methods/Design

The SCOPE 2 trial schema is shown in figure 1.

The study objectives are:

In squamous cell carcinoma (SCC):

1. Does high dose RT (60Gy/25 fractions) improve OS when compared to standard dose RT (50Gy/25 fractions)?
2. In patients who do not respond (as defined by PET) to cisplatin and capecitabine chemotherapy does switching to carboplatin + paclitaxel chemotherapy backbone show activity and toxicity profiles that warrant a Phase III trial? *

In adenocarcinoma (ACA):

1. Does high dose RT (60Gy/25 fractions) show activity and toxicity profiles which warrant taking this strategy forward to a Phase III trial when compared to standard dose RT (50Gy/25 fractions)?
2. In patients who do not respond (as defined by PET) to cisplatin and capecitabine chemotherapy does switching to carboplatin + paclitaxel chemotherapy backbone show activity and toxicity profiles which warrant a later phase trial? *

*Patients undergoing up-front induction carboplatin+ paclitaxel will not participate in PET randomisation

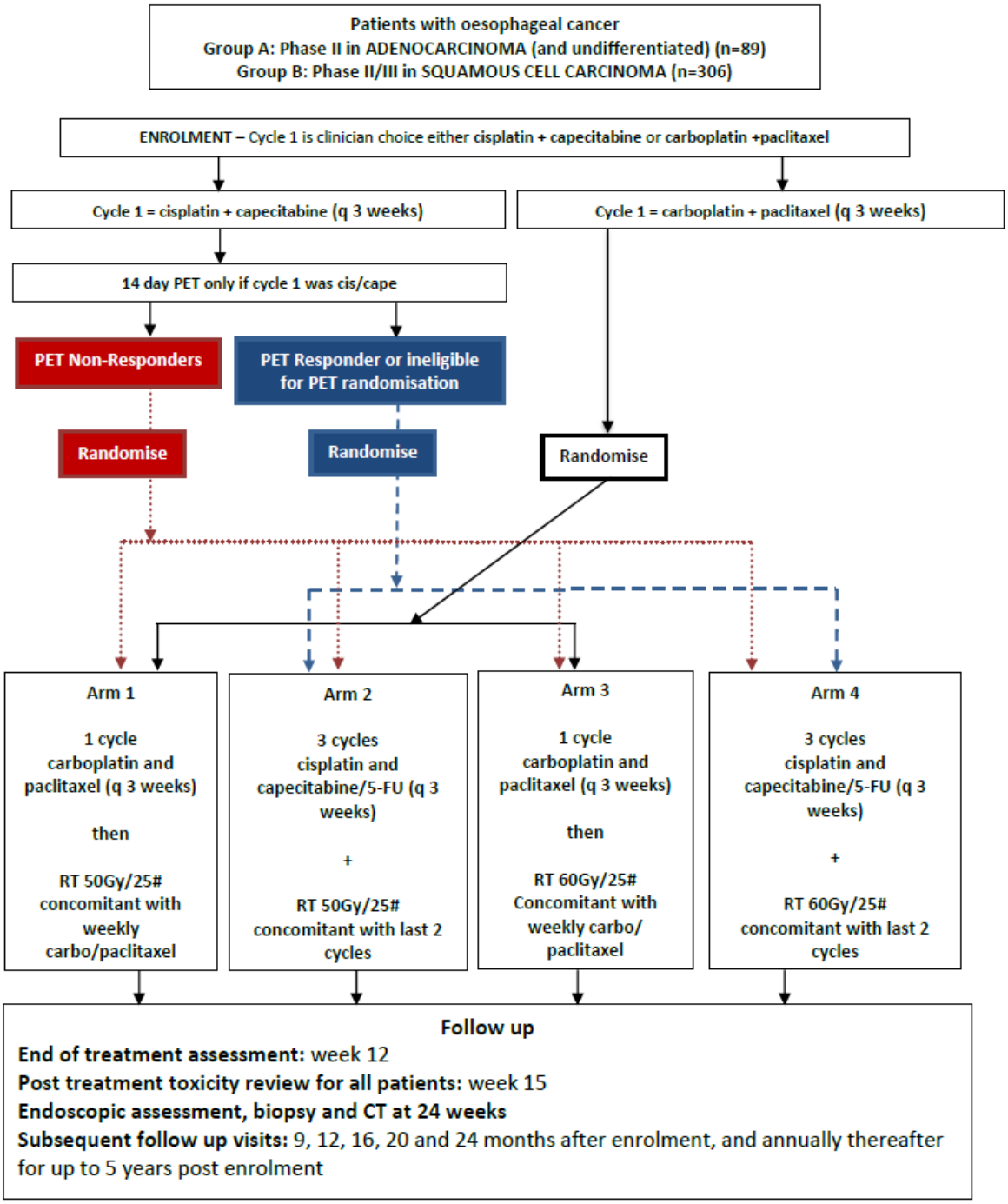



**Figure 1** SCOPE 2-trial schema.

**Amendments made through life of the SCOPE 2 trial**

All recruiting centres are encouraged to send in screening logs to help identify reasons for ineligibility. In response to this feedback, several amendments to the eligibility criteria have taken place. The key amendments are detailed in table 1.

Table 1: key amendments to the SCOPE 2 trial protocol

| | Original protocol | Protocol amendments |
|---|---|---|
| Patient selection | Primary tumour ≤8cm and total disease length ≤10cm | Eligible tumour length extended (primary tumour ≤10cm and total disease length ≤13cm) |
| | GFR ≥ 50 mls/min (by either Cockcroft-Gault or EDTA). Participants whose GFR is 50-<60 ml/min by Cockcroft-Gault should have a formal GFR estimation (EDTA or 24 hour clearance) | GFR eligibility updated to provide clarity to sites and allow local institutional equivalent of EDTA, DTPA renal scan or 24 hour clearance |
| | Haemoglobin (Hb) ≥ 100g/L | Haemoglobin can be corrected to (Hb) ≥ 100g/L (if necessary through blood transfusion) in patients with low haemoglobin before start of treatment |

| | | |
|---|---|---|
| Treatment | Patients with known DPD deficiency excluded | DPD testing strongly recommended. If DPD deficiency detected carboplatin and paclitaxel should be given from outset |
| | All participants will receive cisplatin and capecitabine for the first cycle | Carboplatin (AUC 5) allowed in patients either with a contra-indication to cisplatin or by choice of local investigator<br><br>Carboplatin and paclitaxel based chemotherapy allowed as the upfront treatment of choice** |
| Investigations | EUS required as screening assessment | Increased flexibility with screening EUS requirement (COVID concession due to pressures on endoscopy capacity) |
| Follow up | Face to face appointments | Allowance of telephone assessments |

Abbreviations

GFR: Glomerular filtration rate

EDTA: Ethylenediaminetetraacetic acid

DTPA: Diethylenetriamine pentaccetate

DPD: Dihydropyrimidine dehydrogenase

EUS: Endoscopic ultrasound

** The comparable survival data for this regimen [5] means a change in the baseline parameters of the sample size calculations is not necessary, however patients undergoing up-front induction carboplatin and paclitaxel will not undergo PET response randomisation as we predict the number of patients in this arm will be low.

**Rationale for the SCOPE 2 trial**

The SCOPE1 trial reported unprecedented outcomes in the standard dCRT arm with a median OS (mOS) of 25.4 months and 2-yr OS of 56% [1], rising to 34.5 months in the long term follow up [6], with low rates of long-term toxicity. Despite this study demonstrating that with a detailed protocol and robust RT trials quality assurance (RTTQA) programme, high quality dCRT can be delivered throughout the UK and lead to outcomes equivalent to that seen in published surgical series, outcomes remain poor. In line with priorities for future direction of oesophageal RT research [7], in the era of intensity modulated RT (IMRT), volumetric intensity-modulated arc therapy (VMAT) and enhanced image guided RT (IGRT) we felt it was time to revisit the role and safety of RT dose escalation in OC. The PET-CT sub study will also investigate optimisation and personalisation of systemic treatment by adapting the chemotherapy regimen depending on metabolic response.

