SMGroup

Radiation Therapy for Cancer of the Oesophagus and Pancreas

Emma Mathews*, Caitlin Bowden, Owen Nicholas, Ricky Frazer and Sarah Gwynne
South West Wales Cancer Centre, Singleton Hospital, Swansea, UK

***Corresponding author:** Emma Mathews, South West Wales Cancer Centre, Singleton Hospital, Swansea, UK, Email: emma.elizabeth.mathews@wales.nhs.uk

Published Date: June 20, 2016

RADIOTHERAPY FOR OESOPHAGEAL CANCER

Radiation therapy is increasingly utilised in the management of oesophageal cancer, both in the definitive and adjuvant setting. While surgery has been the mainstay of curative treatment in early and locally advanced oesophageal cancers, 20-30% of patients have microscopically positive resection margins (R1), contributing in part to 5 year survival rates rarely exceeding 40% in surgical series [1]. As a result, there has been increasing interest recently in the use of radiation as part of neo-adjuvant therapy to improve outcomes. Radiation remains the mainstay of non surgical curative treatment for those who do not undergo surgery for reasons of being medically inoperable, locally advanced disease or from patient choice [2].

NEO-ADJUVANT CHEMORADIOTHERAPY (NACRT)

Rationale

NACRT is internationally recognised as a standard of care. Giving NACRT rather than adjuvant (post operative) CRT has several postulated advantages. It can allow early eradication of micrometastatic disease and downsizing of the primary tumour. Practically speaking, Tumour Volume Delineation **(TVD)** is easier with the primary tumour in-situ.

Evidence

Gwynne et al conducted a systematic review in 2014, [3] demonstrating that 3 recent Randomised Control Trials **(RCT)** and 3 recent meta-analyses favoured NACRT for overall survival, over surgery alone. However conflicting evidence exists regarding the impact on postoperative complications. Of note all the RCTs that showed survival advantage for NACRT came in the era of conformal radiotherapy.

CROSS Trial

The CROSS trial is a Dutch study, that randomised 368 patients with potentially resectable oesophageal cancers, both Adenocarcinoma **(AC)** and Squamous Cell Carcinoma **(SCC)**, to either NACRT with paclitaxel/carboplatin or to surgery alone. Patients followed a rigorous staging protocol using lung function tests, upper endoscopy and Endoscopic Ultrasound **(EUS)** and neck ultrasound. Radiotherapy was standardised to 41.4 Gy in 23#. The results showed survival of 49 months for the CRT arm *vs*. 24 months in the surgery arm (HR 0.657, 95% confidence interval, 0.495 to 0.871; P=0.003). The R0 rate in the CRT group was 92% *vs*. 69% (p<0.001) in the surgery only group. Complete pathological response **(pCR)** rate was 23% in the AC and 49% in the SCC groups respectively. Postoperative complications were similar in both groups [4].

META-ANALYSES

Three recent meta-analyses demonstrate survival advantage with CRT but conflicting results on postoperative complications. The results are summarised below (Table 1).

Table 1: Meta-analyses of CRT for oesophageal cancer.

Study	Number of studies/patients	Conclusions
Zheng *et al* 2013 [5]	7/523	Survival benefit with CRT High incidence of related complications Lower incidence of loco regional recurrence Similar incidence of distant recurrence No comment on histological subtype
Wang 2012 [6]	12/1529	Improved 1,3 and 5 years survival Greater benefit for SCC No increase in post-operative complications
Sjoquist 2011 [7]	24/4188	Both NA chemo and NA CRT have survival advantage over surgery alone Benefit of NA CRT over NA chemo not established Survivals similar in AC and SCC

NeoSCOPE

NeoSCOPE is a randomised UK phase II study of 85 patients using two NA CRT regimens (two cycles of Oxaliplatin and Capecitabine followed by RT, 45Gy in 25 fractions with either concurrent Oxaliplatin and Capecitabine or Paclitaxel and Carboplatin), before surgery, for resectable AC of the oesophagus/oesophagogastric junction. Reported in early 2016, it showed a pathological Complete Response **(pCR)** rate in the Carboplatin/Paclitaxel arm of 27.9% *vs* 11.9% in the Oxaliplatin/Capecitabine arm. The R0 rate in Carboplatin/Paclitaxel arm was 80.35% *vs*. 72.2% for Oxaliiplatin/Capecitabine. Postoperative complications were comparable to previously reported trials although Carboplatin/Paclitaxel arm showed significantly greater haematological toxicities. A Phase III study is now being planned [8].

Definitive CRT (dCRT)

Historically, dCRT was reserved for patients deemed medically unfit for surgical resection due to co-morbidities or extent of locally advanced disease, or patient choice. In the SCOPE 1 trial 38% of patients chose to undergo non surgical treatment [2]. In recent years, dCRT has emerged as a treatment option in patients with resectable SCC. This reflects the increasing trend seen in SCC in other sites such as the anus, cervix and head and neck tumours, where dCRT has become the treatment of choice, reserving salvage surgery for relapsed disease [9]. It is also increasingly being considered as a curative non surgical option in AC for those who do not wish to undergo surgery.

Evidence

Stahl et al reported a German RCT comparing dCRT *vs*. Surgery in patients with locally advanced SCC of mid/upper oesophagus [10]. Patients were randomised to either induction chemotherapy followed by CRT (40 Gy) followed by surgery or the same induction chemotherapy followed by CRT (at least 65 Gy) without surgery. The surgical arm demonstrated improved progression free survival but not in overall survival. (Survival at 3 years, surgical arm, 31.3%; dCRT arm, 24.4%; P = .02). In a similar study, Bedene et al showed no survival advantage for surgery either [11]. SCOPE 1 was a multicentre UK phase II/III trial of dCRT with 50 Gy in 25

fractions of RT concurrent with four cycles of cisplatin/capecitabine with or without the addition of cetuximab, an anti EGFR monoclonal antibody. This trial included patients with both SCC and AC. Even though the trial closed early as the addition of cetuximab found to be detrimental, the the overall survival data for the standard arm exceeed that seen in previous studies of surgery and neo-adjuvant chemotherapy [2]. A study from the Netherlands found that carboplatin and taxol were equally efficacious as cisplatinum and 5 Fluorouracil in this setting, with the former associated with lower rates of toxicity [12]. The currently recruiting SCOPE 2 trial will also use these two regimens and will examine the role of dose escalation in the setting of dCRT to try and further improve outcomes. Further data from randomised trials is needed to determine if dCRT is equivalent to surgery in AC.

