Quality Assurance of Radical Lung Cancer Radiotherapy

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the Faculty of Biology, Medicine, and Health

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List of Abbreviations

2D	Two-dimensional
2D RT	Two-dimensional radiotherapy
3D	Three-dimensional
3D CRT	Three-dimensional conformal radiotherapy
AAPM	American Association of Physicists in Medicine
ACDS	Australian Clinical Dosimetry Service
ASTRO	American Society of Radiation Oncology
AvIP	Average image projection
CBCT	Cone-beam computed tomography
CCTG	Canadian Cancer Trials Group
CONSORT	Consolidated Standards of Reporting Trials
CPM	Clinical prognostic model
CRUK	Cancer Research United Kingdom
CTAAC	Clinical Trials Awards and Advisory Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTRad	Clinical and Translational Radiotherapy
CTV	Clinical target volume
DIR	Deformable image registration
DVH	Dose volume histogram
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQD_2	Equivalent dose in 2Gy fractions
ESTRO	European Society for Radiotherapy and Oncology
GHG	Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group
GTV	Gross tumour volume
Gy	Gray
HR	Hazard ratio
IAEA	International Atomic Energy Agency
IGRT	Image guidance radiotherapy
IMRT	Intensity-modulated radiotherapy
IQR	Interquartile range
irAE	Immune-related adverse events
IROC	Imaging and Radiation Oncology Core
ITAC	Intra-thoracic anatomical changes
JCOG	Japan Clinical Oncology Group
MTD	Maximum tolerated dose

NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NHS	National Health Service
NIHR	National Institute of Health Research
NIHR CRN	National Institute of Health Research Clinical Research Network
NPL	National Physical Laboratory
NSCLC	Non-small cell lung cancer
NTCP	Normal tissue complication probability
OAR	Organ at risk
OS	Overall survival
OTT	Overall treatment time
PBT	Proton beam therapy
PFS	Progression free survival
PHE	Public Health England
PRV	Planning organ at risk volume
PTV	Planning target volume
QA	Quality assurance
QOL	Quality of life
QUANTEC	Quantitative analysis of normal tissue effects in the clinic
RD	Dose file
RDS	Radiation Dosimetry Services
RCT	Randomised controlled trial
RO-ILS	Radiation Oncology Incident Learning System
ROI	Region of interest
ROSEIS	Radiation Oncology Safety and Education Information System
RP	Plan file
RS	Structure set
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RT QA	Radiotherapy quality assurance
RTT	Radiation therapy technologists
RTTQA	Radiotherapy Trials Quality Assurance
SABR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiation therapy
SCLC	Small cell lung cancer
sCT	Synthetic computed tomography
SEER	Surveillance Epidemiology and End Results
SRS	Stereotactic radiosurgery
TD	Total dose
TG	Task Group

TMG	Trial Management Group
TPS	Treatment planning system
TROG	Trans Tasman Radiation Oncology Group
TV	Target volume
TVD	Target volume delineation
UK	United Kingdom
VODCA	Visualization and Organization of Data for Cancer Analysis

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Abstract

RTOG 73-01 and RTOG 0617 established 60 Gray (Gy) in 30 daily fractions over six weeks as the optimal radiotherapy dose and fractionation for the radical treatment of locally advanced non-small cell lung cancer. RTOG 0617 randomised between standard dose 60 Gy and high-dose 74 Gy; survival detriment was noted in the 74 Gy arm, however only half of the cohort received radiation with modern delivery techniques and the impact of unwanted radiation dose to the heart and unintended mediastinal structures remains under investigation. Technological advances now enable radiotherapy dose delivery to the target beyond 60Gy with scope for dose intensification and sparing of the organs at risk.

Accurate radiotherapy delivery is a multi-faceted process, and in the United Kingdom, the National Radiotherapy Trials Quality Assurance (RTTQA) Group provides radiotherapy quality assurance (QA) for all National Institute of Health Research Clinical Research Network (NIHR CRN) portfolio studies which involve a radiotherapy component. A key aim of the RTTQA Group is to standardise radiotherapy delivery and reporting across clinical trials.

This thesis aims to review the variability in radical lung cancer radiotherapy processes and proposes standardisation of radiotherapy QA processes with a focus on the radical treatment of lung cancer.

Total word count

17306 words in the main body of text, excluding tables, figures, and references.

Declaration

I declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Introduction

RTOG 73-01 [1] and RTOG 0617 have [2] established 60 Gray (Gy) in 30 daily fractions over six weeks as the optimal radiotherapy dose and fractionation for the radical treatment of locally advanced non-small cell lung cancer (NSCLC).

Advances in diagnostic imaging and the transition from two-dimensional (2D) to three-dimensional conformal radiotherapy (3D CRT), and now intensity-modulated radiotherapy (IMRT) enable radiotherapy dose delivery beyond 60Gy equivalent dose in 2Gy fractions with sparing of adjacent organs at risk (OAR).

In this era of multi-modality sequential therapy, it is paramount that the ensuing toxicities from the individual components of a treatment schedule are considered in tandem as toxicity is cumulative, impacts quality of life, and impedes progression through the intended optimal treatment programme. Quantitative analysis of normal tissue effects in the clinic (QUANTEC) defines OAR dose-volume constraints, which if exceeded increase the probability of the patient developing high-grade toxicity [3]. The OAR dose-volume constraints are based on historical data sets; the application of these constraints may not be appropriate in the context of modern image-guidance, contemporary drug-radiotherapy combinations, or radiotherapy dose-intensification [4].

The National Radiotherapy Trials Quality Assurance (RTTQA) Group provides radiotherapy quality assurance (QA) for all National Institute of Health Research Clinical Research Network (NIHR CRN) portfolio studies involving a radiotherapy component. A key aim of the RTTQA Group is to standardise radiotherapy delivery and reporting across clinical trials.

Aims

This thesis aims to review the variability in radiotherapy processes and to propose standardisation of radiotherapy QA processes with a focus on the radical treatment of lung cancer.

The thesis is comprised of five packages of work:

1) Review of quality assurance of radical lung cancer radiotherapy in the post-QUANTEC era [Paper 1]
2) Provision of Organ at Risk Contouring Guidance in United Kingdom Radiotherapy Clinical Trials [Paper 2]
3) Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group Consensus Guidelines [Paper 3]
4) Associations between radiotherapy protocol deviations and outcome in the CONVERT trial [Paper 4]
5) Pilot analysis of daily variation on dose to organs at risk within Isotoxic IMRT trial [Paper 5]

The conclusions from the packages of work contribute to the discussion, with proposal of a radiotherapy QA reporting framework for lung cancer in line with the Consolidated Standards of Reporting Trials principles.

Paper 1: Quality assurance of radical lung cancer radiotherapy in the post-QUANTEC era

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Conception or design of the work: RM
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Abstract

Introduction

Radiotherapy quality assurance (QA) is a multi-faceted process where all components impact upon the validity of the reported trial outcome. This paper reports the extent of radiotherapy QA, toxicity, and outcome reporting within published novel radical intent fractionated NSCLC radiotherapy studies in the post-QUANTEC era and highlights areas of unmet need.

Methods

An electronic search strategy was performed on 16th June 2019 and identified radical intent fractionated NSCLC radiotherapy delivered with treatment delivered with photons, with or without platinum-based systemic chemotherapy. The presence and level of radiotherapy QA was recorded. If radiotherapy QA was not reported in the published paper, the corresponding author was contacted and allowed 28 days to respond.

Results

8026 abstracts were screened; 11 studies were identified as containing at least one component of radiotherapy QA. 8/11 described how contours were applied. 8/11 employed planning QA. 9/11 encouraged IGRT. Variability was noted in the approach to each QA component highlighting a lack of consistency.

Conclusion

This systematic review of radiotherapy QA in radical NSCLC radiotherapy trials in the post-QUANTEC era highlights the heterogeneity in clinical trial reporting and the lack of consistent radiotherapy QA. Areas of unmet need highlighted by this systematic review include standardisation of OAR outlining, clinical trial endpoint reporting, and mechanisms for the evaluation of IGRT and treatment delivery.

Introduction

Advances in diagnostic imaging alongside the transition in radiotherapy planning techniques enable the delivery of radical radiotherapy to patients whose disease burden would have ordinarily precluded them from radical intent treatment [5].

Disease burden, performance status, and patient-related factors guide the decision-making process and allow the clinician to choose between radical intent and palliative intent treatment. For non-small cell lung cancer (NSCLC) the additional parameters of baseline lung function and volume of irradiated normal lung predict an increased risk of radiotherapy-related toxicity [6]. QUANTEC evaluated normal tissue effects to radiation in terms of organ-specific threshold tolerance and 3D dose volume-outcome data. QUANTEC acknowledges the inherent limitations of the guidance; particularly as patient-related factors and novel radiotherapy approaches such as hypo/hyperfractionation, and dose-intensification were not evaluated [3].

Toxicity predictors in radiotherapy are created through mathematical models, with toxicity and dosimetric endpoints as inputs into the respective formulae. The granularity and accuracy of the data inputs may impact the final recommendation.

Guidance improving the quality and reporting of randomised clinical trials (RCT) is in place. The Consolidated Standards of Reporting Trials (CONSORT) statement specifies twenty-five items to be included when reporting an RCT [7] (table 1). In radiotherapy, the additional variable of radiotherapy delivery should be considered separately as radiotherapy QA is known to impact upon patient outcomes [8], and so the author proposes radiotherapy QA should be reported alongside clinical trial endpoints to fully appreciate the trial outcome(s).

This paper reports the extent of radiotherapy QA, toxicity, and outcome reporting within published novel radical intent fractionated NSCLC radiotherapy studies in the post-QUANTEC era and highlights areas of unmet need.

Table 1. The CONSORT 2010 Statement 25 item checklist to aid reporting of a randomised clinical trial

Section/topic	Item number	Checklist item	Reported on page number
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[21,31])	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% CI)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[28])	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration[13] for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials,[11] non-inferiority and equivalence trials,[12] non-pharmacological treatments,[32] herbal interventions,[33] and pragmatic trials.[34] Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

Table: **CONSORT 2010 checklist of information to include when reporting a randomised trial***

Materials and methods

An electronic search strategy was performed on Scopus, Medline, Pubmed, and the Cochrane Library. The searches were performed on 16th June 2019. The databases were searched from 2010 to present day, with keywords: “radiotherapy” and “constraint” with “heart”, “cardiac”, “oesophagus”, “esophagus”, or “lung”. A further search with the keyword “toxicity” in place of “constraint” was run. The search was limited to English language material only.

Studies were deemed eligible if related to radical intent fractionated NSCLC radiotherapy delivered with photons, with or without platinum-based systemic chemotherapy. Studies with stereotactic body radiotherapy or concurrent or adjuvant immunotherapy were excluded; the latter due to the potential impact of immune-related adverse events confounding the reported toxicity rates. Eligible studies employed dose-fractionations beyond standard 60Gy in 2Gy per fraction schedules.

Abstracts were initially screened for relevance, followed by the eligibility of full-length articles.

Radiotherapy QA was defined as independent or institutional, prospective, or retrospective review of target volume (TV) and OAR contours, review of radiotherapy plan, and comment on treatment delivery with detail of verification and image-guidance action levels. Compliance to clinical trial or departmental protocol was recorded.

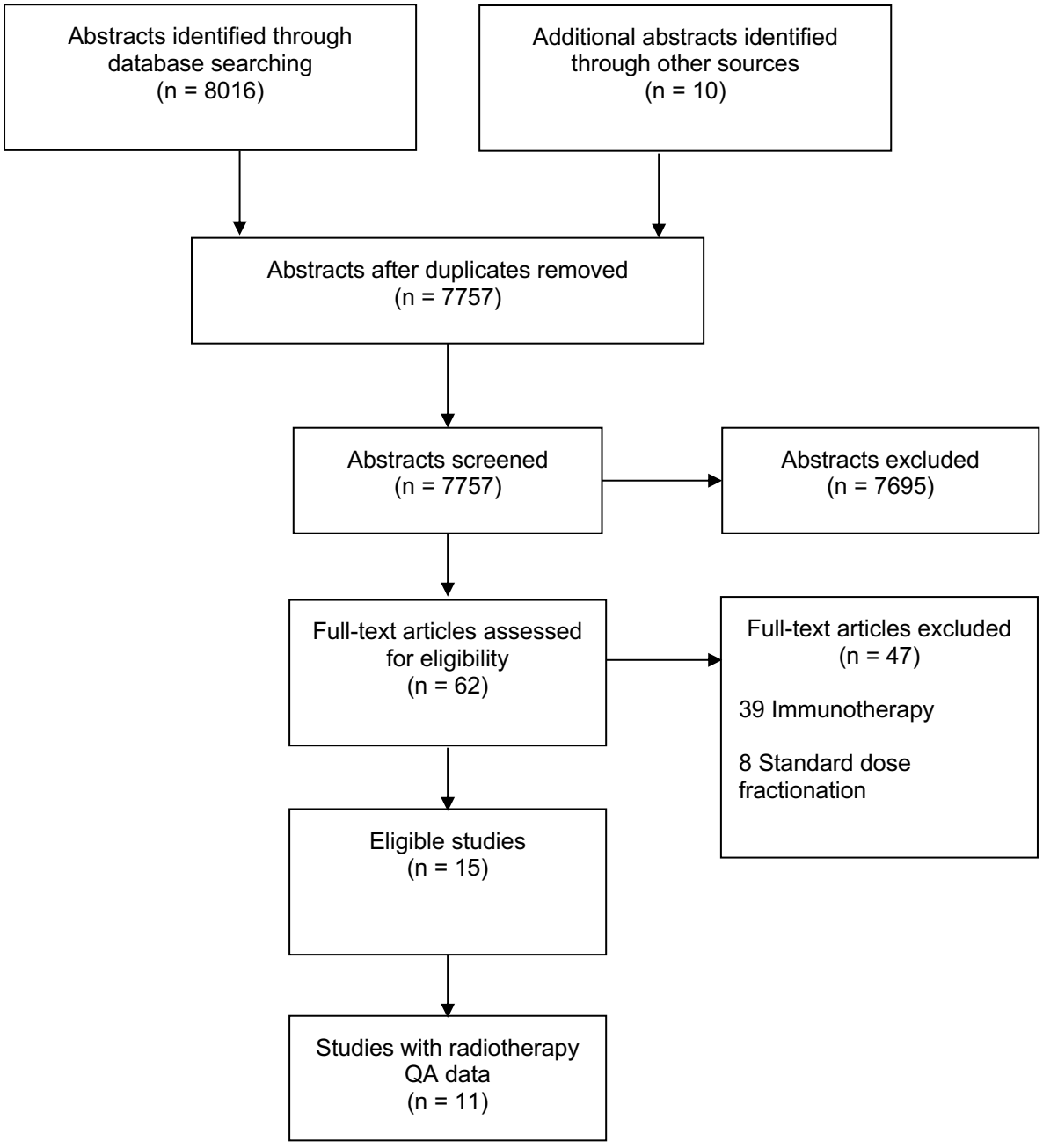
The following data was collected from the studies: inclusion criterion, study design, recruitment period interval (years), number of recruited patients, radiotherapy technique, total dose, use of 4D planning CT, QA approach to contouring and planning, IGRT approach, study endpoint(s), toxicity pertaining to OAR, and outcome(s).

Corresponding authors were contacted by email to provide radiotherapy QA details not described in the publication relating to contouring, planning, and image guidance (IGRT). Corresponding authors were given a period of 28 days to respond. In instances where the study did not report on radiotherapy QA and no email correspondence was returned, the study was excluded from the second stage of the review process.

Results

A total of 8026 abstracts were identified (figure 1); fifteen full-length articles (table 2) met the pre-specified inclusion criteria. Patients were recruited from 2004 – 2014. All studies were reported in peer-reviewed journals. Eleven studies, either within the publication or following contact with the corresponding author had radiotherapy QA details.

Figure 1. Search outcomes



The four studies excluded from the second stage of analysis due to lack of radiotherapy QA details were van Baardwijk [11], SOCCAR [13], Sekine et al [15], and Hallqvist [18].

3D CRT was used as the sole radiotherapy delivery technique in five studies; IMRT was the sole technique in five studies. The remaining five studies allowed both 3D CRT and IMRT. Studies recruiting patients from 2008 onwards employed IMRT, with the 2010 CHART-ED [9] trial as the only exception.

Thirteen (86.7%) studies employed dose escalation, beyond or equal to 66Gy EQD_2, with five trials reporting isotoxic or randomised to radiotherapy dose-intensification to the planning target volume (PTV) dependent on the planned dose to the OAR.

Eight (53.3%) studies reported data on forty patients or fewer; in one instance this was due to the suspension of the clinical trial due to high-grade toxicity.

Four studies reported on large, retrospective single centre patient cohorts. Two studies were randomised controlled trials.

Table 2. Summary of the studies

Study & Recruitment dates	Ph	n	TNM	Aim	Total dose +/- chemotherapy	OAR planning constraints	Technique	4D CT	Toxicity Assessment	≥G3 Toxicity^	Outcome
RTOG 0117 [10] 2004	I	17	I-III	Establish MTD	Level 1 75.25Gy in 35# Level 2* 74Gy in 37# Weekly paclitaxel 50mg/m2 and carboplatin AUC 2	Lung – PTV V20 ≤30% Oesophagus Mean dose ≤34Gy V55 ≤30%	3D CRT	NR	Acute CTCAE v2.0 Late RTOG	Level 1 Acute 4/8 lung Late 2/8 lung Level 2 Acute 1/9 lung Late 2/7 oesophagus & lung	MTD 74Gy/37#
Van Baardwijk et al [11] 2004-2007	Prospective single centre cohort	166	I-III	Establish toxicity of individualised maximum tolerable dose	Individual dose escalation until normal tissue constraints were reached Maximum dose+ 79.2Gy in 22# (30d)	Lung MLD 10-19Gy ± 1Gy£ Oesophagus No constraint Great vessels & bronchi Dmax 70.2Gy	3D CRT	NR	CTCAE v3.0	Acute 8/166 Oesophagus 20/166 Lung Late 5/166 Lung	MLD was dose limiting in 33.1% Severe oesophagitis was observed in <5% and was transient in all instances
Bral et al [12]	II	40	III	Assess feasibility and toxicity of moderately	70.5Gy in 30#	Lung V20 ≤30% MLD ≤17Gy	Tomo	NR	Acute RTOG & CTCAE v3.0	Acute 1/40 oesophagus 6/40 lung	MLD (UVA) >18Gy & V20 >32% predictive of ≥G3 lung toxicity (p=0.04)

2005-2008				hypofractionated EBRT		Oesophagus Dmax 70Gy when ⅓ <66Gy and when ½ <35Gy			Late RTOG	Late 5/31 lung	
SOCCAR [13] 2005-2010	II RCT	130	IIIA-IIIB	Comparison of sCRT and cCRT	55Gy in 20# sCRT 4 cycles of cisplatin 80mg/m2 day 1. Vinorelbine 25mg/m2 days 1 and 8 cCRT Cisplatin 20mg/m2 with fractions 1-4 and 16-10. Vinorelbine 15mg/m2 with fractions 1, 6, 15, and 20.	Whole lung – GTV V20 ≤30% Oesophagus ≤12cm in PTV	3D CRT	One centre	CTCAE v3.0	Oesophagus sCRT 5/59 cCRT 6/69 Lung sCRT 3/59 cCRT 2/69	No increased risk of toxicity with cCRT and hypofractionated RT when compared with sCRT
Kwint et al [14] 2008-2010	Prospective single centre cohort	139	Locally advanced NSCLC	Establish dose-effect relationship between acute oesophageal toxicity & dose volume parameters	66Gy in 24# Concurrent cisplatin 6mg/m2 daily	Lung MLD ≤20% Oesophagus V35 <65% Heart	IMRT	NR	CTCAE v3.0	Acute 22% oesophagitis	V50 identified as the most accurate predictor of ≥grade 3 acute oesophageal toxicity

						Total ≤40Gy, ⅔ ≤50Gy, ⅓ ≤66Gy					
Sekine et al [15] 2005-2008	I	31	Unresectable stage III	Establish MTD	Level 1 66Gy in 33# Level 2 72Gy in 36# Level 3 78Gy in 39# Concurrent cisplatin 80mg/m2 day 1. Vinorelbine 20mg/m2 day 1 and 8	Lung V20 ≤30% Oesophagus Dmax 66Gy	3D CRT	NR	CTCAE v3.0 Lung toxicity defined as the highest grade: cough, dyspnoea, obstruction, pneumonitis, fibrosis	Level 1 1/12 oesophagitis Level 2 1/12 Oesophagitis Level 3 1/6 lung	3D CRT with concurrent cisplatin and vinorelbine at 72Gy in 36# is feasible. Lung V20 ≤30% should be used for cCRT trials
RTOG 0617[@] [2] 2007-2011	III RCT	482	IIIA-IIIB	Two-by-two factorial design	60Gy in 30# 74Gy in 37# Concurrent weekly paclitaxel 45mg/m2 and carboplatin AUC 2 ± cetuximab	NR	3D CRT (53%) IMRT (47%)	Encouraged	CTCAE v3.0	Oesophagitis 3d CRT : 39/254 IMRT : 30/228 Lung 3d CRT : 20/254 IMRT: 8/228	Substantial differences in dosimetry and target volumes between 3d CRT and IMRT 5-year OS and PFS 32.1% (60Gy) and 23% (74Gy) (p=0.007). Established 60Gy in 30# as SOC.
Kelsey et al [16]	I	24	III, local	Establish MTD	58Gy in 29#[$] 62Gy in 31#	Lung	IMRT	Y	CTCAE v4.0	Acute Oesophagitis	DLT developed in patients with tumour

2009-2014			recurrence		66Gy in 33# 70Gy in 35# 74Gy in 37# Concurrent cisplatin 50mg/m2 day 1, 8, 29, 36, and etoposide 50mg/m2 days 1-5 and 29-33	V5<50%, V20<35% Oesophagus V20<50% V60<25%			FACT	58Gy 1/6 70Gy 1/6 Late Oesophagitis 66Gy 1/3	abutting the oesophagus 74Gy is the MTD
CHART-ED [9] 2010-2012	I	18	Inoperable I-III	Determine MTD with dose-escalation beyond CHART	CHART + 2, 4, and 6, 1.8Gy fractions on days 15-17 57.6Gy in 38# (15 d) 61.2Gy in 40# (16 d) 64.8Gy in 42# (17 d)	Whole lung – GTV V20<35% Oesophagus Dmax<105% Heart V100%<30% V50%<50%	3D CRT	NR	CTCAE v4.0	Oesophagitis 3/18	No DLT reported
IDEAL-CRT [17] 2010-2013	I/II	84	IIA-IIIB	Report toxicity and survival for dose-escalated cCRT Determine oesophageal MTD	Participants received the highest prescribed tumour dose between 63 – 73Gy while meeting OAR constraints. Concurrent cisplatin 75mg/m2 day 1 and	Whole lung – GTV EQD_{2mean} 18.2Gy $D_{oesoph1cc}$ 65-71`Gy	3D CRT (96%) IMRT (4%)	Y (34)	CTCAE v4.0	Oesophagitis 5/84	68Gy is the oesophageal MTD Average prescribed tumour dose 67.7Gy in 30#. (15% increase in EQD_2 above 60Gy in 30#)

					20. Vinorelbine 15mg/m2 days 1, 8, 29, and 36.						
PLANET [18] 2011-2013	II	35	IIIA - IIIB	Establish if radiation dose escalation based on individual normal tissue constraints improves outcome	Standard: 68Gy in 34# Experimental: CTV dose escalated up to 84Gy dependent on constraint of lung and spinal canal. Concurrent cisplatin 75mg/m2 day 1 and 20. Vinorelbine 25mg/m2 days 1 and 8.	Lung DLCO > 60%, then V20 <50% DLCO 40-60%, then V20 <35%	3D CRT IMRT	Y	CTCAE v4.0 QLQ 30 LC14	Standard Oesophagitis 1/17 Experimental Oesophagitis 4/18	Trial terminated early due to oesophageal perforation in the high dose region.
CALGB 31102 [19] 2012-2014	I	21	IIIA-IIIB	Determine MTD for hypofractionated cCRT and describe toxicity	RT dose maintained at 60Gy, with increasing fraction size 1: 60Gy in 27# 2: 60Gy in 24# 3: 60Gy in 22# 4: 60Gy in 20# Concurrent weekly paclitaxel 45mg/m2 and carboplatin AUC2	Lung V20≤35% Oesophagus Dmax 105% V55 <30% Heart Dmax 62Gy 55Gy <⅓ 40Gy <⅔ V100%<30Gy	3D CRT IMRT	Y	CTCAE v4.0	Acute 5/19 Late Level 2 1 fatal haemoptysis Level 3 1 fatal haemoptysis 1 fatal pneumonitis	MTD cCRT 60Gy in 24# 18/21 completed consolidation chemotherapy

de Ruysscher et al [20] 2009-2012	Prospective single centre cohort	185	III	Establish if INDAR delivery with cCRT improves OS	Ph1: 45Gy in 30# (1.5Gy/#, 21d) Ph2: 2Gy/# Dose escalation to OAR constraint Concurrent cisplatin 40-50mg/m2 and vinorelbine 15-20mg/m2 day 1.	Lung MLD 19 ± 1Gy Oesophagus V35≤35% Dmax 74Gy Heart Mean 46Gy Mediastinal structures Dmax 69Gy	IMRT	Y	CTCAE v4.0	Acute Lung: 6/185 Oesophagitis: 41/185 No late oesophageal toxicity	Mean tumour dose 66±12.8Gy Mediastinal structures were dose limiting in 67%
PET-Boost [21] 2010-2015	II RCT	107	II-III	Establish toxicity of dose escalation to entire primary tumour or sites of high FDG uptake	≥72Gy in 24# over 32d with SIB to the PTV or limited to areas of FDG uptake Maximum boost dose is determined individually on OAR constraints of isotoxicity cCRT, sCRT, or RT alone were permitted	Lung MLD <20Gy Oesophagus V35 <80% D0.1% <94Gy Heart D0.1% <94Gy	IMRT	Y	CTCAE v3.0	72% cCRT Acute Oesophagitis[%] cCRT 14.3% sCRT/RT 3.3% Late Oesophagitis cCRT 15.6%	43 patients not randomised due to OAR constraints

						Mediastinal envelope D0.1% <94Gy				sCRT/RT 3.3%	
Chajon et al [22] 2011-2014	Prospective single centre cohort	21	III	Evaluate SMART with cCRT in order to reduce oesophagitis and maintain local control	SMART 66Gy in 30# to the primary GTV with SIB 54Gy in 30# to the CTV Concurrent platinum based chemotherapy	Whole lung – CTV V5 <65% V20 <30% MLD <20Gy Oesophagus V50 ≤30%	IMRT	Y	CTCAE v4.0	Acute 1/21 Oesophagitis	OAR dose reduced with SMART cf IMRT reference group

*dose fractionation schedule adjusted during recruitment of cohort 1; ^reported grade 3 or greater toxicity related to lung, oesophagus, or heart; [£]dependent on FEV_1 and DLCO; [+]twice daily fractions of 1.8Gy with 8-hour interval; [$]6 fractions per week, including 2 fractions 6 hours apart on Friday; [%]2 patients developed acute dysphagia which continued as late toxicity. Symptoms resolved at 6 and 10 months respectively; [@]secondary analysis IMRT compared with 3d CRT; BED = Biological Effective Dose; cCRT, Concurrent Chemo-radiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; CTV, Clinical Target Volume; d, day; DLCO, Carbon Monoxide Diffusion Capacity; Dmax, Maximum Dose; FDG, ^{18}F-fluoro-2-deoxy-glucose; GTV, Gross Tumour Volume; Gy, Gray; INDAR, Individualised Accelerated Isotoxic Dose Escalation; LX, Length of organ exceeding Xgy; NR, Not Reported; NSCLC, Non-Small Cell Lung Cancer; OAR, Organ at risk; OS, Overall Survival; PFS, Progression Free Survival; Ph, Phase; PI, Principle Investigator; PTV, Planning Target Volume; QA, Quality Assurance; QARC, Quality Assurance and Review Centre, Rhode Island; RCT, Randomised Controlled Trial; RT, Radiotherapy; RTOG, Radiation Therapy Oncology Group; RTTQA Group, National Radiotherapy Trials Quality Assurance Group; sCRT, Sequential Chemoradiotherapy; SIB, Simultaneous Integrated Boost; SMART, Simultaneously Modulated Accelerated Radiation Therapy; Tomo, TomoTherapy; VX, Volume of organ at or exceeding Xgy; w, weeks; 3D CRT, three dimensional conformal radiotherapy; 4D CT, 4-dimensional planning CT

Contouring radiotherapy QA

Eight studies defined how contours were applied (table 3). OAR structures were contoured by radiation therapy technologists (RTT) or dosimetrists in two trials. Formalised, either text descriptions or trial-specific contouring atlas were supplied to centres in four studies.

Quality Assurance and Review Centre, Rhode Island (QARC) and the United Kingdom RTTQA Group both provide independent radiotherapy QA. The respective groups supplied pre-trial benchmark cases, with the prospective on-trial review of TV and OAR in two trials.

To date (16th June 2019), none of the studies included in this paper have reported contouring radiotherapy QA and compliance to the clinical trial or departmental protocol.

Planning radiotherapy QA

Eight studies performed planning radiotherapy QA. In three instances, planning reviews were performed prospectively, either in a weekly departmental planning meeting (1) or by an independent radiotherapy QA group (2).

Three studies describe either ‘central review’ or ‘physicist QA review’, without specifying the parameters or radiotherapy QA metrics used for assessment.

Treatment delivery radiotherapy QA

Nine studies encouraged IGRT.

Five studies specified treatment delivery radiotherapy QA: three studies mandated daily orthogonal imaging with weekly cone-beam computed tomography (CBCT); two studies mandated daily CBCT.

Three studies specified an action level of 5mm, above which adjustment as per local policy was recommended.

One study employed the shrinking action level off-line protocol, whereby the average of the systematic uncertainty is measured, compared to a predefined action level, followed by correction on subsequent fractions.

Table 3. Contouring, planning, and treatment delivery radiotherapy QA

Study & Recruitment dates	Contouring QA	Planning QA	Treatment delivery QA
RTOG 0117 [10] 2004	NR	Stored centrally and checked by PI	NR.
Bral et al [12] 2005-2008	NR	NR	Daily CBCT with correction.
Kwint et al [14] 2008-2010	RTTs trained to contour OAR and follow a clear protocol	Physicists QA planning	In-house IGRT protocol: off-line shrinking action level and setup correction protocol. CBCTs acquired for the first 3 fractions, if no correction was necessary weekly follow-up scans were acquired, with reversion to daily CBCT if correction was required. 4D CBCT were acquired if the motion of the tumour, measured on the 4DCT, was ≥ 8 mm. The CBCT's were registered to the MidV-CT based on the bony anatomy of the vertebrae. The CBCT registrations were performed by two RTTs.
RTOG 0617@ [2] 2007-2011	Central review	Central review	IGRT encouraged.
Kelsey et al [16] 2009-2014	OAR delineated by dosimetrists. Physicians will sign off the volume, particularly oesophagus – but this is informal.	Plans reviewed weekly at QA meeting as per SOC. As this was a single institution study – no formal QA process was employed.	Daily OBI. Weekly CBCT. Daily CBCT was employed if OBI and CBCT did not match well.
CHART-ED [9] 2010-2012	Independent QA through RTTQA Group	Independent QA through the RTTQA Group	EPI used to confirm accuracy <5mm. Refer to local guidance when discrepancy ≥5mm
IDEAL-CRT [17] 2010-2013	Pre-trial benchmark submitted to the RTTQA Group and prospective review. OAR delineation guidance with atlas in guideline document.	Retrospective QA through the RTTQA Group	Recommended that EPIs or 3D kv or MV imaging be used to confirm the accuracy of treatment to within 5mm. If a discrepancy ≥5mm, setup should be adjusted according to departmental protocol. CBCT with on-line correction is encouraged where clinically available.
CALGB 31102 [19] 2012-2014	Pre-trial benchmark submitted to QARC Written contouring guidance for OAR	QARC prospective review of all treatment plans	Daily setup with kv, CBCT, or fiducial tracking.

De Ruysscher et al [20] 2009-2012	All OAR and TVD contours check independently by a second radiation oncologist. Trial specific contouring atlas.	Not performed	No trial specific IGRT process. Standard practice is MV CBCT.
PET-Boost [21] 2010-2015	OAR delineated according to Amstersdam-Maastrict normal tissue atlas	NR	Daily CBCT. Setup corrections were performed according to local policy.
Chajon et al [22] 2011-2014	NR	NR	CBCT day 1-3, then weekly. If discrepancy ≥5mm, adjustment and daily imaging with correction was allowed.

QA, Quality Assurance; IGRT, Image-Guided Radiotherapy; PI, Principle Investigator; NR, Not reported; CBCT, Cone Beam Computed Tomography; RTT, Radiation Technology Therapist; OAR, Organ at Risk; 4D, Four-dimensional; Mid V-CT, Mid-ventilation Computed Tomography; Gy, Gray; SOC, Standard of care; NR, Not reported; OBI, Onboard imaging; RTTQA, National Radiotherapy Trials Quality Assurance Group; EPI, Electronic portal imaging; kV, kilovoltage; MV, Megavoltage; QARC, Quality Assurance and Review Centre, Rhode Island; TVD, Target Volume Delineation; d, days

Toxicity

Toxicity was consistently recorded as either acute, within 90 days of radiotherapy, or late as per Radiation Therapy Oncology Group (RTOG) guidance [23]. Toxicity was graded as per the worst organ-specific symptom within the most recently published National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading classification [24].

Published toxicity symptoms were pooled, for example, the highest graded symptom of cough, dyspnoea, obstruction pneumonitis, or fibrosis, defined the grade of lung toxicity.

The studies listed in this summary (table 2) are heterogeneous in trial design, patient recruitment, systemic therapy regimen, and in radiotherapy dose, fractionation, and planning technique. Despite this variation, there has been a focus on determining the maximum tolerated dose (MTD) of the oesophagus as an OAR, with 68Gy to D1cc highlighted as the MTD for the oesophagus and V50 as a predictor for high-grade oesophageal toxicity respectively [14,17].

One clinical trial was terminated early due to high-grade oesophageal toxicity [18].

The proximity of the treated volume to the mediastinum or oesophagus limited dose-intensification in two studies [16,20], with one study unable to dose-intensify radiotherapy in 28.7% of recruited patients [21].