Building on an established network of UK centres who participated in the SCOPE series of trials, we have shown that we continue to have an engaged and collaborative oesophagogastric community and can recruit and deliver high quality clinical trials in this area. However there have been a broad range of challenges in the development and running of this trial and we have included a 'lessons learnt' section (table 2) highlighting not only the difficulties we have encountered during this unprecedented time but also lessons we have learnt along the way.

Table 2

| Theme | Topic | Issues | Positive | Recommended practice/successful implementation |
|---|---|---|---|---|
| Early collaboration | Building on established network of UK centres/principle investigators (SCOPE1, NeoSCOPE trial) | | Engaged and very collaborative community | |
| | Investigator meetings to inform design | | Meeting post SCOPE1 to seek feedback on design/ideas for future trials<br>Consensus meeting re SCOPE 2 soon after grant awarded<br>Radiotherapy workshop between grant approvals and opening at sites | Enabled focus<br>Helped inform grant<br>Helped inform protocol to be in line with current standard of care |
| Educational provision | Radiotherapy (RT) | | Many centres adopted SCOPE 1 protocol as their standard for oesophageal RT. Made development of SCOPE 2 protocol easier<br>Provided educational events such as workshops and webinars to support | SCOPE1 standardised and modernised RT techniques so was key to build on for SCOPE2<br>Developments in RT techniques at sites driven by the developments in trial protocols e.g. 4DCT, IMRT/VMAT with simultaneous integrated boost |

| | | | | |
|---|---|---|---|---|
| | | | implementation of new technical advances in RT | |
| Radiotherapy Trials Quality Assurance Team (RTTQA) | Radiotherapy (RT) | QA requirements can add to workload and timescales | Streamlining of RTTQA: Outlining from NeoSCOPE acceptable for SCOPE2<br>RT guidance document amended through learning from RTTQA process | Relationships built between trial team, RTTQA team and participating centres<br>Focus on being an iterative and collaborative process, guiding and supporting implementation and ensuring consistency with individualised feedback<br>Targets for turnaround time to avoid delays to the treatment pathway |
| Ongoing collaboration | Principal Investigator feedback<br>Investigator meetings | Ensure the trial maintains its academic / scientific integrity and remains relevant and applicable to clinical practice<br>Time/personnel required to produce the trial amendments | Pragmatically respond to issues at sites | Responsive Trial Management Group (TMG) to discuss the adaptation of the trial protocol<br>Enables alignment of the protocol with standard clinical care<br>Ongoing prioritisation in workload to balance amendments and support sites |
| Co-ordination | Site set up | Set up times significantly delayed by resource at sites | Consistent Trial Management Group (TMG) members and Trials Unit staff helped with | Previous SCOPE trials have allowed us to build relationship with sites and provide support to set-up |

| | | | | |
|---|---|---|---|---|
| | | Overcoming challenges of prioritisation of complex trials at individual centres | building relationships with sites | Provide a supportive environment and deal with queries promptly<br>NHS research resource in all departments remains an ongoing problem across all trials |
| | Low recruitment | Lack of eligibility following the initial protocol design lead to low recruitment | Changes to eligibility following conversations with sites | Improvement of recruitment |
| | Slow recruitment | Time pressures in clinic are barrier to complex consent process<br>Increasing elderly population and complexities of decision making in this context<br>Pathways not in line with best practice | | Adapting protocol to fit the patient population based on review of queries, screening logs and deviations. |
| Changing environment | COVID-19 | Access to diagnostics/staging tests reduced<br>Need to reduce physical face to face consultations | Aligned trial risk with national guidelines as they were released<br>Flexibility to eligibility criteria and allowed virtual consultations | Challenge for all trials<br>Importance of listening to feedback and supporting sites |

| | | | | |
|---|---|---|---|---|
| | | Recruitment was slow to recover to pre-COVID levels | | |

**PET-CT sub-study: PET scanning in response assessment**

The optimal role of PET in detecting 'non-responders' to systemic treatment is still uncertain [7]. Gillies et al [8], in a single centre phase two trial of 48 patients, demonstrated a relationship between metabolic response seen on fluorodeoxyglucose (FDG) PET and histopathological response and survival. Meanwhile, the MUNICON [9] and MUNICON II [10] studies have demonstrated the feasibility of using PET-CT response to guide neo-adjuvant (NA) therapy. Patients in the MUNICON study underwent a PET scan on day 14 of platinum/fluorouracil chemotherapy with median OS and major histopathological response favouring metabolic responders. The MUNICON II study confirmed an early PET-CT response may select out patients with a better outcome but also suggested that the addition of standard dose RT to a "failing" chemotherapy backbone may not be able to reverse treatment resistance, and a change in concurrent chemotherapy should be simultaneously investigated. The CALGB 80803 trial showed using PET imaging as a biomarker to individualize therapy for patients with resectable oesophageal ACA was an effective way of improving pathological complete response (pCR) rates in PET non-responders [11]. SCOPE 2 has adopted the PET sensitivity sub-study to adapt the systemic therapy backbone during treatment based on assessment of early response to cisplatin/fluoropyrimidine therapy.

**PET-CT sub-study: Alternative chemotherapy regimen**

In both NA CRT and dCRT studies, distant failure remains an issue even in the presence of LC, suggesting the need to refine systemic treatment in addition to local treatment intensification [6,12,13,14,15]. Toxicities associated with systemic treatment can lead to lower doses of standard therapy (both chemotherapy and RT) and has been implied as a potential cause of inferior survival in the experimental arms in the REAL3 and the SCOPE1 trials [16],[1]. It is therefore imperative that the systemic therapy used in dCRT is effective and tolerable.

Cisplatin and fluorouracil (5FU) became the standard of care in dCRT following the publication of the RTOG 85-01 trial [17], albeit at the cost of increased toxicity, and was used in the standard arm of the SCOPE 1 trial where survival was amongst the best in published literature on dCRT [1, 6]. However, as only 40-50% of OC patients respond to platinum-5FU based chemotherapy [18] work is needed to identify patients who may be more appropriately treated with an alternative regimen. Historically, in the UK, patients were only offered carboplatin and paclitaxel if had contraindications to cisplatin and/or 5FU but it is now considered standard in many parts of North America and Europe, as exemplified by its inclusion within the ART DECO trial [4]. Several phase II studies have shown that carboplatin and paclitaxel given concurrently with RT in OC is both tolerable and active [19] [20]. The largest study using carboplatin/paclitaxel based CRT was the CROSS trial of NA CRT vs surgery alone [21]. The pCR rate was 23% (18/121) in the ACA group and 49% (18/37) in the SCC group, comparing favourably with trials using cisplatin and fluoropyrimidine regimens, and with a favourable toxicity profile. In addition, long-term results of the NeoSCOPE trial demonstrated that in patients with resectable disease OS and progression free survival favoured NA carboplatin and paclitaxel over platinum and 5FU concurrent with RT [22]. Retrospective UK data also suggests that OS is comparable to those undergoing cisplatin and 5FU chemotherapy [5]. Similarly, Chen et al. [23] randomised to either cisplatin 5FU or paclitaxel 5FU in their study of dose-escalated oesophageal RT and found no difference between the two arms.

**Dose escalation**

The optimal dose/fractionation for oesophageal dCRT remains uncertain, with patterns of relapse often being loco-regional and in most instances this occurs within the irradiated field [13,14,15]. Cancers in other regions of the aero-digestive tract are treated safely with higher doses of RT [24, 25]. This has led to the hypothesis that RT dose escalation may improve outcomes in OC, which has been tested in both modelling studies and clinical trials. A systematic overview of preoperative CRT by Geh et al. [26] found that increasing the RT

dose increased the probability of a pathological complete response (pCR) (p=0.006), whereas increasing duration of treatment was found to be detrimental (p=0.035). This suggests that RT dose escalation could improve outcome if the overall treatment time is not increased as a consequence.

A planning study using data on 10% of UK SCOPE 1 [1] patients found that by using a simultaneous integrated boost (SIB) technique, a dose of 60Gy in 25 fractions could be delivered to gross tumour volume (GTV) whilst maintaining lung and heart constraints in most patients [28]. Using the radiobiological model described by Geh at al [26] it was predicted that the higher dose of radiotherapy increased tumour control probability by an estimated 18.6% (from 38.2% to 56.3%) [28].