In summary, for patients with resectable disease NACRT is now considered a standard of care for both AC and SCC. For patients with a SCC histological, subtype, dCRT can be considered as equivalent treatment option to surgery, but further work is needed to define the role of dCRT in AC.

PLANNING TECHNIQUE FOR OESOPHAGEAL CARCINOMA

Patients should undergo CT in the supine position, ideally within 2 weeks of starting NA chemotherapy (if used). 3mm CT slices should be performed from 1cm above the lung apices to L2 using IV contrast. A stomach filling protocol should be followed for anatomical reproducibility. Upper third/cervical oeso phagus tumours will need a thermoplastic shell and are often planned similarly to head and neck cancers. While middle and lower third oesophageal tumours patients should be scanned supine with arms above the head. The legs should be immobilised with a knee fix and one anterior and two lateral tattoos placed to prevent lateral rotation. In lower and junctional tumours, tumour motion can be significant and therefore 4D CT can be considered. This is used in the Neo-SCOPE clinical trial.

TARGET VOLUME DELINEATION

Prior to the opening of the SCOPE 1 trial, there was considerable variation in the treatment approach to oesophageal cancer with dCRT [13]. SCOPE 1 standardised the outlining technique and this is now widely accepted as the radiotherapy protocol in the majority of UK centres.

GTV Delineation

GTV outlining should take into account the diagnostic information from CT, PET and Endoscopic Ultrasound **(EUS).** As summarised by Rackley et al [9], EUS may underestimate the extent of disease if passage is limited by oesophageal stricture. PET can then provide useful information to guide the length of disease. PET has a moderate sensitivity but high specificity and therefore the GTV should not be reduced if regions that are positive on other imaging modalities are shown to be PET negative. Positive disease on any imaging modality should be included in the GTV.

CTV Delineation

After delineation of the GTV, the CTV is grown using the following steps.

For tumours that do not extend within 2cm of the gastro-oesophageal junction: [2]

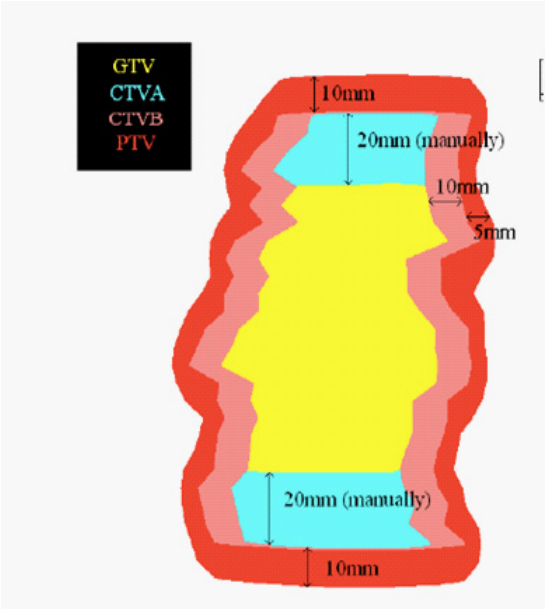


Figure 1: Planning technique for tumours that do not extend within 2cm of the gastro-oesophageal junction. (Images courtesy of S.Gwynne.)

Manually adding a 2cm margin along the oesophagus superiorly and inferiorly (CTVA).

Adding to this a 1cm margin anteriorly, posteriorly, right and left directions (CTVB).

CTVB – can be edited if the dose constraints of the PRV for the cord can't be met by reducing the posterior margin but the CTVA to CTVB margin should stay above 0.5cm.

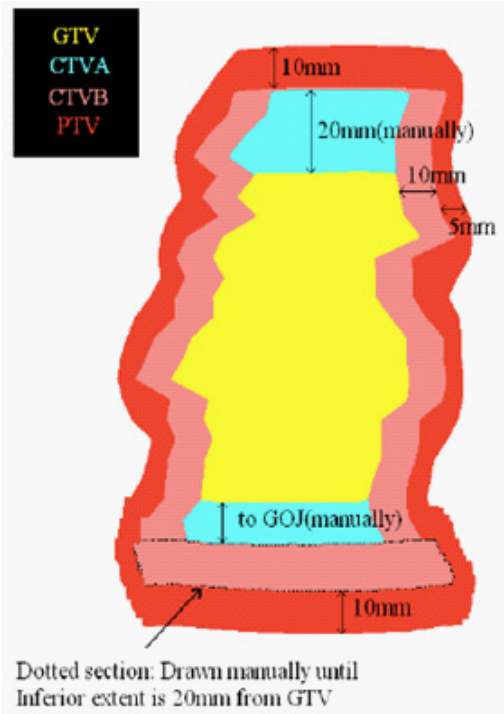


Figure 2: Planning technique for tumours within 2 cm of GOJ (Images courtesy of S. Gwynne).

GTV is copied and expanded manually 2cm superiorly (CTVA)

CTVA is expanded inferiorly as far as the GOJ.

This is then expanded 1cm anteriorly, posteriorly, right and left (CTVB)

CTVB is then manually expanded inferiorly so that the total inferior extension from GTV to CTVB is 2cm.

This extension should aim to include the mucosa of the stomach in the direction of the lymph node stations along the lesser curve including the para-cardial and left gastric lymph nodes.