Discussion

This systematic review of dose-intensified, hypo, and hyperfractionated radical NSCLC radiotherapy studies reported in the post-QUANTEC era highlights the heterogeneity of the evidence base, in terms of radiotherapy dose and fractionation, planning technique, and reported toxicity endpoints.

Of fifteen eligible studies, eleven defined the underlying process behind at least one radiotherapy QA component, with five studies detailing the radiotherapy QA approach to all three components of contouring, planning, and treatment delivery. Eight of the evaluated studies specified their approach to contouring, with three studies employing independent radiotherapy QA. The four studies excluded from the second stage of analysis due to absence of radiotherapy QA details were van Baardwijk [11], SOCCAR [13], Sekine et al [15], and Hallqvist [18]; the radiotherapy QA practices within these studies are unknown, the absence of these studies may have introduced bias.

Contouring is the most influential radiotherapy QA component; the quality of contouring directly impacts reported dosimetry [25]. In clinical practice, tumour site experts agree on a single gold standard contouring benchmark from which submitted contours are assessed against. In the phase III CONVERT trial, pre-trial review of submitted “dummy-run” heart contours demonstrated the heart contours were not protocol compliant in 79.7% of reviewed cases. Retrospective radiotherapy QA of fifty recruited patients again demonstrated that the heart contours were not protocol compliant in 76% of the evaluated cohort [26].

To date, four clinical trials of radical radiotherapy for NSCLC had published on radiotherapy QA: CHART [27], GFPC-IFCT 02.01 [28], PROCLAIM [29], and PET-Plan [30]. In PROCLAIM, the reported radiotherapy QA parameters were limited to four dosimetric parameters: PTV coverage, dose homogeneity, the volume of lung receiving ≥20Gy, and maximum point dose to the spinal cord. Trial-defined major radiotherapy QA violations were noted in 7.2% of recruited patients and centres recruiting two or greater patients with major dosimetric violations had reduced progression free survival and overall survival. Radiotherapy QA is a multi-faceted process; from the verification of linear accelerator output to retrospective review of the final radiotherapy treatment plan, consequently, radiotherapy QA parameters should be reported as a continuum rather than isolated components as each component is likely to impact the reporting of the subsequent component.

Although IGRT was encouraged in the examined studies, specific guidance concerning action once the 5mm setup tolerance was exceeded was lacking; the impact of IGRT in NSCLC is well described [31]. LARTIA [32], NARLAL 2 [33], and the ARTNET Group [34] describe intra-thoracic anatomical changes and the subsequent impact on target volume and OAR dosimetry in fractionated and stereotactic radiotherapy delivery. The thorax, a body cavity with tissue heterogeneity and moving organs has added treatment delivery and radiotherapy QA complexities; the IGRT lessons learnt from comprehensively reported clinical trials will inform routine practice.

Clinical trial toxicity endpoints were reported consistently in line with RTOG acute and late toxicity criteria alongside the most recently published NCI CTCAE toxicity grading classification. The evaluated studies pooled

toxicity gradings to create a composite score for lung and oesophageal toxicity respectively, with this approach there is data loss; the author recommends clinical trials should report raw data rather than pooled, composite toxicity scores, so that output data may be more reflective of the different toxicities and underlying pathophysiologies driving toxicity [4].

This systematic review of radiotherapy QA in radical NSCLC radiotherapy trials in the post-QUANTEC era is limited by the respective study recruitment dates; the systematic review however highlights the heterogeneity in clinical trial reporting and the lack of consistent radiotherapy QA.

The 1996 CONSORT Statement, updated in 2001 and 2010, was developed by an international group of clinical trialists, statisticians, epidemiologists, and biomedical editors aiming to improve the reporting of a randomised controlled trial so that the trial is transparently reported to the reader [7]. The CONSORT Statement reduced ambiguity in reporting, which has historically been associated with bias in estimating the effectiveness of interventions [35]. The quality of radiotherapy delivered is known to impact patient outcome; this review highlights the heterogeneity in radiotherapy QA reporting. In response to the findings, the author supports standardised reporting of radiotherapy QA in line with CONSORT principles.

Radiation Oncology is a fast-moving field which directly develops new technologies to improve patient outcomes. With the advances in radiotherapy technology, clinical trials involving radiotherapy should adopt comprehensive radiotherapy QA and be reported to a consistent standard [36]. Areas of unmet need highlighted by this systematic review include standardisation of OAR outlining, clinical trial endpoint reporting, and mechanisms for the evaluation of IGRT and treatment delivery; this thesis explores the variation in radiotherapy delivery from a QA perspective and proposes radiotherapy reporting metrics based on the CONSORT Statement to promote standardisation of future practice.

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Paper 2: Provision of Organ at Risk Contouring Guidance in UK Radiotherapy Clinical Trials

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Abstract

Introduction

Accurate delineation of organs at risk (OAR) is vital to the radiotherapy planning process. Inaccuracies in OAR delineation arising from imprecise anatomical definitions may impact plan optimisation and risk inappropriate dose delivery to normal tissues. We reviewed the provision of existing OAR contouring guidance in National Institute of Health Research Network (NIHR CRN) portfolio clinical trials and evaluated OAR nomenclature and contouring guidance.

Method

The National Radiotherapy Trials Quality Assurance (RTTQA) Group accessed all recruiting and in setup clinical trials in the NIHR CRN portfolio, which involve radiotherapy Quality Assurance (QA). The OAR nomenclature and contouring guidance were recorded. Twelve expert members of the RTTQA Group provide their expert opinion as to whether each unique OAR description provided optimal information to contour the OAR through a two-round Delphi method with a priori determined threshold for consensus agreement.

Results

Eighty-four clinical trials involving radiotherapy QA were identified as either in recruitment or in setup within the NIHR CRN portfolio. Fifty-nine trials mandated OAR contouring. In total there were four hundred and twelve OAR; one hundred and seventy-one were uniquely named. One hundred and fifty-nine OAR had more than one name associated with a single structure, with the greatest nomenclature variation seen for the femoral head ± neck, the parotid gland, and bowel. The two-round Delphi assessment determined forty-two OAR descriptions as providing optimal contouring guidance.

Conclusion

This report identifies the need for OAR nomenclature and contouring guidance consistency across clinical trials. In response to this report and in conjunction with the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonisation Group (GHG) (https://rtqaharmonization.com), the RTTQA Group is in collaboration with international partners to provide consensus recommendations for OAR delineation in clinical trials.

Introduction

Accurate delineation of organs at risk (OAR) is vital to the radiotherapy planning process [1]. United Kingdom (UK) radiotherapy trials define site-specific OAR within the trial protocol and, where required, the associated radiotherapy guideline document [2]. In practice, the definition accuracy of each OAR varies between tumour-specific trial protocols in terms of nomenclature and anatomical description.

Inaccuracies in OAR delineation arising from imprecise definitions may impact plan optimisation and risk inappropriate dose delivery to normal tissues [3]. Furthermore, in clinical trials, delineation inconsistencies impact radiotherapy dose-reporting, cross-trial comparison of results, and limit the validity of pooled analyses from clinical trial data.

The American Society of Radiation Oncology (ASTRO) Clinical Affairs and Quality Council [4] adopt standardised nomenclature from the reports of Santanam et al [5] and American Association of Physicists in Medicine (AAPM) Task Group 263 [6]. Neither Santanam nor AAPM provide or report on the provision of OAR contouring guidance within clinical trial protocols or radiotherapy guideline documents.

The National Radiotherapy Trials Quality Assurance (RTTQA) Group, centrally funded since 2010, provides radiotherapy quality assurance (QA) for all UK National Institute of Health Research Clinical Research Network (NIHR CRN) portfolio studies, which include a radiotherapy component. To evaluate OAR nomenclature and to achieve consensus on an optimal OAR description, we employed the Delphi method. The Delphi method of consensus building involves anonymised participant response to a formalised question followed by controlled feedback to create group opinion. This approach captures the individual opinions within a geographically dispersed group, minimises the biasing effects of dominant participants and irrelevant communications, and reduces group pressure towards conformity [7].

This report evaluates the provision and extent of OAR contouring guidance in NIHR CRN portfolio studies involving radiotherapy QA and presents a consensus opinion on optimal OAR descriptions.

Materials and Methods

Between the 26th of September 2018 and the 3rd of October 2018, the RTTQA Group accessed all recruiting and in setup clinical trials on the UK NIHR CRN portfolio, which involve radiotherapy QA.

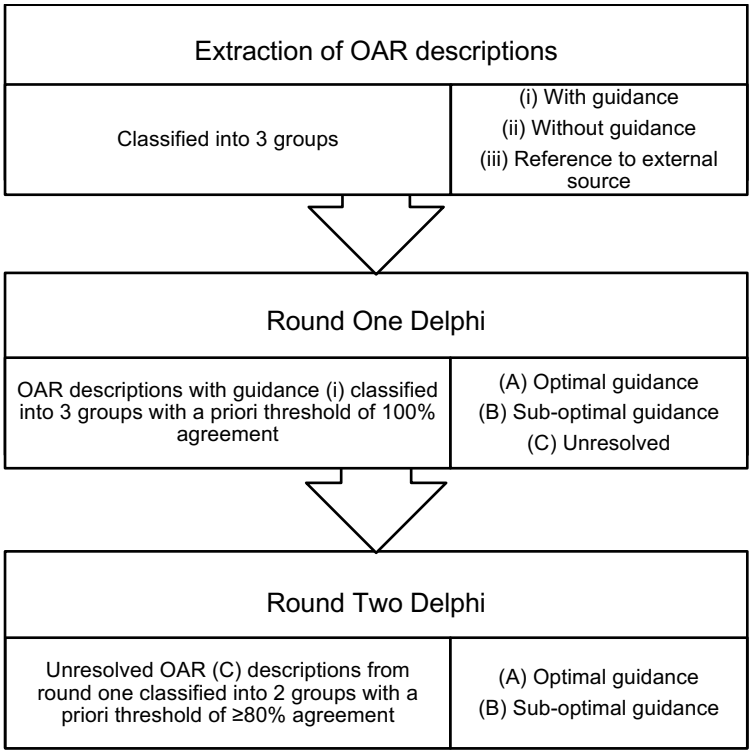
As demonstrated in figure 1, clinical trial protocols and, where provided, the associated radiotherapy guideline documents were reviewed. The OAR nomenclature and contouring guidance were recorded and classified into 3 groups: (i) with guidance, (ii) without guidance, and (iii) guidance referred solely to an external source. The Delphi method was used to evaluate the OAR descriptions in group (i), to establish a consensus opinion on an OAR description.

Twelve members of the RTTQA Group (four clinical oncologists, four therapy radiographers, and four radiotherapy physicists) with expertise in advanced techniques (intensity-modulated radiotherapy (IMRT), dose-intensification, adaptive radiotherapy, stereotactic ablative body radiotherapy (SABR)) and critique of OAR contours across a breadth of tumour sites were invited to provide their expert opinion as to whether each unique OAR description provided optimal information to contour the OAR. A minimum of ten respondents were required for the Delphi method to capture the expertise of the RTTQA Group [8].

In round one, participants were provided with OAR nomenclature and the associated description. Participants were instructed to independently categorise each unique description as providing (A) optimal guidance, or (B) sub-optimal guidance. OAR descriptions which achieved 100% consensus agreement or disagreement as providing optimal or sub-optimal guidance for OAR contouring in round one, were considered resolved and excluded from round two. The remaining OAR descriptions were classified as (C) unresolved and entered round two.

Four weeks later, the same participants were instructed to categorise the unresolved OAR. An a priori threshold of ≥80% agreement was required in round two, for the OAR description to achieve consensus.

Figure 1. Data extraction, classification, and Delphi grouping



Participants were always blinded to the clinical trial source of the OAR descriptions.

Ethical approval was not required when producing this report.

Results

Eighty-four clinical trials involving radiotherapy QA were identified as either recruiting or in setup within the NIHR CRN portfolio. Fifty-nine of these (70.2%) mandated OAR contouring, while the remainder (29.8%) made no reference to OAR in the clinical trial protocol or radiotherapy guideline document. In total, there were 412 OAR descriptions with 64 distinct organ structures across the evaluated clinical trial protocols.

As illustrated in table 1, the most frequent treatment site was the pelvis, with 16 clinical trials mandating 2 – 8 OAR. Breast and pelvis treatment sites had the lowest variation in number of mandated OAR (breast: median 3, range 2 – 4, SD 1; pelvis: median 3, range 2 – 8, SD 1.75). Seven clinical trials involved radiation delivery to a range of anatomical sites; these clinical trials had the largest variation in mandated OAR (median 12, range 8 – 29, SD 7.54). Four of these trials involved SABR as the treatment modality for oligometastatic or oligoprogressive disease; the remaining trials included patients with haematological malignancies or sarcoma.

Table 1. Provision of OAR contouring guidance for 59 clinical trials according to the anatomical site of radiation delivery

Anatomical site	**Brain**	**Head & Neck**	**Thorax**	**Breast**	**Abdomen**	**Pelvis**	**Whole body**
Trials n (%)	8 (13.6)	7 (11.9)	10 (16.9)	5 (8.5)	6 (10.2)	16 (27.1)	7 (11.9)
OAR							
Median	7.5	5	6.5	3	6	3	12
Range	5 – 19	3 – 14	4 – 10	2 – 4	6 – 11	2 – 8	8 – 29
SD	4.7	4	2.02	1	2.04	1.75	7.54

SD = Standard Deviation

Nomenclature

Of the four hundred and twelve OAR, one hundred and seventy-one were uniquely named. One hundred and fifty-nine (93.0%) had more than one structure name with the greatest nomenclature variation seen in the femoral head ± neck, the parotid gland, and the bowel (table 2). In comparison, the bladder structure had only two structure names.

Table 2. Variation in OAR nomenclature

Structure	**Trials (n)**	**Nomenclature variations**
Femoral head ± neck	18	FemHeadNeck_X, Femoral Head_X, Femoral heads, Femoral Heads, Femoral Neck, FemoralHead_X, FemoralHeadNeck, FemoralJoint_X, Femur_Head_X, Right and left femoral heads
Parotid gland	10	Contralateral parotid and Ipsilateral parotid, Ipsilateral and contralateral parotid, Parotid_IL, Parotid_X, Parotid glands
Bladder	16	Bladder, Bladder Wall
Bowel	22	Bowel, Bowel Bag, Bowel_cavity, Gut, Other_Bowel

X, laterality; IL, Ipsilateral

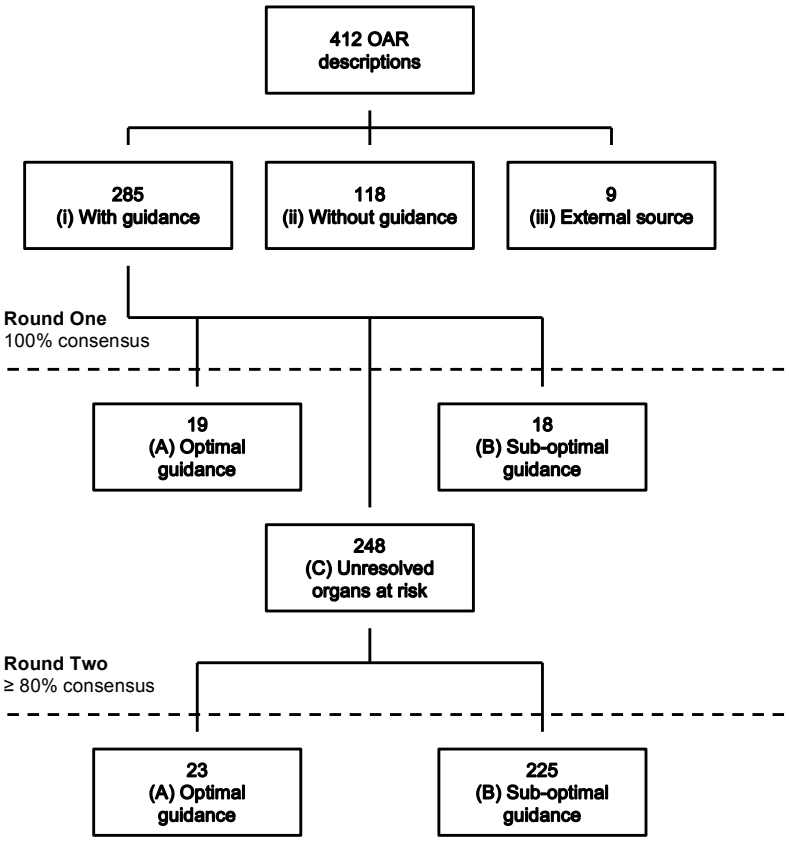
The nomenclature used in two hundred and eleven (51.2%) OAR descriptions was consistent with AAPM TG 263 [6] standardised nomenclature e.g. Femur_Head_L, Parotid_L, Bag_Bowel.

In the one hundred and thirty-one instances where laterality was important to identify the OAR, thirty-eight (29.0%) were named with the suffix left or right, consistent with AAPM TG 263 [6]. Of the remaining ninety-three OAR instances, twenty-two (16.8%) were identified with the prefix contra- or ipsi-: nine in the head and neck (eye, parotid gland), two in the abdomen (kidney), and 11 in the thorax (breast, lung). Seventy-one (54.2%) OAR had no reference to laterality, whether that be left or right, or with the prefix contra- or ipsi-; the majority of these OAR were in the head and neck: brachial plexus, eye, hippocampus, lens, cochlea.

OAR Descriptions

One hundred and eighteen (28.6%) OAR had no associated description or contouring guidance (figure 2); nine (2.2%) had no associated description, but referred to either a pre-existing clinical trial protocol or radiotherapy guideline document (5) or published contouring atlas (4). Two hundred and eighty-five (69.2%) had an associated description and were classified into the (i) with guidance group. Within this group, one hundred and four OAR descriptions included wording directly from either a contouring atlas (34), an existing clinical trial radiotherapy guideline document (35), or published contouring guidance (35).

Figure 2. Schematic of the Delphi Method



Twelve RTTQA Group members were invited to participate in the Delphi. Ten individuals (four clinical oncologists, four therapy radiographers, and two radiotherapy physicists) returned both round one and round two questionnaires.

In round one, all participants agreed nineteen descriptions provided optimal guidance and eighteen descriptions provided sub-optimal guidance for accurate OAR delineation. These OAR descriptions were excluded from round two. Examples are given in table 3.

Round two included the remaining two hundred and forty-eight unresolved OAR descriptions; twenty-three of these met the a priori threshold of ≥80% consensus agreement and therefore were considered to provide optimal guidance to contour the OAR.

Overall, forty-two (14.7%) of UK NIHR CRN portfolio trial OAR descriptions provided optimal contouring guidance. This Delphi assessment deemed two hundred and forty-three (85.3%) OAR descriptions as sub-optimal.

Table 3. Examples of OAR guidance, which achieved 100% consensus, whether optimal or sub-optimal

Organ at risk	**Consensus**	
	Optimal Guidance	**Sub-optimal Guidance**
Bowel	Individual bowel loops visible on relevant levels of the planning scan will be outlined. Outlining will include the small bowel, large bowel and the sigmoid colon down to the level of the rectosigmoid junction. The superior extent should be 2cm beyond the superior extent of the CTV.	Superior limit 2cm above the PTV.
Heart	The heart will be contoured along with the pericardial sac. The superior aspect is defined as the superior aspect of the pulmonary artery and the caudal border should be defined by the lowest part of the left ventricle inferior wall that is distinguishable from the liver.	Outlined to the extent of the pericardial sac. The major blood vessels are excluded.
Lung(s)	The right and left lungs can be contoured separately, but they should be considered as one structure for lung dosimetry. All inflated and collapsed, fibrotic and emphysematous lungs should be contoured, small vessels extending beyond the hilar region should be included; however, hilars and trachea/main bronchus should be excluded.	Both lungs from apices to diaphragm.

Organ-specific OAR varied in their description; the greatest variation is seen between bowel descriptors (table 4).

Table 4. Examples of variation in bowel nomenclature and description

Nomenclature	**Description**
Bowel	Bowel (small bowel and colon) is outlined on all slices from 3cm above the upper limit of the PTV
Bowel	Above rectum, within 15cm of PTV for Cyberknife SBRT and within 4cm PTV for gantry based SBRT and IMRT. Bowel may be outlined as a "bowel bag"
Bowel Bag	Inferiorly from the most inferior small or large bowel loop or above the anorectum, whichever is most inferior. Outline as one continuous structure to include duodenum, small and large bowel. Contour the abdominal contents excluding muscle and bones. Subtract any overlapping non-GI normal structures. Please outline at least 3cm above and below the PTV.
Bowel_cavity	Contouring of the potential bowel cavity volume including 2cm above the superior extent of the PTV. This includes the abdominal contents excluding major vasculature, muscles and bones as well as other pelvic organs (eg bladder, prostate, vagina, uterus). The bowel cavity is not delineated in inferior axial slices where there is no visible small bowel or colon.
Gut	Outline as one continuous structure, like a sac, which includes the stomach, duodenum, small and large bowel down to anus. It is not necessary to outline each loop of bowel individually or to separate the different components.
Other_Bowel	The small and large bowel (including sigmoid colon) will be outlined as a single structure. The entire small and large bowel visible on relevant levels of the planning scan will be outlined as individual bowel loops. The superior extent of outlining should be 2cm beyond the superior extent of the PTV.

OAR descriptions varied in superior and inferior borders; with variation seen in the definition of the brachial plexus, brainstem, heart, and rectum amongst others. Examples are shown in table 5.

Table 5. Examples of variations in superior and inferior OAR borders

Structure	**Superior border**	**Inferior border**
Brachial plexus	C7	2nd rib
	C4	2nd rib
	C7	Axilla
Brainstem	Mesencephalon	Foramen magnum
	Bottom of the lateral ventricles	Tip of the dens of C2
	Ponto-medullary junction	Tip of the dens of C2
Heart	Superior aspect of the pulmonary artery	Lowest part of the left ventricle that is indistinguishable from the liver
	The first slice at which the right and left pulmonary arteries separate	Apex of the heart
	Infundibulum of the right ventricle and apex of both atria	Lowest part of the left ventricle that is indistinguishable from the liver
Rectum	Rectosigmoid junction	Anal margin
	Sigmoid colon	Anal sphincter
	Rectosigmoid junction	Bottom of ischial tuberosities

Discussion

Well-conducted clinical trials inform and shape routine clinical practice. The international radiotherapy community promotes a culture of safety [9]. Consistency in radiotherapy target volume (TV) and OAR terminology enhances safety, reduces variation within clinical trials, and ensures future cross-trial comparisons are appropriate and generalisable to the non-clinical trial population [3]. Additionally, OAR dose-volume parameters correlated with prospective toxicity outcome data collected through clinical trials, are used to define constraints for future radiotherapy planning protocols [10].

This report on the provision of contouring guidance in clinical trials within the UK NIHR CRN portfolio highlights the need for the standardisation of OAR nomenclature along with the associated anatomical descriptions. Eighty-four clinical trial protocols and, where available, radiotherapy guideline documents were reviewed; fifty-nine clinical trial protocols stipulated OAR for radiotherapy treatment planning. There is variation in the number of mandated OAR for each clinical site, with the largest variation seen in clinical trials in which radiotherapy could be delivered to any anatomical site within the body (table 1). Twenty-five clinical trials did not mandate OAR for radiotherapy treatment planning. The reasons for clinical trial protocols not stipulating OAR were not investigated as part of this report but is an area for future research. Clinical trials which elected not to refer to OAR are speculated to be either due to the lack of impact of toxicity upon the trial endpoint(s) or that the radiotherapy dose prescription was below established OAR dose constraints.

Four hundred and twelve individual OAR descriptions were reviewed. Of the uniquely named OAR, 93% had more than one identifier, with approximately half (51.2%) of the nomenclature consistent with AAPM TG 263 [6] recommendations. On review of the individual descriptions and as a result of the two-round Delphi, the RTTQA Group consensus opinion deemed 42 (14.7%) OAR clinical trial descriptions as providing optimal guidance for contouring. The discrimination for OAR descriptions providing optimal guidance is subjective. In the absence of robust guidance, this two-round Delphi assessment, performed by expert members of a multi-professional radiotherapy QA group provides insight into current provision. OAR descriptions deemed optimal included superior and inferior organ contouring limits with defined anatomical landmarks, inclusion and exclusion structures and, where appropriate, recommendations on imaging modality and windowing. These parameters should be specified when defining an OAR.

The ASTRO Clinical Affairs and Quality Council [4] published guidance standardising which OAR are contoured for each disease site. Although not prescriptive or exhaustive, the guidance is instructive and incorporation into OAR contouring recommendations should be considered to combat the variation seen in the number of OAR in use (table 1). Standardisation of radiotherapy practice is also recommended in the 2019 National Health Service (NHS) England Modernising Radiotherapy Services Consultation and subsequent Radiotherapy Service Specification Report. Both documents outline working arrangements between the eleven newly formulated NHS England radiotherapy networks [11]. The service specifications include improving access to modern, advanced, and innovative radiotherapy techniques; reducing variation in quality by adopting best practice protocols; and increasing participation in research and clinical trials by 15% over 3 years. Standardisation of terminology and

participation in multi-centre clinical trials improves departmental workflow, supports communication and collaboration between networks, and enables the implementation of advanced techniques [12]. The benefit of a comprehensive clinical trial QA programme extends to the research activities of staff, impacts local radiotherapy facilities, and ultimately improves treatment for non-clinical trial patients [13-15].

The approach used to minimise OAR contouring variation and the impact on clinical trial endpoints and the individual patient vary. The RTTQA Group implements a stepwise QA process of benchmark, prospective, and retrospective case review, which monitors and capture variation from the clinical trial protocol. Pre-trial benchmark QA identifies major discrepancies or misinterpretations of the trial protocol or radiotherapy guideline document before centres are open to recruitment. On trial prospective case review monitors variation from protocol and enables corrective action before radiotherapy delivery. Timely retrospective review monitors ongoing adherence to protocol. This stepwise QA review process, with active feedback to clinical oncologists, radiotherapy physicists, and therapy radiographers, aims to limit the impact of variation in OAR contouring on clinical trial endpoints.

Variation in TV and OAR delineation is recognised [16-20]. In clinical practice, over- and under-contouring may impact treatment plan optimisation and potentially limit the dose delivered to the TV or underestimate the dose received by the OAR respectively [20]. Evaluation of the impact of the variation in organ-specific OAR descriptions is beyond the scope of this report. Imprecise OAR definitions providing poor contouring guidance may result in the wider interpretation of contouring guidance and subsequently increase contour variation. Overall, forty (9.7%) OAR descriptions referred to a pre-existing clinical trial protocol or radiotherapy guideline document, thirty-eight (9.2%) referred to a contouring atlas, and thirty-five (8.5%) referred to published contouring guidance. Reference to pre-existing clinical trial protocols should be avoided, as normal tissue contouring atlases are constantly refined so that guidance remains contemporary and clinically relevant [21].

Discrepancies in organ-specific OAR superior and inferior border descriptions exist, seen in the brachial plexus, brainstem, heart, and rectum (table 5). Large variations such as those seen in bowel descriptions (table 4) make cross-trial comparisons and extrapolation of dose constraint findings from the trial setting to the non-trial patient population challenging [22]. Pre-trial benchmark QA of heart contouring in the 2008-2013 CONVERT trial [23] (NCT00433563) demonstrated the heart was not outlined according to the protocol in 79.7% of cases [24]. The on-trial prospective review was not performed as part of the QA programme for this trial. Retrospective application of the gold-standard heart contours to fifty recruited CONVERT patients revealed the heart was not outlined according to the protocol in 76% of cases [25]. In both the pre-trial and retrospective QA reviews, the superior border of the heart was too low, resulting in a median increase of heart $V_{5\%}$ and $V_{30\%}$ in 77.3% and 82.1% of evaluated plans respectively [25]. The increase in $V_{5\%}$ and $V_{30\%}$ was reflective of radiation delivery to the un-contoured superior aspect of the organ. The long-term effects of heart irradiation are not clear. Big data analyses imply dose delivered to superior heart substructures may impact patient survival [26] and residual shifts towards the mediastinum have a negative impact on patient outcome [27]. While translational data is awaited, consistent OAR delineation, accurate OAR dosimetry, and retrospective dosimetric analysis will, in part, identify the true long-term effects of heart irradiation. Furthermore, individualised radiotherapy delivered

through dose intensification is increasingly incorporated into the clinical trial design [28-30]. These radiotherapy plans are often optimised *isotoxically*; therefore, precise OAR delineation enables optimal dose delivery and avoids inappropriate “dose-dumping” to anatomical regions that are not defined during the planning process.

In response to this report and in conjunction with the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonisation Group (GHG) (https://rtqaharmonization.com), the RTTQA Group is in collaboration with international partners European Organisation for Research and Treatment of Cancer (EORTC), Imaging and Radiation Oncology Core (IROC-NRG), Japan Clinical Oncology Group (JCOG), and Trans-Tasman Radiation Oncology Group (TROG) in reviewing OAR definitions, intending to provide a comprehensive resource for delineation of OAR in clinical trials.

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Paper 3: Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group Consensus Guidelines

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Abstract

Introduction

The Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG) is a collaborative group of Radiation Therapy Quality Assurance (RTQA) Groups harmonizing and improving RTQA for multi-institutional clinical trials. The objective of the GHG OAR Working Group was to unify OAR contouring guidance across RTQA groups by compiling a single reference list of OARs in line with AAPM TG 263 and ASTRO, together with peer-reviewed, anatomically defined contouring guidance for integration into clinical trial protocols independent of the radiation therapy delivery technique.

Methods

The GHG OAR multi-professional Working Group comprised of 22 members from 6 international RTQA Groups and affiliated organisations conducted the work in 3 stages: 1) Clinical trial documentation review and identification of structures of interest 2) Review of existing contouring guidance and survey of proposed OAR contouring guidance 3) Review of survey feedback with recommendations for contouring guidance with standardised OAR nomenclature.

Results

157 clinical trials were examined; 222 OAR structures were identified. Duplicates, non-anatomical, non-specific, structures with more specific alternative nomenclature, and structures identified by one RTQA group were excluded leaving 58 structures of interest. 6 OAR descriptions were accepted with no amendments, 41 required minor amendments, 6 major amendments, 20 developed as a result of feedback, and 5 structures excluded in response to feedback. The final GHG consensus guidance includes 73 OARs with peer-reviewed descriptions.

Conclusion

We provide OAR descriptions with nomenclature for use in clinical trials. A more uniform dataset supports the delivery of clinically relevant and valid conclusions from clinical trials.

Introduction

Clinical research in radiation therapy is conducted two-fold: through analysis of high-level evidence generated from well-conducted prospective clinical trials, or retrospective evaluation of real-world data extracted from big data repositories [1,2]. The dosimetric, toxicity, and endpoint reporting parameters from these datasets inform the development of normal tissue complication probability (NTCP) models and define organ at risk (OAR) constraints for future radiation therapy planning protocols [3]. In these approaches, variability in the reporting standards of OAR-specific metrics reduces the ability to draw robust conclusions and impacts the validity of the recommendations [4-6].

Data pooling from institutions is impeded by inconsistencies in nomenclature [1,7-9]. Inconsistency in contouring guidance for OARs may increase contour variability [10]. Consistency and accuracy in structure nomenclature and contouring guidance not only minimizes variation but also improves departmental workflow and safety [9,11-14], with a positive impact on clinician peer-review [9]. Miscommunication and lack of well-defined operating procedures have been highlighted as key causative factors in the origin of radiation incidents, particularly during transfers of care [11-16]. Specific target volume (TV) and OAR radiation therapy errors and near misses were seen in 80/1565 incidents voluntarily reported to Public Health England (PHE) from August – November 2019 [16].

Standardisation of terminology facilitates data pooling, scripting, and automation of reports; whether that is for departmental quality assurance (QA), data capture in national registries, or wider inter-institutional radiation therapy research. Data pooling and data sharing agreements between investigators and institutions make research more efficient and increase the value of the initial clinical trial investment [3]. Standardisation of data allows the robust derivation of dose constraints and the development of dose-response relationship models [1-7].

The transition from two-dimensional radiation therapy (2D RT) treatment planning and delivery to volumetric three-dimensional conformal radiation therapy (3D CRT), inverse-planned intensity-modulated radiation therapy (IMRT) and proton beam radiation therapy (PBT) have enabled dose-intensification to the TV while sparing dose delivered to the OARs [17,18]. Inverse-planned radiation therapy is driven by user-defined planning objectives. Under-contouring of the OAR leads to inferior OAR sparing [19] with potential for increased or unanticipated toxicity; over-contouring could result in unnecessary dose compromises to the TV. Given the growing use of sequential and multi-modality anti-cancer therapies, inaccuracies in OAR contouring and hence plan optimisation risk inappropriate dose delivery to an OAR, with greater potential for “dose-dumping” in normal tissues and subsequent unanticipated toxicity during a patient’s treatment pathway.

The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) review proposed OAR tolerances and defined OAR constraints; with the acknowledgement that progress in radiation oncology accelerates only when we understand how treatment decisions impact patient outcomes [1,3].

The need for consistent language and terminology has been highlighted, as well as the positive impact of consistency on process improvement and workflow management infrastructure [9]. Since inception in 1925, the International Commission on Radiation Units and Measurements (ICRU) has developed and implemented internationally accepted recommendations, enabling the multi-professional radiation oncology team to use standardised target volume and dose reporting nomenclature [20]. The international radiation therapy community continually promotes a culture of safety. Organisations including, but not limited to, the Pennsylvania Patient Safety Authority [11], Radiation Oncology Safety and Education Information System (ROSEIS) [13], Radiation Oncology Incident Learning System (RO-ILS) [15], PHE [16], and American Society of Radiation Oncology (ASTRO) [14] report inaccurate and incomplete communication as causative themes in the origin of radiation incidents [16].

The American Association of Physicists in Medicine (AAPM) has been a driving force for the implementation of improvements in patient safety. AAPM task group (TG) reports 113 [21] and 263 [2] both recommend the use of standardised nomenclature, with the latter publishing standardized TV and OAR nomenclature, reducing variability in naming and enabling multi-vendor platforms to interact easily.

The ASTRO Clinical Affairs and Quality Council provides guidance on which OARs should be contoured per anatomical treatment site, defining those essential OARs that consensus *recommends* regardless of treatment scenario, thus providing a basic minimum standard of care, and those OARs which should be *considered* dependent on the clinical situation for contouring in anatomical site-specific clinical trials [18].