## Results

### Current clinical evidence for dose escalation

INT 0123 trial (RTOG 94-05) [27], was opened in 1995 in the era of two-dimensional (2D) RT planning and randomised patients to a sequential boost of 64.8Gy/36 fractions. The trial was discontinued prematurely for futility after recruiting 236 patients and showed an excess of treatment related deaths in the high dose arm. However, most of the deaths (7/11) occurred before a cumulative dose of 50Gy was delivered and only one death could be directly attributable to high dose radiation. The reason for lack of benefit in the high dose arm was not clear, but it is postulated that the early deaths and significant prolongation of treatment time due to toxicity may have contributed to this outcome.

Subsequent studies of dose escalation have focused on attempting to reduce toxicity by escalating dose to smaller volume, taking advantage of the progress in RT techniques.

### Prospective Phase I-II studies

A US single-institution phase I study conducted between 2007 and 2013 by Vlacich et al was recently published in abstract form [30]. Gross disease received 60Gy with SIB. The primary objective was to assess feasibility as determined by a <15% rate of grade 4 or 5 toxicity. While the feasibility threshold for the study was achieved, toxicity to therapy was still

significant and treatment compliance was relatively poor, with outcomes otherwise comparable to historical controls.

Another US single institution phase I-II single-arm trial recruited 46 patients from 2010-2015 [31]. 63Gy was delivered to the gross tumour and involved nodes with SIB and concurrent docetaxel and fluoropyrimidine. No patients experienced grade 4 or 5 toxicities. Comparison with 97 contemporaneous controls who received a standard dose of RT showed superior LC and OS in the high dose arm.

Long-term outcomes of a single arm phase II study from China of dCRT with SIB in oesophageal SCC was presented in abstract form in ESTRO 2020 [32]. Between 2012 and 2015, 87 patients received 66Gy to the primary tumour concurrent with cisplatin and 5FU. 1, 3 and 5 year loco-regional control rates and survival were high at 78%, 72.4% and 72.4% and 82.8%, 60.8% and 58.3 % but there were 16 cases (18.4%) of severe late toxicities, including 4 cases (4.6%) of grade 5 oesophageal ulceration, 7 cases (8.0%) of Grade 3 oesophageal ulceration and 3 cases (3.4%) of Grade 3 oesophageal stricture.

A single institution phase I study from Japan published in 2021 [33] aimed to estimate the maximum tolerated CRT dose for locally advanced oesophageal SCC using SIB IMRT via the standard 3+3 radiation dose-escalation trial design. Dose to the primary tumour was escalated from 66Gy to a planned maximum dose of 72Gy in 3Gy increments with an elective nodal irradiation (ENI) dose of 48Gy. Nine patients were recruited. Two of the three patients allocated to the II dose level (69Gy) experienced pre-defined dose limiting toxicities and no patients were able to progress to dose level III. The authors recognise that the size of their ENI field, which encompassed large areas of the mediastinum and thus increased the volume of irradiated oesophagus contributed to being unable to proceed with a higher than 66Gy dose to the primary tumour.

**Prospective Phase II-III studies**

In the era of modern RT, there are two main studies to consider in addition to SCOPE 2. These are detailed in table 3~~2~~.

The phase II-III French CONCORDE study (PRODIGE 26) [34] has been published in abstract form only and has shown no improvement in loco-regional progression free survival with dose escalated chemoradiotherapy~~closed to recruitment and we await results~~. The phase III Dutch ART DECO trial has recently been published in full [4] and disappointingly showed no improvement in 3 year loco-regional control or OS in the experimental arm. There was evidence of (non-statistically significant) higher toxicity in the experimental arm with 61% grade 3 toxicity (versus 55%) and 8 deaths (versus 4 deaths) secondary to haemorrhage, perforation, respiratory failure and sepsis. The authors acknowledge that toxicities make studying the effect of higher radiation doses more challenging.

**Table 3~~2~~**

Table comparing trial protocol for ART DECO, CONCORDE (PRODIGE 26) and SCOPE 2, all looking at dose escalation in oesophageal radiotherapy.

| | ART DECO | CONCORDE (PRODIGE 26) | SCOPE 2 |
|---|---|---|---|
| Phase | III | II-III | II-III |
| Histology | SCC and ACA stratified | SCC and ACA stratified | SCC (III) and ACA (II) separated out |
| Chemotherapy | Carboplatin and paclitaxel<br>Concurrent with RT weekly (x6) | Platinum/5FU<br>3 cycles concurrent with RT followed by 3 cycles adjuvant | Platinum/5FU or<br>Carboplatin and paclitaxel<br>2 cycles of induction chemotherapy followed by concurrent CRT<br>(PET sensitivity sub-study with change of |

| | | | |
|---|---|---|---|
| | | | chemotherapy based on response) |
| RT dose in standard arm | 50.4Gy in 1.8Gy fractions | 40Gy in 2Gy fractions ENI and sequential boost 10Gy in 2Gy fractions to primary and involved nodes | 50Gy in 2Gy fractions |
| RT dose in experimental arm | 50.4Gy ENI in 1.8Gy fractions<br>61.6Gy SIB to primary in 2.2Gy fractions | 40Gy in 2Gy fractions ENI and sequential boost 26Gy in 2Gy fractions to the primary and involved nodes | 50Gy ENI in 2Gy fractions<br>60Gy SIB to primary in 2.4Gy fractions |
| Maximum length of tumour (if known) | Maximum length of primary tumour 10cm | Not defined | Maximum length of primary tumour ≤10cm and total tumour length ≤13cm |

| | | | |
|---|---|---|---|
| TVD | *CTV:*GTV + **3cm** superior-inferior<br><br>Inclusion of periesophageal fatty tissue, aorta pulmonary window, sub carinal area, bilateral supraclavicular area and fatty tissue along the left gastric artery in the hepatogastric ligament (if these regions within the 3 cm superior-inferior extension).<br>If positive cervical nodes all jugular nodes included (II, III, IV and VI)<br><br>*PTV*<br><br>CTV +1cm all directions. | *CTV:*<br><br>CTV 1: GTV **+ 5cm** superior-inferior<br><br>Inclusion of lymph node stations with ≥ 20% risk of involvement as defined by RTOG atlas<br><br>CTV 2: GTV +**3cm** superior-inferior<br><br>*PTV*<br><br>CTV1 + 1cm all directions | *CTV*: GTV + **2cm** superior-inferior, 10mm radially<br><br>Inclusion of fatty perioesophageal tissue, edited for normal structures,<br>minimum GTV-to-CTV margin of 5mm<br><br>Bilateral SCF region if positive SCF node. Below diaphragm ELNI along lesser curve of stomach, left gastric artery and coeliac region (within 2cm inferior of GTV)<br><br>ITV: (4DCT only): composite of CTV volumes from all phases of respiratory cycle<br><br>*PTV*<br><br>3DCT: CTV +1cm superior, 1-1.5cm inferior, 0.5cm radially |

| | | | |
|---|---|---|---|
| | <u>Boost</u><br><br>primary tumour GTV + 1cm in all directions | <u>Boost</u><br><br>CTV2 +1cm all directions | 4DCT – ITV plus 0.5cm in all directions<br><br><u>Boost</u><br>GTV primary + 5mm in all directions |
| RTTQA | No | Pre-accrual benchmark case | Pre accrual benchmark case<br><br>Real time review of outline and planning of first cases from all centres and all high dose cases during the initial toxicity assessment stage.<br><br>Timely retrospective review of a 10% sample of cases<br><br>All planning scans and dose cubes collected centrally for retrospective analysis. |

Abbreviations

SCC - Squamous cell carcinoma

ACA - Adenocarcinoma

ENI - Elective nodal irradiation

SIB - Simultaneous integrated boost

RTOG – Radiation Therapy Oncology Group

TVD – Tumour volume delineation

GTV - Gross tumour volume

CTV - Clinical tumour volume

PTV – Planning tumour volume

ITV – Internal target volume

TVD – Tumour volume delineation

RTTQA - Radiotherapy trials quality assurance

4DCT – Four-dimensional Computed Tomography

SCF – Supraclavicular fossa

## Discussion

### Where now for dose escalation?

The results of the ART DECO trial have raised questions as to the continued relevance of the SCOPE 2 trial. The latter is overseen by a Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC). The IDMC have reviewed the SCOPE 2 data regularly and at its most recent review was in August 2021, where the full ART DECO data was discussed and the decision has been to continue the dose escalation component of the trial.