CTVB may be edited posteriorly as previous to meet PRV cord constraints maintain at least a 0.5c margin between CTVA and CTVB.

PTV Delineation

PTV is created by expansion of CTVB in the superior and inferior directions by 1cm and by 0.5cm anteriorly, laterally and posteriorly.

Neo-SCOPE and SCOPE 2 build on the principles of TVD detailed in the SCOPE 1 protocol by editing the CTV for normal structures [14]. CTVB is edited off lung, pericardium, great vessel, vertebral bodies, trachea and main bronchi. This reduces the amount of normal tissue in the PTV. Neo-SCOPE also defines limited elective lymph node irradiation for lower third and gastro-

oesophageal junctional tumours within 2cm of the gross tumour volume and exclusion of lymph nodes at the splenic hilum for type 2 GOJ incorporating the EORTC guidelines published in 2009 [3,15]. A standardised 4DCT protocol is also used. SCOPE 2 is a dose escalation trial also has a detailed radiotherapy protocol and involves similar modifications.

Standard beam arrangement for conformal 3D radiotherapy consists of an Anterior-Posterior **(A-P)** pair, plus right and left posterior oblique beams to keep the dose to OAR' within tolerance. IMRT and proton therapy can improve conformality and dose distribution to OAR's and will be discussed later.

4D CT

The lower oesophagus and GOJ can move significantly during respiration. There is also movement due to swallowing, peristalsis gastric filling and emptying, vascular and cardiac pulsations, all of which can lead to geographical miss [16]. 4DCT can account for intrafraction variation of GTV during respiration. An INTERNAL TARGET VOLUME **(ITV)** is created to reduce the geographical miss of the target volume and to individualise margins to spare normal tissues. Wang et al [17] investigated oesophgeal motion using 4DCT and found that with mid and distal oesophagus there is significant motion. To cover the motion of the distal oesophagus a margin of 0.4 cm left-right, 0.58 in the A-P direction and 0.82 cm in superior-inferior direction would be needed to create an ITV on 3DCT. If an ITV was created by outlining on each of the 10 phases of the respiratory cycle obtained by 4DCT there is a 39.8% decrease in ITV for middle oesophageal cancer and a 59.37% decrease in ITV for distal tumours. This confirms that individualized margins can decrease the target volume being irradiated whilst ensuring adequate coverage. The NeoSCOPE trial neoscope protocol and the awaited SCOPE2 trial include 4DCT protocols so that radiotherapy margins are more individualized for patients.

OAR

The lungs, spinal cord and heart are the major dose limiting organs in oesophageal planning and should be contoured. The liver and kidneys should also be contoured if the inferior edge of the PTV overlaps with the superior edge of the organ. V20Gy and mean lung dose has been shown to be the best predictor of pneumonitis [9]. Recent Quantec data estimates myelopathy risk at <1% at dose of 54Gy and less than 10% at 61Gy [18]. More conservative limits are often used in oesophageal cancer due to concurrent chemotherapy acting as a radiosensitiser [9]. Table 2 summarises the dose constraints for OAR's used in the recent UK SCOPE 1 and Neo-SCOPE trials.

Table 2: OAR dose constraints for Oesophageal Cancer [2,14].

OAR	Dose Constraints
Cord Max dose	40Gy
Cord PRV D1cm³	D1cm³ = 40Gy
Lung	V20Gy <25%
Heart	V40 = <30Gy V25 = <50%
Liver	V30 = <60%
Kidneys	V20= <25%

PLANNING ALGORITHMS

The type of planning algorithms used in radiotherapy planning can significantly affect the calculation of accurate dose distributions. In particular the areas of tissue inhomogeneity such as the lungs type a algorithms do not take into account lateral electron travel and therefore give less accurate dose calculations than type b algorithms [19]. Wills et al compared type a (pencil kernel) algorithm and type b (collapsed cone) algorithm dose distributions for a number of oesophageal plans. They concluded that plan optimisation with type b algorithms results in improved PTV V95%. This does require compromise on the level of dose to low density PTV in the lungs. They recommended that type b algorithms be used in oesophageal planning.

INTENSITY MODULATED RADIATION THERAPY (IMRT)

Dose escalation in the thorax can be difficult due to the oesophagus lying in close proximity to critical structures such as the spinal cord, heart and lungs. IMRT allows both sparing of normal tissues and a more homogeneous dose to be delivered to the tumour [16]. IMRT has been mainly studied in dosimetric analyses for oesophageal cancer. There have been 9 dosimetric studies in recent years investigating IMRT and VMAT. These have been summarised in a review paper by Yap et al [20] and a further paper by Yang et al [21] though these studies contained a small number of patients. A reduction in lung V18 to V30 with IMRT compared to 3D conformal planning was shown, but also an increase in V5 to V10. The effect of an increased low dose to a larger volume of lung is not known but Japanese studies suggest that these may increase rates of pneumonitis [9]. NeoSCOPE did not recommend IMRT in the pre-operative setting, due to concerns over lung toxicity in the post-operative period [16]. Recent data from the MD Anderson Cancer Centre comparing the outcome of oesophageal cancer patients treated with conformal RT and IMRT [22] found an excess of non-cancer related deaths in the conformal RT arm, postulated to be due to cardiac deaths secondary to cardiac irradiation.

Wang et al reported a retrospective case series of early outcomes as well as dosimetric evaluations using IMRT [23]. 6 Out of 7 patients, who completed treatment, all had a complete response on endoscopic biopsies. Two were clear of tumour at 13 and 17 months. A further two developed local recurrence; one was successfully treated with photodynamic therapy. A further two developed distant metastatic disease.