The National Radiotherapy Trials Quality Assurance (RTTQA) Group reported on the provision of OAR-specific contouring guidance in the United Kingdom (UK) National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio studies [10]. Variation was seen in OAR nomenclature and in the OARs contoured across anatomical site-specific clinical trials. The study found that 71.0% of bilateral OAR were not denoted with laterality and 85.3% of OAR-specific descriptions provided sub-optimal guidance for contouring [10]. Implementation of standardised OAR nomenclature and contouring guidance will address miscommunication between multi-professional teams caused by lack of confidence and ambiguity in structure nomenclature.

The Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG) (https://rtqaharmonization.com) is a collaborative member group of radiation therapy QA organisations: European Organisation for Research and Treatment of Cancer (EORTC), Imaging and Radiation Oncology Core (IROC), Japan Clinical Oncology Group (JCOG), the National Radiotherapy Trials Quality Assurance (RTTQA) Group, and Trans Tasman Radiation Oncology Group (TROG). The GHG is also associated with the following observer groups: Australian Clinical Dosimetry Service (ACDS), Canadian Cancer Trials Group (CCTG), European Society for Radiotherapy and Oncology (ESTRO), International Atomic Energy Agency (IAEA), National Physical Laboratory (NPL), Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials (QUARTET), and the Radiation Dosimetry Services (RDS).

The objective of the GHG is to enhance the quality of radiation therapy in multi-institutional clinical trials through harmonisation of QA to reduce ambiguity in trial reporting, interpretation, and translation of clinical outcomes. The GHG identified an unmet need for the standardisation of OAR nomenclature along with peer-reviewed contouring guidance for use in clinical trials involving adult patients with a radiation therapy component.

The GHG OAR Working Group is a multi-professional collaborative initiative, formed of twenty-two members from six international radiation therapy QA groups and affiliated organisations, assuring broad representation across the radiation therapy community.

The objective of the GHG OAR Working Group was to unify OAR contouring guidance across all the QA groups by compiling a single reference list of OARs, together with peer-reviewed, anatomically defined contouring guidance for integration into future clinical trial protocols independent of the radiation therapy delivery technique.

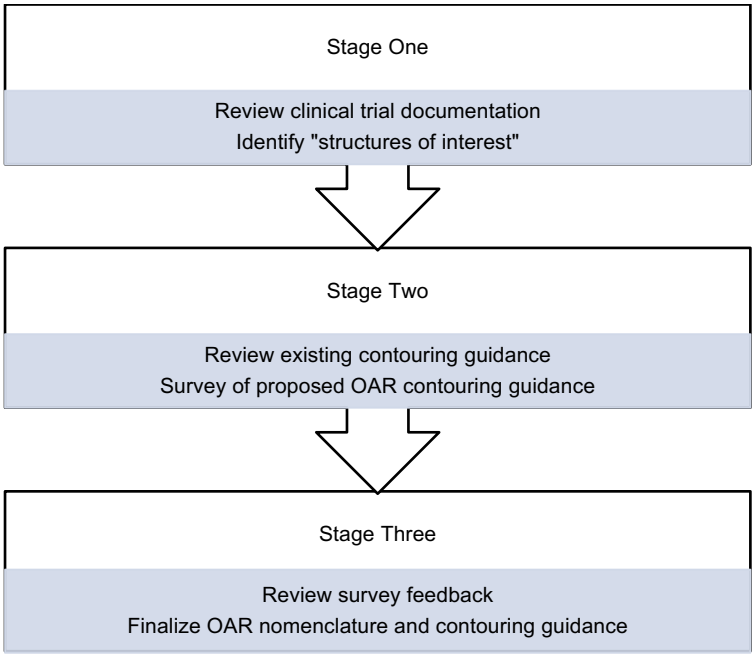
Materials and Methods

The GHG OAR Working Group conducted the work in three stages (figure 1).

Stage One

Between August and November 2018, representatives of the EORTC, IROC, RTTQA, and TROG QA groups reviewed documentation from clinical trials with a radiation therapy QA component, that were either in recruitment or in setup. Data collected included: the date of clinical trial opening, radiation therapy technique, anatomical site of radiation therapy delivery, OAR nomenclature, and associated contouring guidance.

Figure 1. Work stages one, two, and three



Following the application of standardised nomenclature [2], OARs in use were collated and combined with those OARs identified as recommended and considered for contouring from the ASTRO Clinical Affairs and Quality Council guidance [18]. Duplicates, non-anatomical, non-specific structures, and structures with more specific alternatives were excluded. Structures identified by two or more radiation therapy QA groups were included, thus creating the “structures of interest”.

Stage Two

Contouring guidance associated with each structure of interest were collated, whether from the clinical trial protocol, an external reference, or a pre-existing alternative clinical trial document. The contouring guidance elements were reviewed according to GHG OAR Working Group's pre-defined objectives (figure 2) and applied to each structure of interest.

Proposed contouring guidance with OAR nomenclature consistent with AAPM TG 263 [2] were created and disseminated to each of the QA groups, who then distributed the proposed nomenclature and contouring guidance to radiation therapy clinical trial investigators within each respective QA network. Investigators were selected by each QA group as those who were most active within radiation oncology clinical trials; two investigators were selected with experience within each respective tumour site. The investigators participating in the survey were instructed to provide written free-text feedback on the proposed OAR contouring guidance.

Figure 2. Pre-defined objectives for the development of the GHG OAR Working Group consensus contouring guidance

1. One name and one description for each OAR[$]
2. OARs are anatomically defined; the same description should be used for all treatment scenarios
3. OAR contouring guidance applies to adults with standard anatomy
4. Laterality is defined on all relevant OARs
5. Contouring guidance incorporates anatomical landmarks and border* definitions. Cranial and caudal terminology used in preference to superior and inferior so guidance is unambiguous regardless of patient positioning
6. Optimal windowing and imaging modality are incorporated into contouring guidance where relevant
7. The clinical trial protocol will define
    a. patient preparation and use of contrast
    b. patient positioning and immobilisation
    c. motion management technique(s)
    d. the extent to which the OAR will be delineated beyond the limit of the PTV
8. Consider[$] addition of ~ suffix to denote contouring of a partial structure i.e. SpinalCord~

[$]consistent with AAPM TG 263 recommendation; *border definitions: cranial, caudal, medial, lateral, anterior, posterior; OAR, Organ at risk; PTV, Planning Target Volume

Stage Three

Anonymised feedback from surveyed individuals was centrally reviewed by the GHG OAR Working Group, reviewed against the pre-defined objectives, and incorporated into consensus OAR contouring guidance. The proposed OAR guidelines were either; accepted, accepted with minor amendment, or accepted with a major amendment. Major amendment involved complete revision of the OAR description including modification of borders, whereas minor amendment involved the inclusion of omitted landmarks, refinement of borders, or adjustment of sentence structure for user clarity.

The central review process allowed exclusion of OARs and the development of new OAR nomenclature (if not available in AAPM TG 263) and contouring guidance in response to the survey feedback received from the international clinical community.

Ethical approval was not required when producing this consensus report.

Results

One hundred and fifty-seven clinical trials including radiation therapy were identified from the QA groups as recruiting or in setup: fourteen (8.9%) from EORTC, thirty-eight (24.2%) from IROC, eighty-four (53.5%) from RTTQA, and twenty-one (13.4%) from TROG.

The earliest clinical trial included in this analysis opened in November 2004. Overall, two clinical trials included 2D RT, sixty-one included 3D CRT, and one hundred and three included IMRT as the permitted radiation therapy technique(s). Stereotactic body radiation therapy (SBRT), stereotactic radiosurgery (SRS), and PBT were included in the randomisation(s) in twenty-nine, three, and seven clinical trials, respectively.

Table 1. Anatomical treatment site and permitted radiation therapy delivery technique(s)

	CNS	H&N	Thorax	Abdomen	Pelvis	Any*
2D RT						2
BT					1	
3D CRT	11	3	16	9	12	10
IMRT	15	24	20	9	31	4
SBRT			6	6	5	12
SRS	3					
PBT	2	1	2	2		

*Radiation therapy delivery to any anatomical site; BT, Brachytherapy; CNS, Central Nervous System; H&N, Head and Neck; IMRT, Intensity-Modulated Radiation Therapy; PBT, Proton Beam Radiation Therapy; SBRT, Stereotactic Body Radiation Therapy; SRS, Stereotactic Radiosurgery; 2D RT, Two-dimensional Radiation Therapy; 3D CRT, Three-Dimensional Conformal Radiation Therapy

Two hundred and six instances of OARs were identified from the clinical trial documentation. When combined with the recommended and considered ASTRO structures, 16 additional structures were highlighted as listed within ASTRO guidance, but not identified within clinical trial documentation. Following the exclusion of duplicates (table 2), 117 distinct structures remained. Exclusion of non-anatomical, non-specific structures, structures with more specific alternatives, and structures specified in clinical trials monitored by one or fewer radiation therapy QA groups resulted in 58 structures of interest.

Table 2. Examples of excluded structures

Reason for exclusion	Structure	Comment
Non-anatomical	Bag_ostomy	Ostomy bag
	Pacemaker	
Non-specific	Bronchus_Adj	Bronchus adjacent to PTV
	RVR	Remaining volume at risk
More specific alternative nomenclature	Bronchus_Main	Incorporated into Trachea and Bronchus_Prox
	Bronchus_L/R	
	Reprod^Female	Encompassing structure of the ovary, uterus, and vagina
Identified by one radiation therapy QA group	Ear_L/R	
	Liver^Ves	Liver vessels

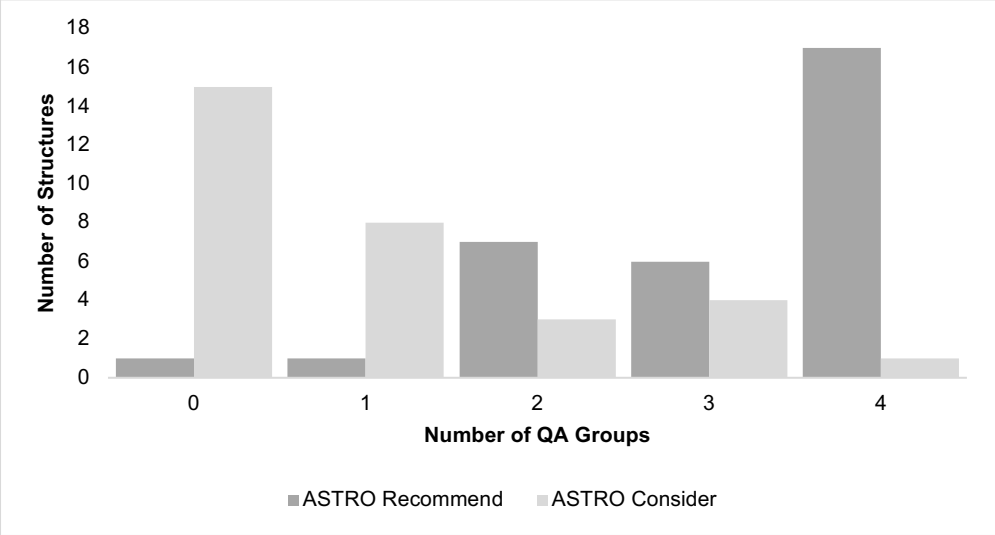
Structures of interest

Of the fifty-eight structures of interest, 39 (67.2%) were consistent with the ASTRO recommended and considered OAR structures [18]. Sixteen structures were identified for contouring in the ASTRO guidance, but were not included within clinical trial documentation from the QA groups. The cauda equina was the only structure (figure 3) listed as recommended for contouring by ASTRO, which was not described in clinical trial documentation across the QA groups.

The brachial plexus was identified by all four radiation therapy QA groups for contouring but recognised as a structure only to be considered for contouring by ASTRO for treatment involving the cervical spine, nasopharynx, oropharynx, larynx, hypopharynx, cervical oesophagus, neck, breast, supraclavicular fossa, axilla, or lung.

Of the thirty-two ASTRO recommended structures, thirty (93.8%) were identified in trials monitored by two or more QA groups; seventeen structures (53.1%) were identified in trials monitored by all four QA groups (figure 3). The ASTRO considered structures of the breast, chest wall, great vessels, and trachea were identified by three QA groups; genitals, hippocampus, and ovary were identified by two QA groups.

Figure 3. QA Groups identifying each ASTRO structure

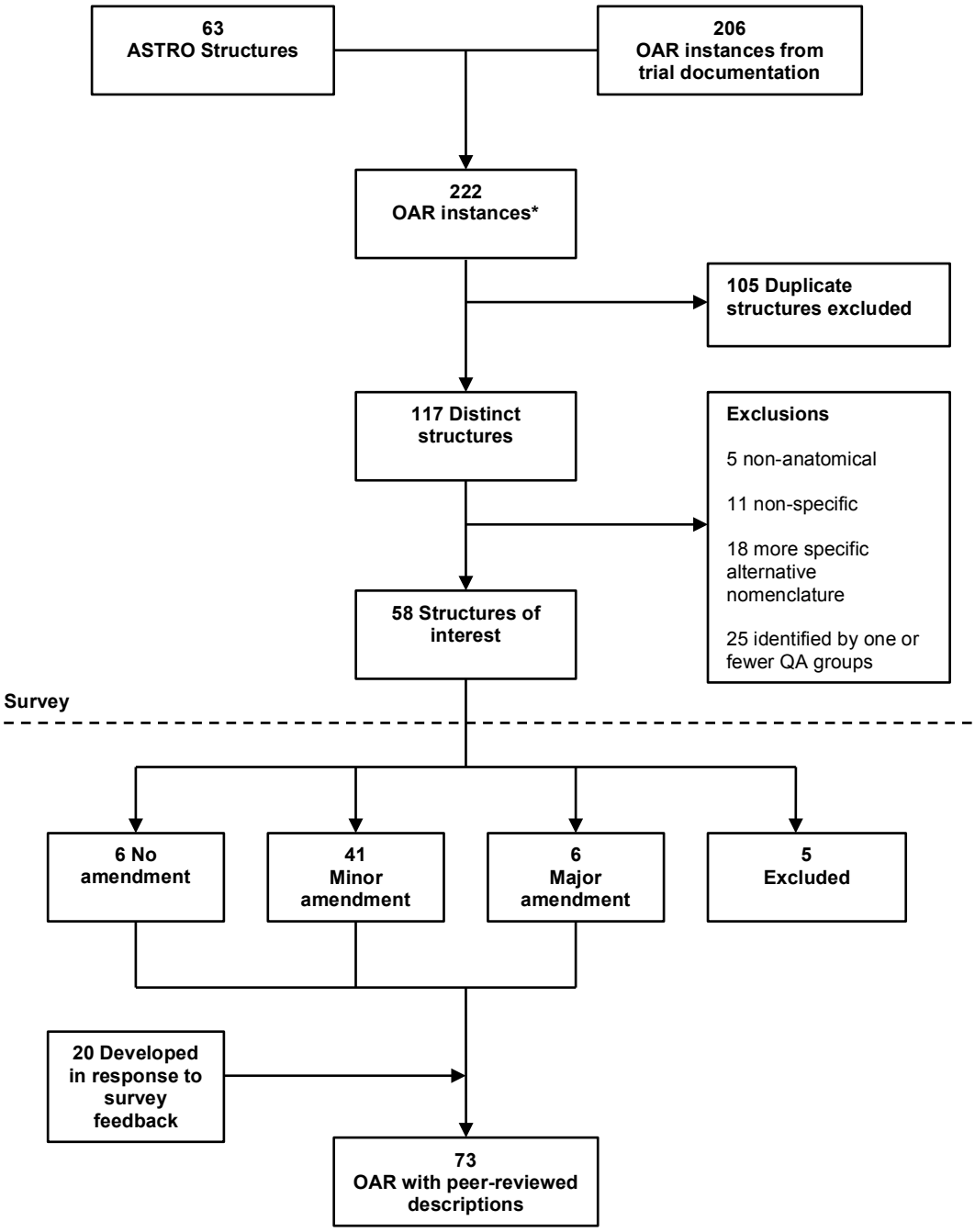


Survey

Forty-one radiation oncologists and six radiation therapists (RTT) from thirty-eight institutions across fifteen countries participated in the survey and commented on the fifty-eight structures of interest. The mean number of responses per OAR was 17.72 (IQR 14 – 21); the surveyed participants varied by specialist site: nine gastrointestinal and head and neck malignancies respectively, seven lung, six breast, central nervous system, and urological malignancies respectively, five sarcoma, and four gynae-oncology.

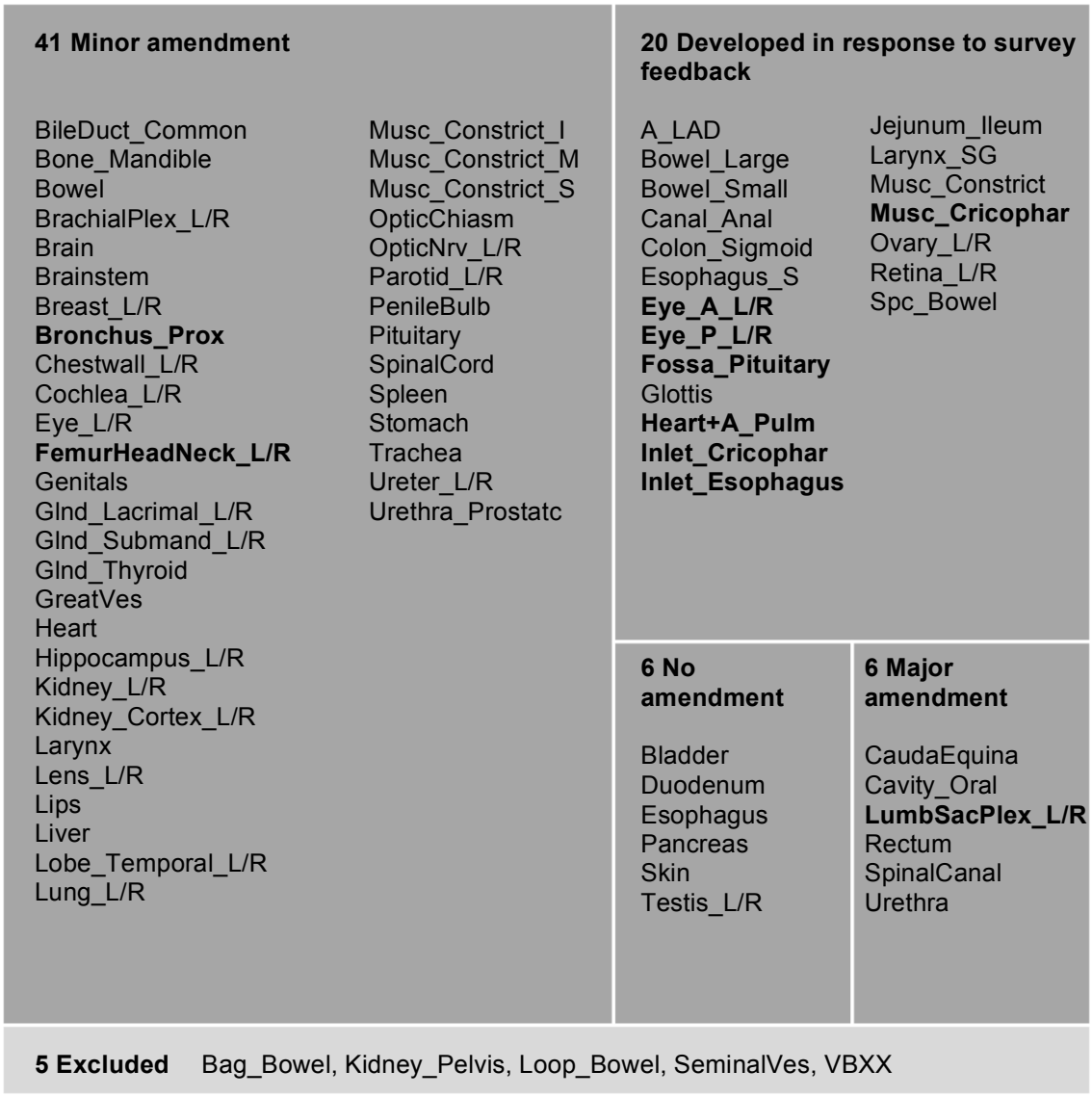
On review of survey responses, six OAR descriptions were accepted with no amendments, forty-one were accepted with minor amendments, and six underwent major amendment (figure 4). The existing nomenclature choices within AAPM TG 263 did not fulfil requirements for three of the surveyed structures, and so new nomenclature were created: *Bronchus_Prox, FemurHeadNeck_L/R,* and *LumbsacPlexs (LumbSacPlex_L/R* with laterality designation). Twenty descriptions were developed in response to survey feedback (figure 5), seven of which did not have standardised nomenclature pre-defined by AAPM TG 263 [2].

Figure 4. OAR description survey and feedback responses



*Includes 206 OAR instances and 16 OAR structures listed within ASTRO [18] consensus guidance, which did not appear in clinical trial documentation

Figure 5. GHG consensus OAR



Treemap displaying the 73 GHG consensus OAR in dark grey and 5 excluded OAR in light grey, with classifications of no amendment, minor amendment, major amendment, and developed in response to survey feedback. Structures in bold denote nomenclature not pre-existing within AAPM TG 263

Heart

The description of the cranial border of the heart differed between clinical trials. Six landmarks for the cranial border are in use: superior aspect of the pulmonary artery, aorta-pulmonary window, origin of the ascending aorta, inferior to the left pulmonary artery, point at which the pulmonary trunk and right pulmonary artery are seen as separate structures, and the infundibulum of the right ventricle, respectively. The uppermost cranial borders were predominantly used in clinical trials pertaining to fractionated radical radiation therapy for lung cancer or SBRT to the lung for either primary lung cancer or oligo-progressive disease, or oligometastatic

disease from any primary cancer. The point at which the pulmonary trunk and right pulmonary artery were seen as separate structures was used in clinical trials for lymphoma and primary tumours arising from the breast.

AAPM TG report 101 [22] and UK Consensus on Normal Tissue Dose Constraints [23] recommend the toxicity endpoint for heart irradiation in the setting of SBRT is ≥ grade three pericarditis. To ensure the pericardium is encompassed fully, in the context of SBRT, the cranial heart border is extended to the top of the pulmonary artery to include the attachment of the fibrous pericardium at the adventitia of the great vessels [24].

Considering the information above, surveyed investigators had a preference for two of the cranial heart borders described: the superior aspect of the pulmonary artery and the point at which the pulmonary trunk and right pulmonary artery are seen as separate structures. In response to survey feedback and as an exception to the pre-defined objectives (figure 2), two distinct heart structures are defined within the GHG OAR consensus guidance, *Heart+A_Pulm* and *Heart*.

Skin

The skin structure was highlighted in clinical trial documentation or external references as “should be outlined”, “exclude”, or “include”; either in support of the radiation therapy planning and optimisation process or as a distinct OAR. This request was seldom accompanied by contouring guidance. A review of clinical and dosimetric evaluation studies demonstrates variation in practice [25-33]. Recommended skin thickness for contouring from clinical trial documentation ranged from 3 – 6mm; anatomically the thickness of the skin is dependent on the location, ranging from 1.5 – 5mm [34]. Contouring guidance specifies the skin structure as a 5mm inner rind automatically created from the external contour [35]; GHG OAR consensus guidance reflects the published contouring guidance, with the caveat that skin thickness will vary depending on region of interest.

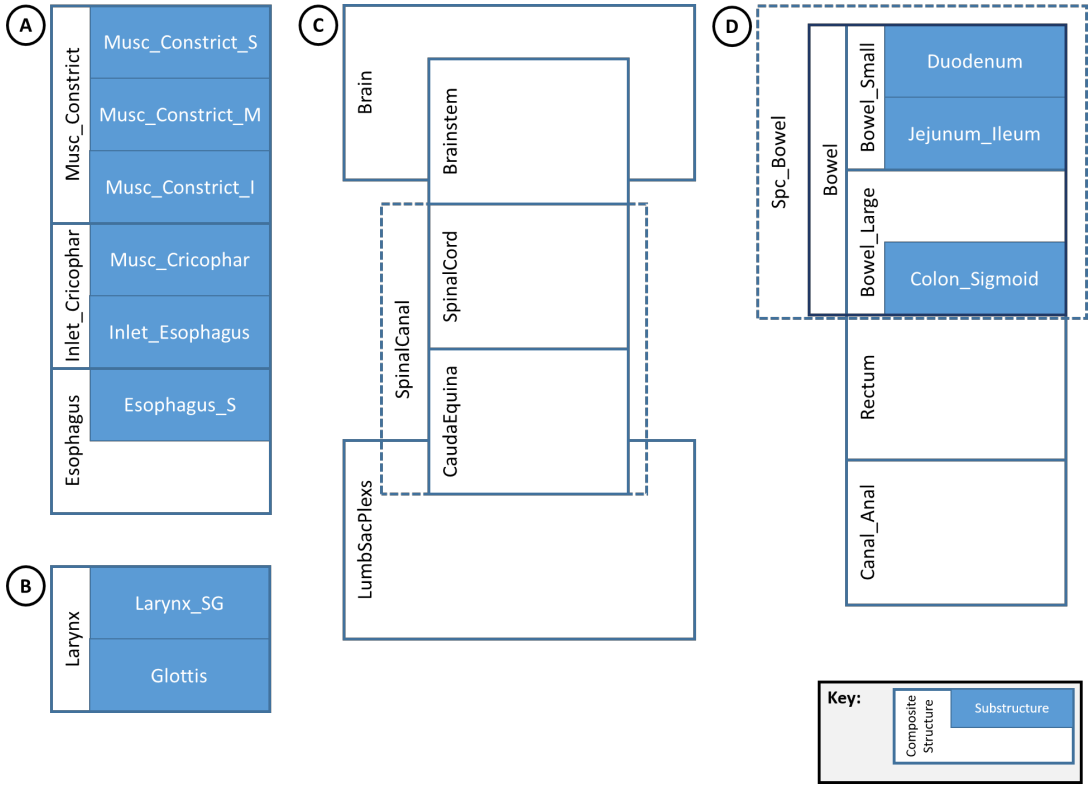
Bowel

The survey distributed to investigators described the bowel as an encompassing structure from the pylorus to the recto-sigmoid junction; the composite structure was reflective of the current contouring practice [10]. The overwhelming feedback from the radiation therapy community was to allow the bowel to be contoured as individual substructures, and so *Jejunum_Ileum, Bowel_Small, Bowel_Large, Colon_Sigmoid,* and *Canal_Anal* were defined, whilst retaining the original *Duodenum* and *Bowel* structure. Investigators are encouraged to choose the most appropriate structures to contour within a given treatment protocol.

Bag_Bowel nomenclature was excluded in favour of *Spc_Bowel* as the nomenclature for the former was inconsistent with the associated contouring guidance [36].

The schematic (figure 6) demonstrates the relationship between composite e.g. *Bowel* and individual substructures of the neck, central nervous system, and sub-diaphragmatic gastro-intestinal tract e.g. *Jejunum_Ileum, Colon_Sigmoid*.

Figure 6. Relationship between composite and individual substructures



A, swallowing structures of the neck; B, laryngeal structures; C, the central nervous system; D, the sub-diaphragmatic gastrointestinal tract

New nomenclature

The GHG OAR Working Group adopted AAPM TG 263 [2] recommendations as the nomenclature standard for this work. The existing nomenclature choices did not fulfil requirements for ten structures; the GHG OAR central reviewers established new nomenclature to align with the currently contoured OAR (table 3).

Table 3. New nomenclature and AAPM TG 263 anatomic group

	AAPM TG 263 Anatomic Group	New Nomenclature	OAR
1	Eye	Eye_A_L Eye_A_R	Anterior segment of the eye
2	Eye	Eye_P_L Eye_P_R	Posterior segment of the eye
3	Head & Neck	Fossa_Pituitary	Pituitary fossa
4	Head & Neck	Inlet_Cricophar	Cricopharyngeal inlet
5	Head & Neck	Inlet_Esophagus	Oesophageal inlet
6	Head & Neck	Musc_Cricophar	Cricopharyngeal muscle
7	Thorax	Bronchus_Prox	Proximal bronchial tree
8	Thorax	Heart+A_Pulm	Heart (extended cranial border)
9	Pelvis	FemurHeadNeck_L FemurHeadNeck_R	Femoral head and neck
10	Pelvis	LumbSacPlex_L LumbSacPlex_R LumbSacPlexs	Lumbar-sacral plexus with laterality, bilateral lumbar-sacral plexus

GHG consensus guidance on seventy-three OARs, with standardised nomenclature and peer-reviewed descriptions are detailed in the appendix with an example of implementation of this consensus guidance.

Discussion

With the advances in the precision and delivery of radiation therapy, the importance of accurate and consistent OAR delineation cannot be understated. This GHG OAR Working Group report from an international collaborative network of radiation therapy QA groups provides consensus guidance on the OAR descriptions and nomenclature for use in clinical trials, intending to promote consistency in OAR contouring and dosimetric reporting.

Seventy-three OARs have been defined by the GHG OAR Working Group; 48 (65.8%) are included in the ASTRO Clinical Affairs and Quality Council guidance [18]. Thirty (93.8%) of the ASTRO recommended structures were identified by two or more QA groups; seventeen structures (53.1%) were identified by the four QA groups (figure 3), thereby validating the consensus guidance and OAR contouring recommendation provided by ASTRO [18].

Six OAR descriptions underwent major amendments following review of survey feedback (figure 5); the rectum, a commonly contoured OAR in urological and gynaecological clinical trials, was one such structure. Existing rectal contouring guidance varied in the cranial and caudal border, with the use of the ischial tuberosities as a bone surrogate for the caudal border [10]. With the move away from 2D orthogonal radiation therapy planning, it is inaccurate to identify soft tissue structures based on variably positioned bone surrogates, the GHG OAR consensus guidance identifies the levator muscles, the puborectalis sling, and the disappearance of perirectal fat as landmarks for the caudal rectal border.

Five OARs were excluded in response to survey feedback; reasons for exclusion were the incorporation of the OAR into alternative nomenclature or survey respondents deeming the structure as a TV as opposed to an OAR.

New OAR nomenclature was created for ten previously un-defined structures (table 3). For clarity, the femoral head and neck structure is renamed as *FemurHeadNeck_L/R,* the *Cricopharyngeus* structure is renamed as the encompassing *Inlet_Cricophar* with the division to the substructures *Musc_Cricophar* and *Inlet_Esophagus* to discriminate between the muscle and inlet components (figure 6). The eye is subdivided into anterior and posterior components with nomenclature consistent with AAPM TG 263 [2] guidance. The *Fossa_Pituitary* defines the inner bony limits of the sella turcica, which in clinical practice is used as an alternative structure for the *Pituitary* gland. The *Bronchus_Prox* describes the proximal bronchial tree, a well-established structure when delivering SBRT to the thorax. *LumbSacPlexs* replaces *SacralPlex*, as established contouring guidance is available for the former.

The GHG OAR Working Group pre-specified objectives for the development of consensus OAR descriptions (figure 2). One name and one description should be used for each OAR. The GHG OAR Working Group was unable to meet this objective for the heart structure due to the variation in contouring guidance across clinical trials. As an exception, the GHG OAR Working Group has provided two heart OAR descriptions with distinct

nomenclature: *Heart+A_Pulm* and *Heart*. Clinical trial protocols and investigators must be clear on which heart contour is used within the respective clinical trial and use the appropriate nomenclature.

The heart as an OAR is of increasing importance. Historical series of Hodgkin's Lymphoma survivors quantify the risk of heart toxicity following large-field mediastinal radiation therapy [37,38]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) review of Surveillance Epidemiology and End Results (SEER) cancer registries identified an excess of cardiac deaths following left-sided versus right-sided 2D planned tangential breast radiation therapy (cardiac mortality ratio 1.58 95% CI 1.29 – 1.95 p=0.03) [39]. In the context of contemporary 3D planned radical radiation therapy delivered in the treatment of non-small cell lung cancer and oesophageal cancer, big-data analyses imply residual shifts towards the mediastinum [40] and dose to the base of the heart structure [41] negatively impact overall survival. With the increasing awareness of cardiac toxicity and the clinical application of SABR for refractory ventricular tachycardia,[42] the GHG OAR Working Group anticipates dose constraints to heart substructures: the ventricles, atria, valves, and conduction pathways [41-43] to be prospectively evaluated in forthcoming clinical trials.

The RTTQA Group identified the lack of OAR laterality in 54.2% of instances of relevant nomenclature within United Kingdom clinical trials, the predominance of these OAR were within the head and neck anatomical site [10]. AAPM TG 263 recognizes the inconsistent approach when designating OAR laterality and recommends the use of the suffix _L or _R following the primary structure name [2]. The GHG OAR Working Group unanimously agrees with AAPM TG 263 with the inclusion of the laterality suffix on paired OAR over contra- or ipsi- prefix, as laterality is unambiguous, avoids non-formalised assumptions, and is logical for all multi-professional members of a radiation oncology department. The application of contra- or ipsi- prefix is uncertain for midline or bilateral TV, and laterality designation provides user clarity in the event of TV re-irradiation.

Automated tools implementing AAPM TG 263 nomenclature, either applied retrospectively or prospectively to institutional datasets improve structure name compliance, with structure naming consistency reported as greater than 99.0% [44,45]. Consistency of the guidance underlying the nomenclature choices was not evaluated; this GHG OAR consensus guidance aims to internationally and prospectively implement a globally agreed standard for OAR contouring.

Auto-segmentation for OAR contouring, particularly based on deep learning algorithms are attractive as once they have achieved a reliable and consistent quality in OAR contouring these processes may offer time-saving efficiencies during the radiation therapy planning process. Deep learning is reliant on consistent expert contours over the normal variation of patient anatomies; this GHG OAR consensus guidance defines OAR anatomically, which could aid the generation of robust auto-segmentation models [46,4].

The impact of standardised nomenclature on treatment planning systems (TPS) and end-to-end accuracy has been estimated. AAPM TG 263 limits OAR nomenclature to sixteen characters to ensure compatibility with the majority of TPS [2]. Three TPS compatible special characters have been included in this consensus report: plus, included in *Heart+A_Pulm* nomenclature; underscore, distinguishing OAR laterality from the primary or root name; and tilde, designating where a structure has not been contoured in entirety (figure 2). User uptake of

these special characters and the impact on compatibility between multi-vendor platforms and end-to-end accuracy will be recorded with an ongoing audit.

There are limitations to this work. The GHG OAR Working Group elected to exclude structures which were not listed within ASTRO contouring consensus guidance and were identified by one or fewer radiation therapy QA groups; structures not frequently contoured such as the *Ear_L/R* and the *Liver^Ves* were excluded from the stage two investigator survey. The consensus OAR are defined in entirety; the consensus guidance may not be suitable when overarching structures are used for optimisation and dose-reporting of substructures of variable radio-sensitivities e.g. optimising to the *SpinalCanal* structure using the dose-constraint of either the underlying *SpinalCord* or *CaudaEquina*. In these circumstances, the GHG OAR Working Group recommend either use of the GHG consensus contouring guidance and nomenclature or the development of situation-specific clinical trial nomenclature.