The ART DECO authors have postulated the reasons for the lack of effect in the high dose arm, which include toxicity [4]. Taking all of the available data on dose escalation into account [4, 23, 26-33] it is possible that increased toxicity seems to be a major obstacle in attempts to dose escalate and could be hypothesised to be the main limitation to date. It is worth noting that grade 5 toxicity in the standard dose arm of the ART DECO trial was 5%, whereas no grade 5 toxicities were seen in the dCRT SCOPE 1 trial using the same dose [5]. Methods to further reduce toxicity, some of which are incorporated into the SCOPE 2 trial, will be important in seeking to minimise this as a cofounder, in fact the lack of significant toxicity in the SCOPE 2 dose earlier in the study were given as reasons for approving the continuation of the trial.

## Methods to minimise toxicity from dose escalation

### Minimising volumes

Theoretically, treatment-related toxicities should decline with smaller irradiated volumes. As summarised in table 1 there are differences in the RT volumes (both the ENI field and boost margins) of the CONCORDE, ART DECO and SCOPE 2 trials. The role of ENI remains uncertain and a survival advantage has not yet been conclusively shown [35]. An analysis of recurrence patterns by Button et al [14] showed only 3/85 (3%) developed isolated out-of-field regional failure without distant metastases, and it was felt that larger field margins would not have been clinically acceptable or effective in these cases; supporting the SCOPE 2 approach of boosting the primary GTV alone with smaller margins.

Ward et al. [36] demonstrated that local recurrences occurred predominantly in the region of high SUV uptake on the diagnostic pre-treatment FDG PET. A recent feasibility study of dose escalation to a PET-defined GTV by Fan et al. [29] showed that selective boosting of sub-volumes appears more feasible than boosting the whole of the GTV due to limitations of failing dose constraints to surrounding organs at risk, but there remains a modest increase in the risk of cardiac and lung toxicities.

### Motion management

Motion of the lower oesophagus, GOJ and the associated regional nodal areas can be marked during respiration because of swallowing, gastric filling and vascular pulsations [7]. Four-dimensional CT (4DCT) planning has the potential to reduce the resulting risk of geographical miss by taking into account internal motion allowing the creation of individualised margins [37]. In addition, it has been shown to result in a smaller median absolute PTV volume and a reduction of dose to surrounding OARs [38]. The SCOPE 2 trial strongly encourages the use of 4DCT for lower oesophageal tumours providing a detailed 4D planning protocol.

### Adaptive radiotherapy

Cone beam CT (CBCT) has significantly enhanced on-set image guided radiotherapy compared to electronic portal imaging [39]. The use of CBCT matched to the planning CT scan is mandated in the SCOPE 2 trial and the minimum protocol for verification is on-line imaging of the initial five fractions and then a minimum of weekly imaging thereafter. The trial team are capturing data on re-planning decisions based on changes identified on-set during treatment introducing an element of real-time adaptive RT. Integration of a linear accelerator with MRI functionality enables high contrast soft-tissue imaging directly at the time of treatment, capturing anatomical changes through inter and intra-fraction motion [40]. Early studies comparing MRI and conventional linear accelerator delivered treatment led to clinically acceptable dose distributions [41]. On-going work in the UK through the RadNet group is currently looking at incorporating MRI-guided RT for oesophageal cancer enabling real time adaptation of treatment, but limitations include longer treatment times at a time when service delivery is already under significant pressure. Another potential effect of utilising MRI would be the integration of functional sequences, which may indicate early or poor responders to potentially allow escalation/de-escalation. Equally important would be the utility of identifying potential predictors of late toxicity, for instance cardiac biomarkers to adapt treatment dose escalation safely for each individual case.

**Radiotherapy Trials Quality Assurance (RTTQA)**

It is well documented that protocol deviations in clinical trials can affect outcome and that non-adherence to protocol-specific RT requirements is associated with reduced LC, survival and can potentially increase toxicity [42] and lead to the benefits of the interventions discussed not being realised. To ensure a high quality of RT is delivered as part of the SCOPE 2 trial we provide a detailed RT planning protocol for upper, mid and lower oesophageal tumours and an associated rigorous RTTQA programme, including a pre-accrual outlining and planning exercise as well as a real time review case. The PRODIGE 26/CONCORDE trial also mandated a pre-accrual benchmark case procedure for each centre with a detailed tumour volume delineation (TVD) protocol. Overall 25% of the pre-accrual test case plans for this trial were rejected based on unacceptable protocol deviations [43]. The main reason for major protocol deviations were under-dosage of the planning tumour volume (PTV) and unacceptable dose to organs at risk.

**Protons**

Due to its unique dose distribution, proton beam therapy (PBT) has the potential to improve outcomes from oesophageal cancer and further systematic evaluation in prospective studies is warranted [44]. PBT exhibits a Bragg peak resulting in a sharp dose fall-off at the distal edge of the beam thereby reducing RT dose to distal organs at risk [45]. Several studies from Japan report outcomes using a dose-escalated schedule with PBT in combination with photon RT with acceptable levels of pulmonary and cardiac toxicity [46-51]. Ono et al. [50] retrospectively evaluated the safety and efficacy of PBT for the treatment of oesophageal cancer using multicentre data in Japan. Over 200 hundred patients were recruited and a median dose of 87.2Gy was delivered. 4% developed grade 3 oesophageal ulceration, 1 patient developed grade 3 pneumonitis and 2 patients developed grade 3 pericarditis however; these patients had also received extensive photon ENI. No grade 4 or 5 toxicities were recorded.

**Where next after dose escalation?**

The results of the ART DECO trial are clearly disappointing and as discussed by the authors, the small excess in toxicity-related deaths in the high dose arm of the trial does not fully explain the lack of improvement in local tumour control [3] and there is a need to explore other areas of research that may form a part of, or all, treatment strategies in the future.

Alongside the optimisation of RT technique, there remains work to be done on optimising systemic therapy as well as stratification of patients based on GTV size [52] and comorbidity alongside a greater focus on prehabilitation to optimise patients for treatment.

The role of molecular biomarkers in predicting response to systemic treatment, thus enabling the development of more personalised treatment strategies, needs to be further explored. For example, the nucleotide excision repair and inter-strand cross-link pathways seem to be key in cellular responses to platinum-induced DNA damage [53]. Further research in this area is essential as only three molecular biomarkers have thus far been demonstrated to predict a response to targeted therapies in this group of patients: HER2

positivity [54], microsatellite instability (MSI) status and PD- L1 expression [55, 56]. Despite this lack of clinically relevant biomarkers, distinct molecular subtypes of oesophageal cancers have been identified and targeted biological therapy and immunotherapy are tested in clinical trials.

The recently published Checkmate 577 study [57] was a global phase III study looking at the role of adjuvant nivolumab following neo-adjuvant CRT and surgical resection in those with residual pathological disease. There was a 31% reduction in the risk of recurrence or death and a doubling in median progression free survival (PFS) in the experimental arm, with an acceptable safety profile. The KEYNOTE-975 phase III trial [58] is currently open to recruitment and is assessing the efficacy and safety of adjuvant pembroluzimab following dCRT in OC.

**Conclusion**

Personalised medicine is the future of cancer treatment. Despite the negative results of the ART DECO trial and the CONCORDE study (PRODIGE 26), we believe the SCOPE 2 trial continues to ask important questions for the oesophageal RT community. In addition, it is hoped that the sub studies within SCOPE 2 exploring the systemic therapy backbone and PET response will also add to the future data in this area to inform future studies. Further work is needed to characterise molecular differences between tumours and integrate better imaging and treatment technology allowing us to stratify patients for treatment and deliver a more personalised adaptive treatment paradigm resulting in better outcomes for this patient group.