PROTONS

Protons have a narrow range and low exit dose and therefore may be a useful radiation modality for oesophageal cancers. Dose distributions comparing protons and IMRT radiotherapy have shown mean lung doses reduced from 9.45Gy with IMRT to 6.03Gy with protons and maximum cord dose from 36.93Gy to 11.61Gy [24]. The clinical evidence for the use of proton therapy is currently small and mainly from United States and Japanese studies. Ishikawa et al reported a case series of 40 patients treated with protons to a dose of 60Gy in 30 fractions concurrently with chemotherapy in a 24-month follow up period. No cardiopulmonary toxicity of grade 3 or higher was observed. There was a 2-year disease specific survival of 77% and loco-regional control rate of 66% [25]. They therefore conclude that protons are a feasible option for oesophageal cancer. Lin et al 26 in the United States also reported their preliminary experience of using combined chemotherapy and proton therapy in 62 patients. They prescribed 50.4Gy in 28 fractions using 2-3 beams and 180-250Mv protons. The median follow up was 20.1 months. They experienced G2-3 dysphagia in 43.6% of patients and oesophagitis in 46.8%. They had three cases of radiation pneumonitis, one of which was grade 5. 3 year OS was 51.7% (CI 95% 0.31-0.69). They conclude there is a theoretical advantage of better sparing of OARs and increased tumour control by 20% with a normal tumour complication probability of 5%. Welsh et al studied intensity modulated proton therapy in order to dose escalate the dose to the tumour where the majority of recurrences occur [27]. They found that normal tissues doses could be further reduced. The efficacy of this treatment with regards to tumour control requires further investigation.

VERIFICATION

With the increasing complexity of oesophageal planning, accurate treatment delivery is essential. Oesophageal plans must be verified on set during treatment. Electronic Portal Imaging **(EPI)** or Cone Beam CT **(CBCT)** are two methods utilised. Standard verification involves imaging on the first three fractions and weekly thereafter unless daily corrections are needed.

Advances in target volume definition accounting for tumour motion and individualised margins has led to an increased need for more accurate treatment verification. Until recently the most common method of verification, EPI, leads to many uncertainties, as vertebral bodies are used as surrogate markers for tumour position [28]. CBCT images add a volumetric dimension to verification. Images are obtained in the treatment position and merged with CT planning scan via automated software. The entire PTV can be visualised against soft tissue marking to ensure that it is being covered prior to treatment [16,28]. Hawkins et al studied EPI *vs*. CBCT verification of oesophageal cancer planning and found that CBCT offer improved accuracy of treatment delivery and recommended this imaging modality be used for oesophageal malignancies [28].

FUTURE DIRECTIONS OESOPHAGEAL CANCER IN THE UK

SCOPE 2 is the next UK based oesophageal trial looking at dose escalation of CRT in oesophageal cancer for definitive CRT. Patients receive standard 50Gy in 25 fractions or standard therapy with a concomitant boost to 60Gy to the primary tumour. Squamous cell and adenocarcinomas will be analysed separately. SCOPE 2 will also look at the role of PET responsiveness and adaptation of chemotherapy depending on this response.

RADIOTHERAPY IN PANCREATIC CANCER

Unlike oesophageal cancer the role of radiation therapy in pancreatic cancer is less well defined. Only 20% of patients present with resectable disease and even then the survival is poor (7-25% 5 year survival) (CRUK website). Radiation has been studied both as adjuvant treatment in resectable, borderline resectable and locally advanced disease (see table 3 for definitions). 30% with locally advanced disease and only 20% with resectable tumours [29]. CT or MRI imaging is required to define the pancreatic cancer status and is based on the relation of the tumour to the vessels surrounding the pancreas.

Table 3: Adapted from the Intergroup Trial A021101 [30].

Locally advanced	An interface between the tumor and the SMA measuring ≥ 180 degrees of the circumference of the vessel wall No interface between the tumor and the aorta Occlusion of the SMV or portal vein without a sufficient cuff of normal vein above and below the level of obstruction with which to perform venous reconstruction Long-segment interface (of any degree) between the tumor and the common hepatic artery or its major tributaries with insufficient artery proximal and distal to the interface to perform reconstruction
Borderline resectable	▪ An interface between the primary tumor and the Superior Mesenteric Vein or Portal Vein **(SMV-PV)** measuring ≥ 180 degrees of the circumference of the vessel wall ▪ •Short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction ▪ •Short segment interface (of any degree) between tumour and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and reconstruction An interface between the tumor and Superior Mesenteric Artery **(SMA)** measuring < 180 degrees of the circumference of the vessel wall

RESECTABLE PANCREATIC CANCER AND THE ROLE OF ADJUVANT CHEMOTHERAPY OR CHEMORADIOTHERAPY

For resectable patients optimal therapy would be surgical resection followed bv chemotherapy [31].

The role of adjuvant Chemoradiotherapy **(CRT)** in this setting remains controversial [32]. The EORTC trial recruited 218 patients with resected pancreatic cancer and randomised the patients to 5FU based chemoradiotherapy versus observation and no survival benefit was demonstrated.

The GITDG 9173 trial randomised 43 patients with resected tumours to adjuvant CRT versus observation alone. This trial showed a survival benefit of CRT but has been criticised for a small

sample size and poor accrual. The median overall survival was 20 months [32,33]. The ESPAC 1 trial [34] aimed to evaluate adjuvant 5-FU chemotherapy versus 5-FU CRT. There were additional randomisations added to the trial (+/- CRT and +/- chemotherapy alone). No quality assurance was conducted leading to concerns about the quality of the radiotherapy planning. Initial analysis showed no significant improvement in survival with adjuvant CRT. CRT was shown to have a detrimental effect compared to observation alone on later analysis.

The RTOG 0848 trials proposes to clarify the role of CRT in the adjuvant setting and has a prospective radiation quality control incorporated. This is to address concerns that the previous adjuvant RT trials used different radiotherapy techniques, often 2 dimensional planning and without any quality assurance programme. The trial will limit recruitment to those patients with head of pancreas tumours and stratification criteria will also include resection margin and nodal status, as these are important prognostic indicators [35].