The GHG OAR Working Group consensus guideline provides peer-reviewed contouring guidance alongside standardised nomenclature for implementation in clinical trials. In addition to this consensus guidance, users should employ good practice and confirm the structure contour on all viewing planes. Image co-registration inaccuracies and artefacts affecting image quality impact contouring accuracy and precision; users should be aware of these potential sources of error and review the final contours on the primary dataset. This consensus guidance describes each OAR in its entirety; in practice, clinical trial protocols may either specify partial OAR contouring or define the extent to which the OAR will be contoured beyond the planning target volume (PTV). The tilde suffix discriminates between a complete and partially contoured OAR and on data analysis identifies the contour to researchers as suitable for point dose measurement reporting, and not suitable for volumetric dose reporting.

The OAR structures within this report are anatomically defined; the GHG OAR consensus contouring guidance of whole organs is unlikely to change. Further work and dosimetric research will identify radiosensitive OAR substructures with respective dose constraints; contouring guidance for these newly identified substructures should be developed with the engagement of the international radiation therapy community.

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Paper 4: Association between radiotherapy protocol variations and outcome in the CONVERT trial

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Abstract

Introduction

Radiotherapy quality assurance (QA) is integral to radiotherapy delivery. Here we report comprehensive contouring, dosimetry, and treatment delivery QA, describe protocol compliance, and detail the impact of protocol variations on acute grade 3 toxicity, progression free survival (PFS), and overall survival (OS) in the phase III CONVERT trial.

Method

Radiotherapy planning data from one hundred randomly selected patients were requested. Members of the CONVERT Trial Management Group recontoured the heart, lung, and spinal cord OARs according to the trial guideline. The existing radiotherapy plan was re-applied to the new structures and the new dosimetric data were recollected. Compliance with radiotherapy QA components were recorded and radiotherapy QA components were pooled into protocol variations acceptable, acceptable variation, and unacceptable variation. Univariable analysis with a Cox proportional hazards model established the relationship between protocol variations and patient outcome.

Results

Ninety-three cases were submitted for retrospective radiotherapy QA review. Demographics of the radiotherapy QA cohort (n=93) matched the non-QA (n=450) cohort. 97.8% of GTV contours were protocol compliant. OAR contours were non-compliant in 79.6% instances of the heart, 37.6% lung, and 75.3% spinal cord. Of the non-compliant heart contours, 86.5% and 2.7% had contours caudal and cranial to the protocol-defined heart borders. 10.8% did not include the pericardial sac, and 2.7% did not include the anterior aspect of the heart. Eleven (11.8%) submissions exceeded protocol-defined dosimetric heart constraints; six of which were only noted on the application of protocol-compliant contours. Unacceptable variations were not associated with an increase in grade 3 toxicity (p=0.808), PFS (p=0.232), or OS (p=0.743).

Conclusion

Non-protocol compliant heart contours were associated with increased dose delivered to the heart OAR, with 11.8% of submitted heart structures exceeding protocol-defined constraints. In this QA cohort of patients with SCLC, unacceptable variations were not associated with acute grade three toxicity, PFS, or OS.

Introduction

The non-surgical, radical management of lung cancer is evolving rapidly [1]. High-quality diagnostic imaging and highly conformal treatment delivery fuel this era of advanced radiotherapy [1-3]. International consensus guidance aims to standardise the processes underlying optimal target volume delineation (TVD), plan dosimetry, and treatment delivery given these technological advances [2,3]. Consequently, the radiotherapy quality assurance (QA) process becomes increasingly complex and the impact of the individual processes within the chain of tumour site-specific QA parameters should be understood.

Radiotherapy QA is a multifaceted process; starting with the verification of linear accelerator output, development of radiotherapy QA guidelines, and pre-trial benchmark evaluation of contours; continuing to patient positioning, determination of optimal motion-management strategies, implementation of on-trial image guidance (IGRT) processes, and retrospective review of the final radiotherapy treatment plan [4].

The quality of radiotherapy delivered directly impacts patient outcomes [5]. The QA parameters for radical lung radiotherapy are described; dosimetric and treatment delivery violations are reported as isolated components, with pooled deviations reported against patient outcome [6,7]. This paper reports the continuum of contouring, dosimetric, and treatment delivery radiotherapy QA for the randomised phase III CONVERT trial in patients with limited-stage small-cell lung cancer (LS-SCLC) and describes protocol compliance and the impact of the protocol variations on acute toxicity, progression free survival (PFS), and overall survival (OS).

Materials and methods

The CONVERT trial was an international, multicentre, phase III randomised controlled trial with the primary aim of establishing a standard chemo-radiotherapy regimen in LS-SCLC. Details of the trial design have been published previously [8].

Patients were randomised to receive either twice-daily radiotherapy (45Gy in 30 fractions over 19 days) or once-daily radiotherapy (66Gy in 33 fractions over 45 days) concurrent with cisplatin-etoposide chemotherapy. Radiotherapy commenced on day twenty-two of the first cycle of chemotherapy. Three-dimensional conformal radiotherapy was the mandatory minimum standard and elective nodal irradiation was not permitted. Patients were followed up until death.

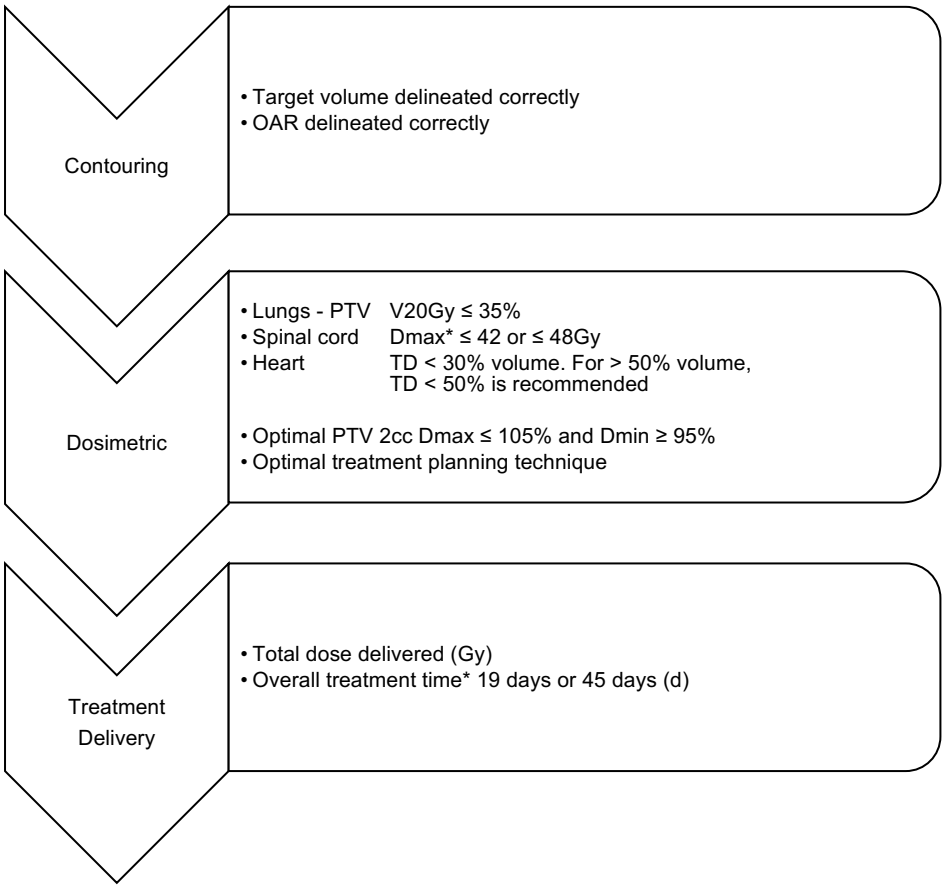
All participants gave written informed consent to participate. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines. The institutional review board or the research ethics committee at each study centre approved the protocol.

The CONVERT QA Programme

The CONVERT radiotherapy QA programme was developed by the CONVERT Trial Management Group (TMG) in conjunction with the RTTQA Group.

The radiotherapy QA programme consisted of two components [8]. Firstly, a pre-trial facility questionnaire recording radiotherapy facilities at each centre, followed by submission of contours and a radiotherapy plan of a previously treated patient who satisfied the eligibility criteria for the CONVERT trial. Secondly, a retrospective review of one hundred randomly selected recruited patients evaluating contouring, dosimetric, and treatment delivery QA (figure 1).

Figure 1. Protocol compliant contouring, dosimetry, and treatment delivery QA parameters



*Dependent on randomisation group; d, days; Dmax, the maximum dose to 2cc; Gy, Gray; OAR, Organs at risk; PTV, Planning Treatment Volume; TD, Total dose; V20Gy, Volume of organ receiving 20Gy

In advance of patient recruitment, all participating centres were provided with the CONVERT radiotherapy planning guidelines including an atlas of protocol-compliant organ at risk (OAR) delineation [8]. The OAR were defined as; lungs: both the right and the left lungs contoured as one structure; spinal cord: the spinal cord contoured based on the bony limits of the spinal canal. The spinal cord was contoured starting at least 10cm

above the superior extent of the planning treatment volume (PTV) and continuing on every CT slice to at least 10cm below the inferior extent of the PTV. Oesophagus: the oesophagus was contoured using mediastinal windowing on the CT scan to correspond to the mucosal, submucosa, and all muscle layers out to the fatty adventitia from the cricoid cartilage to the gastro-oesophageal junction; and heart: the heart was contoured along with the pericardial sac. The superior aspect (or base) started at the level of the superior aspect of the left atrium and extended inferiorly to the apex of the heart.

Patients were treated on a linear accelerator operating at 4 – 10MV. Three-dimensional conformal radiotherapy was mandatory; intensity-modulated radiotherapy (IMRT) was permitted for centres routinely using the technique for the treatment of lung cancer.

The intended radiotherapy total dose (TD) was dependent on the randomisation arm. The radiotherapy dose was specified at the ICRU reference point and corrected for heterogeneity. The optimal PTV planning objective was within ± 5% of the prescribed dose; the mandatory PTV planning objective was ± 7% of the prescribed dose. Normal tissue constraints are described in figure 1; the optimal overall treatment time (OTT) was nineteen days and forty-five days respectively.

Data collection

For both the pre-trial and retrospective QA component, centres were required to anonymise and transfer all treatment-planning data to the RTTQA Group electronically using the secure file transfer protocol. Data were reviewed and analysed with Visualization and Organization of Data for Cancer Analysis (VODCA) version 3.2.7 (Medical Software Solutions GmbH, Hagendorn, Switzerland).

Gross Tumour Volume (GTV) delineation was evaluated by members of the CONVERT TMG and the RTTQA Group in conjunction with the diagnostic imaging report(s) and, where available, the original diagnostic image(s). Expert members of the CONVERT TMG recontoured the heart, the lung, and the spinal cord OARs according to the guideline. The existing dose cube and radiotherapy plan were re-applied. Dosimetric data were collected and compliance with the trial specified normal tissue constraints (figure 1) were recorded; protocol variations were noted (table 1).

Protocol Variation Definition

Individual protocol compliance QA parameters were combined and classified as per the 2015 Global Quality Assurance of Radiotherapy Clinical Trials Harmonization Group (GHG) Protocol Variation Definition version 1.0 (www.RTQAHarmonization.com) recommendation and modified to a) acceptable, b) acceptable variation, c) unacceptable variation – treatment delivered categories [9]. The CONVERT TMG and the RTTQA Group tailored the protocol variation definition criteria for radical lung radiotherapy (table 1).

Table 1. CONVERT protocol variation

A) Acceptable	Radiotherapy was delivered to the patient according to the protocol specifications and meets all the criteria as defined by the protocol. • GTV delineated as per protocol according to diagnostic image(s) • OAR contoured as per protocol and the radiotherapy plan meets protocol defined constraint(s) • PTV coverage achieved optimal objective ± 5% prescription dose • Overall treatment time* 19 days (BD arm) or 45 days (OD arm)
B) Acceptable variation	Radiotherapy was not delivered to the patient according to all of the protocol specifications; no major clinical impact is expected due to the variation(s). • GTV delineated as per protocol according to diagnostic imaging report(s) • OAR contoured not per protocol; with the application of optimal contour(s) and dose cube, the radiotherapy plan meets protocol defined constraint(s) • PTV coverage achieved mandatory objective ± 7% prescription dose • Overall treatment time* 20-21 days (BD arm) or 46-47 days (OD arm)
C) Unacceptable variation – treatment delivered	Radiotherapy delivered to the patient did not meet all the protocol specifications; the variation(s) may impact upon the trial outcome. Radiotherapy is delivered due to clinical necessity as perceived by the treating physician. • GTV delineated not as per protocol according to diagnostic imaging report(s) • OAR contoured not as per protocol; with the application of optimal contour(s) and dose cube, the radiotherapy plan does not meet protocol defined constraint(s) • PTV coverage does not achieve mandatory dose objective • Treatment planning suboptimal – dose not specified at ICRU reference point and not corrected for inhomogeneity • Overall treatment time* ≥ 22 days (BD arm) or ≥ 48 days (OD arm)

*dependent on randomisation group; BD, twice daily; GTV, Gross Tumour Volume; OAR, Organs at risk; OD, once daily; Dmax, the maximum dose to 2cc; QA, Quality Assurance; ICRU, International Commission of Radiation Units and Measurements; PTV, Planning Treatment Volume

Statistical analysis

The CONVERT TMG and the RTTQA Group combined the trial-specific protocol compliance QA parameters (figure 1), into acceptable, acceptable variation, and unacceptable variation – treatment delivered protocol variation categories (table 1). Acceptable and acceptable variation categories were pooled for analysis.

Univariable PFS and OS complete case analysis was performed for selected protocol compliance QA parameters against the pooled acceptable (acceptable and acceptable variation) and unacceptable variation, using the Cox proportional hazards model with and without adjusting for the clinical prognostic model (CPM), which accounted for Eastern Cooperative Oncology Group Performance Status (ECOG PS), gross tumour volume (GTV), and tumour laterality.

Due to the sample size in the QA cohort, a multivariable analysis was not conducted following advice from the study statistician. Hazard ratios (HR) with 95% confidence intervals and p-values are reported.

A univariable logistic regression analysis was conducted for correlating QA variables to any grade three or above toxicity. Odds ratios (OR) with 95% confidence intervals and p-values are reported.

All analyses were conducted in R v 3.5.1.

Results

Between April 2008 and November 2013 five hundred and forty-seven patients from seventy-three centres in eight countries were recruited to the CONVERT trial. Two hundred and seventy-four were randomly assigned to receive twice-daily radiotherapy, and two hundred and seventy-three to receive once-daily radiotherapy. Four patients were lost to follow-up; the modified intention to treat analysis included five hundred and forty-three patients.

The pre-trial QA component has been reported [8,10]. For the retrospective QA component, the CONVERT TMG retrospectively requested treatment-planning data for one hundred randomly selected patients. Ninety-three complete cases were returned: sixty-two (66.7%) from twenty-five centres within the United Kingdom, twenty-five (26.9%) from eighteen European centres across five countries, and six (6.4%) from six centres in the Canadian Provinces.

The baseline characteristics of the QA cohort were well matched to the non-QA cohort (table 2).

Table 2. Baseline and treatment characteristics of the QA and non-QA cohort

	QA Cohort (n=93)	Non-QA Cohort (n=450)
Age (y, range)	63 (34 – 79)	62 (29 – 84)
Sex (n, %)		
M	59 (63)	235 (52)
F	34 (37)	215 (48)
Ethnicity (n, %)		
White	91 (98)	433 (96)
African	0 (0)	2 (<1)
Asian	0 (0)	5 (1)
Other	2 (2)	7 (2)
Not known	0 (0)	3 (1)
ECOG PS (n, %)		
0	43 (46)	205 (46)
1	48 (52)	228 (51)
2	2 (2)	15 (3)
Smoking history (n, %)		
Never smoker	1 (1)	6 (1)
Former smoker	53 (57)	284 (63)
Current smoker	39 (42)	158 (35)
Adverse biochemical factors (n, %)		
LDH > ULN	20 (22)	109 (24)
Hyponatraemia	22 (24)	87 (19)
ALP > 1.5 ULN	1 (1)	10 (2)
Radiotherapy (n, %)		
66Gy once daily	53 (57)	217 (48)
45Gy twice daily	40 (43)	233 (52)
UICC/AJCC Stage (n, %)		
I	1 (1)	3 (1)
II	13 (14)	69 (15)
III	72 (77)	351 (78)

Median gross tumour volume (cc, range)	79.9 (0.5 – 593.0)	83.9 (1.6 – 635.1)
Planned chemotherapy cycles (n, %)		
Four	61 (66)	308 (68)
Six	32 (34)	142 (32)
PET-CT Staging		
Yes	44 (47)	265 (59)
No	48 (52)	183 (41)
IMRT		
Yes	12 (13)	71 (16)
No	81 (87)	331 (74)
Unknown	0 (0)	48 (11)

QA, Quality Assurance; y, years; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate Dehydrogenase; ULN, Upper Limit of Normal; UICC, Union for International Cancer Control; AJCC, American Joint Committee on Cancer; IMRT, Intensity Modulated Radiotherapy; UK, Unknown

Contouring compliance

The GTV contours were deemed as protocol compliant in 90/92 (97.8%) cases (table 3). One case was not evaluable due to the patient having had a complete radiological response to cycle one of cisplatin-etoposide chemotherapy. Two GTV contours were incorrectly labelled as clinical target volumes (CTV).

Table 3. Protocol compliant and non-compliant contours

Structure	Protocol compliant (n, %)	Protocol non-compliant (n, %)
GTV	90 (97.8)	2 (2.2) ▪ Incorrectly labelled as CTV
Heart	19 (20.4)	74 (79.6) ▪ Incorrect cranial heart border ▪ Exclusion of pericardial sac ▪ Anterior border not encompassing heart
Lung	58 (62.4)	35 (37.6) ▪ Incorrectly labelled ▪ Incorrect subtraction of lung – target volume ▪ Lung contour not delineated
Spinal Cord	23 (24.7)	70 (75.3) ▪ Spinal cord contoured instead of spinal canal ▪ Structure insufficiently contoured superior and/or inferior to the PTV

The quality of heart contours varied across the submitted cases; 19/93 (20.4%) contours were protocol compliant; the remaining seventy-four (79.6%) heart contour variations were classified as; i) heart contour either caudal (86.5%) or cranial (2.7%) to the protocol defined upper heart border, ii) heart contour not including the pericardial sac (10.8%), or iii) anterior border not encompassing the most anterior aspect of the heart (2.7%).

Thirty-five (37.6%) lung contours were protocol non-compliant. The right and left lung contours were submitted as individual structures in twenty-seven submissions; the PTV were excluded from either the right or left lung respectively, as opposed to the combined lung contour in two case submissions. One case submission excluded the GTV from the combined lung volume; five submissions did not include the lung contours.

The contouring guidance specified that the spinal cord structure was based on the inner bony limits of the spinal canal, with the contour extending 10cm superior and inferior to the PTV. In sixty-seven (72.0%) instances, the structure was not contoured sufficiently superior or inferior to the PTV. The spinal cord structure encompassed the spinal cord, rather than the spinal canal in three submissions.

Dosimetric compliance

Following the application of protocol-compliant lung, spinal cord, and heart contours to the submitted cases, there were sixteen instances of OAR dosimetric non-compliance; four in lungs – PTV, where V20Gy exceeded 35% (range 35.1 – 38%), eleven in D50% delivered to the heart (range 45Gy arm: 25.7 – 33.3Gy, range 66Gy arm: 35.2 – 48.3Gy), and one in spinal cord Dmax (48.1Gy). The protocol specified spinal cord Dmax was 48Gy.

Six (55%) heart structures were newly noted to exceed protocol-defined dosimetric constraints. In comparison of submitted heart contours and protocol-defined contours, the mean heart V5Gy and V30Gy increased by 4.89% (IQR 0 – 9.56) and 5.24% (IQR 0 – 9.08) in the 45Gy arm and 3.56% (IQR 0 – 6.81) and 4.49% (IQR 0 – 8.97) in the 66Gy arm. The mean D50% was greater at 1.89Gy (IQR 0 – 1.2) and 1.44Gy (IQR 0 – 1.58), respectively (table 4). The mean Dmax increased by 2.10Gy (0 – 1.3) and 1.36Gy (0 – 1.36).

Table 4. Dosimetric impact of the application of protocol non-compliant heart contours

Dosimetric increase from institution supplied and protocol compliant heart contours	**45Gy twice daily (n=40)**	**66Gy once daily (n=53)**
V5Gy (%) (Mean, median, IQR)	4.89, 1.42, 0 – 9.56	3.56, 1.85, 0 – 6.81
V30Gy (%) (Mean, median, IQR)	5.24, 2.73, 0 – 9.08	4.49, 3.8, 0 – 8.97
D50% (Gy) (Mean, median, IQR)	1.89, 0.2, 0 – 1.2	1.44, 0.55, 0 – 1.58
Dmax (Gy) (Mean, median, IQR)	2.10, 0, 0 – 1.3	1.36, 0, 0 – 1.36

V5Gy, Volume of heart receiving 5Gy; V30Gy, Volume of heart receiving 30Gy; D50%, Dose to 50% of the heart; Dmax, Maximum dose to 2cc

87% of the QA cohort were treated with three-dimensional conformal radiotherapy. The maximum and minimum dose to 2cc of the PTV was recorded as a parameter of plan quality with the optimal and mandatory objectives of ±5% and ±7% prescription dose. The optimal objective was achieved in 14/40 (35%) of the 45Gy arm and 30/53 (56.7%) of the 66Gy arm. The mandatory objectives of ≤107% and >93% were not met in 6/40 (15%) and 24/40 (60%) of the 45Gy arm. Similarly, in the 66Gy arm, the maximum dose objective of 2cc PTV was more likely to be achieved compared to the minimum dose objective; 73.5% versus 22.6%.

Overall, treatment planning was optimal in 71/93 (81%) of submitted cases. Examples of sub-optimal planning included variation in beam arrangement resulting in hotspots outside of the PTV and poor beam arrangement resulting in delivery of avoidable radiotherapy dose to the heart. Seven radiotherapy treatment plans were subjectively deemed “too generous” with excessive 90% isodose coverage outside of the PTV.

Treatment delivery compliance

All patients within the QA cohort received the planned radiotherapy dose. The optimal OTT was exceeded in eighteen (19.4%) of the QA cohort; nine (17.0%) in the 66Gy arm and nine (22.5%) in the 45Gy arm.

Impact of protocol variation on outcome

Overall, the unacceptable variation rate was 21.1% across all QA parameters.

Sixty-five (69.9%) patients in the QA cohort had any form of Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 grade 3 or greater toxicity occurring up to three months following completion of treatment. Univariable analysis of instances of grade 3 or greater toxicity demonstrated no significant increase in toxicity in instances of heart, lung, and spinal cord dosimetric non-compliance (table 5). Extension of OTT beyond twenty-two days or forty-eight days was not associated with grade 3 or greater toxicity (OR 2.30 (95% CI 0.68 – 10.63) p = 0.221). Similarly, pooled acceptable variations compared with unacceptable variations (OR 1.26 (95% CI 0.16 – 7.43) p = 0.808) were not associated with grade 3 or greater toxicity.

Table 5. Univariable any grade 3 toxicity analysis and variation from protocol

	OR (95% CI)	**p-value**
Dosimetric non-compliance		
Heart	0.72 (0.20 – 2.97)	0.631
Lung	1.00 (0.01 – 99.99)	0.990
Spinal cord	1.00 (0.01 – 99.99)	0.991
Treatment delivery non-compliance		
OTT	2.30 (0.68 – 10.63)	0.221
Acceptable vs unacceptable variation	1.26 (0.16 – 7.43)	0.808

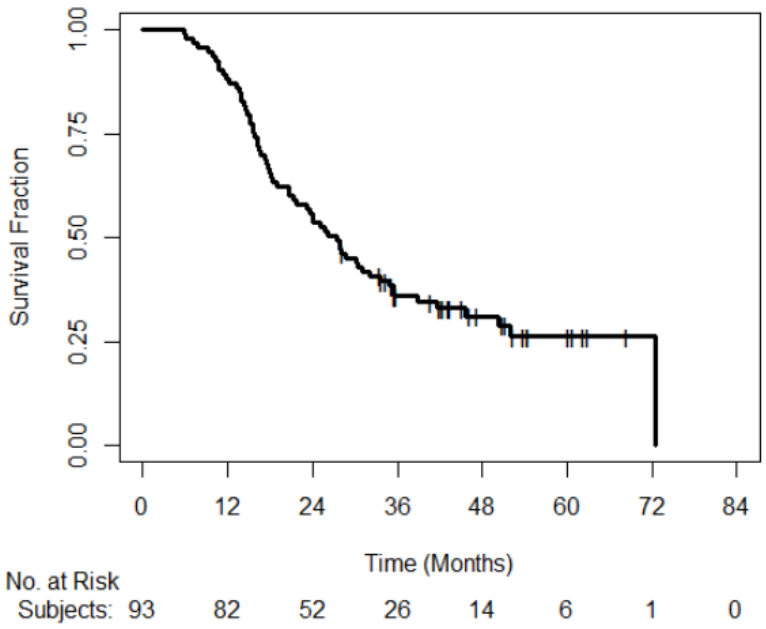
Univariable and CPM-adjusted PFS analysis revealed no detriment with dosimetric non-compliance of the heart, lung, or spinal cord (table 6). OTT over protocol recommendation were not associated with prolonged PFS (HR 1.28 (95% CI 0.69 – 2.35) p = 0.431). Pooled acceptable variations compared with unacceptable variations (HR 0.57 (95% CI 0.23 – 1.43) p = 0.232) were not associated with prolonged PFS.

Table 6. Univariable and CPM adjusted progression free survival analysis with variation from protocol

	Univariable analysis		CPM Adjustment	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Dosimetric non-compliance				
Heart	1.12 (0.57 – 2.20)	0.743	1.05 (0.51 – 2.14)	0.899
Lung	1.28 (0.46 – 3.52)	0.635	1.25 (0.45 – 3.43)	0.672
Spinal cord	1.64 (0.23 – 11.92)	0.626	1.31 (0.18 – 9.82)	0.791
Treatment delivery non-compliance				
OTT	1.13 (0.62 – 2.03)	0.691	1.28 (0.69 – 2.35)	0.431
Acceptable vs unacceptable variation	0.63 (0.25 – 1.57)	0.321	0.57 (0.23 – 1.43)	0.232

Median OS of the QA cohort was twenty-eight months (95% CI 21 – 35; figure 2) and matched the trial cohort of thirty months (95% CI 24–34) in the twice-daily group and twenty-five months (95% CI 21–31) in the once-daily group (HR 1.18 (95% CI 0.95 – 1.45) p = 0.14).

Figure 2. Overall survival in the QA cohort



Univariable and CPM adjusted OS analysis revealed no detriment with dosimetric non-compliance of the heart, lung, or spinal cord (table 7). OTT over protocol recommendation were not associated with reduced OS (HR 1.01 (95% CI 0.99 – 1.03) p = 0.240). Pooled acceptable variations compared with unacceptable variations (HR 0.86 (95% CI 0.34 – 2.16) p = 0.743) were not associated with reduced OS.

Table 7. Univariable and CPM adjusted overall survival analysis with variation from protocol

	Univariable analysis		**CPM Adjustment**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Dosimetric non-compliance				
Heart	1.02 (0.50 – 2.06)	0.962	0.91 (0.43 – 1.93)	0.800
Lung	1.72 (0.62 – 4.76)	0.296	1.71 (0.62 – 4.74)	0.303
Spinal cord	1.13 (0.16 – 8.15)	0.907	0.93 (0.12 – 6.99)	0.946
Treatment delivery non-compliance				
OTT	1.01 (0.99 – 1.03)	0.259	1.01 (0.99 – 1.03)	0.240
Acceptable vs unacceptable variation	0.82 (0.33 – 2.04)	0.674	0.86 (0.34 – 2.16)	0.743

Discussion

This study reporting radiotherapy QA for the international randomised controlled CONVERT trial comprehensively reports radiotherapy QA parameters in radical fractionated lung cancer radiotherapy and relates the continuum of contouring and the dosimetric impact of contour variation, with treatment delivery compliance against patient outcome [6-8,10].

Of five hundred and forty-three recruited patients, ninety-three (17.1%) cases were submitted for retrospective radiotherapy QA. The cases were received randomly and not by stratified selection, the data accrual process will have introduced selection bias, despite this the baseline characteristics of the QA cohort were well matched to the non-QA cohort implying the QA cohort was representative of the entire study population. Modern QA processes employ stratified timely retrospective QA; such process eliminates selection bias. The GTV contours were more likely to be protocol compliant (97.8%) than the associated OARs of the heart (20.4%), the lung (62.4%), and the spinal cord (24.7%). The dosimetric impact of protocol non-compliance of OAR contours are described, with the greatest difference seen in radiation dose received by the heart structure. In eleven (11.8%) instances the heart structure received radiation dose exceeding protocol-defined constraints; half (54.5%) of these protocol variations were detected when protocol-compliant heart contours were applied to the radiotherapy plan and after the participant had completed treatment.

Of the seventy-four non-protocol compliant heart contours, 89.2% had contours terminating either cranial or caudal to the protocol-defined upper heart border, the remainder did not encompass the anterior-most aspect of the heart structure, which may be reflective of the individual not contouring the heart structure with the optimal window or level. The CONVERT trial protocol provided each participating institution with radiotherapy planning guidelines including atlas of protocol-compliant OAR delineation detailing the upper heart border [8]. Despite institutions possessing OAR contouring guidance and submitting contours and radiotherapy plan of a previously treated patient who satisfied the eligibility criteria for the CONVERT trial, on-trial timely prospective QA review may have highlighted heart structure contouring non-compliance to institutions and reduced the incidence of non-compliant heart contours.

Reported heart dosimetry differed between the submitted cases and following application of protocol-compliant heart contours V5Gy, V30Gy, D50%, and Dmax all increased, with the greatest increase in mean V5Gy; 4.89% in the 45Gy arm, 3.56% in the 66Gy arm (table 4). This dosimetric difference is consistent with that seen in RTOG 0617 when auto-segmented heart contours were applied to trial data [11]. The event rate in this CONVERT QA analysis for heart structure dosimetric non-compliance was 11.8 % and too small to proceed with robust statistical analysis to compare radiotherapy dose to the heart structure against participant outcome. There was no difference in univariable and CPM-adjusted acute toxicity, PFS, and OS in patients with unacceptable variations (tables 5-7).

Single centre pooled analysis of one hundred and twelve patients with stage III non-small cell lung cancer (NSCLC) treated with dose-escalated radiotherapy implies cardiac events are independently related to both

baseline cardiac risk and dose delivered to the heart structure, with threshold mean heart dose in patients with cardiologist determined cardiac events as 20Gy and V30Gy of 29% [12].

A meta-analysis of cardiac dosimetric parameters in 5614 clinical trial patients treated for NSCLC determined heart dose should not be prioritised over lung dose given the weaker strength of association between heart dose-volume parameters, toxicity, or mortality, with insufficient evidence to justify compromising tumour dose or coverage [13]. The meta-analysis did not consider the impact of radiotherapy QA, the variation in heart contouring in and across clinical trials, disease-related and cardiac-specific mortality, nor the impact of fraction size, radiotherapy delivery technique, or total radiotherapy dose delivered.

The CONVERT trial specified the heart dose constraint as total dose less than 30% volume, and total dose less than 50% if greater than 50% of the heart structure was irradiated [8]. These constraints are more generous than the constraints proposed by Wang et al. but consistent with radiotherapy lung cancer clinical trials which recruited at a similar time to the CONVERT trial [12]. The CONVERT trial heart dose constraints were in keeping with the best available evidence in the era where the results from RTOG 0617 were not yet known [14]. Contemporary lung cancer clinic trials employ the superior aspect of the pulmonary artery on coronal view as the cranial heart border, as there is variation in the definition of the cranial heart border in historical lung cancer clinical trials, the results from this CONVERT QA analysis may not be generalisable to contemporary lung cancer treatment. The Global Harmonization Group Organ at Risk Consensus Guidance formulates a standard for OAR contouring, so that future datasets are more uniform [15].

Radiation induced heart disease following treatment for lung cancer are multifactorial; patients with lung cancer are older, often with established co-morbidities. Prognostic scales have made attempts to quantify the impact of these individual patient baseline risk factors on outcome [16,17]. Further work will include the prospective collection of patient baseline risk factors, with quality assured dosimetric data collected from the heart structure and heart substructures aided by OAR atlases to establish the true impact of radiotherapy dose to the heart [15,16]. Considering such limitations and unanswered questions as these it is not unsurprising that this study reporting the CONVERT radiotherapy QA did not demonstrate a survival advantage for those trial participants with pooled acceptable protocol variations.

To date, CHART, GFPC-IFCT 02.01, PET-Plan, and PROCLAIM have formally reported radiotherapy QA in the radical treatment of lung cancer [6,7,18,19]. The radiotherapy QA parameters differ between these clinical trials with a variable focus on TV and OAR delineation, dosimetry, and treatment delivery; the radiotherapy QA parameters are reported as isolated components. Comprehensive radiotherapy QA should report these parameters as a continuum - this CONVERT QA study demonstrates contour compliance impacts directly upon reported dosimetry. Radiotherapy QA within the PROCLAIM and PET-Plan studies mandated a prospective review of the first radiotherapy plan from each centre followed by a selective on-trial review [6,7]. In PROCLAIM, based on the four trial-specific QA parameters of PTV coverage, hot spots within and outside the PTV, spinal cord dose, and V20Gy lung, 7.2% (40/554) of cases within the trial were classified with major radiotherapy QA violations [6]. The PET-Plan trial employed extensive radiotherapy QA individual case review (EORTC-

radiotherapy QA level 4) and reported an overall 25% minor, 59% intermediate, and 15% major deviation incidence [7]. Twenty-six of the two hundred and four evaluated radiotherapy records had more than one major deviation. As there is variation across clinical trial reporting, there is an unmet need to systematically define the radiotherapy QA parameters in the radical treatment of lung cancer, along with pre-accrual standardisation of the definitions of a minor and major deviation.