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**Declaration of interests**

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

**Research highlights**

- Building on SCOPE series of trials, shaping UK oesophageal radiotherapy development
- Radiotherapy dose escalation and systemic therapy personalisation in oesophageal cancer
- Role of PET-CT in treatment response assessment
- Future research strategies for oesophageal cancer

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3 literature research T Crosby; S Mukherjee; M Hawkins; S Gwynne; G Radhakrishna'; C Hurt; L Nixon; A Holborow

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Original Article

# SCOPE 2 – Still Answering the Unanswered Questions in Oesophageal Radiotherapy? SCOPE 2: a Randomised Phase II/III Trial to Study Radiotherapy Dose Escalation in Patients with Oesophageal Cancer Treated with Definitive Chemoradiation with an Embedded Phase II Trial for Patients with a Poor Early Response using Positron Emission Tomography/Computed Tomography

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**Abstract**
The SCOPE 2 trial of definitive chemoradiotherapy in oesophageal cancer investigates the benefits of radiotherapy dose escalation and systemic therapy optimisation. The trial opened in 2016. The landscape of oesophageal cancer treatment over the lifetime of this trial has changed significantly and the protocol has evolved to reflect this. However, with the recent results of the Dutch phase III ART DECO study showing no improvement in local control or overall survival with radiotherapy dose escalation in a similar patient group, we sought to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal radiotherapy. Here we discuss the rationale behind the SCOPE 2 trial, outline the trial schema and review current data on dose escalation and outline recommendations for future areas of research.

*Key words:* Dose escalation; oesophagus; radiotherapy

## Introduction (A head)

The SCOPE 2 trial, the second UK multicentre trial of definitive chemoradiotherapy (dCRT) in oesophageal cancer, investigates the benefits of radiotherapy dose escalation and systemic therapy optimisation through assessment of positron emission tomography/computed

tomography (PET/CT) response. It is building on the SCOPE series of trials [1,2], which have shaped the developments of oesophageal radiotherapy in UK centres [3]. The trial opened in 2016 and is currently open in 31 UK centres and to date has recruited 278 patients. The landscape of oesophageal cancer treatment over the lifetime of this trial has changed significantly, and the protocol has evolved to reflect this. However, with the recent results of the Dutch phase III ART DECO study showing no improvement in local control or overall survival with radiotherapy dose escalation in a similar patient group [4], we sought to determine if the SCOPE 2 trial is still answering the key unanswered questions for oesophageal radiotherapy.

## Materials and Methods (A head)

### *Methods/Design (B head)*

The SCOPE 2 trial schema is shown in Figure 1.

Figure 1 here

The study objectives are:

In squamous cell carcinoma (SCC):

(i) Does high-dose radiotherapy (60 Gy/25 fractions) improve overall survival when compared with standard dose radiotherapy (50 Gy/25 fractions)?

(ii) In patients who do not respond (as defined by PET) to cisplatin and capecitabine chemotherapy, does switching to carboplatin + paclitaxel chemotherapy backbone show activity and toxicity profiles that warrant a phase III trial? (Patients undergoing up-front induction carboplatin + paclitaxel will not participate in PET randomisation.)

In adenocarcinoma (ACA):

(i) Does high-dose radiotherapy (60 Gy/25 fractions) show activity and toxicity profiles that warrant taking this strategy forward to a phase III trial when compared with standard dose radiotherapy (50 Gy/25 fractions)?

(ii) In patients who do not respond (as defined by PET) to cisplatin and capecitabine chemotherapy, does switching to carboplatin + paclitaxel chemotherapy backbone show activity and toxicity profiles that warrant a later phase trial? (Patients undergoing up-front induction carboplatin + paclitaxel will not participate in PET randomisation.)

### *Amendments Made Through the Life of the SCOPE 2 Trial (B head)*

All recruiting centres are encouraged to send in screening logs to help identify reasons for ineligibility. In response to this feedback, several amendments to the eligibility criteria have taken place. The key amendments are detailed in Table 1.

Table 1 here

### *Rationale for the SCOPE 2 Trial (B head)*

The SCOPE 1 trial reported unprecedented outcomes in the standard dCRT arm with a median overall survival of 25.4 months and 2-year overall survival of 56% [1], rising to 34.5 months in the long-term follow-up [6], with low rates of long-term toxicity. Despite this study showing that with a detailed protocol and robust radiotherapy trials quality assurance (RTTQA) programme, high-quality dCRT can be delivered throughout the UK and lead to outcomes equivalent to those seen in published surgical series, outcomes remain poor. In line with priorities for future direction of oesophageal radiotherapy research [7], in the era of intensity-modulated radiotherapy, volumetric intensity-modulated arc therapy and enhanced image-guided radiotherapy we felt it was time to revisit the role and safety of radiotherapy dose escalation in oesophageal cancer. The PET/CT substudy will also investigate optimisation and personalisation of systemic treatment by adapting the chemotherapy regimen depending on metabolic response.

Building on an established network of UK centres who participated in the SCOPE series of trials, we have shown that we continue to have an engaged and collaborative oesophagogastric community and can recruit and deliver high-quality clinical trials in this area. However, there have been a broad range of challenges in the development and running of this trial and we have included a 'lessons learnt' section (Table 2) highlighting not only the difficulties we have encountered during this unprecedented time but also lessons we have learnt along the way.

Table 2 here

*Positron Emission Tomography/Computed Tomography Substudy: Positron Emission Tomography Scanning in Response Assessment (B head)*

The optimal role of PET in detecting 'non-responders' to systemic treatment is still uncertain [7]. Gillies *et al*. [8], in a single-centre phase II trial of 48 patients, showed a relationship between metabolic response seen on fluorodeoxyglucose (FDG) PET and histopathological response and survival. Meanwhile, the MUNICON [9] and MUNICON II [10] studies have shown the feasibility of using PET/CT response to guide neoadjuvant therapy. Patients in the MUNICON study underwent a PET scan on day 14 of platinum/5-fluorouracil (5-FU) chemotherapy with median overall survival and major histopathological response favouring metabolic responders. The MUNICON II study confirmed that an early PET/CT response may select out patients with a better outcome but also suggested that the addition of standard dose radiotherapy to a 'failing' chemotherapy backbone may not be able to reverse treatment resistance and a change in concurrent chemotherapy should be simultaneously investigated. The CALGB 80803 trial showed using PET imaging as a biomarker to individualise therapy for patients with resectable oesophageal ACA was an effective way of improving pathological complete response (pCR) rates in PET non-responders [11]. SCOPE 2 has adopted the PET sensitivity substudy to adapt the systemic therapy backbone during treatment based on assessment of early response to cisplatin/fluoropyrimidine therapy.

*Positron Emission Tomography/Computed Tomography Substudy: Alternative Chemotherapy Regimen (B head)*

In both neoadjuvant CRT and dCRT studies, distant failure remains an issue, even in the presence of local control, suggesting the need to refine systemic treatment in addition to

local treatment intensification [6,12–15]. Toxicities associated with systemic treatment can lead to lower doses of standard therapy (both chemotherapy and radiotherapy) and has been implied as a potential cause of inferior survival in the experimental arms in the REAL3 and the SCOPE 1 trials [1,16]. It is therefore imperative that the systemic therapy used in dCRT is effective and tolerable.

Cisplatin and 5-FU became the standard of care in dCRT following the publication of the RTOG 85-01 trial [17], albeit at the cost of increased toxicity, and was used in the standard arm of the SCOPE 1 trial where survival was among the best in published literature on dCRT [1,6]. However, as only 40–50% of oesophageal cancer patients respond to platinum-5-FU-based chemotherapy [18], work is needed to identify patients who may be more appropriately treated with an alternative regimen. Historically, in the UK, patients were only offered carboplatin and paclitaxel if they had contraindications to cisplatin and/or 5-FU, but it is now considered standard in many parts of North America and Europe, as exemplified by its inclusion within the ART DECO trial [4]. Several phase II studies have shown that carboplatin and paclitaxel given concurrently with radiotherapy in oesophageal cancer is both tolerable and active [19,20]. The largest study using carboplatin/paclitaxel-based CRT was the CROSS trial of neoadjuvant CRT versus surgery alone [21]. The pCR rate was 23% (18/121) in the ACA group and 49% (18/37) in the SCC group, comparing favourably with trials using cisplatin and fluoropyrimidine regimens, and with a favourable toxicity profile. In addition, long-term results of the NeoSCOPE trial showed that in patients with resectable disease, overall survival and progression-free survival favoured neoadjuvant carboplatin and paclitaxel over platinum and 5-FU concurrent with radiotherapy [22]. Retrospective UK data also suggest that overall survival is comparable with those undergoing cisplatin and 5-FU chemotherapy [5]. Similarly, Chen *et al.* [23] randomised to either cisplatin 5-FU or paclitaxel 5-FU in their study of dose-escalated oesophageal radiotherapy and found no difference between the two arms.