BORDERLINE RESECTABLE PANCREATIC CANCER: THE ROLE OF CHEMORADIOTHERAPY

The management of borderline resectable patients is still under intense investigation. Neoadjuvant chemotherapy or CRT is not routinely used in the UK, ESPAC 5 is a phase II feasibility trial which is comparing immediate surgery to neoadjuvant chemotherapy (with Gemcitabine and Capecitabine or Folfirinox) or NACRT (50.4Gy in 28 fractions) in borderline resectable pancreatic cancer. This trial opened in the UK in 2014. Golcher et al also studied NA CRT. Patients with resectable disease were randomised to surgery or neoadjuvant CRT (using gemcitabine and cisplatin with conformal 3D radiotherapy to a dose of 55.4Gy). In both arms the patients received adjuvant chemotherapy as per the CONKO-001 trial. Unfortunately this trial closed prematurely due to poor recruitment, but did show a trend towards better median overall survival in the neoadjuvant CRT group [36]. Until the outcomes of ESPAC 5 are known, NA treatment cannot be recommended.

THE MANAGEMENT OF LAPC AND ROLE OF NEOADJUVANT CHEMORADIOTHERAPY

LAPC differs to borderline resectable tumours in that NA treatment rarely leads to downstaging of the tumour and resectability. 5% of patients went on to have a resection in the SCALOP trial) [37]. The goal of treatment is usually prolongation of survival, symptom palliation and disease control. Over recent years there has been much debate over the treatment of this group of patients, with trials differing in recommendations. The current treatment approaches include induction chemotherapy followed by CRT, CRT without induction chemotherapy (+/- adjuvant chemotherapy) or chemotherapy alone.

The most recent trial, LAP 07, randomised patients (n=442) to 4 months of induction chemotherapy with gemcitabine alone or with erlotinib. The patients who did not show

progression (n=269) underwent further randomisation to receive CRT (54Gy with concurrent capecitabine at a dose of 1600mg/m^2) or two further cycles of the same chemotherapy The overall survival between the two groups was not significant (15.2 months *vs* 16.4 months for CRT and chemotherapy alone, respectively, P=0.8) [38]. There is a suggestion that CRT may improve local control but sub-group analysis is awaited [39]. In contrast, the GERCOR study, where 181 patients received gemcitabine-based induction chemotherapy and those who did not progress (n= 128) were randomised to CRT using 55Gy and 5-FU or continuing chemotherapy, the median progression free survival was 10.8 months *vs* 7.4 months and overall survival was 15 months *vs* 11.7 months in favour of the CRT arm [39].

In a third study by Krishnan et al, patients were randomised to gemcitabine (+/- cisplatin) followed by CRT or CRT alone. Patients who received consolidation CRT (after induction chemotherapy) had a better overall survival (11.9 months *vs* 8.5 months, P=<0.001) [40].

The randomised phase 2 SCALOP trial looked at the optimal CRT regimen. All patients underwent 12 weeks of induction chemotherapy (Gemcitabine 1000mg/m^2 on days 1,8 and 15 and capecitabine 830mg/m^2 twice a day, days 1-21 of a 28 day cycle). Patients who did not have progression and who had a tumour of <6cm were randomised to another cycle of Gemcitabine/capecitabine chemotherapy followed by either weekly Gemcitabine (300mg/m^2) or capecitabine (830mg/m^2 twice a day, Monday to Friday only) during radiotherapy (50.4Gy in 28 fractions). The results favoured capecitabine with a median overall survival of 15.2 months *vs* 13.4months (adjusted hazard ratio [HR] 0.39, 95% CI 0.18-0.81; p=0.012). Median progression free survival was 12 months *vs* 10.4 months [37].

The recommendations drawn from these trials suggest that chemotherapy should be the backbone for LAPC management and if patients demonstrate stable disease CRT may be considered to aid local disease control.