This study of CONVERT radiotherapy QA parameters reports an unacceptable variation rate of 21.1%, this is greater than that reported in PET-Plan and PROCLAIM [6,7] where selected QA parameters were reported, indicating the true major QA violation or unacceptable deviation incidence are only appreciated when the processes within the chain of QA parameters are evaluated as a continuum. Radiotherapy treatment planning was deemed optimal in 81% of submitted cases; despite most plans being optimal; optimal radiotherapy treatment planning does not mitigate the impact of non-compliant OAR contouring.

In contrast to this CONVERT QA study, secondary QA analysis of the 2002-2005 TROG 02.02 HeadSTART trial and radiotherapy QA of the PET-Plan and PROCLAIM trial report the negative impact of protocol violation on patient outcome in the cases submitted for QA [5]. Violations of the pre-defined QA parameters as described within TROG 02.02 HeadSTART trial are not likely to be seen in either usual clinical practice or contemporary clinical trials due to robust governance processes including departmental peer-review, prospective QA review, or on-trial correction of protocol non-compliance. With present-day governance and stringent treatment delivery guidance; the magnitude of the impact of radiotherapy QA as reported in the TROG 02.02 HeadSTART trial is not likely to be seen again [5]. Nevertheless, radiotherapy QA remains the cornerstone of good radiotherapy delivery and should be embedded into clinical trial and non-clinical trial practice.

There are limitations to this work. This QA analysis was conducted retrospectively, 17.1% of cases were reviewed having been selected randomly from the total participant cohort. A stratified selection of cases submitted for QA review would have overcome the bias of case selection. 87% of patients in this QA cohort were treated with 3D conformal radiotherapy with the majority planned with type b dose calculation algorithms. With the drive to deliver modern radiotherapy with IMRT, the treatment delivery process is increasingly complex, and the impact of radiotherapy QA is even more important.

Conclusions

This analysis of CONVERT QA parameters with a detailed description of protocol deviations within contouring, planning, and treatment delivery describes an overall unacceptable deviation rate of 21.1%; this is only fully appreciated when the QA components are reported as a continuum rather than isolated components. Protocol deviations in TVD were rarely seen. The OAR structures had higher rates of unacceptable protocol deviations with the greatest impact seen in contouring of the heart structure with a negative impact on heart dosimetry. There is an unmet need to systematically define the radiotherapy QA parameters in the radical treatment of lung cancer, along with pre-accrual standardisation of the definition of a minor and major deviation.

Future clinical trials should report standardised radiotherapy QA parameters alongside clinical trial outcomes.

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Paper 5: Pilot analysis of daily variation on dose to organs at risk within Isotoxic IMRT trial

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Drafting and editing text: RM, RS

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Abstract

Introduction

Radiotherapy QA is a multifaceted process; assessment of the variance in radiotherapy dose delivered to OAR is an area of unmet need. Here, using deformable image registration (DIR), we present pilot data from the Isotoxic IMRT trial and appraise the bi-daily per-fraction 3D CBCTs to report per-fraction and normalised radiotherapy dose delivered to the OAR during the radical radiotherapy treatment.

Method

Once ethical approval was sought, all participating centres in the Isotoxic IMRT trial were approached to transfer the per fraction 3D CBCT data to the RTTQA Group. 3D CBCT were rigidly registered with the AvIP and underwent DIR through Varian Velocity v4.01. The synthetic CBCT (sCT) were exported to Eclipse v16.0 for dose calculation. Dose to the oesophagus and heart OAR were collected from each sCT and normalised to that re-calculated from the AvIP. Descriptive statistics describe the variance between the OAR dose on the re-calculated AvIP and the respective sCT.

Results

Three partial Isotoxic IMRT trial participant datasets were available for analysis; ninety-six CBCTs underwent success DIR. The heart OAR volume varied more than the oesophagus and spinal cord structures. On review of the apparent dose to the OAR, the greatest dose variance was seen at $D50_{\%}$ to $D20_{\%}$; implying small changes in OAR position in the high dose gradient impact most on dose received to the OAR.

Conclusion

The DIR process highlighted the heart OAR volume varied more that the oesophagus and spinal cord structures throughout the radical course of lung cancer radiotherapy. Small changes in OAR position within the high dose gradient may result in the greatest impact on dose received by the OAR. This analysis was limited by the available data and supports upfront collection of clinical trial data, so that all data may be used to its full potential.

Introduction

Radiotherapy quality assurance (QA) is a multifaceted process; assessment of the variance in radiotherapy dose delivered to organs at risk (OAR) is an area of unmet need. Excess dose to OAR impacts upon acute and late toxicity [1,2] and may induce morbidity [3-5]; unanticipated toxicity and morbidity may impact progress through the intended, optimal treatment schedule.

The RAIDER Trial was the first phase III randomised controlled trial to utilise daily soft tissue image guidance associated with a comprehensive radiotherapy QA programme [6]. Daily per-fraction three-dimensional (3D) cone-beam CT (CBCT) informed the on-line selection of the radiotherapy plan of the day; this enabled delivery of tumour focused dose-escalated radiotherapy to the bladder gross tumour volume whilst limiting dose delivery to the remaining bladder, rectum, and surrounding small bowel [6].

Image-guidance and treatment delivery QA in the context of the radical treatment of lung cancer has additional challenges; the thorax is a moving, heterogenous cavity in which anatomical changes develop [7]. In examined radical radiotherapy lung cancer clinical trials (paper one), trial specific guidance and defined action levels for image guidance and treatment delivery QA was lacking. Single institution data reports 47%, 36%, and 17% of patients exhibiting one, two, or three or greater intra-thoracic anatomical changes during a radical course of lung cancer radiotherapy [7]. One third of patients with lung cancer will develop tumour shrinkage by the final fraction with significant shrinkage noted in week two [8-10]. Such changes in the target volume (TV) and normal tissues may additionally impact dosimetry. Big data analyses in the fractionated and stereotactic radical treatment of lung cancer demonstrate residual shifts towards the heart are associated with poor outcome, with identification of radiosensitive heart substructures [3-5].

The Isotoxic intensity modulated radiation therapy (IMRT) trial was a multicentre feasibility study evaluating dose-intensification strategies including hyperfractionation, acceleration, and dose escalation facilitated by IMRT in the radical treatment of stage III lung cancer. The trial design and primary outcomes have been published previously [11,12]. The trial mandated bi-daily per-fraction CBCT with online correction.

Here, using deformable image registration (DIR), we present pilot data from the Isotoxic IMRT trial and appraise the bi-daily per-fraction 3D CBCTs to report per-fraction and normalised radiotherapy dose delivered to the OAR during the radical radiotherapy treatment.

Materials and methods

Participants in the Isotoxic IMRT trial were treated with individualised doses of radiotherapy based on pre-specified normal tissue doses (heart, brachial plexus, lung tissue, spinal cord, great vessels, proximal bronchial tree) up to a maximum dose of 79.2Gy in 44 bi-daily fractions (table 1) [11,12].

Table 1. Organ at risk tolerance doses and target volume dose criteria

Organ at risk	**Dose-volume constraint**
Spinal cord PRV	D_{1cc} < 50Gy
Lungs – GTV	Mean lung dose < 20 Gy
Brachial plexus PRV	D_{1cc} < 75.1Gy
Proximal bronchial tree and great vessels PRV	D_{1cc} < 75.1Gy
Target volume	**Dose-volume objective**
Clinical target volume	$D_{95\%}$ > 95% of prescribed dose 90% < D_{1cc} < 107%
Planning target volume	$D_{95\%}$ >90% of prescribed dose 80% < D_{1cc} < 107%

GTV, Gross tumour volume; PRV, Planning organ at risk volume

All participants were planned using inverse optimised IMRT by an experienced dosimetrist and/or radiotherapy physicist. The National Radiotherapy Trials Quality Assurance (RTTQA) Group conducted the radiotherapy QA programme which involved submission of facility questionnaire, dosimetry audit, prospective review of contours, and timely retrospective review of the radiotherapy plan dosimetry.

Pre-treatment 3D CBCT with online matching (first bone, then carina) and correction was mandated for all bi-daily fractions. On-treatment anatomical changes were anticipated with their management left to the discretion of the local Principal Investigator.

All participants gave written informed consent. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines. The trial was reviewed in the United Kingdom by the National Research Ethics Service Committee, which granted ethical approval for the study on 8th August 2013. The protocol was approved by the review board at each participating institution [11].

Data collection

The bi-daily per-fraction 3D CBCT data were not specified for prospective collection by the Isotoxic IMRT trial protocol, as such the 3D CBCT data were not collected by the RTTQA Group as part of the initial radiotherapy QA program or during trial recruitment. With engagement from the Chief Investigator and following trial specific

Research and Development approvals, in January 2019 written correspondence was sent to each of the seven participating institutions requesting secure file transfer of anonymised participant 3D CBCT data.

Deformable image registration and dose calculation

All radiotherapy data were anonymised and held securely in the Varian Velocity v4.01 platform. Participant data were identified by trial number.

Each CBCT was rigidly registered with the average intensity projection (AvIP) planning CT. Comprehensive dose calculation was not possible on the CBCT due to the short field of view, hence per-fraction synthetic CT (sCT) were created.

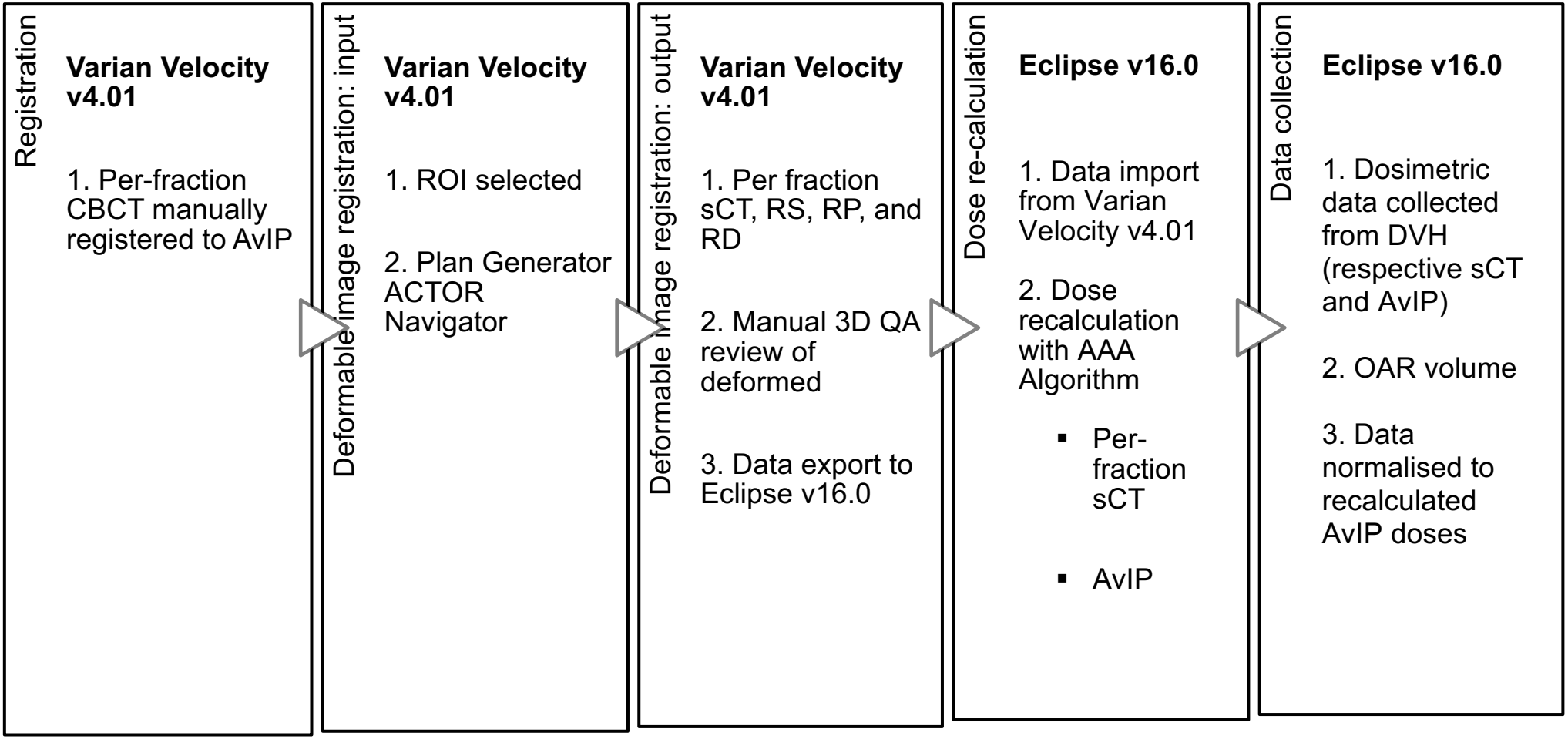
The Varian Velocity v4.01 deformable image registration algorithm was employed to perform the 3D CBCT deformation. A 3D region of interest (ROI) was manually defined on the 3D CBCT to encompass the mediastinal structures and the spinal canal. The structures: external, oesophagus, heart, and spinal canal contours were selected and DIR through the Varian Velocity v4.01 Plan Generator ACTOR navigator was conducted to create the per-fraction sCT along with the associated plan file (RP), dose file (RD), and structure set (RS).

Manual 3D visual review was conducted to ensure the registration and deformation were satisfactory.

The AvIP and the sCT with the associated RP, RD, and RS data were exported into Varian Medical Systems Eclipse v16.0 treatment planning system. To ensure dose comparison was directly comparable, the dose was recalculated with Anisotropic Analytical Algorithm on the initial AvIP planning CT; furthermore, the dose was recalculated on the respective sCT. The monitor units from the initial plan were used for both dose calculations. The dose volume histogram for the initial AvIP planning CT and the respective sCT were examined and doses $D_{95\%}$, $D_{90\%}$, $D_{85\%}$, $D_{80\%}$, $D_{50\%}$, $D_{30\%}$, $D_{20\%}$, $D_{10\%}$, and $D_{5\%}$ to the heart and oesophagus were recorded and normalised to the recalculated doses from the AvIP planning CT. Due to the limitations of DIR, descriptive statistics are reported rather than full dose accumulation [13].

The workflow for the deformable image registration and dose calculation process is displayed in figure 1.

Figure 1. Deformable image registration and dose calculation workflow



CBCT, cone beam computed tomogrpahy; AvIP, average intensity projection; ROI, region of interest; AAA, Anisotropic Analytical Algorithm; sCT, synthetic computed tomography; RS, structure set; RP, plan file; RD, dose file; QA, quality assurance; 3D, three-dimensional; DVH, dose volume histogram; OAR, organ at risk

Statistical analysis

The calculated per-fraction and normalised dose to oesophagus and heart from the respective sCT are reported and contrasted with the recalculated dose on the initial AvIP planning CT.

The mean, standard deviation (SD), variance (var), and co-efficient of the variance (co-var) were calculated for each dose parameter; the variance reports on single parameter variability, the co-efficient of the variance reports on how two variables vary together. All analyses were conducted in Microsoft Excel v16.54.

Results

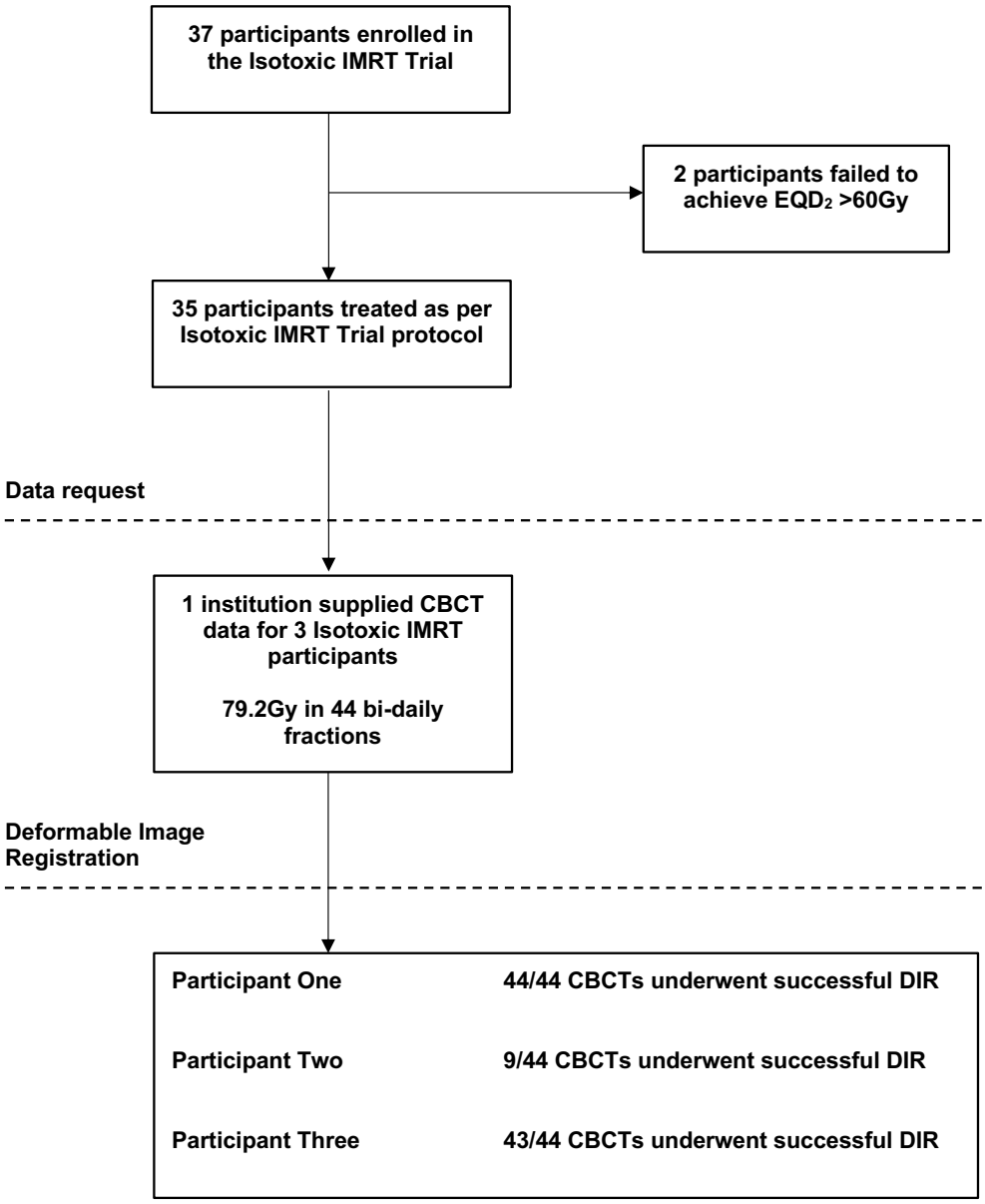
Between June 2014 and March 2016 thirty-seven participants were enrolled from seven United Kingdom institutions to the Isotoxic IMRT Trial. Two participants failed to achieve the planned dose of EQD_2 >60Gy due to large tumour size and inability to achieve OAR constraints; thirty-five participants were treated as per trial protocol.

One institution returned complete 3D CBCT data for three Isotoxic IMRT Trial participants. The three participant data sets were successfully imported into the Varian Velocity v4.01 platform (figure 2).

Despite engagement with all participating institutions, complete 3D CBCT data for the remaining thirty-two trial participants could not be retrieved. The reasons behind these difficulties are explored in the discussion.

The participants included in this pilot analysis received a total dose of 79.2Gy in 44 bi-daily fractions. The optimal planning target volume (PTV) objective of $D_{95\%} \geq 95\%$ was achieved in all evaluated data.

Figure 2. Available data for analysis



OAR metrics and dose re-calculation

One hundred and thirty-two 3D CBCTs relating to three Isotoxic IMRT trial participants from one submitting institution underwent DIR; ninety-six (72.7%) underwent successful DIR (44 Participant One, 9 Participant Two, 43 Participant Three).

The range of the total volume of the heart structure on the AvIP planning CT was 513.6cc (table 2). The range of the volume of the heart structure across participant specific sCT increased as the volume of the heart structure on the AvIP planning CT increased; participant two volume 672.2cc and sCT range 72.3cc, participant one volume 786.9cc and sCT range 109.7cc, participant three volume 1186.1cc and sCT range 128.9cc.

The total volume of the oesophagus and spinal canal on sCT were consistent with the volumes seen on the AvIP planning CT (table 2).

Table 2. OAR total volume characteristics across AvIP and sCT

		Participant One		**Participant Two**		**Participant Three**	
		AvIP	**sCT**	**AvIP**	**sCT**	**AvIP**	**sCT**
Heart (cc)		786.9		672.4		1186.1	
	Mean		775.9		663.8		1277.6
	Range		693.9 – 803.6		634.5 – 706.8		1258.6 – 1387.5
	SD		26.3		25.7		36.0
Oesophagus (cc)		24.0		42.5		40.9	
	Mean		24.7		42.6		39.2
	Range		22.3 – 25.6		42.2 – 44.1		37.4 – 49.9
	SD		0.8		0.6		2.1
Spinal Canal (cc)		62.6		41.7		50.8	
	Mean		62.9		40.2		48.7
	Range		60.6 – 63.1		39.8 – 40.7		43.7 – 53.4
	SD		0.5		0.3		2.6

Participant One

The heart and oesophagus recalculated AvIP doses (Gy) pertaining to participant one are displayed in tables 3 and 4, and figures 3 and 4, respectively. The mean OAR dose across combined sCT was consistently higher than that re-calculated on the AvIP. There was a trend towards increased variance in the heart and oesophageal delivered dose as the dose objective fell (tables 3 and 4).

Table 3. Participant one heart metrics

	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
Recalculated AvIP (Gy)	12.95	16.17	19.51	22.71	34.03	40.96	46.24	56.07	67.58
sCT mean (Gy)	13.48	16.99	20.62	24.05	35.77	43.08	48.71	58.99	71.04
sCT SD	0.46	0.66	0.80	0.83	0.56	0.72	0.92	1.23	2.01
sCT Var	0.21	0.43	0.65	0.69	0.31	0.52	0.84	1.52	4.06
sCT Co-Var	3.43	3.87	3.90	3.46	1.56	1.68	1.88	2.09	2.83

Figure 3. Participant one variation in normalised dose to the heart

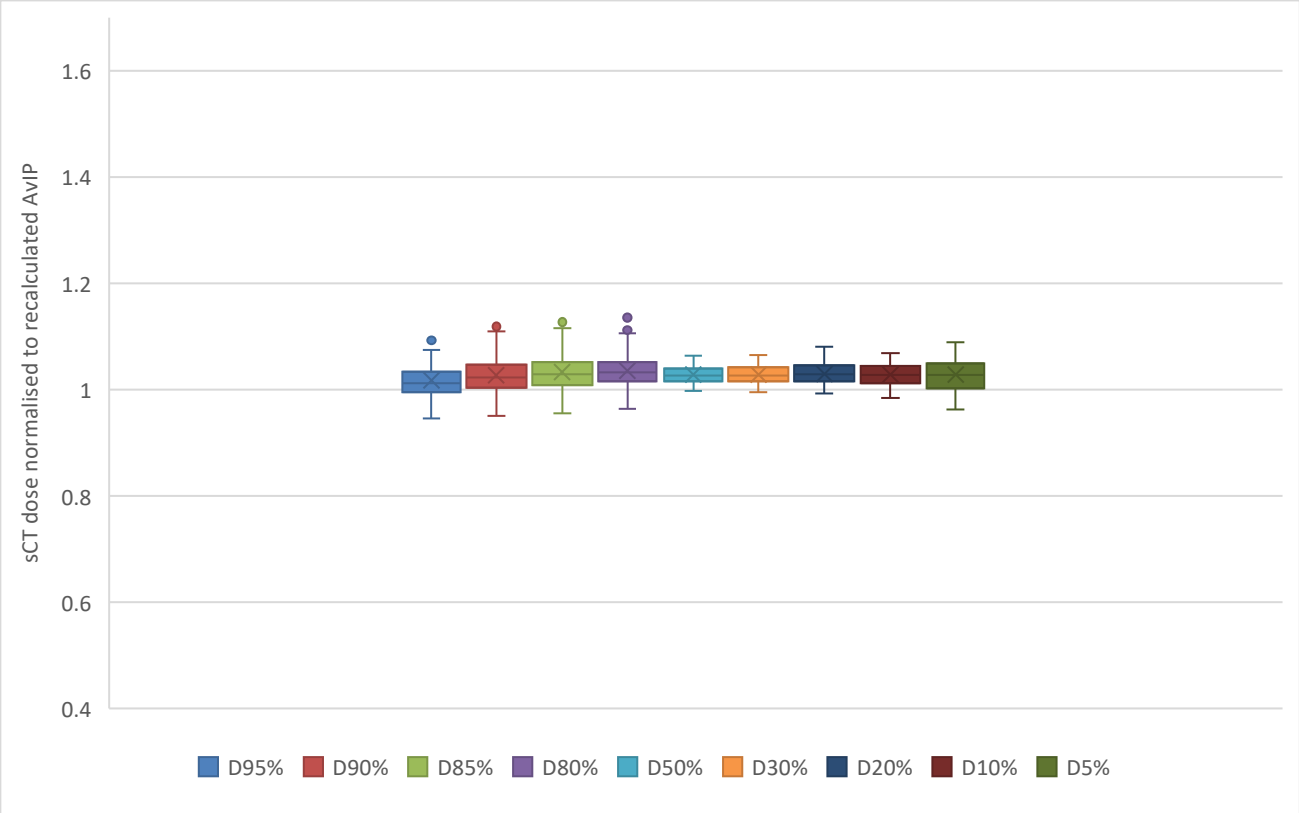
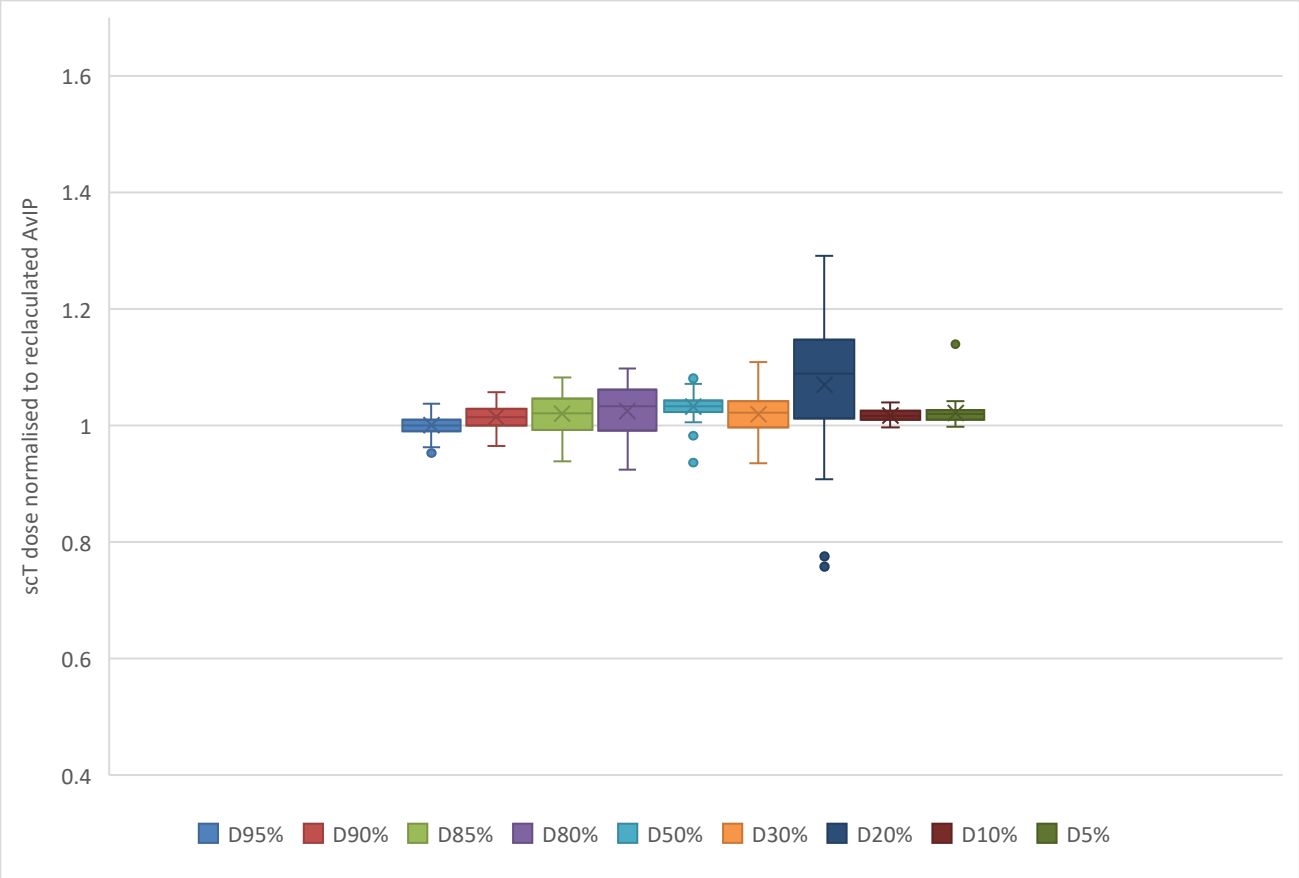


Table 4. Participant one oesophagus metrics

	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
Recalculated AvIP (Gy)	1.06	1.41	1.95	2.76	16.37	26.49	47.92	79.62	80.49
sCT mean (Gy)	1.08	1.46	2.03	2.89	17.28	27.62	52.43	82.82	84.05
sCT SD	0.02	0.03	0.07	0.11	0.36	0.89	5.67	0.83	1.68
sCT Var	0.00	0.00	0.00	0.01	0.13	0.79	32.10	0.69	2.82
sCT Co-Var	1.76	2.07	3.27	3.97	2.10	3.21	10.81	1.01	2.00

Figure 4. Participant one variation in normalised dose to the oesophagus



Participant Two

The heart and oesophagus re-calculated doses pertaining to participant two are displayed in tables 5, 6 and figures 5, and 6, respectively. The mean OAR dose across the combined sCT was consistently higher than that re-calculated on the AvIP. The variance in dose delivered to the heart was highest at D50%; the result is influenced by outliers within the dataset (figure 5). The oesophagus dose variance was highest at D30% (figure 6).

Table 5. Participant two heart metrics

	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
Recalculated AvIP (Gy)	0.81	1.08	1.36	1.66	10.80	42.54	51.65	67.72	78.95
sCT mean (Gy)	0.81	1.07	1.36	1.67	13.38	43.72	53.05	69.70	80.09
sCT SD	0.03	0.03	0.04	0.05	2.49	0.69	0.94	1.88	0.75
sCT Var	0.00	0.00	0.00	0.00	6.20	0.48	0.89	3.52	0.57
sCT Co-Var	3.74	3.25	2.93	2.93	18.62	1.58	1.78	2.69	0.94

Figure 5. Participant two variation in normalised dose to the heart

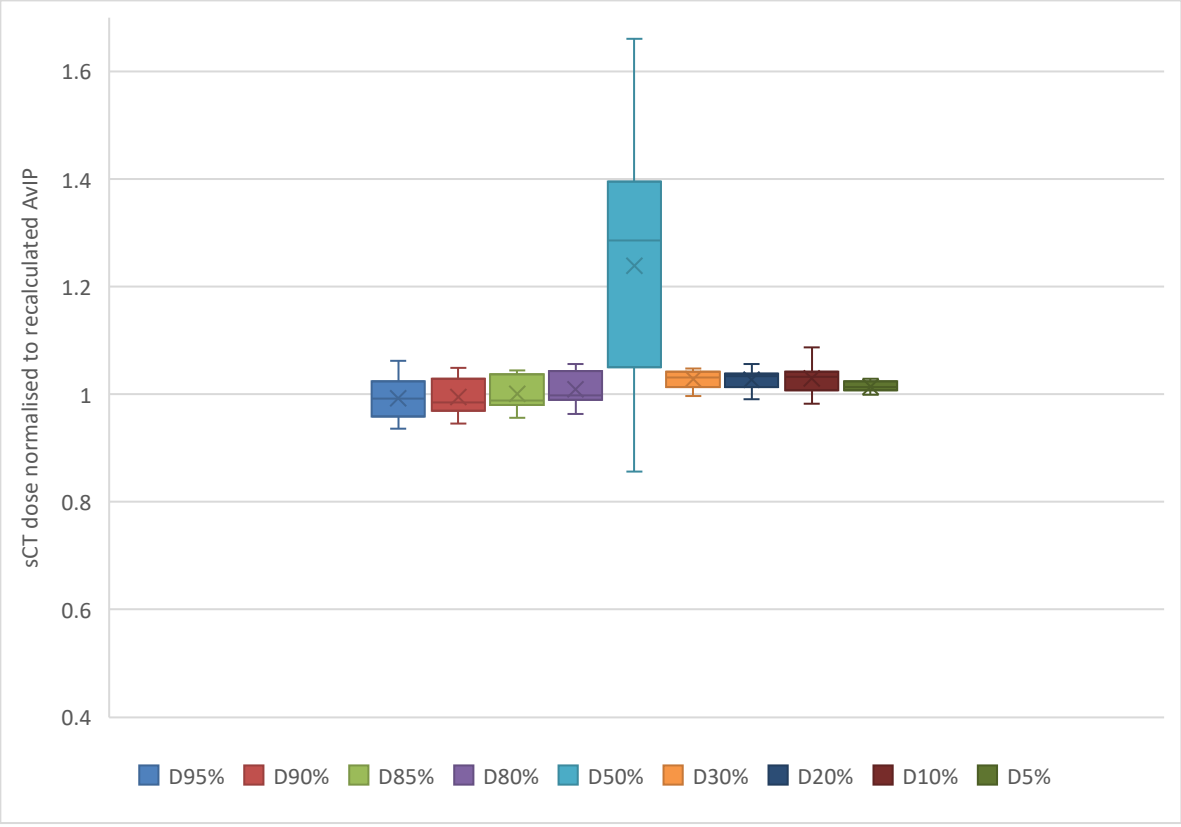
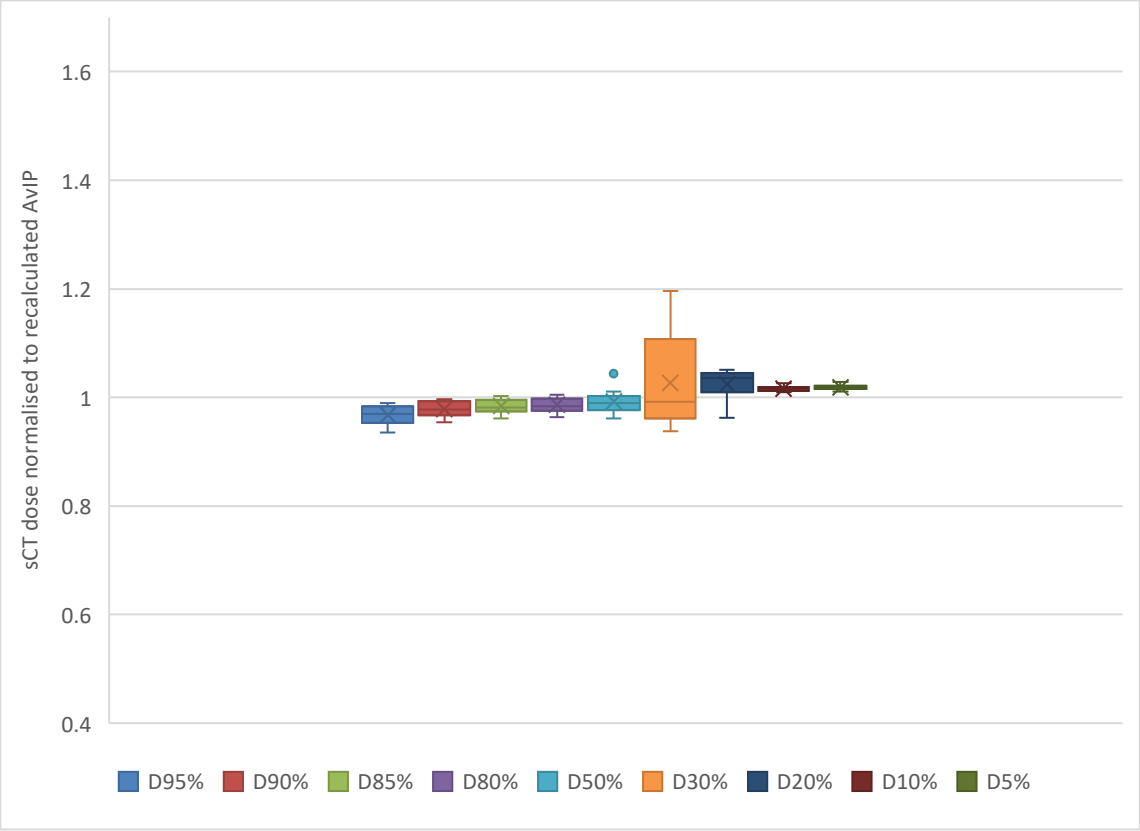


Table 6. Participant two oesophagus metrics

	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
Recalculated AvIP (Gy)	0.94	1.04	1.12	1.21	2.67	9.08	74.03	79.98	80.37
sCT mean (Gy)	0.91	1.02	1.10	1.19	2.65	9.33	75.83	81.31	81.90
sCT SD	0.02	0.01	0.01	0.02	0.06	0.76	1.98	0.39	0.41
sCT Var	0.00	0.00	0.00	0.00	0.00	0.57	3.91	0.15	0.17
sCT Co-Var	1.87	1.39	1.31	1.33	2.26	8.12	2.61	0.48	0.50

Figure 6. Participant two variation in normalised dose to the oesophagus



Participant Three

The heart and oesophagus re-calculated doses pertaining to participant three are displayed in tables 7 and 8 and figures 7 and 8, respectively. The greatest variance in dose for both the heart and oesophagus was at D50%, D30%, and D20%.