*Dose Escalation (B head)*

The optimal dose/fractionation for oesophageal dCRT remains uncertain, with patterns of relapse often being locoregional and in most instances this occurs within the irradiated field [13–15]. Cancers in other regions of the aerodigestive tract are treated safely with higher doses of radiotherapy [24,25]. This has led to the hypothesis that radiotherapy dose escalation may improve outcomes in oesophageal cancer, which has been tested in both modelling studies and clinical trials. A systematic overview of preoperative CRT by Geh *et al.* [26] found that increasing the radiotherapy dose increased the probability of a pCR ($P$ = 0.006), whereas increasing the duration of treatment was found to be detrimental ($P$ = 0.035). This suggests that radiotherapy dose escalation could improve outcome if the overall treatment time is not increased as a consequence.

A planning study using data on 10% of UK SCOPE 1 [1] patients found that by using a simultaneous integrated boost (SIB) technique, a dose of 60 Gy in 25 fractions could be delivered to the gross tumour volume (GTV) while maintaining lung and heart constraints in most patients [27]. Using the radiobiological model described by Geh *et al.* [26] it was predicted that the higher dose of radiotherapy increased tumour control probability by an estimated 18.6% (from 38.2 to 56.3%) [27].

**Results (A head)**

*Current Clinical Evidence for Dose Escalation (B head)*

INT 0123 trial (RTOG 94-05) [28], was opened in 1995 in the era of two-dimensional radiotherapy planning and randomised patients to a sequential boost of 64.8 Gy/36 fractions. The trial was discontinued prematurely for futility after recruiting 236 patients and showed an excess of treatment-related deaths in the high-dose arm. However, most of the deaths (7/11) occurred before a cumulative dose of 50 Gy was delivered and only one death could be directly attributable to high-dose radiation. The reason for lack of benefit in the high-dose arm was not clear, but it is postulated that the early deaths and significant prolongation of treatment time due to toxicity may have contributed to this outcome. Subsequent studies of dose escalation have focused on attempting to reduce toxicity by escalating dose to a smaller volume, taking advantage of the progress in radiotherapy techniques.

*Prospective Phase I–II Studies (B head)*

A US single-institution phase I study conducted between 2007 and 2013 by Vlacich *et al*. [29] was recently published in abstract form. Gross disease received 60 Gy with SIB. The primary objective was to assess feasibility as determined by a <15% rate of grade 4 or 5 toxicity. Although the feasibility threshold for the study was achieved, toxicity to therapy was still significant and treatment compliance was relatively poor, with outcomes otherwise comparable with historical controls.

Another US single-institution phase I–II single-arm trial recruited 46 patients from 2010 to 2015 [30]. 63 Gy was delivered to the gross tumour and involved nodes with SIB and concurrent docetaxel and fluoropyrimidine. No patients experienced grade 4 or 5 toxicities. A comparison with 97 contemporaneous controls who received a standard dose of radiotherapy showed superior local control and overall survival in the high-dose arm.

Long-term outcomes of a single-arm phase II study from China of dCRT with SIB in oesophageal SCC was presented in abstract form in ESTRO 2020 [31]. Between 2012 and 2015, 87 patients received 66 Gy to the primary tumour concurrent with cisplatin and 5-FU. One-, 3- and 5-year locoregional control rates and survival were high at 78%, 72.4% and 72.4% and 82.8%, 60.8% and 58.3%, respectively, but there were 16 cases (18.4%) of severe late toxicities, including four cases (4.6%) of grade 5 oesophageal ulceration, seven cases (8.0%) of grade 3 oesophageal ulceration and three cases (3.4%) of grade 3 oesophageal stricture.

A single-institution phase I study from Japan published in 2021 [32] aimed to estimate the maximum tolerated CRT dose for locally advanced oesophageal SCC using SIB intensity-modulated radiotherapy via the standard 3+3 radiation dose-escalation trial design. Dose to the primary tumour was escalated from 66 Gy to a planned maximum dose of 72 Gy in 3 Gy increments with an elective nodal irradiation (ENI) dose of 48 Gy. Nine patients were recruited. Two of the three patients allocated to dose level II (69 Gy) experienced pre-defined dose-limiting toxicities and no patients were able to progress to dose level III. The authors recognise that the size of their ENI field, which encompassed large areas of the mediastinum and thus increased the volume of irradiated oesophagus, contributed to being unable to proceed with a higher than 66 Gy dose to the primary tumour.

*Prospective Phase II–III Studies (B head)*

In the era of modern radiotherapy, there are two main studies to consider in addition to SCOPE 2. These are detailed in Table 3.

Table 3 here

The phase II–III French CONCORDE study (PRODIGE 26) [33] has been published in abstract form only and has shown no improvement in locoregional progression-free survival with dose-escalated CRT. The phase III Dutch ART DECO trial has recently been published in full [4] and disappointingly showed no improvement in 3-year locoregional control or overall survival in the experimental arm. There was evidence of (non-statistically significant) higher toxicity in the experimental arm, with 61% grade 3 toxicity (versus 55%) and eight deaths (versus four deaths) secondary to haemorrhage, perforation, respiratory failure and sepsis. The authors acknowledge that toxicities make studying the effect of higher radiation doses more challenging.

**Discussion (A head)**

*Where Now for Dose Escalation? (B head)*

The results of the ART DECO trial have raised questions as to the continued relevance of the SCOPE 2 trial. The latter is overseen by a Trial Management Group, Trial Steering Committee and Independent Data Monitoring Committee. The Independent Data Monitoring Committee have reviewed the SCOPE 2 data regularly and its most recent review was in August 2021, where the full ART DECO data were discussed and the decision has been to continue the dose-escalation component of the trial.

The ART DECO authors have postulated the reasons for the lack of effect in the high-dose arm, which include toxicity [4]. Taking all of the available data on dose escalation into account [4,23,26–32,34] it is possible that increased toxicity seems to be a major obstacle in attempts to dose escalate and could be hypothesised to be the main limitation to date. It is worth noting that grade 5 toxicity in the standard dose arm of the ART DECO trial was 5%, whereas no grade 5 toxicities were seen in the dCRT SCOPE 1 trial using the same dose [5]. Methods to further reduce toxicity, some of which are incorporated into the SCOPE 2 trial, will be important in seeking to minimise this as a cofounder, in fact the lack of significant toxicity in the SCOPE 2 dose earlier in the study were given as reasons for approving the continuation of the trial.

*Methods to Minimise Toxicity from Dose Escalation (B head)*

*Minimising volumes (C head)*

Theoretically, treatment-related toxicities should decline with smaller irradiated volumes. As summarised in Table 1 there are differences in the radiotherapy volumes (both the ENI field and boost margins) of the CONCORDE, ART DECO and SCOPE 2 trials. The role of ENI remains uncertain and a survival advantage has not yet been conclusively

shown [35]. An analysis of recurrence patterns by Button *et al*. [14] showed only 3/85 (3%) developed isolated out-of-field regional failure without distant metastases, and it was felt that larger field margins would not have been clinically acceptable or effective in these cases; supporting the SCOPE 2 approach of boosting the primary GTV alone with smaller margins.

Ward *et al.* [36] showed that local recurrences occurred predominantly in the region of high standardised uptake value on the diagnostic pre-treatment FDG PET. A recent feasibility study of dose escalation to a PET-defined GTV by Fan *et al.* [34] showed that selective boosting of subvolumes appears more feasible than boosting the whole of the GTV due to limitations of failing dose constraints to surrounding organs at risk (OARs), but there remains a modest increase in the risk of cardiac and lung toxicities.