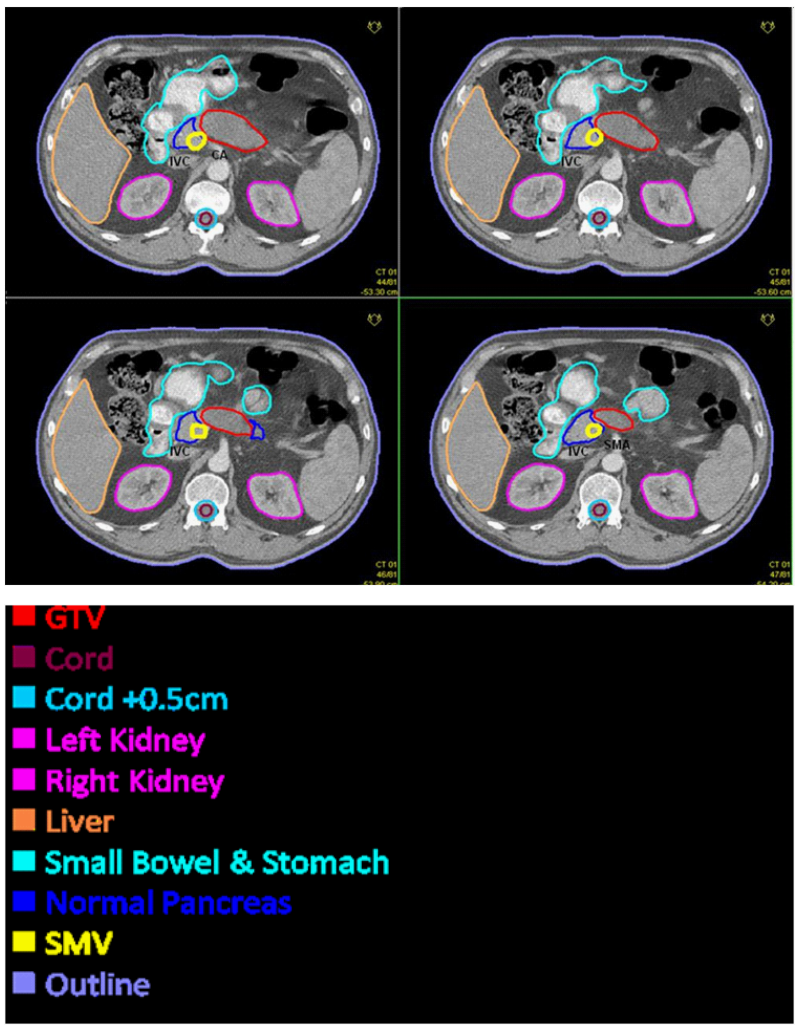
PLANNING STRATEGIES FOR RADIOTHERAPY TO THE PANCREAS

There is a move towards using Intensity-Modulated Radiotherapy **(IMRT)** and 4D-CT rather than conventional 3D planning. The aim of IMRT is to allow radiotherapy dose escalation whilst avoiding high doses to organs at risk. Milano et al showed in 25 patients with pancreatic or bile duct cancer that those treated with IMRT versus 3D conventional plans (4 field technique) had a lower mean dose to the liver, kidneys, stomach and small bowel. 80% of patients in the IMRT group received grade 2 or less upper gastrointestinal toxicity and local control rates were not compromised [41].

The current technique used for LAPC radiotherapy is as follows:

- All patients will need a renogram scan to ensure their kidney function is sufficient prior to radiotherapy (GFR should be >50ml/min/1.73^3).

- Patients should have a CT planning scan with the patient supine, arms raised above their head (with arm supports) and immobilised with the help of vacuum bags. A chest-board and knee-fix is often used. IV contrast should be used.
- The GTV tumour and nodes (>1cm) are outlined on the planning scan and where possible both an oncologist and radiologist should be involved.
- If a 3D CT is used the PTV is the GTV plus 15mm anterior-posterior and 20mm in the inferior-superior directions.
- If a 4D CT is used (recommended) then the ITV is created by combining GTV outlines from multiple phases of respiration (at least 3 phases used such as maximum inspiration and expiration and the time-weighed average). PTV is ITV plus a 1cm isotropic margin.



Outlining for pancreatic radiotherapy. (Images courtesy of S. Mukherjee.)

3D conformal plans usually 3 or 4 coplanar fields are used (anterior-posterior beams and lateral beams which are angled to reduce renal dose). IMRT is a preferred technique as there is increased dose conformality. The dose delivered is 50.4-54Gy in 28-30 fractions, 1.8Gy/fraction using 10MV photons. In 3D planning the minimum dose to the PTV should not be under 95% and the maximum should not be above 107% of the prescription dose. The pancreas moves with respiration [42] and 4DCT can account for this intrafraction variation of GTV. An INTERNAL TARGET VOLUME **(ITV)** is created to reduce the geographical miss of the target volume and to individualise margins to spare normal tissues.

Dose Constraints to Organs at Risk:

Region of Interest/OAR	Dose Constraint
PTV	V95% (47.9Gy) >99%
DMAX	<107%
Spinal cord PRV	V40Gy <0%
Liver	V30 <40%
Ipsilateral kidney	V20 <40%
Combined kidney	V40 <30%

EMERGING RADIOTHERAPY TECHNIQUES IN PANCREATIC CANCER

Gastrointestinal toxicity is an important side effect in pancreatic irradiation. These observed toxicities correlate with dose-volume histograms for the duodenum and stomach [43]. A method to reduce this toxicity is to reduce the PTV volume, however this requires imaging strategies and respiration control [44].

Stereotactic Ablative Body Radiotherapy **(SABR)** delivers a very intensive dose of radiotherapy to the tumour whilst limiting dose to the surrounding tissues. The GTV is outlined and a small margin (2mm) is added to create the PTV. Brunner et al [44] analysed the toxicity of SABR and found that many observed fractionation regimes could be used to interpret estimated toxicity according to EQD2/BED prescription doses. Dose constraints for the duodenum were derived from this data paving the way for further SABR trials. Results of some pancreas SABR trials are shown in table 4.

Table 4:

Study	Patients (n)	Dose/#	Local control	OS	PFS
Koong et al 2004[45]	15	15-25 Gy 1 #	100	Median 11 months	Median 2 months
Koong et al 2005[46]	16	25Gy x 1 as boost	94	Median 8.3 months	1 year 8%,
Schellenberg et al 2011[47]	16	25Gy x 1#	81	Median 11.4 months	Median 9.2 months 1 year 50%
Hoyer et al 2005[48]	22	15Gy x 3	57	Median 5.7 months	Median 4.8 months
Mahedevan et al 2010[49]	36	8-12Gy x 3	79	Median 14.3 months	Median 9.6 months
Goyal et al 2012[50]	20	20-30Gy in 1-3 #	81	1 year 56%	Median 14 months 1 year 65%

Proton therapy is an area of emerging interest. A current trial in the United States (NCT01683422) is investigating the role of Gemcitabine and Erlotinib plus proton therapy versus capecitabine and oxaliplatin for locally advanced pancreatic cancer [51]. The attraction with protons, as for SABR is reducing dose to surrounding organs and to aid dose escalation and better loco-regional control.

FUTURE DIRECTIONS IN THE MANAGEMENT OF PANCREATIC CANCER

The SCALOP II trial is a phase II study of patients with locally advanced pancreatic cancer: patients are treated with three cycles of induction gemcitabine and nab-paclitaxel. Those who have stable or responding disease will then be randomised to continuing the same chemotherapy for a further three cycles or to receive one further cycle of the same chemotherapy followed by one of four CRT regimes: 50.4Gy with capecitabine, 50.4Gy with capecitabine and nelfinavir, 60Gy with capecitabine and 60Gy with capecitabine and nelfinavir. This trial will help to determine whether dose escalation in pancreatic cancer produces better overall survival and whether the addition of nelfinavir (a protease inhibitor) to CRT produces better progression free survival.