Table 7. Participant three heart metrics

	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
Recalculated AvIP (Gy)	0.60	0.76	0.91	1.08	3.37	19.28	36.86	56.91	76.93
sCT mean (Gy)	0.62	0.79	0.96	1.16	4.39	22.55	36.50	53.40	72.37
sCT SD	0.01	0.02	0.02	0.03	0.42	2.50	3.00	3.71	3.54
sCT Var	0.00	0.00	0.00	0.00	0.18	6.24	8.99	13.74	12.56
sCT Co-Var	2.02	2.11	2.37	2.80	9.65	11.08	8.22	6.94	4.90

Figure 7. Participant three variation in normalised dose to the heart

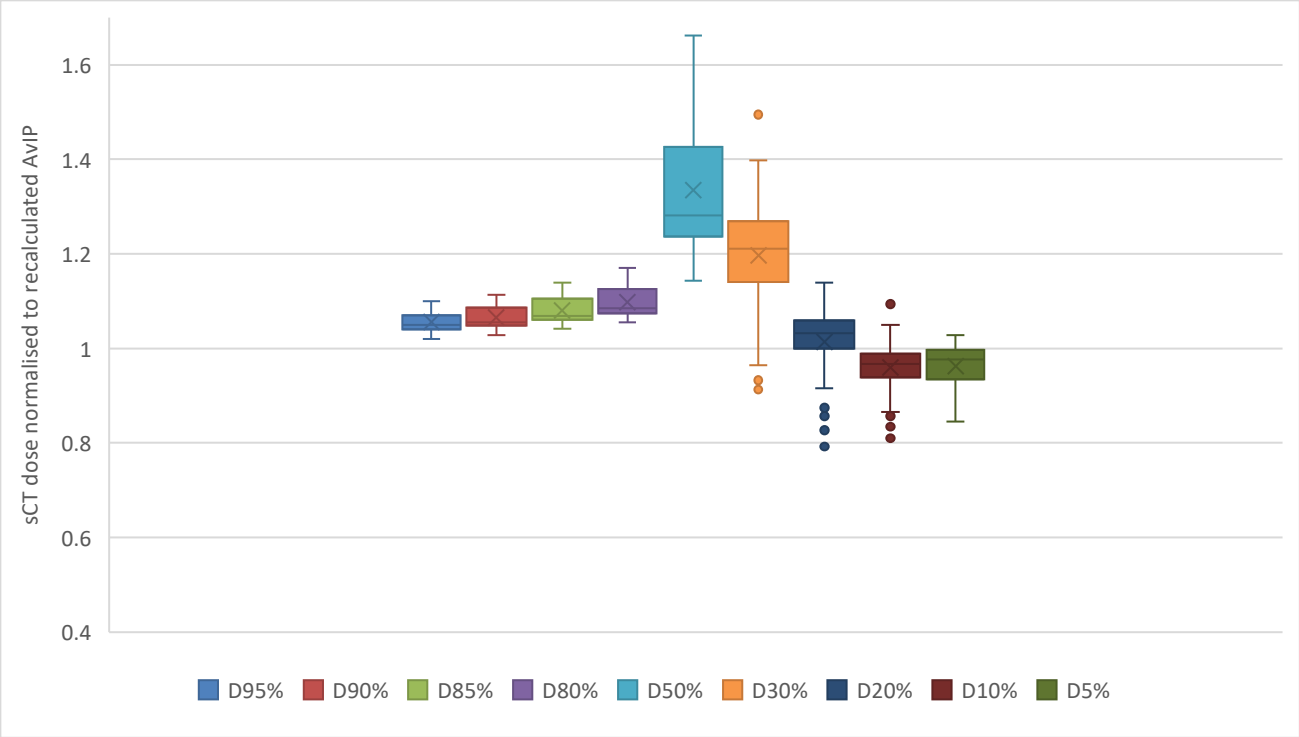
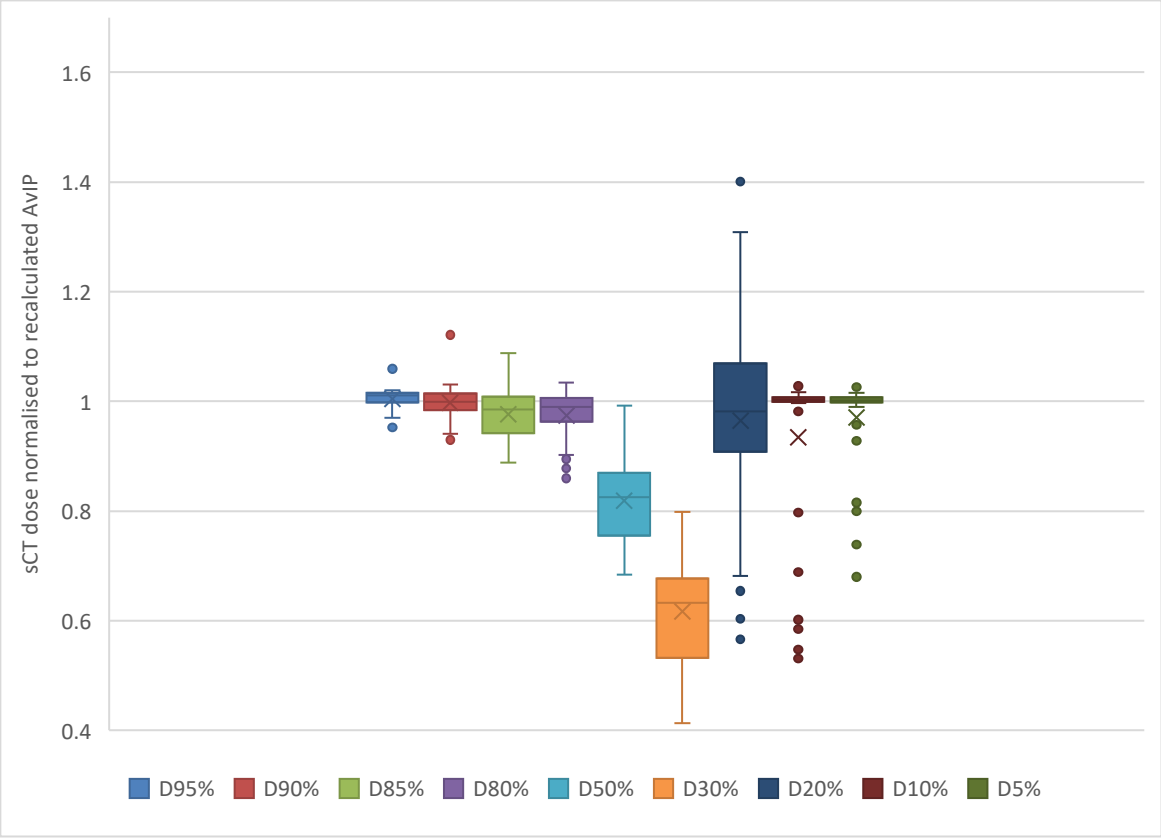


Table 8. Participant three oesophagus metrics

	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
Recalculated AvIP (Gy)	0.78	0.91	1.14	1.37	4.46	25.29	43.67	78.46	79.10
sCT mean (Gy)	0.77	0.89	1.08	1.30	3.57	15.23	41.18	71.59	75.02
sCT SD	0.01	0.03	0.05	0.06	0.31	2.47	8.20	12.13	6.42
sCT Var	0.00	0.00	0.00	0.00	0.10	6.13	67.31	147.05	41.27
sCT Co-Var	1.91	3.19	4.68	4.93	8.81	16.25	19.92	16.94	8.56

Figure 8. Participant three variation in normalised dose to the oesophagus



The raw dosimetric data is displayed in the appendix.

Discussion

The pilot data herein reports the AvIP and normalised dose to the heart and the oesophagus throughout a course of fractionated radical lung cancer radiotherapy for three Isotoxic IMRT study participants.

Ninety-six 3D CBCTs underwent successful deformation. The heart OAR varied the most in volume throughout treatment when compared to the oesophagus or spinal canal; this effect is observed during radical lung and oesophageal cancer radiotherapy, where variation and progressive reduction in heart volume was not associated with impairment of cardiac function [14,15]. There was no appreciable variation in the volume of the oesophagus or spinal canal; volume review of the deformed fixed bony spinal canal structure along with manual clinician review of deformation in three planes provided QA for the DIR process.

The quality of the DIR process was not sufficiently robust to allow cumulative dose calculation. On review of the descriptive statistics, the instances where apparent dose variation was seen was commonly between $D50_{\%}$ and $D20_{\%}$; it is likely these dose levels represent the high dose gradient and hence small shifts in OAR position result in greater variance in dose delivered.

To our knowledge this exploratory analysis is the first to use DIR through the Varian Velocity platform to appraise dose per fraction as re-calculated on sCT. With further work and process QA, this technique could be employed to create a pathway for on-line dose analysis in the clinical setting. Such pathway may avoid the requirement to re-expose a patient to the additional radiotherapy exposure from a repeat planning CT if wishing to estimate radiotherapy dose during treatment and may additionally provide a pathway for retrospective review of dose delivery.

Due to the small number of participants, no meaningful conclusions can be sought from the three examined datasets; it is reassuring to note that when reviewing specific OAR doses there was no significant or persistent increase in radiotherapy dose delivered to the heart and oesophagus, as high doses to these structures has been associated with high grade toxicity [16].

The thorax is a heterogenous cavity with TV and OAR moving independent of each other. Radiotherapy planning for lung cancer can be challenging as the TV may be i) fixed to the chest wall, ii) adjacent to a radiosensitive OAR (the spinal cord), iii) or tethered to the diaphragm with significant internal motion. The anatomical location of the TV should be considered in the treatment planning process. Attempts at ensuring the radiotherapy plan achieves target coverage and OAR constraints include predictive planning and plan robustness; these planning processes however do not predict for anatomical changes which are reported in 72% of lung cancer patients during radical radiotherapy [7]. The impact of anatomical changes on dosimetry has not been fully quantified; dosimetric analysis of large datasets will build the evidence base to help to define action levels for replanning.

As discussed in thesis papers one and three, the Quantitative Analyses of Normal Tissue Effects in the Clinic review proposed OAR tolerances and defined OAR constraints with the acknowledgement that progress in

radiation oncology accelerates only when we understand how treatment decisions impact upon patient outcomes [17-19]. All clinical trial data should be used to the full potential to understand how clinical decisions impact upon patient outcomes. The first author along with patient and public involvement initiatives encourage Chief Investigators and Clinical Trial Units to support prospective collection of all trial data, so that trial data may be held as a resource for future radiotherapy research [20-22].

There are limitations to this work. Conclusions from this exploratory analysis are limited by the small data set. The 3D CBCT data for this analysis were not prospectively collected during trial accrual. Despite best efforts just three of thirty-five requested datasets were available for analysis; 72.7% of the collated CBCTs were successfully deformed, the data for the remainder of collated CBCTs were corrupted and for technical reasons the data were not evaluable.

At the outset, clinical trials define a clear research question with primary and secondary objectives designed to address the research question. Clinical trial data is collected prospectively in response to the clinical trial objectives. In the Isotoxic IMRT Trial there was no requirement to collect the bi-daily CBCT data as the trial objectives did not include a research question mandating per-fraction dosimetric analysis. Retrospective data collection was conducted for this pilot analysis, in practice retrospective collection is challenging as i) data may not have been retained or be readily available ii) trial-specific permission for data use must be sought retrospectively, iii) participating institutions require time and resource to package data and send on for analysis. For this exploratory analysis trial specific approval was sought prior to this exploratory analysis, however most of the requested data were not retained nor available for electronic transfer. A secondary limitation is that the QA of the DIR process was conducted two-fold: i) volumetric assessment of the spinal canal structure and ii) manual review of the deformation by a QA experienced clinician; no metrics were available to quantify the accuracy of the DIR process.

Future work will concentrate on refining the DIR process to include dosimetry of the TV in addition to the OAR, with end-to-end QA and streamlining of the pathway so that it may be employed to robustly analyse large clinical trial datasets.

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Concluding remarks and proposed QA reporting metrics

The aim of this thesis was to review the variability in radiotherapy processes and to propose standardisation of radiotherapy quality assurance QA with a focus on the radical treatment of lung cancer.

Five distinct pieces of work are presented: i) the variation in QA reporting in the post-QUANTEC era with areas of unmet need highlighted, ii) identification of variation in nomenclature and OAR descriptions, iii) presentation of international consensus OAR nomenclature and OAR contouring guidance, iv) presentation of the clinical impact of variable OAR contouring with recommendations for future practice, v) and appraisal of OAR dose throughout the radical lung radiotherapy program.

The work presented in this thesis successfully examines radiotherapy QA processes and has positively impacted on radiotherapy QA processes in the international arena.

Paper one reports the variation in QA reporting in the post-QUANTEC arena. Eight thousand and twenty-six abstracts were screened; eleven met the pre-specified criteria and contained at least one aspect of radiotherapy QA. Variation was noted in the quality and extent of radiotherapy QA reporting. Paper two reports the provision of contouring guidance in clinical trials within the United Kingdom National Institute of Health Research Clinical Research Network (NIHR CRN) portfolio and highlights the need for the standardisation of OAR nomenclature along with the associated anatomical descriptions. Of the examined data 14.7% of nomenclature were deemed as providing optimal guidance for contouring; variation in the cranial and caudal borders of selected OAR were seen – such variation directly impacts on dose reporting with the clinical impact of dose reporting detailed in paper four.

Paper three is the most cited paper and presents standardised OAR nomenclature and peer reviewed OAR contouring guidance for the clinical trial and non-clinical trial setting. Paper four reports a retrospective QA analysis of the phase III CONVERT Trial and quantifies the impact of contour variation on radiotherapy dose reporting; the QA cohort were randomly selected; the paper discusses how modern radiotherapy QA processes overcome selection bias when selecting cases for QA review.

Paper five presents pilot data from deformable image registration of the per-fraction three-dimensional (3D) cone-beam CT (CBCT) from the Isotoxic IMRT Trial. Descriptive statistics reporting dose delivered to respective OAR are presented. The analysis was hampered by difficulties in transferring raw and analysed data between the variety of radiotherapy treatment planning systems; the discussion explores the pitfalls with retrospective data collection and analysis.

Radiotherapy workflows employ complex multistep processes in which all multi-professional members of the radiotherapy team input; radiotherapy QA processes must be robust and transparent so that all multi-professional members understand terminology thus making communication safe. Target volume nomenclature and definitions are clearly defined by the International Commission on Radiation Units and Measurements

(ICRU); the internationally agreed and accepted terminology enables the multi-professional radiotherapy team to use the same language when referring to complex radiotherapy processes.

The work presented in this thesis identifies and resolves the difficulties seen with respect to the variation in OAR nomenclature and OAR definitions. From a dosimetric perspective, the work presented herein is an invaluable resource which will aid the development of standardised radiotherapy datasets; more uniform datasets will deliver clinically relevant and valid conclusions from clinical trials, a key aim of the National Radiotherapy Trials Quality Assurance (RTTQA) Group.

In 2019 NHS England formulated eleven Radiotherapy Operational Delivery Networks. These collaborative networks were designed to facilitate meaningful partnership working between established radiotherapy departments, to support provision of modern radiotherapy services across England, and to reduce variation in quality by adopting standardised best practice protocols thereby improving outcomes. Similar to the implementation of the ICRU target volume and dose reporting definitions, I hope the international OAR consensus guidance presented in this thesis is utilised to full potential. It is a personal goal of mine for the work to be implemented in England across all Radiotherapy Operational Delivery Networks so that the quality of OAR nomenclature and contouring is standardised across the country.

This thesis has several limitations. In paper one, the analysis of variation in QA reporting is limited by that which is formally published. The analysis will not have captured the processes or protocols employed in individual departments. The development and presentation of OAR nomenclature and contouring guidance is robust, but as new data emerges, radiosensitive OAR substructures will be defined i.e., heart substructures, brain substructures, pharyngeal swallowing structures. Furthermore, in the future, OAR may be defined by intrinsic function i.e., segments of parallel OAR may be delineated to allow radiotherapy dose delivery to regions which lack function and therefore accommodate higher radiotherapy dose deposition, in preference to functional OAR segments, where the OAR function may be comparatively preserved by applying a dose limiting constraint. Lastly, contouring guidance was adapted from established guidance; additional radiology specific support was not sought. The OAR consensus paper acknowledges the above and recommends OAR contouring guidance should be developed with the engagement of the international radiotherapy community.

The retrospective analysis of the CONVERT Trial QA data is impacted by case selection. One hundred randomly selected cases were requested retrospectively with ninety-three complete evaluable data sets. Modern QA processes employ stratified selection so that selection bias is avoided. The methodology underlying the CONVERT QA analysis is comprehensive, however the selection bias and number of cases within the QA cohort limit the validity of the analysis. The CONVERT QA analysis did not demonstrate a toxicity, progression free, or overall survival gain in those patients who were treated to the standard of acceptable variation; this is not surprising as with present-day governance and stringent treatment delivery guidance; the magnitude of the impact of radiotherapy QA as reported in the TROG 02.02 HeadSTART trial will not be seen again. Despite this, radiotherapy QA remains the cornerstone of good radiotherapy delivery and should be embedded into clinical trial and non-clinical trial practice.

The final paper presents pilot data from the Isotoxic IMRT Trial. Per-fraction 3D CBCT underwent deformable image registration to create synthetic CT followed by dose-recalculation to the heart and oesophagus OAR. The process was hampered by data-transfer difficulties, initially with acquiring raw data which had been archived in most participating centres, and lastly when transferring raw and analysed data between radiotherapy treatment planning systems. Dose accumulation was not possible and descriptive statistics are presented; descriptive statistics do not confidently represent dose delivered to the OAR and so there are no meaningful conclusions with respect to variation in OAR radiotherapy dose from the deformable image registration and dose recalculation process. The deformable image registration workflow was not quality assured, but once the process has been finessed, the workflow may enable radiotherapy departments to perform target volume and OAR dose analysis without rescanning the patient.

The work presented in this thesis was conducted as part of a two-year fellowship with the National RTTQA Group; a key aim of the RTTQA Group is to standardise reporting across clinical trials, the aim has been achieved with respect to OAR nomenclature and contouring, but moving forward, clinical trials with a radiotherapy component will benefit from standardised reporting so that clinical trials with the added variable of radiotherapy delivery are comprehensively reported.

Paper one introduced the CONSORT Statement. Devised in 1996 and updated in 2001 and 2010, the CONSORT Statement was developed by an international group of clinical trialists, statisticians, epidemiologists, and biomedical editors aiming to improve the reporting of a randomised controlled trial so that the trial is transparently reported to the reader. The quality of radiotherapy delivered is known to impact patient outcome and this thesis demonstrates existing variation in practice and the clinical impact of variability, I support standardised reporting of radiotherapy QA in line with CONSORT principles.

Table 1 proposes a lung cancer specific framework for use when reporting a radical radiotherapy lung cancer clinical trial; reference to relevant thesis papers are highlighted against the itemised reporting framework.

Table 1: Radiotherapy quality assurance for radical lung cancer: A CONSORT framework proposal

Section/Topic	Item No	Checklist item	Checklist parameters	Thesis reference
Pre-trial quality assurance				
	1	Facility questionnaire	Anatomical site specific and technique specific record of practice within the participating centre	
	2	Dosimetry audit	External report of linear accelerator output	
	3	IMRT Credentialing	Test of treatment technique and treatment planning system algorithm	Paper 4
	4a	Protocol	Radiotherapy technique Plan objective OAR constraints and target volume objectives Process for verification	Papers 2, 3
	4b	Variation	Pre-accrual definition of acceptable and unacceptable variation(s)	Papers 1, 3
	4c	Toxicity	Protocol to pre-define acute and late toxicity as per RTOG definition and in line with CTCAE 4.0	Paper 1
	5	Benchmark and/or dummy run	Submission of contouring and planning benchmark case and/or dummy run	Paper 3
On-trial quality assurance				
	6	Set up	Motion management technique	
	7	Contouring	Standardised organs at risk and associated nomenclature Use of atlas/contouring guidance Protocol compliant diagnostic imaging +/- image Fusion Prospective and/or stratified timely retrospective review of submitted target volumes and organs at risk	Papers 1-4
	8	Dosimetry	Prospective and/or stratified timely retrospective review of submitted radiotherapy plans Dose objectives and dosimetry Integral dose Beam arrangement Technique	Paper 4
	9	Verification	CBCT or Kv imaging Frequency of verification Action level Replanned	Papers 1 and 5
	10	Outcomes	Number of participants completing the protocol defined treatment program Overall treatment time Total dose delivered	Paper 4
Post-trial quality assurance				
	11	Retrospective review	Retrospective review of submitted target volumes and organs at risk Retrospective review of submitted radiotherapy plan	Paper 4
	12	Data collection	Defined by the protocol	Paper 5

Appendices

Global Harmonization Group organ at risk consensus contouring guidance

Example of implementation of Global Harmonization Group organ at risk consensus contouring guidance References

Existing reference: wherever available existing consensus guidance descriptions and atlases form the basis for the final organ at risk descriptions

Amendment: amendment of the proposed descriptions following review of survey feedback

Standardised Nomenclature	Existing Reference	Amendment	Consensus Contouring Guidance
A_LAD	2011 Feng [1] 2017 Duane [2]	Developed in response to survey feedback	The left anterior descending artery originates at the left main coronary artery and passes between the left and right ventricles in the anterior inter-ventricular groove. The caudal limit is located at the apex of the heart. The diameter of the coronary artery decreases from proximal to distal; angiographic studies show the average diameter to be 3.2mm, therefore use a 4mm diameter tool to contour the structure throughout the entire length.
BileDuct_Common	2014 Jabbour [3]	Minor	The common bile duct is usually 8-10cm in length and 5-6mm in diameter. The contour begins at the union of the common hepatic duct and the cystic duct and extends caudally to the second section of the duodenum. The common bile duct passes posterior and medial to the duodenum and joins with the pancreatic duct to form the ampulla of vater.
Bladder	2012 Gay [4]	No amendment	The bladder should be contoured in entirety from base to dome. The lateral extent is the outer bladder wall.
Bone_Mandible	2014 Sun [5] 2015 Brouwer [6]	Minor	The mandible should be contoured in entirety from the temporo-mandibular junction to the symphysis menti. The teeth are excluded from the contour. Contour on bone windows.
Bowel	2012 Gay [4] 2016 Standring [7]	Minor	The bowel encompasses the small (duodenum, jejunum and ileum) and large bowel (caecum, ascending, transverse, descending, and sigmoid colon) structures in one contour. Delineate from the pylorus to the recto-sigmoid junction adhering closely to the outer boundary of the external bowel wall, including bowel contents. Ensure small bowel in the lower pelvis caudal to the recto-sigmoid junction is included.

			Investigators wishing to contour the bowel space should refer to the *Spc_Bowel* structure.
Bowel_Large	2016 Standring [7]	Developed in response to survey feedback	The large bowel encompasses the caecum, ascending colon, transverse colon, descending colon, and sigmoid colon in one contour. Contour from the ileocaceal junction to the recto-sigmoid junction. The large bowel can be discriminated from the small bowel by the appearance of bowel contents, presence of haustra, sacculations, and appendices epiploicae. The contour adheres closely to the outer boundary of the external wall and includes large bowel contents.
Bowel_Small	2016 Standring [7]	Developed in response to survey feedback	The small bowel encompasses the duodenum, jejunum, and ileum in one contour. Contour from the pylorus to the ileocaecal junction. Ensure small bowel in the lower pelvis caudal to the recto-sigmoid junction is included. The small bowel can be discriminated from the large bowel by the appearance of bowel contents and the presence valvulae conniventes. The contour adheres closely to the outer boundary of the external wall and includes small bowel contents.
BrachialPlex_L BrachialPlex_R BrachialPlexs	2008 Hall [8] 2011 Kong [9] 2015 Brouwer [6] 2016 Standring [7]	Minor	Each brachial plexus should be contoured separately. The brachial plexus originates at the spinal nerve root foraminae C5, C6, C7, C8, and T1 and terminates at the medial limit of the second rib. Begin contouring with a 5mm diameter tool at the C5, C6, C7, C8, and T1 neural foramina and continue caudally, contouring the region from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles. At the levels where no neural foramina are present, contour the space or soft tissue between the anterior and middle scalene muscles. The middle scalene muscle, and therefore brachial plexus structure will terminate in the region of the subclavian neurovascular bundle one or two slices below the clavicular head. The first and second ribs serve as the medial limit of the brachial plexus contour.

			Co-registration with MRI and/or the use of intravenous contrast can help distinguish between nerves and vessels. Be aware that patient positioning may influence the position of the underlying anatomy and the brachial plexus. *BrachialPlexs* is a summation of the right and left brachial plexus and may be used for dose reporting purposes.
Brain	2015 Brouwer [6] 2018 Eekers [10]	Minor	The brain is the whole brain including the cerebellum, cerebrospinal fluid, and small brain vessels. Contour from the tentorium to the foramen magnum including the temporal lobes bilaterally. The brainstem, carotid canal, cavernous, sigmoid, transverse, and superior sagittal sinuses are excluded. Contour on brain soft tissue windows on CT. Use sagittal viewing planes and consider MRI co-registration to support identification of the cranial border of the brainstem.
Brainstem	2015 Scoccianti [11] 2018 Eekers [10]	Minor	The brainstem includes the midbrain, pons, and medulla oblongata. The cranial border is the substantia nigra at the cerebral peduncle; the cranial aspect of the posterior clinoid process may be used as a bony landmark. Continue contouring to the caudal limit at the level of the tip of the dens of the C2 vertebra. Contour on brain soft tissue windows on CT. Use sagittal viewing planes and consider MRI co-registration to support identification of the cranial border of the brainstem.
Breast_L Breast_R Breasts	2013 Nielsen [12] 2016 Offersen [13]	Minor	Each breast should be contoured separately as a glandular tissue structure. The cranial border is at the upper most aspect of visible breast tissue and is not expected to extend beyond the lower edge of the sterno-clavicular joint. The caudal border is that with visible glandular tissue. The breast extends laterally to the lateral thoracic artery and medially to the lateral aspect of the sternum. The breast excludes skin anteriorly. Posteriorly, the anterior aspect of the major pectoral muscles and exterior surface of the ribs are excluded. *Breasts* is a summation of the right and left breast and may be used for dose reporting purposes.

Bronchus_Prox	2011 Kong [9]	Minor	The proximal bronchial tree is contoured using mediastinal windows and includes the external aspect of the cartilage rings. The cranial border is 2cm cranial to the carina. Caudally, the proximal bronchial tree includes the bilateral proximal airways: the carina, right and left mainstem bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi should end immediately at the site of a segmental bifurcation. Lung windows may assist in identification of the segmental bifurcations.
Canal_Anal	2016 Standring [7] 2018 Nyholm [14]	Developed in response to survey feedback	The anal canal originates at the anorectal junction where the perirectal fat can no longer be seen, coinciding with the insertion of the levator muscles and the pubo-rectalis sling; these structures are best visualised on coronal viewing planes. The anal canal continues caudally to the anal verge. A radio-opaque marker may be used to define the external limit of the anal canal. The contour adheres closely to the outer boundary of the external anal wall, and includes sphincter muscles and anal contents.
CaudaEquina	2012 Yi [15] 2018 Berg [16]	Major	The cauda equina is defined by the thecal sac within the spinal canal. The cranial border of the cauda equina is located at the caudal limit of the spinal cord, usually at the level of L1-2 vertebral bodies. The spinal cord thickens into the conus medullaris at this level and can be used as a landmark. The caudal limit is at the termination of the thecal sac usually at the caudal limit of the S1 vertebral body, however extension to the caudal limit of the S2 vertebral body or beyond is not unusual. The thecal sac is best defined on MRI.
Cavity_Oral	2015 Brouwer [6]	Major	The cranial extent of the oral cavity is defined by the hard palate mucosa and mucosal reflections near the maxilla.

	2016 Standring [7]		The posterior border is the posterior edge of the hard palate and should be extended to the level of the caudal border, where the first slice of the tubercle of the hyoid bone is visible. Antero-laterally, the structure includes the inner soft tissue surface of the mandible and maxilla.
Chestwall_L Chestwall_R Chestwall	2011 Kong [9]	Minor	Each chest wall should be contoured separately. The chest wall is a 2cm rind of the hemi-thorax outside of the thoracic cavity. The structure includes ribs, intercostal vessels, nerves and muscles, and excludes vertebral bodies, sternum, and skin. The anterior-medial border is at the lateral edge of the sternum; the posterior-medial border is the lateral aspect of the vertebral body. *Chestwall* is a summation of the right and left chestwall and may be used for dose reporting purposes.
Cochlea_L Cochlea_R Cochlea	2013 Kojima [17] 2015 Brouwer [6] 2018 Eekers [10]	Minor	Each cochlea should be contoured separately. The cochleae appear as small curved or round lucencies in the petrous portion of the temporal bone. The cochleae lie caudal to the semicircular canals, lateral to the internal auditory meatus, anterior to the vestibular apparatus, and medial to the middle ear. The structure is small and measures up to 0.6cc. Contour on CT using bone windows. Exclude the semi-circular canals. *Cochlea* is a summation of the right and left cochlea and may be used for dose reporting purposes.
Colon_Sigmoid	2016 Standring [7]	Developed in response to survey feedback	The sigmoid colon is an S-shaped structure that is mobile on its own mesentery. The cranial border is where the structure meets the descending colon and can be identified where the colon curves medially at the level of the left iliac crest. The caudal border is at the recto-sigmoid junction, approximately at the level of the S3 vertebral body; this can best be identified using sagittal viewing planes.

			The contour adheres closely to the outer boundary of the external wall and includes sigmoid bowel contents.
Duodenum	2014 Jabbour [3]	No amendment	The duodenum should be contoured from the pylorus to the duodenojejunal junction/ligament of Treitz. The majority of the structure is fixed to the retroperitoneum and follows a C-shaped course around the head of the pancreas. The contour follows four anatomical sections: 1) 5cm in length and anterolateral to the body of the L1 vertebra 2) 7-10cm descending adjacent to the L1-3 vertebral bodies 3) 6-8cm in length, turning medially and crossing the L3 vertebral body. The aorta and inferior vena cava are posterior; the superior mesenteric artery and vein lie anteriorly 4) 5cm in length and ascending from the L3 vertebral body to the cranial border of the L2 vertebral body The contour adheres closely to the outer boundary of the external wall and includes duodenal contents. Take care to distinguish the duodenum from the head of the pancreas as the structures are in close proximity.
Esophagus	2010 Wasik [18] 2011 Kong [9]	No amendment	The esophagus is contoured on mediastinal windows to include all muscle layers out to the fatty adventitia. Contour from the lower edge of the cricoid cartilage to the gastro-esophageal junction.
Esophagus_S	2009 Li [19] 2010 Wasik [18] 2011 Kong [9] 2015 Brouwer [6]	Developed in response to survey feedback	The cervical esophagus is contoured on mediastinal windows to include all muscle layers out to the fatty adventitia. The cranial border is 10mm caudal to the lower edge of the cricoid cartilage. The cervical esophagus abuts the esophageal inlet at the cranial border. The caudal border is at the lower edge of the C7 vertebral body.
Eye_A_L Eye_A_R	2015 Brouwer [6]	Developed in response to survey feedback	Each anterior segment of the eye should be contoured separately; the structure consists of the cornea, iris, ciliary body, and lens. Exclude the extra-ocular muscles.
Eye_L Eye_R Eyes	2015 Brouwer [6]	Minor	Each eye should be contoured separately.