*Motion management (C head)*

Motion of the lower oesophagus, gastro-oesophageal junction and the associated regional nodal areas can be marked during respiration because of swallowing, gastric filling and vascular pulsations [7]. Four-dimensional computed tomography planning has the potential to reduce the resulting risk of geographical miss by taking into account internal motion allowing the creation of individualised margins [37]. In addition, it has been shown to result in a smaller median absolute planning target volume and a reduction of dose to surrounding OARs [38]. The SCOPE 2 trial strongly encourages the use of four-dimensional computed tomography for lower oesophageal tumours providing a detailed four-dimensional planning protocol.

*Adaptive radiotherapy (C head)*

Cone beam computed tomography (CBCT) has significantly enhanced on-set image-guided radiotherapy compared with electronic portal imaging [39]. The use of CBCT matched to the planning CT scan is mandated in the SCOPE 2 trial and the minimum protocol for verification is online imaging of the initial five fractions and then a minimum of weekly imaging thereafter. The trial team are capturing data on re-planning decisions based on changes identified on-set during treatment introducing an element of real-time adaptive radiotherapy. Integration of a linear accelerator with magnetic resonance imaging (MRI) functionality enables high contrast soft-tissue imaging directly at the time of treatment, capturing anatomical changes through inter- and intra-fraction motion [40]. Early studies comparing MRI and conventional linear accelerator-delivered treatment led to clinically acceptable dose distributions [41]. On-going work in the UK through the RadNet group is currently looking at incorporating MRI-guided radiotherapy for oesophageal cancer, enabling real-time adaptation of treatment, but limitations include longer treatment times at a time when service delivery is already under significant pressure. Another potential effect of utilising MRI would be the integration of functional sequences, which may indicate early or poor responders to potentially allow escalation/de-escalation. Equally important would be the utility of identifying potential predictors of late toxicity, for instance cardiac biomarkers to adapt treatment dose escalation safely for each individual case.

*Radiotherapy Trials Quality Assurance (B head)*

It is well documented that protocol deviations in clinical trials can affect outcome and that non-adherence to protocol-specific radiotherapy requirements is associated with reduced local control, survival and can potentially increase toxicity [42] and lead to the benefits of the interventions discussed not being realised. To ensure a high quality of radiotherapy is delivered as part of the SCOPE 2 trial, we provide a detailed radiotherapy planning protocol for upper, mid and lower oesophageal tumours and an associated rigorous RTTQA programme, including a pre-accrual outlining and planning exercise as well as a real-time review case. The PRODIGE 26/CONCORDE trial also mandated a pre-accrual benchmark case procedure for each centre, with a detailed tumour volume delineation protocol. Overall, 25% of the pre-accrual test case plans for this trial were rejected based on unacceptable protocol deviations [43]. The main reason for major protocol deviations were under-dosage of the planning target volume and unacceptable dose to OARs.

*Protons (B head)*

Due to its unique dose distribution, proton beam therapy (PBT) has the potential to improve outcomes from oesophageal cancer and further systematic evaluation in prospective studies is warranted [44]. PBT exhibits a Bragg peak resulting in a sharp dose fall-off at the distal edge of the beam, thereby reducing radiotherapy dose to distal OARs [45]. Several studies from Japan report outcomes using a dose-escalated schedule with PBT in combination with photon radiotherapy with acceptable levels of pulmonary and cardiac toxicity [46–51]. Ono *et al.* [50] retrospectively evaluated the safety and efficacy of PBT for the treatment of oesophageal cancer using multicentre data in Japan. Over 200 patients were recruited and a median dose of 87.2 Gy was delivered. Four per cent developed grade 3 oesophageal ulceration, one patient developed grade 3 pneumonitis and two patients developed grade 3 pericarditis; however, these patients had also received extensive photon ENI. No grade 4 or 5 toxicities were recorded.

*Where Next after Dose Escalation? (B head)*

The results of the ART DECO trial are clearly disappointing and, as discussed by the authors, the small excess in toxicity-related deaths in the high-dose arm of the trial does not fully explain the lack of improvement in local tumour control [3] and there is a need to explore other areas of research that may form a part of, or all, treatment strategies in the future.

Alongside the optimisation of radiotherapy technique, there remains work to be done on optimising systemic therapy as well as stratification of patients based on GTV size [52] and comorbidity alongside a greater focus on prehabilitation to optimise patients for treatment.

The role of molecular biomarkers in predicting the response to systemic treatment, thus enabling the development of more personalised treatment strategies, needs to be further explored. For example, the nucleotide excision repair and inter-strand cross-link pathways seem to be key in cellular responses to platinum-induced DNA damage [53]. Further research in this area is essential, as only three molecular biomarkers have thus far been shown to predict a response to targeted therapies in this group of patients: HER2 positivity [54], microsatellite instability status and PD-L1 expression [55,56]. Despite this lack of clinically relevant biomarkers, distinct molecular subtypes of oesophageal cancers have been identified and targeted biological therapy and immunotherapy are being tested in clinical trials.

The recently published Checkmate 577 study [57] was a global phase III study looking at the role of adjuvant nivolumab following neoadjuvant CRT and surgical resection in those with residual pathological disease. There was a 31% reduction in the risk of recurrence or death and a doubling in median progression-free survival in the experimental arm, with an acceptable safety profile. The KEYNOTE-975 phase III trial [58] is currently open to recruitment and is assessing the efficacy and safety of adjuvant pembroluzimab following dCRT in oesophageal cancer.

**Conclusion (A head)**

Personalised medicine is the future of cancer treatment. Despite the negative results of the ART DECO trial and the CONCORDE study (PRODIGE 26), we believe the SCOPE 2 trial continues to ask important questions for the oesophageal radiotherapy community. In addition, it is hoped that the substudies within SCOPE 2 exploring the systemic therapy backbone and PET response will also add to the future data in this area to inform future studies. Further work is needed to characterise molecular differences between tumours and integrate better imaging and treatment technology, allowing us to stratify patients for treatment and deliver a more personalised adaptive treatment paradigm resulting in better outcomes for this patient group.

**Conflicts of interest**

The authors declare no conflicts of interest

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**Ethics Approval**

SCOPE 2 has full ethical approval from Wales Research Ethics Committee 3 (dated 22 January 2016, with subsequent approval of each amendment; REC reference 15/WA/0395), and is conducted in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments, and the Declaration of Helsinki 1996. Written informed consent has been obtained from all study participants.

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**Fig 1.** SCOPE 2 trial schema.

**Table 1**
Key amendments to the SCOPE 2 trial protocol

| | Original protocol | Protocol amendments |
|---|---|---|
| Patient selection | Primary tumour ≤8 cm and total disease length ≤10 cm | Eligible tumour length extended (primary tumour ≤10 cm and total disease length ≤13 cm) |
| | GFR ≥ 50 ml/min (by either Cockcroft-Gault or EDTA). Participants whose GFR is 50–<60 ml/min by Cockcroft-Gault should have a formal GFR estimation (EDTA or 24-h clearance) | GFR eligibility updated to provide clarity to sites and allow local institutional equivalent of EDTA, DTPA renal scan or 24-h clearance |
| | Haemoglobin ≥ 100 g/l | Haemoglobin can be corrected to ≥100 g/l (if necessary through blood transfusion) in patients with low haemoglobin before start of treatment |
| Treatment | Patients with known DPD deficiency excluded | DPD testing strongly recommended. If DPD deficiency detected carboplatin and paclitaxel should be given from outset |
| | All participants will receive cisplatin and capecitabine for the first cycle | Carboplatin (AUC 5) allowed in patients either with a contraindication to cisplatin or by choice of local investigator |

| | | |
|---|---|---|
| | | Carboplatin and paclitaxel-based chemotherapy allowed as the upfront treatment of choice* |
| Investigations | EUS required as screening assessment | Increased flexibility with screening EUS requirement (COVID concession due to pressures on endoscopy capacity) |
| Follow-up | Face to face appointments | Allowance of telephone assessments |

DPD, dihydropyrimidine dehydrogenase; DTPA, diethylenetriamine pentaccetate; EDTA, ethylenediaminetetraacetic acid; EUS, endoscopic ultrasound; GFR, glomerular filtration rate.