The four-arm phase III CONKO-7 trial will evaluate the efficacy of neoadjuvant chemotherapy plus chemoradiation versus chemotherapy alone in an estimated 830 unresectable LAPC patients. The chemotherapy options in this trial include either FOLFIRINOX or gemcitabine. This trial will guide us on which induction chemotherapy regime to use and the added benefit of CRT versus chemotherapy alone.

RADIOTHERAPY QUALITY ASSURANCE IN OESOPHAGEAL AND PANCREATIC CANCER CLINICAL TRIALS

Radiotherapy Trial Quality Assurance **(RTQA)** is important to ensure that radiotherapy delivered in trials is of high quality and does not adversely impact on trial outcomes. Abrams et al found that protocol deviations in the RTOG 9704 study of adjuvant chemoradiotherapy for pancreas cancer were associated with worse survival [52]. QA aims to reduce inter-observer and standardise treatment volumes with the use of protocols.. The SCOPE 1 trial reported a median overall survival of 25.4 months in the standard radiotherapy arm, which exceeded expectations.

This may in part be due to the detailed protocol and quality assurance of this trial including a pre-accrual benchmark case.

The UK Neo-SCOPE trial, recently presented at GI ASCO 2016, showed that prospective review of outlining within the trial enabled the identification and correction of unacceptable variations in protocols in 11% of patients without causing treatment delays [53].

The SCALOP trial, participating investigators outlined a pre-trial benchmark case as per the radiotherapy protocol. The accuracy of the investigators GT*Vs* and PT*Vs* were evaluated by Fokas et al [54] (using qualitative and geometric analyses). There were no major protocol deviations, however this study showed that there were variations in GTV delineation, particularly with the recognition of peri-pancreatic lymph nodes, despite a detailed RT protocol, educational atlas and radiologist input [54].

These studies have shown that RTQA workshops and real-time central review of delineations is needed in future trials.

References

1. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998; 339: 1979-1984.
2. Crosby T, Hurt C, Falk S, Gollins S, Mukherjee S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol. 2013; 14: 627-637.
3. Gwynne S, Wijnhoven BP, Hulshof M, Bateman A. Role of chemoradiotherapy in oesophageal cancer -- adjuvant and neoadjuvant therapy. Clin Oncol (R Coll Radiol). 2014; 26: 522-532.
4. Van Hagen P, Hulshof MC, Van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012; 366: 2074-2084.
5. Zheng B, Zheng W, Zhu Y, Lin XY, Xu BH, et al. Role of adjuvant chemoradiotherapy in treatment of resectable esophageal carcinoma: a meta-analysis. Chinese Med. 2013; 126: 1178-1182.
6. Wang DB, Zhang X, Han HL, Xu YJ, Sun DQ, et al. Neoadjuvant chemoradiotherapy could improve survival outcomes for esophageal carcinoma: a meta-analysis. Digest Dis Sci. 2012; 57: 3226-3233.
7. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Australasian Gastro-Intestinal Trials Group , et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011; 12: 681-692.
8. S Mukherjee, C Hurt, S Gwynne, A Bateman, S Gollins, et al. NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. ASCO GI 2016 Oral Presentation. 2016.
9. Rackley T, Leong T, Foo M, Crosby T. Definitive chemoradiotherapy for oesophageal cancer -a promising start on an exciting journey. Clin Oncol (R Coll Radiol). 2014; 26: 533-540.
10. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005; 23: 2310-2317.
11. Bedenne L, Michel P, Bouché O, Milan C, Mariette C, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007; 25: 1160-1168.
12. Honing J, Smit JK, Muijs CT, Burgerhof JG, de Groot JW, et al. A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. Ann Oncol. 2014; 25: 638-643.
13. Button MR, Staffurth J, Crosby TDL. National variation in the treatments of oesophageal cancer with chemoradiotherapy. Clinical Oncology. 2007; 73: S25.
14. Mukherjee S, Hurt CN, Gwynne S, Bateman A, Gollins S, et al. NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. BMC Cancer. 2015; 15: 48.

15. Matzinger O, Gerber E, Bernstein Z, Maingon P, Haustermans K, et al. EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neo-adjuvant radiation of adenocarcinomas of the gastro-oesophageal junction and the stomach. Radiother Oncol. 2009; 92: 164-175.

16. Gwynne S, Falk S, Gollins S, Wills L, Bateman A, et al. Oesophageal Chemoradiotherapy in the UK-current practice and future directions. Clin Oncol (R Coll Radiol). 2013; 25: 368-377.

17. Wang W, Li J, Zhang Y, Li F, Xu M, et al. Comparison of patient-specific internal gross tumour volume for radiation treatment of primary esophageal cancer based separately on three-dimensional and four-dimensional computed tomography images. Diseases of the oesophagus. 2014: 27; 348-354.

18. Marks L, Yorke ED, Jackson A, Ten Haken RK, Constine LS, et al. Use of normal tissue complication probability models in the clinic. Int. J. Radiation Oncology Biol. Phys. 2010; 76: S10-S19.

19. Wills L, Millin A, Paterson J, Crosby T, Staffurth J. The effect of planning algorithms in oesophageal radiotherapy in the context of the SCOPE 1 trial. Radiother Oncol. 2009; 93: 462-467.

20. Yap JC, Harish K. Malhotra, Gary Y Yang. Intensity modulated radiation therapy in the treatment ofesophageal cancer. Thoracic Cancer. 2010; 1: 62-69.

21. Yang GY, McClosky SA, Khushalani NI. Principles of Modern Radiation Techniques for Esophageal and Gastroesophageal Junction Cancers. Gastrointestinal Cancer Research. 2009; 3: S6-S10.

22. Myles BA, SH Lin, SL Tucker, JA Ajani, WL Hofstetter, et al. "Long Term Outcomes Comparing Three-dimensional Conformal Radiation Therapy to Intensity Modulated Radiation Therapy with Concurrent Chemotherapy for the Treatment of Esophageal Cancer: The MD Anderson Experience." International Journal of Radiation Oncology Biology Physics. 2011; 81: S127.