			Contour the entire eye to include the anterior and posterior segments. Anteriorly, the structure consists of the cornea, iris, ciliary body, and lens. Posteriorly, the eye includes the anterior hyaloid membrane, vitreous humor, retina, and choroid. Exclude the optic nerve and extra-ocular muscles. *Eyes* is a summation of the right and left eye and may be used for dose reporting purposes.
Eye_P_L Eye_P_R	2015 Brouwer [6]	Developed in response to survey feedback	Each posterior segment of the eye should be contoured separately. The posterior segment of the eye consists of the anterior hyaloid membrane, vitreous humor, retina, and choroid. Exclude the optic nerve and extra-ocular muscles.
FemurHeadNeck_L FemurHeadNeck_R	2012 Gay [4]	Minor	Each femoral head and neck should be contoured separately. The structure includes the ball of the femur, femoral neck, greater trochanter, and proximal shaft to the caudal limit of the lesser trochanter. Contour on bone windows.
Fossa_Pituitary	2015 Brouwer [6] 2018 Eekers [10]	Developed in response to survey feedback	Contour the inner bony limits of the sella turcica as an alternative anatomical structure for the pituitary gland. Make use of sagittal viewing planes and contour on bone windows.
Genitals	PLATO Trial Development Group, United Kingdom [20] 2015 Brooks [21]	Minor	The female genitals structure encompasses the clitoris, labia major and minora, mons pubis, and the surrounding fat. The male genitals structure encompasses the entire penis, scrotum, perineal body, and the surrounding fat. Both structures extend laterally to the inguinal creases. A useful landmark for the cranial border is midway through the symphysis pubis. Consider MRI co-registration to support delineation.
Glnd_Lacrimal_L Glnd_Lacrimal_R	2006 Hughes [22] 2015 Freedman [23] 2015 Scoccianti [11] 2018 Eekers [10]	Minor	Each lacrimal gland should be contoured separately. The lacrimal gland lies in the cranio-lateral extraconal portion of the orbit, medial to the zygomatic process of the frontal bone. The structure is hyperdense when compared to the surrounding fat.

			The caudal border is at the level of the lateral rectus muscle; the superior rectus muscle lies laterally. The gland is almond shaped, concave against the eye and measures approximately 20 x 15 x 5mm. Contour on soft tissue windows.
Glnd_Submand_L Glnd_Submand_R Glnd_Submands	2009 van de Water [24]	Minor	Each submandibular gland should be contoured separately. The submandibular glands lie within the submandibular space and appear hypodense on CT compared to the surrounding structures. The submandibular glands are composed of a large superficial lobe and a smaller deep lobe, which are continuous with each other around the posterior border of the mylohyoid muscle. The cranial border is located at the caudal edge of the medial ptyergoid muscle at the level of the C3 vertebral body. Continue contouring caudally until fatty tissue appears. The lateral border is the platysma muscle and the mandibular surface. The medial border is the lateral surface of the mylohyoid muscle and the anterior belly of the digastric muscle. *Glnd_Submands* is a summation of the right and left submandibular gland and may be used for dose reporting purposes.
Glnd_Thyroid	2014 Sun suppl [5] 2015 Brouwer [6]	Minor	The thyroid gland appears hyperdense on CT compared to the surrounding structures. The cranial border is the caudal edge of the piriform sinus, the caudal border is usually found at level of the C5-7 vertebral bodies. Anteriorly the gland is bordered by the sternocleidomastoid muscles. The cervical vessels, cricoid cartilage, and esophagus lie posterior-medially. The thyroid gland is a soft tissue structure and therefore the thyroid cartilage and cricoid cartilage should be excluded.
Glottis	2011 Christianen [25] 2015 Brouwer [6] 2016 Standring [7]	Developed in response to survey feedback	The glottis structure is the true vocal cords. Contour from the cranial edge of the arytenoid cartilages to the caudal edge of the anterior part of the thyroid cartilage. Posteriorly the glottis is bordered by the cricoid cartilage and anterior border of the arytenoid cartilages.

			The thyroid cartilage is antero-lateral and the pharyngeal lumen is medial to the structure. Air should be excluded from the structure.
GreatVes	2011 Kong suppl [9] 2016 Standring [7]	Minor	The great vessels are contoured on mediastinal windows to include the vascular wall and muscle layers out to the fatty adventitia. The structure abuts the *Heart+A_Pulm* contour. Intravenous contrast may be helpful in distinguishing the great vessels from adjacent structures. Contour the superior vena cava and the aorta. The branches of the aortic arch: the brachiocephalic artery, the left common carotid artery, and the left subclavian artery may be included. The inferior vena cava is included in the great vessels structure. The cranial aspect is where the inferior vena cava is clearly separate from the right atrium of the heart. The cranial, caudal, and lateral extent to which the great vessels structure is contoured beyond this guidance is defined by the clinical trial protocol.
Heart	2011 Feng [1]	Minor	The heart is contoured on mediastinal windows to include the pericardial sac. The cranial border is where the pulmonary trunk and right pulmonary artery are seen as separate structures. The caudal extent is at the apex of the heart where the left ventricle blends with the diaphragm. Major vessels, including the inferior vena cava should be excluded. The pulmonary arteries are excluded below the main bronchi. Investigators wishing to contour the heart with cranial border at the cranial aspect of the pulmonary artery should refer to *Heart+A_Pulm*.
Heart+A_Pulm	2016 Haslett [26] 2016 Standring [7]	Developed in response to survey feedback	The heart is contoured on mediastinal windows to include the pericardial sac. The cranial border is at the cranial aspect of the pulmonary artery. The caudal extent is at the apex of the heart where the left ventricle blends with the diaphragm. Major vessels, including the inferior vena cava should be excluded. The pulmonary arteries are excluded below the main bronchi.

			Investigators wishing to contour the heart with cranial border at the bifurcation of the pulmonary artery should refer to *Heart.*
Hippocampus_L Hippocampus_R Hippocampi	2009 Chera [27] 2010 Gondi [28] 2015 Scoccianti [11] 2016 Standring [7] 2017 di Biase [29] 2018 Eekers [10]	Minor	Each hippocampus should be contoured separately. The hippocampus is a small, seahorse shaped, complex gray matter structure located in the medial temporal lobe. Delineation using co-registered T1-weighted MRI with use of sagittal viewing planes is essential. Hippocampal size (2.8-4.0cc) and location may vary. Begin the contour at the most caudal hypointense gray matter located medial to the cerebrospinal fluid hypointensity/temporal horn of the lateral ventricle. Continue to contour cranio-posteriorly avoiding the amygdala and uncus, which are located anterior to the tip of the temporal horn of the lateral ventricle. The hippocampus terminates when the T1-hypointense structure no longer borders the lateral ventricle at the level of the pons and the pituitary gland. At this point, the crux of the fornix emerges anteriorly and the splenium of the corpus callosum can be visualised posteriorly. The medial border is the ambient and quadrigeminal cisterns. *Hippocampi* is a summation of the right and left hippocampus and may be used for dose reporting purposes.
Inlet_Cricophar	2009 Li [19] 2011 Christianen [25] 2015 Brouwer [6]	Developed in response to survey feedback	The cricopharyngeal inlet encompasses the cricopharyngeal muscle and the esophageal inlet. The cricopharyngeal inlet originates at the first slice caudal to the arytenoid cartilage and extends to 10mm caudal to the lower edge of the cricoid cartilage. The cricopharyngeal muscle component is confined by the posterior edge of the cricoid cartilages anteriorly and by the prevertebral muscle posteriorly. The lateral border is the thyroid cartilage, fatty tissue, and thyroid gland. All muscle layers should be included.
Inlet_Esophagus	2009 Li [19] 2015 Brouwer [6]	Developed in response to survey feedback	The esophageal inlet measures 10mm cranio-caudally and originates at the caudal edge of the cricoid cartilage. The caudal border abuts the cervical esophagus. Contour on mediastinal windows to include all muscle layers.

Jejunum_Ileum	2014 Jabbour [3] 2016 Standring [7]	Developed in response to survey feedback	This structure combines the jejunum and ileum as the anatomical distinction between the two small bowel structures is not easily identified on CT or MRI. Contour from the duodenojejunal junction/ligament of Treitz located at the cranial border of the L2 vertebral body and continue to the ileocaecal junction. The jejunum and ileum can be discriminated from the large bowel by the appearance of bowel contents and the presence valvulae conniventes. The contour adheres closely to the outer boundary of the external wall and includes bowel contents.
Kidney_L Kidney_R Kidneys	2014 Jabbour [3] 2016 Standring [7]	Minor	Each kidney should be contoured separately from the upper to the lower pole. The kidney is easily distinguished from surrounding adipose tissue and is located at the level of the T12 and L3 vertebral bodies. The structure excludes cysts, pararenal fat, and the adrenal gland. The kidney cortex may be delineated as a separate structure. *Kidneys* is a summation of the right and left kidney and may be used for dose reporting purposes.
Kidney_Cortex_L Kidney_Cortex_R Kidney_Cortex	2016 Standring [7]	Minor	Each kidney cortex should be contoured separately from the upper to the lower pole. The kidney cortex structure is the kidney parenchyma and includes the fibrous capsule surrounding the kidney, the kidney cortex, and the kidney medulla. The structure excludes cysts, the kidney pelvis, pararenal fat, and the adrenal gland. *Kidney_Cortex* is a summation of the right and left kidney cortex and may be used for dose reporting purposes.
Larynx	2007 Sanguineti [30] 2011 Christianen [25] 2014 Sun [5] 2015 Brouwer [6]	Minor	The larynx is comprised of supraglottic and glottic components: epiglottis, supraglottic adductor muscles, aryepiglottic folds, arytenoid cartilages, and the true and false vocal cords. Contour from the tip of the epiglottis to the caudal edge of anterior part of the thyroid cartilage. The hyoid bone, pre-epiglottic space, and thyroid cartilage lie anteriorly.

	2016 Standring [7]		The inferior pharyngeal constrictor muscles, pharyngeal lumen, and cricoid cartilage define the posterior border. The thyroid cartilage is antero-lateral and the pharyngeal lumen is medial to the structure.
Larynx_SG	2011 Christianen [25] 2015 Brouwer [6] 2016 Standring [7]	Developed in response to survey feedback	The supraglottic larynx is a soft tissue structure, which includes the epiglottis, supraglottic adductor muscles, aryepiglottic folds, arytenoid cartilages, and false vocal cords. The cranial border is at the tip of the epiglottis and extends caudally to the cranial edge of the arytenoid cartilages. The hyoid bone, pre-epiglottic space, and thyroid cartilage lie anteriorly. The inferior pharyngeal constrictor muscles and pharyngeal lumen define the posterior border. The thyroid cartilage is antero-lateral and the pharyngeal lumen is medial to the structure.
Lens_L Lens_R	2015 Scoccianti [11] 2018 Eekers [10]	Minor	Each lens should be contoured separately. The lens is a clearly visible biconvex, avascular structure located between the vitreous humor and the iris. The diameter measures up to 10mm.
Lips	2015 Brouwer [6] 2016 Standring [7]	Minor	The lip contour extends from the caudal aspect of the nasal columella to the cranial border of the mandibular body. The lateral border is at the lateral commissure. The lip contour includes the inner surface of the lip. A radio-opaque marker may aid identification of the external borders.
Liver	2010 Pan [31] 2014 Jabbour [3]	Minor	The liver should be contoured in entirety from the cranial diaphragmatic aspect to the caudal tip of the right lobe, using soft tissue windows. The inferior vena cava should be excluded from the liver contour when it is clearly separate from the liver. The gall bladder should be excluded. Intravenous contrast may be helpful in distinguishing the left border of the liver from adjacent structures.
Lobe_Temporal_L Lobe_Temporal_R	2014 Sun suppl [5] 2016 Standring [7]	Minor	Each temporal lobe should be contoured separately. The temporal lobe includes the hippocampus, parahippocampal gyrus, and uncus.

			Begin contouring at the cranial edge of the sylvian fissure and continue caudally to the base of the middle cranial fossa. The greater wing of sphenoid and temporal bone define the anterior border. Posteriorly the temporal lobe abuts the petrous part of the temporal bone and cerebellar tentorium. The medial border is the cavernous sinus, sphenoid sinus, and sylvian fissure. The lateral surface of the temporal lobe is caudal to the lateral fissure and lies adjacent to the squamous portion of the temporal bone. Contour on CT using brain soft tissue windows, MRI co-registration may aid delineation.
LumbSacPlex_L LumbSacPlex_R LumbSacPlexs	2012 Yi [15]	Major	*LumbSacPlexs* is the entire lumbo-sacral plexus including bilateral nerve roots. When separated, *LumbSacPlex_L/R* should be used to denote structure laterality. The lumbosacral plexus should be contoured from the L4 nerve root to the cranial most portion of the femoral neck. The L4 nerve root should be contoured by including the space defined by the psoas muscle anterior and laterally, and the facet joint/posterior vertebral body elements posteriorly. The L5 nerve root is contoured using the common iliac vein and psoas muscle anteriorly, the iliacus muscle laterally, and the vertebral body, and sacrum posteriorly. Below the level of the L5 foramen, the sacroiliac joint should serve as the lateral border. Beginning at the level of the S1 foramen, the lumbosacral plexus and S1 lie in the area bounded by the iliac vessels anteriorly, the iliacus muscle/iliac wing laterally, and piriformis muscle posteriorly. At the caudal margin of the greater sciatic foramen, contour the space bounded by the obturator internus muscle/ischial spine anteriorly, piriformis muscle laterally, and gluteus maximus muscle posteriorly. The medial portion of the obturator internus muscle should serve as the medial extent. Below the piriformis muscle, contour the space between the obturator internus muscle anteriorly and the gluteus maximus muscle posteriorly. The medial and lateral extent should be 1-2 cm in length.
Lung_L Lung_R Lungs	2011 Kong [9]	Minor	Each lung should be contoured separately on lung windows.

			Contour the whole lung, from the apex to the diaphragm including all inflated and collapsed lung. Small vessels less than 10mm in diameter and vessels beyond the hilar region are included. Exclude the proximal bronchial tree and the trachea. *Lungs* is a summation of the right and left lung and may be used for dose reporting purposes.
Musc_Constrict	2011 Christianen [25]	Developed in response to survey feedback	The muscle constrictor structure encompasses the superior, middle, and inferior pharyngeal constrictor muscles in a single structure. Contour from the caudal tips of the pterygoid plates to the caudal limit of the arytenoid cartilages. The pre-vertebral muscle defines the posterior border. The lateral borders are the medial pterygoid muscle cranially and the hyoid and thyroid cartilages caudally. The anterior border at the cranial aspect is the pterygoid hamulus. The hyoid bone and posterior border of the thyroid cartilage define the anterior border for the middle and inferior pharyngeal constrictor muscles.
Musc_Constrict_I	2011 Christianen [25]	Minor	The inferior pharyngeal constrictor muscle is the thickest of the three constrictor muscles. The inferior pharyngeal constrictor muscle originates at the lower edge of the hyoid bone and extends caudally to the lower edge of the arytenoid cartilages. Anteriorly the inferior pharyngeal constrictor muscle attaches to the posterior edge of the thyroid cartilage and the posterior border is defined by the prevertebral muscles. The superior horn of the thyroid cartilage marks the lateral border.
Musc_Constrict_M	2011 Christianen [25]	Minor	The middle pharyngeal constrictor muscle originates at the lesser and greater horns of the hyoid bone. The cranial border is at the upper edge of the C3 vertebral body, in continuation with the superior pharyngeal constrictor muscle. The insertion of all fibres unites in the median pharyngeal raphe, the caudal border is defined as the lower edge of the hyoid bone. Anteriorly it is bordered by the tongue base and hyoid bone. Posteriorly the border is defined by the prevertebral space. The pharyngeal lumen is excluded.

Musc_Constrict_S	2011 Christianen [25]	Minor	The superior pharyngeal constrictor muscle originates at the lower aspect of the pterygoid plates and continues caudally to the lower edge of the C2 vertebral body. The posterior border is defined by the prevertebral muscles and fascia, from which it is separated by the retropharyngeal space. Anteriorly, the superior pharyngeal constrictor muscle is attached to the pterygoid hamulus, the pterygoidmandibular raphe, the posterior end of the mandible, and the base of tongue. The pharyngeal lumen is excluded.
Musc_Cricophar	2011 Christianen [25]	Developed in response to survey feedback	The cricopharyngeal muscle originates at the first slice caudal to the arytenoid cartilages and extends caudally to the lower edge of the cricoid cartilages. Anteriorly, the structure is confined by the posterior edge of the cricoid cartilage and posteriorly by the prevertebral muscles. The lateral border is the thyroid cartilage, fatty tissue, and the thyroid gland.
OpticChiasm	2015 Brouwer [6] 2015 Scoccianti [11] 2018 Eekers [10]	Minor	The optic chiasm is located in the subarachnoid space of the suprasellar cistern, 10mm cranial to the pituitary gland and anterior to the pituitary stalk. Laterally the optic chiasm is bordered by the internal carotid artery and the anterior communicating artery. The contour meets the optic nerves anteriorly and includes the divergence of the optic tracts posteriorly. The optic chiasm measures 14mm transversely, 8mm anterior-posteriorly, and 2-5mm cranio-caudally. Co-registration with T1-weighted MRI is recommended. Ensure the structure is contoured in continuity with the optic nerves.
OpticNrv_L OpticNrv_R	2015 Brouwer [6] 2018 Eekers [10]	Minor	Each optic nerve should be contoured separately. The optic nerve is 2-5mm diameter structure originating at the posterior aspect of the eye, passing through the bony optic canal and terminating at the optic chiasm. To better identify the nerve beyond the bony canal, consider co-registration with T1-weighted MRI. Ensure the

			structure is contoured in continuity with the eye and the optic chiasm.
Ovary_L Ovary_R Ovaries	1992 Olson [32] 2006 Hauth [33] 2012 Peters [34] 2016 Standring [7]	Developed in response to survey feedback	Each ovary should be contoured separately. In reproductively mature, pre-menopausal women, the ovaries are ovoid structures measuring 4 x 3 x 2cm. The ovaries are situated in the ovarian fossae, which are adjacent to the lateral pelvic wall. Cranio-lateral to the right ovary are the ileocaecal junction, caecum, and appendix. The sigmoid colon passes over the left ovary. The posterior border is free, faces the peritoneum and overlies the upper part of the internal iliac artery and vein, and ureters. Co-registration with T2-weighted MR and the use of both sagittal and axial viewing planes is advised to aid delineation. *Ovaries* is a summation of the right and left ovary and may be used for dose reporting purposes.
Pancreas	2014 Jabbour [3]	No amendment	The pancreas lies at the level of the L1-L3 vertebral bodies and is identified by its unique glandular appearance. The structure should be contoured in entirety. The pancreatic head is located to the right of the superior mesenteric artery. The uncinate process, an extension of the pancreatic head is posterior to the superior mesenteric vein. The pancreatic body is located between the coeliac trunk and superior mesenteric artery, where it lies anterior to the aorta. Take care to distinguish the pancreatic head from the duodenum as the structures are in close proximity.
Parotid_L Parotid_R Parotids	2009 van de Water [24] 2013 Hoebers [35]	Minor	Each parotid gland should be contoured separately. The parotid gland is an irregular shaped gland wedged between the ramus of the mandible and the mastoid process. The cranial border is the zygomatic arch, the gland extends caudally to the angle of the mandible. The anterior border is the masseter muscle; in 20% of cases the parotid gland extends anteriorly over the surface of the masseter muscle. The posterior border is the anterior aspect of the sternocleidomastoid muscle.

			The parotid gland is laterally confined by the platysma muscle and medially by the posterior belly of the digastric muscle, styloid process, and the parapharyngeal space. The retromandibular vein should be included in the parotid gland contour. Please note, volume and position of the gland can vary. Ensure inclusion of the superficial and deep lobes. *Parotids* is a summation of the right and left parotid gland and may be used for dose reporting purposes.
PenileBulb	2012 Gay [4]	Minor	The penile bulb is the portion of the bulbous spongiosum of the penis immediately caudal to the genito-urinary diaphragm. The structure is bright on T2 weighted MRI. On CT, the structure is posterior to the urethra and has a round shape. The structure is normally 9-10mm in the cranial-caudal direction. The contour should not continue in to the shaft of the penis.
Pituitary	2015 Brouwer [6] 2015 Scoccianti [11] 2018 Eekers [10]	Minor	The pituitary gland is best defined using sagittal viewing planes on brain soft tissue windows. The pituitary gland is oval shaped and lies in the sella turcica, measuring up to 12mm cranio-caudally. The pituitary gland is bordered laterally by the cavernous sinuses. The pituitary gland is connected to the hypothalamus by the pituitary stalk, which lies posterior to the crossing fibres of the optic chiasm. If the pituitary gland cannot be visualised on CT soft tissue windows, consider MRI co-registration. Investigators may consider contouring the inner bony limits of the sella turcica, *Fossa_Pituitary*, as an alternative structure.
Rectum	2012 Gay [4] 2016 Standring [7] 2018 Nyholm [14]	Major	The rectum should be contoured to the outer boundary of the external rectal wall, including rectal contents. Contour from the rectosigmoid flexure, approximately at the level of the S3 vertebral body, the rectosigmoid flexture is best visualised on sagittal viewing planes. The caudal border is at the anorectal junction where the perirectal fat can no longer be seen, coinciding with the insertion of the levator muscles and the pubo-rectalis sling;

			these structures are best visualised on coronal viewing planes.
Retina_L Retina_R Retinas	2015 Scoccianti [11]	Developed in response to survey feedback	Each retina should be contoured separately. The retina is a thin neurosensorial membrane, which lines the posterior wall of the eye. The contour should extend from the insertion of the lateral rectus muscle to the contralateral medial rectus muscle, encompassing the posterior wall of the eye. *Retinas* is a summation of the right and left retina and may be used for dose reporting purposes.
Skin	2016 Standring [7] 2018 Eekers [10]	No amendment	The skin is the 5mm inner rind of the external body contour. Please note actual skin thickness will vary dependent on region of interest.
Spc_Bowel	2008 Sanguineti [36] 2012 Gay [4]	Developed in response to survey feedback	The bowel space represents the space in which the bowel may occupy from the level of the pylorus to the recto-sigmoid junction. The contour extends to the abdominopelvic sidewalls and should include the pelvis caudal to the recto-sigmoid junction as small bowel can occupy this region. The stomach, pancreas, spleen, liver, kidneys, ureters, bladder, reproductive organs, muscles, and major vessels are excluded. Investigators wishing to contour the bowel should refer to the *Bowel* structure.
SpinalCanal	2011 Kong [9] 2015 Brouwer [6] 2016 Standring [7]	Major	The spinal canal is contoured according to the inner limits of the spinal canal using bone windows. The cranial border is at the level of the tip of the dens of the C2 vertebra. The caudal border is the most caudal slice where the spinal canal is visualised, usually at the level of the L5-S1 vertebral bodies.
SpinalCord	2015 Brouwer [6] 2016 Standring [7] 2018 Berg [16]	Minor	The spinal cord is contoured as the true spinal cord, not the spinal canal. The cranial border is at the level of the tip of the dens of the C2 vertebra, where the structure meets the brainstem.

			The caudal border is where the spinal cord thickens into the conus medullaris at the level of L1-2 vertebral bodies i.e. the cranial border of the cauda equina.
Spleen	2016 Standring [7] 2018 Chaudhry [37]	Minor	The spleen varies in size and shape, but is usually 12 x 7 x 3cm and located at the left upper abdominal quadrant. The stomach lies anterior to the spleen. Posteriorly, the spleen is surrounded by left 9th to 11th ribs and diaphragm. The left kidney is medial to the spleen and the caudal border is the left colic flexure. The peritoneum surrounds the spleen and should be excluded from the structure. The shape of the spleen will be affected by the surrounding organs and adjustment of CT window and level may be necessary to better distinguish the border of the spleen against adjacent structures.
Stomach	2014 Jabbour [3]	Minor	The stomach should be contoured from the gastro-esophageal junction to the pylorus. Contour to the outer extent of the external wall, including stomach contents.
Testis_L Testis_R	2016 Standring [7]	No amendment	Each testis should be contoured separately. The testes are ovoid organs covered by the tunica albuginea and the tunica vaginalis. Contour the each testis along with the tunica vaginalis and epididymis. The spermatic cord is excluded from the structure.
Trachea	2011 Kong [9] 2014 Sun [5]	Minor	The trachea should be contoured on mediastinal windows. Contour from the caudal edge of the cricoid cartilage continuing to 2cm cranial to the carina. Contour to the outer boundary of the cartilage, including the lumen, and trachealis muscle. The esophagus lies posteriorly and should be excluded.
Ureter_L Ureter_R Ureters	2016 Standring [7]	Minor	Each ureter should be contoured separately. The cranial border is at the medial aspect of the kidney. The abdominal parts of the ureter are retroperitoneal and lie anterior to the psoas muscle. The ureters continue to run caudally over the pelvic brim at the bifurcation of the common iliac arteries. At the level of the ischial spine, the ureter turns anterior and medial to enter the postero-lateral wall of the urinary

			bladder, before opening into the urinary bladder at the ureteric orifice. The structure should be contoured to include all fibromuscular layers. *Ureters* is a summation of the right and left ureter and may be used for dose reporting purposes.
Urethra	2016 Kataria [38] 2016 Standring [7] 2019 Zakian [39]	Major	The urethra extends from the internal urethral orifice at the bladder neck and continues caudally to the external urethral orifice. In females, the urethra is 4cm in length. In males it is 17.5-20cm in length. The urethra is not visible on CT and should be contoured on T2-weighted MRI where it is moderately hyperintense. Contour to include all muscle layers and use sagittal viewing planes to aid identification of the structure. Be aware that placement of a urinary catheter may distort the position and shape of the urethra.
Urethra_Prostatc	2016 Kataria [38] 2016 Standring [7] 2019 Zakian [39]	Minor	The prostatic urethra is 3-4cm in length and tunnels through the prostate gland. The cranial and caudal borders are defined by the limits of the prostate gland. This structure is not visible on CT and should be contoured on T2-weighted MRI where it is moderately hyperintense. Contour to include all muscle layers and use sagittal viewing planes to aid identification. Be aware that placement of a urinary catheter may distort the position and shape of the prostatic urethra.

Example of implementation of Global Harmonization Group organ at risk consensus contouring guidance

In the XXX Trial participants are positioned supine and immobilised with a knee rest with arms placed out of the radiation therapy field i.e. across the chest.

The radiation therapy CT planning scan will be performed with an empty bladder. The rectum should be empty of faeces and flatus and measure less than Xcm anterior-posteriorly. If the rectum is larger than Xcm, ask the participant to void and re-attempt the scan.

The use of intravenous or oral contrast is not mandatory in XXX Trial. The radiation therapy CT planning scan level is from L4-5 interspace to Xcm caudal to the lesser trochanter.

The descriptions below have been adopted from the Global Harmonization Group organ at risk consensus contouring guideline [REF].

Please note the study specific amendment to the standardised description(s) below where structures are not contoured in entirety due to the radiation therapy CT planning scan levels; partially contoured structures are denoted with the tilde (~) suffix.

Standardised Nomenclature	**Consensus Contouring Guidance**
Bladder	The bladder should be contoured in entirety from base to dome. The lateral extent is the outer bladder wall.
Bowel~	The bowel encompasses the small (duodenum, jejunum and ileum) and large bowel (caecum, ascending, transverse, descending, and sigmoid colon) structures in one contour. Delineate from the pylorus to the recto-sigmoid junction adhering closely to the outer boundary of the external bowel wall, including bowel contents. Ensure small bowel in the lower pelvis caudal to the recto-sigmoid junction is included. The Bowel structure should be contoured Xcm cranial and Xcm caudal to the PTV.
FemurHeadNeck_L FemurHeadNeck_R	Each femoral head and neck should be contoured separately. The structure includes the ball of the femur, femoral neck, greater trochanter, and proximal shaft to the caudal limit of the lesser trochanter. Contour on bone windows.

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Paper 5: Participation letter

National Radiotherapy Trials QA Group
Mount Vernon Cancer Centre
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5th February 2019

Dear Dr XXXX and Team

Thank you for participating in Isotoxic IMRT. It was great to have your involvement in this important study.

To fully evaluate the secondary endpoint of acute and late high-grade toxicity, we request the 4D-CT and bi-daily CBCTs taken throughout radiotherapy to be transferred to RTTQA for analysis.

Please could your team transfer the outstanding data by SFT for the participants listed below. I have enclosed the transfer instructions for ARIA and Elekta (XVI) centres.

Patient	Data
XX	CBCT, AVIP (CT), dose cube (RD), plan (RP), structure set (RS)

Should you have any questions about this work, please contact me directly at RTTQA.

With best wishes

Dr Romaana Mir
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Quick Reference Guide Exporting CBCTs from Aria

These steps are for guidance only. Please contact RTTQA if you have difficulties exporting data.

1. Load patient in Aria, go to Offline review and select one (any is ok) of the CBCTs to load.
2. Select 'Session Timeline' tab at the bottom of the screen.
3. Right click on the CBCT to export and select 'Export to DICOM' >> 'To 'DICOM Export to Pinnacle/External Anonymisation Software/Patient Destination Folder''. (As per standard departmental practice).
4. The Import Export window loads. Select the 'Show/Hide Tree' button to bring up a list of all CBCTs and registration objects.
5. Select the radio buttons next to the CBCTs to export, using the date to identify them.
6. Click on the + to expand the folder called 'Registrations':

7. Select the radio buttons of the registration objects that have the same date as the CBCTs you wish to export.
8. Click the right arrow to export to the export folder/destination.
9. In windows explorer navigate to the export folder/destination and select the CBCTs and registration object files. Copy them to the DICOM anonymiser folder and run through your anonymiser to anonymise as per standard departmental working instructions. **Please check the anonymisation software does not remove the registration objects.** If this occurs please contact RTTQA.
10. Save in a folder ready for export to RTTQA.

Please note, for ease, whole patient exports can be submitted to RTTQA. Furthermore RTTQA can provide more detailed information for ARIA exports, if required.

Quick Reference Guide Exporting CBCTs from Elekta (XVI)

Images need to be exported individually, not as a treatment.

1. On the XVI acquisition PC select the image to be exported.

2. Select IMAGE from the tool bar
   2.1. EXPORT
   2.2. DICOM SERVER 'select TPS/online server'
   2.3. OK

3. The next screen gives 3 options:

   - Option 1 – In the Option 1 list, select a multiple of the voxel size in the reconstructed volume for the CT slice thickness. This can be done without a reference dataset being available and hence imports the CBCT into pinnacle without any co-ordinates related to the reference image. This is not likely to be useful.

   - Option 2 – Only available if image registration was done and approved for this reference image. The position of the VolumeView™ exported is the position **before** registration.

   - Option 3 – Only available if image registration was done and approved for this reference image. The position of the VolumeView™ exported is the position **after** registration.

   3.1 **Select Option 3** as the information required is as the patient was treated i.e. after registration (e.g. if patient was treated with correction). NB Registration has to be performed for option 3 to be available.

   3.2. In the Export options area, click the Create CT button.

4. EXPORT.
   Run data through your anonymiser to anonymise as per standard departmental working instructions.

Please contact RTTQA if you have difficulties exporting data or require further assistance.