*The comparable survival data for this regimen [5] means a change in the baseline parameters of the sample size calculations is not necessary. However, patients undergoing up-front induction carboplatin and paclitaxel will not undergo positron emission tomography response randomisation as we predict the number of patients in this arm will be low.

**Table 2**

| Theme | Topic | Issues | Positive | Recommended practice/successful implementation |
|---|---|---|---|---|
| Early collaboration | Building on established network of UK centres/principal investigators (SCOPE 1, NeoSCOPE trial) | | Engaged and very collaborative community | |
| | Investigator meetings to inform design | | Meeting post SCOPE 1 to seek feedback on design/ideas for future trials<br>Consensus meeting re SCOPE 2 soon after grant awarded<br>Radiotherapy workshop between grant approvals and opening at sites | Enabled focus<br><br>Helped inform grant<br><br>Helped inform protocol to be in line with current standard of care |
| Educational provision | Radiotherapy | | Many centres adopted SCOPE 1 protocol as their standard for oesophageal radiotherapy. Made development of SCOPE 2 protocol easier<br>Provided educational events such as workshops and webinars to support implementation of new technical advances in radiotherapy | SCOPE 1 standardised and modernised radiotherapy techniques so was key to build on for SCOPE 2<br>Developments in radiotherapy techniques at sites driven by the developments in trial protocols, e.g. 4DCT, IMRT/VMAT with simultaneous integrated boost |
| RTTQA | Radiotherapy | Quality assurance requirements can add to workload and timescales | Streamlining of RTTQA: outlining from NeoSCOPE acceptable for SCOPE 2 radiotherapy guidance document amended through learning from RTTQA process | Relationships built between trial team, RTTQA team and participating centres<br>Focus on being an iterative and collaborative process, guiding and supporting implementation and ensuring consistency with individualised feedback<br>Targets for turnaround time to avoid delays to the treatment pathway |
| Ongoing collaboration | Principal investigator feedback<br>Investigator meetings | Ensure the trial maintains its academic/scientific integrity and remains relevant and applicable to clinical practice<br>Time/personnel required to produce the trial amendments | Pragmatically respond to issues at sites | Responsive Trial Management Group to discuss the adaptation of the trial protocol<br>Enables alignment of the protocol with standard clinical care<br>Ongoing prioritisation in workload to balance amendments and support sites |
| Co-ordination | Site set up | Set up times significantly delayed by resource at sites<br>Overcoming challenges of prioritisation of complex trials at individual centres | Consistent Trial Management Group members and Trials Unit staff helped with building relationships with sites | Previous SCOPE trials have allowed us to build relationship with sites and provide support to set-up<br>Provide a supportive environment and deal with queries promptly<br>National Health Service research resource in all departments remains an ongoing problem across all trials |
| | Low recruitment | Lack of eligibility following the initial protocol design leads to low recruitment | Changes to eligibility following conversations with sites | Improvement of recruitment |
| | Slow recruitment | Time pressures in clinic are barrier to complex consent process<br>Increasing elderly population and complexities of decision making in this context<br>Pathways not in line with best practice | | Adapting protocol to fit the patient population based on review of queries, screening logs and deviations. |
| Changing environment | COVID-19 | Access to diagnostics/staging tests reduced<br>Need to reduce physical face to face consultations<br>Recruitment was slow to recover to pre-COVID levels | Aligned trial risk with national guidelines as they were released<br>Flexibility to eligibility criteria and allowed virtual consultations | Challenge for all trials<br>Importance of listening to feedback and supporting sites |

4DCT, four-dimensional computed tomography; IMRT/VMAT, intensity-modulated radiotherapy/volumetric modulated arc therapy; RTTQA, radiotherapy trials quality assurance.

**Table 3**

Table comparing trial protocol for ART DECO, CONCORDE (PRODIGE 26) and SCOPE 2, all looking at dose escalation in oesophageal radiotherapy

| | ART DECO | CONCORDE (PRODIGE 26) | SCOPE 2 |
|---|---|---|---|

| Phase | III | II–III | II-III |
|---|---|---|---|
| Histology | SCC and ACA stratified | SCC and ACA stratified | SCC (III) and ACA (II) separated out |
| Chemotherapy | Carboplatin and paclitaxel<br>Concurrent with radiotherapy weekly (×6) | Platinum/5-FU<br>3 cycles concurrent with radiotherapy followed by 3 cycles adjuvant | Platinum/5-FU or<br>Carboplatin and paclitaxel<br>2 cycles of induction chemotherapy followed by concurrent CRT<br>(PET sensitivity substudy with change of chemotherapy based on response) |
| Radiotherapy dose in standard arm | 50.4 Gy in 1.8 Gy fractions | 40 Gy in 2 Gy fractions ENI and sequential boost 10 Gy in 2 Gy fractions to primary and involved nodes | 50 Gy in 2 Gy fractions |
| Radiotherapy dose in experimental arm | 50.4 Gy ENI in 1.8 Gy fractions<br>61.6 Gy SIB to primary in 2.2 Gy fractions | 40 Gy in 2 Gy fractions ENI and sequential boost 26 Gy in 2 Gy fractions to the primary and involved nodes | 50 Gy ENI in 2 Gy fractions<br>60 Gy SIB to primary in 2.4 Gy fractions |
| Maximum length of tumour (if known) | Maximum length of primary tumour 10 cm | Not defined | Maximum length of primary tumour ≤10 cm and total tumour length ≤13 cm |
| TVD | CTV: GTV + 3 cm superior–inferior<br>Inclusion of perioesophageal fatty tissue, aorta pulmonary window, subcarinal area, bilateral supraclavicular area and fatty tissue along the left gastric artery in the hepatogastric ligament (if these regions within the 3 cm superior–inferior extension).<br>If positive cervical nodes all jugular nodes included (II, III, IV and VI)<br><br>PTV<br>CTV + 1 cm all directions.<br><br>Boost<br>Primary tumour GTV + 1 cm in all directions | CTV:<br>CTV 1: GTV + 5 cm superior–inferior<br>Inclusion of lymph node stations with ≥20% risk of involvement as defined by RTOG atlas<br><br>CTV 2: GTV + 3 cm superior–inferior<br><br>PTV<br>CTV 1 + 1 cm all directions<br><br>Boost<br>CTV 2 + 1 cm all directions | CTV<br>GTV + 2 cm superior–inferior, 10 mm radially<br><br>Inclusion of fatty perioesophageal tissue, edited for normal structures, minimum GTV-to-CTV margin of 5 mm<br><br>Bilateral SCF region if positive SCF node.<br>Below diaphragm ELNI along lesser curve of stomach, left gastric artery and coeliac region (within 2 cm inferior of GTV)<br><br>ITV (4DCT only)<br>Composite of CTV from all phases of respiratory cycle<br><br>PTV<br>3DCT: CTV + 1 cm superior, 1–1.5 cm inferior, 0.5 cm radially<br><br>4DCT – ITV plus 0.5 cm in all directions<br><br>Boost<br>GTV primary + 5 mm in all directions |
| RTTQA | No | Pre-accrual benchmark case | Pre-accrual benchmark case<br><br>Real-time review of outline and planning of first cases from all centres and all high-dose cases during the initial toxicity assessment stage.<br><br>Timely retrospective review of a 10% sample of cases<br>All planning scans and dose cubes collected centrally for retrospective analysis. |

4DCT, four-dimensional computed tomography; 5-FU, 5-fluorouracil; ACA, adenocarcinoma; CRT, chemoradiotherapy; CTV, clinical tumour volume; ENI, elective nodal irradiation; GTV, gross tumour volume; ITV, internal target volume; PET, positron emission tomography; PTV, planning tumour volume; RTOG, Radiation Therapy Oncology Group; RTTQA, radiotherapy trials quality assurance; SCC, squamous cell carcinoma; SCF, supraclavicular fossa; SIB, simultaneous integrated boost; TVD, tumour volume delineation.

Author query

Table 2: please supply a legend for the table

**Highlights**

- Building on SCOPE series of trials, shaping UK oesophageal radiotherapy development
- Radiotherapy dose escalation and systemic therapy personalisation in oesophageal cancer
- Role of PET/CT in treatment response assessment
- Future research strategies for oesophageal cancer