23. Wang S et al. Intensity-modulated radiation therapy with concurrent chemotherapy for locally advanced cervical and upper thoracic esophageal cancer. World Journal Gastroenterology. 2006: 12; 5501-5508.

24. Ling T, Jerry M. Slater, Prashanth Nookala, Rachel Mifflin, Roger Grove, et al. Analysis if Intensity Modulated Radiation Therapy (IMRT), proton and 3D conformal radiotherapy (3D-CRT) for reducing peri-operative cardiopulmonary complications in oesophageal cancer patients. Cancers. 2014: 6; 2356-2368.

25. Ishikawa H, Hashimoto T, Moriwaki T, Hyodo I, Hisakura K, et al. Proton beam therapy combined with concurrent chemotherapy for esophageal cancer. Anticancer Res. 2015; 35: 1757-1762.

26. Lin S, Komaki R, Liao Z, Wei C, Myles B, et al. Proton beam therapy and concurrent chemotherapy for oesophageal cancer. International Journal Radiation Oncology Biology Physics. 2012; 83: e345-351.

27. Welsh, Gomez D, Palmer MB, Riley BA, Mayankkumar AV, et al. Intensity Modulated proton therapy further reduces normal tissue exposure during definitive radiotherapy for locally advanced distal oesophageal tumours- a dosimetric study. International Journal Radiation Oncology Biology Physics. 2011: 81; 1336-1342.

28. Hawkins MA, Aitken A, Hansen VN, McNair HA, Tait DM. Set-up errors in radiotherapy for oesophageal cancers--is electronic portal imaging or conebeam more accurate? Radiother Oncol. 2011; 98: 249-254.

29. Huguet F, Mukherjee S, Javle M. Locally advanced pancreatic cancer: the role of definitive chemoradiotherapy. Clin Oncol (R Coll Radiol). 2014; 26: 560-568.

30. Intergroup Trial A021101, led by the Alliance for Clinical Trials in Oncology (NCT01821612; Chemotherapy and Radiation Therapy Before Surgery Followed by Gemcitabine in Treating Patients With Pancreatic Cancer).

31. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013; 310: 1473-1481.

32. Sen N, Falk S, Abrams RA. Role of chemoradiotherapy in the adjuvant and neoadjuvant settings for resectable pancreatic cancer. Clin Oncol (R Coll Radiol). 2014; 26: 551-559.

33. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985; 120: 899-903.

34. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004; 350: 1200-1210.

35. National Cancer Institute: Gemcitabine Hydrochloride With or Without Erlotinib Hydrochloride Followed By the Same Chemotherapy Regimen With or Without Radiation Therapy and Capecitabine or Fluorouracil in Treating Patients With Pancreatic Cancer That Has Been Removed By Surgery.

36. Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer. Strahlenther Onkol. 2015; 191: 7-16.

37. Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol. 2013; 14: 317-326.

38. Hammel, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. Journal of Clinical Oncology, 2011 ASCO Annual Meeting Abstracts. 2011; 29: 15.

39. Huguet F, André T, Hammel P, Artru P, Balosso J, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol. 2007; 25: 326-331.

40. Krishnan S, Rana V, Janjan NA, Varadhachary GR, Abbruzzese JL, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer. 2007; 110: 47-55.

41. Milano MT, Chmura SJ, Garofalo MC, Rash C, Roeske JC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys. 2004; 59: 445-453.

42. Gwynne S, Wills L, Joseph G, John G, Staffurth J, et al. Respiratory movement of upper abdominal organs and its effect on radiotherapy planning in pancreatic cancer. Clin Oncol (R Coll Radiol). 2009; 21: 713-719.

43. Cattneo GM, Passoni P, Longobardi B, Slim N, Reni M, et al. Dosimetric and clinical predictors of toxicity following combined chemotherapy and moderately hypofractionated rotational radiotherapy of locally advanced pancreatic adenocarcinoma. Radiother Oncol. 2013; 108: 66-71.

44. Brunner TB, Nestle U, Grosu AL, Partridge M. SBRT in pancreatic cancer: what is the therapeutic window? Radiother Oncol. 2015; 114: 109-116.

45. Koong AC, Le QT, Ho A, Fong B, Fisher G, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004; 58: 1017-1021.

46. Koong AC, Christofferson E, Le QT, Goodman KA, Ho A, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2005; 63:320-323.

47. Schnellnberg, Kim J, Christman-Skieller C, Chun CL, Columbo LA, et al. Single-Fraction Stereotactic Body Radiation Therapy and Sequential Gemcitabine for the Treatment of Locally Advanced Pancreatic Cancer International Journal of Radiation Oncology Biology Physics. 2011: 81; 181-188.

48. Hoyer M, Roed H, Sengelov L, Traberg A, Ohlhuis L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol. 2005; 76: 48-53.

49. Mahadevan A, Jain S, Goldstein M, Miksad R, Pleskow D, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2010; 78: 735-742.

50. Goyal K, Einstein D, Ibarra RA, Yao M, Kunos C, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. J Surg Res. 2012; 174: 319-325.

51. Yang G. Chemotherapy Plus Proton-chemotherapy for Locally Advanced Pancreatic Cancer. 2016.

52. Abrams RA, Winter KA, Regine WF, Safran H, Hoffman JP, Lustig R, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704-A phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys. 2012; 82: 809-816.

53. Evans E. On-trial radiotherapy quality assurance in NeoSCOPE: A randomised phase II trial of chemoradiotherapy in oesophageal cancer. GI ACSO Poster. 2016.

54. Fokas E, Clifford C, Spezi E, Joseph G, Branagan J, et al. Comparison of investigator-delineated gross tumor volumes and quality assurance in pancreatic cancer: Analysis of the pretrial benchmark case for the SCALOP trial. Radiotherapy and Oncology. 2015; 117: 432-437.