Paper 5: Raw dosimetric data

Participant one raw data table

	Heart									Oesophagus								
	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
AvIP	**12.95**	**16.17**	**19.51**	**22.71**	**34.03**	**40.96**	**46.24**	**56.07**	**67.58**	**1.06**	**1.41**	**1.95**	**2.76**	**16.37**	**26.49**	**47.92**	**79.62**	**80.49**
sCT #1	13.27	16.68	20.29	23.41	34.16	41.06	46.37	56.06	67.27	1.08	1.45	2.07	2.95	16.83	27.15	58.34	79.41	80.29
sCT #2	14.22	18.17	21.99	25.05	34.62	41.51	46.77	56.28	66.62	1.06	1.44	1.95	2.79	17.21	27.28	58.71	79.64	80.54
sCT #3	13.84	17.51	21.18	24.47	34.57	41.57	46.89	57.11	69.23	1.04	1.39	1.92	2.68	16.88	28.67	61.87	79.9	80.63
sCT #4	13.92	17.6	21.26	24.54	34.65	41.76	47.15	57.13	69.2	1.02	1.38	1.88	2.64	16.75	27.22	55.11	80.62	81.5
sCT #5	13.28	16.58	20.04	23.33	34.46	41.55	49.96	56.88	68.7	1.06	1.43	1.98	2.8	16.7	26.96	49.72	80.49	81.28
sCT #6	13.55	17.18	20.7	23.89	34.73	41.69	47.01	56.83	67.87	1.07	1.4	2.01	2.85	16.96	26.32	53.47	79.93	80.78
sCT #7	13.38	16.73	20.29	23.71	34.94	42.07	47.57	58	70.81	1.03	1.4	1.92	2.71	16.72	26.86	50.62	80.76	81.63
sCT #8	13.04	16.48	20.09	23.52	34.62	41.68	47.1	57.25	69.11	1.09	1.47	2.07	2.94	16.72	25.85	48.32	79.6	80.62
sCT #9	12.63	15.88	19.28	22.47	34.31	41.21	46.5	56.18	66.98	1.1	1.49	2.09	2.98	17.12	26.84	46.78	79.38	80.61
sCT #10	12.5	15.63	18.9	22.15	33.95	40.9	46.18	55.91	66.96	1.07	1.45	2.02	2.87	16.89	27.32	48.33	80.42	81.26
sCT #11	12.79	16	19.36	22.63	34.51	41.65	47.14	57.51	69.82	1.09	1.48	2.08	2.97	17.02	26.82	47.8	80.17	81.23
sCT #12	13.05	16.51	19.94	23.23	34.38	41.27	46.56	56.36	67.66	1.09	1.49	2.11	3.03	16.46	24.88	36.31	79.78	80.99
sCT #13	13.28	16.69	20.16	23.43	34.73	41.86	47.3	57.5	69.58	1.07	1.45	2.01	2.86	16.89	27.16	53.29	80.35	81.36
sCT #14	13.05	16.57	20.05	23.37	34.44	41.38	46.65	56.42	67.48	1.05	1.41	1.95	2.77	16.94	27.1	54.1	80.65	81.5
sCT #15	13.05	16.46	19.99	23.41	34.38	41.37	46.67	56.33	67.27	1.06	1.42	1.93	2.71	16.91	26.29	49.93	80.17	81.14
sCT #16	12.91	16.19	19.67	23.11	34.6	41.67	47.03	57.01	68.67	1.07	1.44	1.99	2.82	16.64	27.17	55.17	80.71	81.58
sCT #17	12.25	15.38	18.79	22.22	34.17	41.02	46.16	55.39	65.1	1.06	1.4	1.91	2.71	16.73	26.34	53.25	80.92	91.73
sCT #18	12.65	15.85	19.23	22.54	34	40.78	45.92	55.21	65.48	1.06	1.42	1.95	2.75	17.07	27.75	51.79	81.11	82.06
sCT #19	13.01	16.43	19.99	23.46	34.72	41.84	47.35	57.84	70.61	1.06	1.43	1.98	2.8	16.88	26.73	52.25	80.81	81.62
sCT #20	13.15	16.62	20.28	23.75	34.93	41.99	47.31	57.15	68.17	1.07	1.45	2.02	2.87	16.82	27.68	61.89	80.88	81.6
sCT #21	12.46	15.46	18.64	21.89	34.87	42.23	47.82	58.4	70.89	1.08	1.46	2.06	2.93	16.74	26.35	48.91	80.43	81.38
sCT #22	12.57	15.72	19.12	22.53	35.01	42.24	47.67	57.78	69.43	1.08	1.45	2.02	2.89	16.77	26.97	52.31	81.67	82.84
sCT #23	12.88	16.08	19.46	22.79	34.65	41.74	47.15	57.09	68.5	1.08	1.47	2.07	2.97	17.13	26.45	52.21	80.82	82
sCT #24	13.14	16.57	20.3	23.89	35.27	42.58	48.15	58.64	71.32	1.07	1.45	2.02	2.88	16.79	26.16	49.12	81.26	82.33
sCT #25	13.4	16.94	20.57	23.91	34.99	42.14	47.59	57.8	69.59	1.07	1.44	1.99	2.81	16.62	27.17	55.11	80.75	81.78
sCT #26	13.15	16.55	20.17	23.66	35.29	42.53	48.04	58.32	70.37	1.06	1.44	1.99	2.82	17.16	26.6	47.81	81.36	82.48
sCT #27	12.79	15.97	19.34	22.62	34.75	41.92	47.43	57.64	69.37	1.07	1.45	2.03	2.89	16.57	26.54	44.66	81.05	82.22
sCT #28	12.56	15.78	19.12	22.39	35.49	43.03	48.76	59.85	73.63	1.07	1.45	2.08	3.01	17.04	26.95	48.67	82.28	83
sCT #29	13.13	16.5	19.95	23.32	35.49	42.92	48.66	59.53	72.67	1.07	1.45	2.05	2.94	17.22	26.3	46.98	81.29	82.25
sCT #30	13	16.41	19.88	23.29	35.14	42.27	47.65	57.61	69.08	1.07	1.46	2.08	2.99	17.54	27.85	61.25	81.6	82.37
sCT #31	13.09	16.68	20.3	23.68	35.17	42.35	47.83	57.99	69.78	1.06	1.43	2.02	2.89	16.98	26.17	51.19	81.17	81.94
sCT #32	13.1	16.41	19.99	23.46	35.44	42.76	48.37	59.08	72.11	1.05	1.41	1.92	2.71	16.75	27.95	50.03	81.71	82.72
sCT #33	13.11	16.35	19.8	23.19	35.25	42.53	48.07	58.41	70.51	1.05	1.42	1.95	2.75	17.05	27.84	55.85	81.35	82.33
sCT #34	13.28	16.8	20.4	23.81	35.3	42.46	47.89	58.04	69.75	1.06	1.43	2	2.86	17.02	28.3	55.29	81.57	82.18
sCT #35	12.96	16.28	19.68	23.02	35.47	42.96	48.71	59.58	72.62	1.06	1.43	2	2.85	16.96	27.07	52.84	81.39	82.16
sCT #36	13.3	16.93	20.47	23.75	35.57	42.88	48.4	58.73	70.89	1.07	1.46	2.09	3.01	17.4	27.38	55.63	81.84	82.51

	Heart									Oesophagus								
	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
sCT #37	13.56	17.13	20.8	24.17	35.11	42.24	47.67	57.73	69.3	1.04	1.39	1.88	2.63	16.91	27.67	49.47	81.26	82.16
sCT #38	13.09	16.55	19.92	23.09	34.78	41.72	46.91	56.27	66.71	1.02	1.37	1.9	2.7	16.08	25.29	37.17	82.73	83.84
sCT #39	13.85	17.5	21.2	24.48	35.73	43.07	48.69	59.31	71.77	1.05	1.41	1.93	2.72	16.96	27.41	53	81.66	82.63
sCT #40	12.77	16.26	20.07	23.74	35.32	42.22	47.36	56.68	67	1.05	1.41	1.94	2.75	15.33	24.78	36.43	80.64	83.61
sCT #41	13.91	17.72	21.67	25.25	35.84	42.99	48.41	58.45	69.93	1.05	1.42	1.96	2.78	17.17	27.87	49.78	81.87	83.05
sCT #42	14.2	18.09	22.12	25.79	36.22	43.65	49.29	59.91	72.53	1.01	1.36	1.83	2.55	17.35	29.37	54.85	81.97	82.54
sCT #43	13.55	17.04	20.71	24.19	35.97	43.38	48.99	59.61	72.29	1.06	1.43	1.99	2.93	17.02	26.64	43.52	81.8	82.85
sCT #44	14.15	17.95	21.77	25.13	35.87	43.17	48.73	59.14	71.33	1.03	1.38	1.89	2.66	17.06	28.19	53.16	82.27	83.38

Participant two raw data table

	Heart									Oesophagus								
	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%	D95%	D90%	D85%	D80%	D50%	D30%	D20%	D10%	D5%
AvIP	0.812	1.078	1.355	1.657	10.801	42.542	51.649	67.716	78.951	0.935	1.04	1.121	1.208	2.674	9.082	74.027	79.981	80.374
sCT #1	0.862	1.131	1.412	1.726	15.091	42.415	51.176	66.533	78.886	0.915	1.037	1.124	1.214	2.657	9.976	77.651	80.74	81.204
sCT #2	0.811	1.076	1.354	1.662	13.889	43.885	53.378	70.469	80.536	0.903	1.023	1.113	1.207	2.602	8.95	76.839	81.434	82.091
sCT #3	0.774	1.038	1.324	1.636	11.201	44.195	53.437	69.885	79.926	0.92	1.03	1.115	1.204	2.623	9.043	77.788	81.288	81.935
sCT #4	0.76	1.019	1.295	1.596	9.246	43.416	53.092	69.946	80.031	0.919	1.017	1.097	1.183	2.645	8.517	73.897	81.352	81.86
sCT #5	0.829	1.101	1.397	1.732	17.94	44.549	54.541	73.602	81.212	0.874	1	1.088	1.177	2.791	10.867	71.237	81.138	82.038
sCT #6	0.805	1.062	1.339	1.644	11.492	42.762	51.888	67.82	79.217	0.925	1.035	1.118	1.205	2.654	8.867	75.81	80.768	81.297
sCT #7	0.783	1.051	1.333	1.646	11.89	44.399	53.575	69.81	79.966	0.905	1.012	1.095	1.18	2.634	8.6	76.621	81.394	81.905
sCT #8	0.834	1.116	1.415	1.75	15.038	43.714	52.78	68.574	79.8	0.907	1.016	1.1	1.189	2.57	9.006	77.062	81.636	82.053
sCT #9	0.799	1.06	1.338	1.653	14.594	44.123	53.622	70.667	81.233	0.879	0.993	1.078	1.164	2.704	10.137	75.551	82.083	82.672

Participant three raw data table

	Heart									Oesophagus								
	D95%	**D90%**	**D85%**	**D80%**	**D50%**	**D30%**	**D20%**	**D10%**	**D5%**	**D95%**	**D90%**	**D85%**	**D80%**	**D50%**	**D30%**	**D20%**	**D10%**	**D5%**
AvIP	0.598	0.757	0.911	1.079	3.367	19.283	36.857	56.914	76.93	0.779	0.91	1.137	1.368	4.458	25.286	43.665	78.456	79.096
sCT #1	0.639	0.819	1.002	1.211	4.815	23.379	36.326	51.889	69.618	0.775	0.886	1.071	1.318	3.223	13.478	41.862	79.48	80.025
sCT #2	0.653	0.843	1.038	1.263	5.594	26.23	39.026	56.26	76.087	0.789	0.907	1.104	1.359	3.365	14.388	48.703	78.932	79.593
sCT #3	0.621	0.794	0.966	1.158	4.235	23.559	39.021	56.265	76.014	0.788	0.919	1.146	1.388	3.92	17.103	45.282	78.373	78.949
sCT #4	0.622	0.795	0.968	1.163	4.32	23.628	38.956	56.13	75.329	0.787	0.914	1.131	1.378	3.829	17.053	48.206	78.553	79.007
sCT #5	0.624	0.795	0.965	1.156	4.094	22.794	38.238	55.56	75.114	0.794	0.928	1.162	1.396	3.983	18.772	42.064	78.489	79.086
sCT #6	0.625	0.798	0.97	1.164	4.25	23.032	38.353	55.488	75.198	0.792	0.926	1.161	1.367	3.946	17.598	43.507	78.494	78.979
sCT #7	0.626	0.799	0.971	1.165	4.214	22.549	37.896	54.634	73.957	0.789	0.92	1.148	1.352	3.857	17.946	45.032	78.917	79.426
sCT #8	0.615	0.784	0.952	1.14	4.007	21.778	37.455	54.432	73.982	0.782	0.904	1.114	1.359	3.85	17.142	43.226	79.039	79.499
sCT #9	0.65	0.835	1.024	1.241	4.802	23.534	36.457	51.52	68.423	0.782	0.896	1.089	1.345	3.415	16.934	43.823	79.732	80.318
sCT #10	0.617	0.789	0.96	1.151	4.11	22.907	38.079	54.881	74.21	0.795	0.936	1.164	1.363	3.846	15.655	40.839	78.604	79.113
sCT #11	0.628	0.804	0.981	1.18	4.487	24.466	38.996	56.845	76.675	0.786	0.907	1.11	1.328	3.589	16.254	46.688	78.833	79.284
sCT #12	0.658	0.835	1.015	1.22	4.734	19.044	32.221	49.231	69.068	0.772	0.894	1.028	1.201	3.264	12.821	30.129	45.864	64.465
sCT #13	0.627	0.798	0.968	1.159	4.1	22.497	37.51	53.884	73.385	0.791	0.926	1.166	1.364	3.935	15.992	37.531	78.652	79.18
sCT #14	0.648	0.825	1.005	1.209	4.667	20.755	33.742	50.797	71.822	0.779	0.902	1.06	1.264	3.321	12.32	32.398	62.541	75.689
sCT #15	0.64	0.822	1.009	1.224	5.151	25.284	39.661	57.754	77.471	0.787	0.902	1.094	1.348	3.282	11.901	45.701	78.753	79.239
sCT #16	0.652	0.828	1.007	1.212	4.644	18.602	31.564	48.001	66.619	0.76	0.869	1.035	1.224	3.144	11.929	28.551	46.467	64.537
sCT #17	0.624	0.795	0.965	1.155	4.068	22.743	38.034	54.57	73.618	0.787	0.912	1.127	1.357	3.834	16.836	42.12	78.55	79.139
sCT #18	0.639	0.822	1.011	1.228	5.332	26.887	40.791	59.771	77.679	0.794	0.916	1.12	1.39	3.536	14.033	49.593	78.204	78.81
sCT #19	0.644	0.826	1.013	1.227	5.225	26.961	41.996	63.055	78.576	0.795	0.922	1.137	1.397	3.696	15.818	49.442	78.657	79.565
sCT #20	0.625	0.798	0.973	1.169	4.309	23.486	38.02	54.985	75.161	0.792	0.931	1.142	1.345	3.87	16.617	39.654	78.525	79.036
sCT #21	0.652	0.829	1.009	1.215	4.768	19.616	32.788	50.491	71.882	0.768	0.885	1.028	1.206	3.273	12.438	29.774	47.888	63.214
sCT #22	0.615	0.786	0.958	1.15	4.165	23.353	38.325	55.472	75.5	0.788	0.917	1.13	1.313	3.577	14.929	42.907	78.596	79.098
sCT #23	0.651	0.835	1.025	1.242	5.017	23.883	37.511	53.397	71.766	0.786	0.899	1.089	1.341	3.489	19.802	48.479	79.778	80.231
sCT #24	0.645	0.83	1.018	1.234	5.192	28.817	41.174	59.319	77.919	0.825	1.02	1.237	1.414	3.864	10.429	31.229	77.026	78.314
sCT #25	0.623	0.794	0.966	1.157	4.094	21.999	37.188	53.935	73.225	0.787	0.915	1.139	1.41	4.032	18.806	44.193	78.772	79.23
sCT #26	0.623	0.795	0.967	1.16	4.198	23.305	38.032	54.903	75.025	0.791	0.929	1.172	1.379	3.97	16.844	40.981	78.685	79.21
sCT #27	0.628	0.801	0.974	1.169	4.251	23.791	38.154	55.118	74.894	0.792	0.929	1.155	1.354	4.423	19.06	41.154	78.523	79.074
sCT #28	0.619	0.79	0.961	1.153	4.15	22.719	37.982	55.059	74.997	0.79	0.924	1.157	1.367	3.875	16.428	42.883	78.536	79.075
sCT #29	0.639	0.821	1.007	1.221	4.987	25.432	39.58	57.264	76.915	0.787	0.906	1.105	1.354	3.522	15.468	51.923	78.877	79.4
sCT #30	0.62	0.793	0.966	1.16	4.269	23.747	38.628	55.739	75.879	0.794	0.938	1.17	1.371	4.004	16.464	41.999	78.499	79.061
sCT #31	0.639	0.82	1.005	1.216	5.086	26.393	40.165	58.274	77.31	0.794	0.923	1.145	1.384	3.677	18.62	61.175	79.037	79.632
sCT #32	0.63	0.81	0.995	1.207	4.994	25.957	41.175	62.241	79.086	0.789	0.909	1.11	1.394	3.772	19.037	55.399	79.318	80.257
sCT #33	0.642	0.814	0.987	1.182	4.322	19.28	31.908	47.505	65.065	0.753	0.859	1.01	1.191	3.049	12.197	28.701	47.197	65.055
sCT #34	0.614	0.785	0.959	1.148	3.851	23.122	37.743	55.063	75.263	0.783	0.907	1.121	1.336	4.119	16.684	43.552	78.743	79.743
sCT #35	0.625	0.798	0.972	1.168	4.326	23.853	38.303	54.833	74.743	0.787	0.917	1.143	1.358	3.88	16.081	41.369	79.053	79.549
sCT #36	0.635	0.806	0.979	1.174	4.202	17.985	30.478	47.54	67.996	0.752	0.856	1.022	1.191	3.068	11.057	24.718	42.944	58.422
sCT #37	0.633	0.811	0.994	1.202	4.768	25.894	40.161	57.597	76.975	0.788	0.913	1.121	1.374	3.647	15.814	55.22	78.923	79.63
sCT #38	0.638	0.809	0.981	1.178	4.239	17.602	29.21	46.109	66.6	0.742	0.846	1.01	1.176	3.164	12.648	26.335	41.648	53.752

	Heart									Oesophagus								
	D95%	**D90%**	**D85%**	**D80%**	**D50%**	**D30%**	**D20%**	**D10%**	**D5%**	**D95%**	**D90%**	**D85%**	**D80%**	**D50%**	**D30%**	**D20%**	**D10%**	**D5%**
sCT #39	0.629	0.799	0.969	1.161	4.154	18.68	31.973	48.744	67.694	0.756	0.864	1.038	1.235	3.352	13.452	31.926	54.015	73.405
sCT #40	0.61	0.778	0.949	1.139	4.015	21.993	36.837	54.959	76.7	0.762	0.873	1.062	1.321	3.668	15.181	43.804	80.687	81.347
sCT #41	0.623	0.797	0.972	1.17	4.273	22.252	37.489	55.498	76.754	0.768	0.876	1.057	1.323	3.582	15.284	41.198	80.611	81.134
sCT #42	0.621	0.793	0.967	1.161	4.312	23.501	38.244	55.326	75.765	0.777	0.895	1.093	1.305	3.376	12.652	41.679	79.386	79.876
sCT #43	0.617	0.792	0.97	1.17	4.454	25.001	40.465	59.481	78.392	0.786	0.905	1.103	1.377	3.798	20.188	57.154	79.662	80.239

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Original Article

Provision of Organ at Risk Contouring Guidance in UK Radiotherapy Clinical Trials

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Abstract

Aims: Accurate delineation of organs at risk (OAR) is vital to the radiotherapy planning process. Inaccuracies in OAR delineation arising from imprecise anatomical definitions may affect plan optimisation and risk inappropriate dose delivery to normal tissues. The aim of this study was to review the provision of OAR contouring guidance in National Institute of Health Research Clinical Research Network (NIHR CRN) portfolio clinical trials.
Materials and methods: The National Radiotherapy Quality Trials Assurance (RTTQA) Group carried out a two-round Delphi assessment to determine which OAR descriptions provided optimal guidance.
Results: Eighty-four clinical trials involving radiotherapy quality assurance were identified as either in recruitment or in setup within the NIHR CRN portfolio. Fifty-nine trials mandated OAR contouring. In total there were 412 OAR; 171 were uniquely named; 159 OAR had more than one name associated with a single structure, with the greatest nomenclature variation seen for the femoral head ± neck, the parotid gland, and bowel. The two-round Delphi assessment determined 42 OAR descriptions as providing optimal contouring guidance.
Conclusions: This study identified the need for OAR nomenclature and contouring guidance consistency across clinical trials. In response to this study and in conjunction with the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonisation Group, the RTTQA Group is in collaboration with international partners to provide consensus recommendations for OAR delineation in clinical trials.

Key words: Constraint; contouring; delineation; organ at risk; radiotherapy

Introduction

Accurate delineation of organs at risk (OAR) is vital to the radiotherapy planning process [1]. UK radiotherapy trials define site-specific OAR within the trial protocol and, where required, the associated radiotherapy guideline document [2]. In practice, the definition accuracy of each OAR varies between tumour-specific trial protocols in terms of nomenclature and anatomical description.

Inaccuracies in OAR delineation arising from imprecise definitions may affect plan optimisation and risk inappropriate dose delivery to normal tissues [3]. Furthermore, in clinical trials, delineation inconsistencies affect radiotherapy dose-reporting, cross-trial comparison of results and limit the validity of pooled analyses from clinical trial data.

The American Society of Radiation Oncology (ASTRO) Clinical Affairs and Quality Council [4] adopt standardised nomenclature from the reports of Santanam *et al.* [5] and

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the American Association of Physicists in Medicine (AAPM) Task Group 263 [6]. Neither Santanam *et al.* [5] nor the AAPM [6] provide or report on the provision of OAR contouring guidance within clinical trial protocols or radiotherapy guideline documents.

The National Radiotherapy Trials Quality Assurance (RTTQA) Group, centrally funded since 2010, provides radiotherapy quality assurance for all UK National Institute of Health Research Clinical Research Network (NIHR CRN) portfolio studies that include a radiotherapy component. To evaluate OAR nomenclature and to achieve consensus on an optimal OAR description, we used the Delphi method. The Delphi method of consensus building involves an anonymised participant response to a formalised question followed by controlled feedback to create group opinion. This approach captures the individual opinions within a geographically dispersed group, minimises the biasing effects of dominant participants and irrelevant communications, and reduces group pressure towards conformity [7].

This study evaluated the provision and extent of OAR contouring guidance in NIHR CRN portfolio studies involving radiotherapy quality assurance. Here, consensus opinion on optimal OAR descriptions is presented.

Materials and Methods

Between 26 September 2018 and 3 October 2018, the RTTQA Group accessed all recruiting and in setup clinical trials on the UK NIHR CRN portfolio that involved radiotherapy quality assurance.

As shown in Figure 1, clinical trial protocols and, where provided, the associated radiotherapy guideline documents were reviewed. The OAR nomenclature and contouring guidance were recorded and classified into three groups: (i) with guidance, (ii) without guidance, (iii) guidance referred solely to an external source. The Delphi method was used to evaluate the OAR descriptions in group (i), to establish consensus opinion on an OAR description.

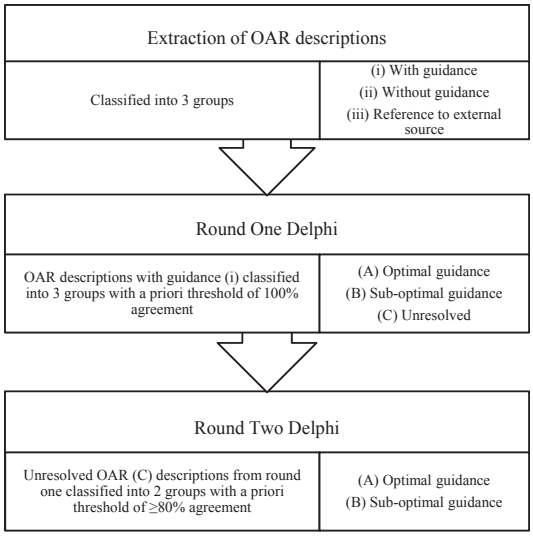

Fig 1. Data extraction, classification and Delphi grouping.

Twelve members of the RTTQA Group (four clinical oncologists, four therapy radiographers, four radiotherapy physicists) with expertise in advanced techniques (intensity-modulated radiotherapy, dose-intensification, adaptive radiotherapy, stereotactic ablative body radiotherapy) across a breadth of tumour sites were invited to provide their expert opinion as to whether each unique OAR description provided optimal information to contour the OAR. A minimum of 10 respondents was required for the Delphi method to capture the expertise of the RTTQA Group [8].

In round one, participants were provided with OAR nomenclature and the associated description. Participants were instructed to independently categorise each unique description as providing (A) optimal guidance or (B) suboptimal guidance. OAR descriptions that achieved 100% consensus agreement or disagreement as providing optimal or suboptimal guidance for OAR contouring in round one were considered resolved and excluded from round two. The remaining OAR descriptions were classified as (C) unresolved and entered into round two.

Four weeks later, the same participants were instructed to categorise the unresolved OAR. An *a priori* threshold of ≥80% agreement was required at round two for the OAR description to achieve consensus.

Participants were blinded to the clinical trial source of the OAR descriptions at all times.

Ethical approval was not required when producing this report.

Results

Eighty-four clinical trials involving radiotherapy quality assurance were identified as either recruiting or in setup within the NIHR CRN portfolio. Fifty-nine of these (70.2%) mandated OAR contouring, whereas the remainder (29.8%) made no reference to OAR in the clinical trial protocol or radiotherapy guideline document. In total, there were 412 OAR descriptions with 64 distinct organ structures across the evaluated clinical trial protocols.

As shown in Table 1, the most frequent treatment site was the pelvis, with 16 clinical trials mandating between two and eight OAR. Breast and pelvis treatment sites had the lowest variation in number of mandated OAR (breast: median 3, range 2–4, SD 1; pelvis: median 3, range 2–8, SD 1.75). Seven clinical trials involved radiation delivery to a range of anatomical sites; these clinical trials had the largest variation in mandated OAR (median 12, range 8–29, SD 7.54). Four of these trials involved stereotactic ablative body radiotherapy as the treatment modality for oligometastatic or oligoprogressive disease; the remaining trials included patients with haematological malignancies or sarcoma.

Table 1
Provision of organ at risk contouring guidance for 59 clinical trials according to the anatomical site of radiation delivery

Anatomical site	Brain	Head and neck	Thorax	Breast	Abdomen	Pelvis	Whole body
Trials *n* (%)	8 (13.6)	7 (11.9)	10 (16.9)	5 (8.5)	6 (10.2)	16 (27.1)	7 (11.9)
Organs at risk							
Median	7.5	5	6.5	3	6	3	12
Range	5–19	3–14	4–10	2–4	6–11	2–8	8–29
Standard deviation	4.7	4	2.02	1	2.04	1.75	7.54

Nomenclature

Of the 412 OAR, 171 were uniquely named. One hundred and fifty-nine (93.0%) had more than one structure name with the greatest nomenclature variation seen in the femoral head ± neck, the parotid gland, and bowel (Table 2).

The nomenclature used in 211 (51.2%) OAR descriptions was consistent with AAPM TG 263 [6] standardised nomenclature, e.g. Femur_Head_L, Parotid_L, Bag_Bowel.

In the 131 instances where laterality was important to identify the OAR, 38 (29.0%) were named with the suffix left or right, consistent with AAPM TG 263 [6]. Of the remaining 93 OAR instances, 22 (16.8%) were identified with the prefix contra- or ipsi-: nine in the head and neck (eye, parotid gland), two in the abdomen (kidney), and 11 in the thorax (breast, lung). Seventy-one (54.2%) OAR had no reference to laterality, whether left or right, or with the prefix contra- or ipsi-; most of these OAR were in the head and neck: brachial plexus, eye, hippocampus, lens, cochlea.

Organ at Risk Descriptions

One hundred and eighteen (28.6%) OAR had no associated description or contouring guidance (Figure 2); nine (2.2%) had no associated description, but made reference to either a pre-existing clinical trial protocol or radiotherapy guideline document (five) or published contouring atlas (four). Two hundred and eighty-five (69.2%) had an associated description and were classified into the (i) with guidance group. Within this group, 104 OAR descriptions included wording directly from either a contouring atlas (34), an existing clinical trial radiotherapy guideline document (35) or published contouring guidance (35).

Table 2
Variations in organ at risk nomenclature

Structure	Trials (*n*)	Nomenclature variations
Femoral head ± neck	18	FemHeadNeck_X, Femoral Head_X, Femoral heads, Femoral Heads, Femoral Neck, FemoralHead_X, FemoralHeadNeck, FemoralJoint_X, Femur_Head_X, Right and left femoral heads
Parotid gland	10	Contralateral parotid and Ipsilateral parotid, Ipsilateral and contralateral parotid, Parotid_IL, Parotid_X, Parotid glands
Bowel	22	Bowel, Bowel Bag, Bowel_cavity, Gut, Other_Bowel

X, laterality; IL, ipsilateral.

Twelve RTTQA Group members were invited to participate in the Delphi. Ten individuals (four clinical oncologists, four therapy radiographers, two radiotherapy physicists) returned both round one and round two questionnaires.

In round one, all participants agreed that 19 descriptions provided optimal guidance and 18 descriptions provided suboptimal guidance for accurate OAR delineation. These OAR descriptions were excluded from round two. Examples are given in Table 3.

Round two included the remaining 248 unresolved OAR descriptions; 23 of these met the *a priori* threshold of ≥80% consensus agreement and were therefore considered to provide optimal guidance to contour the OAR.

Overall, 42 (14.7%) of UK NIHR CRN portfolio trial OAR descriptions provided optimal contouring guidance. This Delphi assessment deemed 243 (85.3%) OAR descriptions as suboptimal.

Organ-specific OAR varied in their description; the greatest variation was seen between bowel descriptors (Table 4).

OAR descriptions varied in superior and inferior borders, with variation seen in the definition of the brachial plexus, brainstem, heart, and rectum, among others. Examples are shown in Table 5.

Discussion

Well-conducted clinical trials inform and shape routine clinical practice. The international radiotherapy community promotes a culture of safety [9]. Consistency in radiotherapy target volume and OAR terminology enhances safety, reduces variation within clinical trials and ensures future cross-trial comparisons are appropriate and generalisable to the non-clinical trial population [3]. Additionally, OAR dose-volume parameters, correlated with prospective toxicity outcome data collected through clinical trials, are used to define constraints for future radiotherapy planning protocols [10].

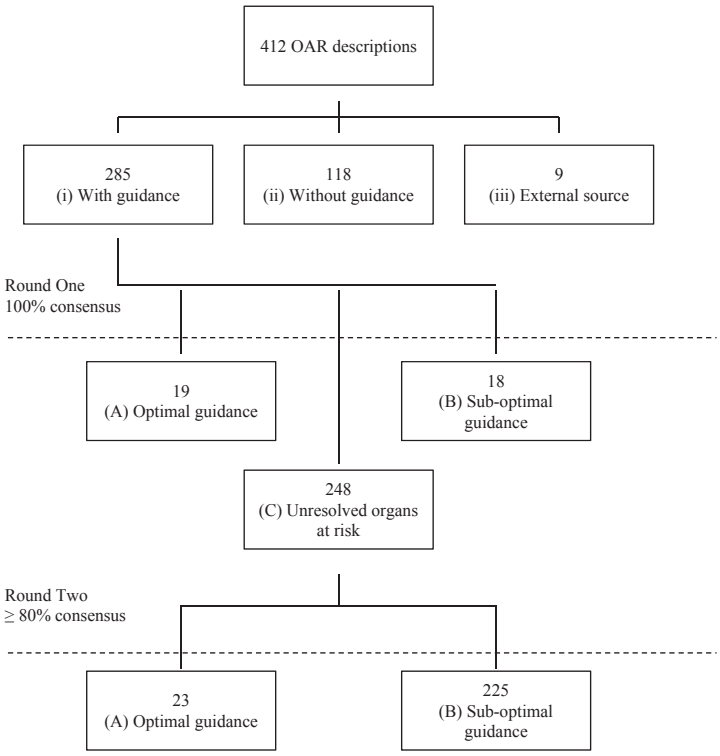

Fig 2. Schematic of the Delphi method.

This study on the provision of contouring guidance in clinical trials within the UK NIHR CRN portfolio highlights the need for the standardisation of OAR nomenclature together with the associated anatomical descriptions. Eighty-four clinical trial protocols and, where available, radiotherapy guideline documents were reviewed; 59 clinical trial protocols stipulated OAR for radiotherapy treatment planning. There was variation in the number of mandated OAR for each clinical site, with the largest variation seen in clinical trials in which radiotherapy could be delivered to any anatomical site within the body (Table 1). Twenty-five clinical trials did not mandate OAR for radiotherapy treatment planning in the clinical trial protocol; the reasons were not investigated as part of this study. The reasons clinical trials elected not to make reference to OAR could be due to either the lack of impact of toxicity on the trial end point(s) or that the radiotherapy dose prescription was below established OAR dose constraints.

Four hundred and twelve individual OAR descriptions were reviewed. Of the uniquely named OAR, 93% had more than one identifier, with about half (51.2%) of the nomenclature consistent with AAPM TG 263 [6] recommendations. On review of the individual descriptions and as a result of the two-round Delphi, the RTTQA Group consensus opinion deemed 42 (14.7%) OAR clinical trial descriptions as providing optimal guidance for contouring. The discrimination for OAR descriptions providing optimal guidance is subjective. In the absence of robust guidance, this two-round Delphi assessment, carried out by expert members of a multiprofessional radiotherapy quality assurance group provides insight into current provision. OAR descriptions deemed optimal included superior and inferior organ contouring limits with defined anatomical landmarks, inclusion and exclusion structures and, where appropriate, recommendations on imaging modality and windowing. These parameters should be specified when defining an OAR.

The ASTRO Clinical Affairs and Quality Council [4] published guidance standardising which OAR are contoured for each disease site. Although not prescriptive or exhaustive, the guidance is instructive and incorporation into OAR contouring recommendations should be considered to combat the variation seen in the number of OAR in use (Table 1). Standardisation of radiotherapy practice is recommended in the 2019 National Health Service (NHS) England Modernising Radiotherapy Services Consultation and subsequent Radiotherapy Service Specification Report. Both documents outline the working arrangements between the 11 newly formulated NHS England radiotherapy networks [11]. The service specifications include improving access to modern, advanced and innovative radiotherapy techniques;

Table 3
Examples of organ at risk guidance that achieved 100% consensus, whether optimal or suboptimal

Organ at risk	Consensus	
	Optimal guidance	Suboptimal guidance
Bowel	Individual bowel loops visible on relevant levels of the planning scan will be outlined. Outlining will include the small bowel, large bowel and the sigmoid colon down to the level of the rectosigmoid junction. The superior extent should be 2 cm beyond the superior extent of the clinical target volume.	Superior limit 2 cm above the planning target volume.
Heart	The heart will be contoured along with the pericardial sac. The superior aspect is defined as the superior aspect of the pulmonary artery and the caudal border should be defined by the lowest part of the left ventricle inferior wall that is distinguishable from the liver.	Outlined to the extent of the pericardial sac. The major blood vessels are excluded.
Lung(s)	The right and left lungs can be contoured separately, but they should be considered as one structure for lung dosimetry. All inflated and collapsed, fibrotic and emphysematous lungs should be contoured, small vessels extending beyond the hilar region should be included; however, hilars and trachea/main bronchus should be excluded.	Both lungs from apices to diaphragm.

Table 4
Examples of variation in bowel nomenclature and description

Nomenclature	Description
Bowel	Bowel (small bowel and colon) is outlined on all slices from 3 cm above the upper limit of the PTV
Bowel	Above rectum, within 15 cm of the PTV for Cyberknife SBRT and within 4 cm of the PTV for gantry-based SBRT and IMRT. Bowel may be outlined as a 'bowel bag'
Bowel Bag	Inferiorly from the most inferior small or large bowel loop or above the anorectum, whichever is most inferior. Outline as one continuous structure to include duodenum, small and large bowel. Contour the abdominal contents excluding muscle and bones. Subtract any overlapping non-gastrointestinal normal structures. Please outline at least 3 cm above and below the PTV.
Bowel_cavity	Contouring of the potential bowel cavity volume including 2 cm above the superior extent of the PTV. This includes the abdominal contents excluding major vasculature, muscles and bones as well as other pelvic organs (e.g. bladder, prostate, vagina, uterus). The bowel cavity is not delineated in inferior axial slices where there is no visible small bowel or colon.
Gut	Outline as one continuous structure, like a sac, which includes the stomach, duodenum, small and large bowel down to anus. It is not necessary to outline each loop of bowel individually or to separate the different components.
Other_bowel	The small and large bowel (including sigmoid colon) will be outlined as a single structure. The entire small and large bowel visible on relevant levels of the planning scan will be outlined as individual bowel loops. The superior extent of outlining should be 2 cm beyond the superior extent of the PTV.

IMRT, intensity-modulated radiotherapy; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

reducing variation in quality by adopting best practice protocols; and increasing participation in research and clinical trials by 15% over 3 years. The standardisation of terminology and participation in multicentre clinical trials improve departmental workflow, support communication and collaboration between networks, and enable the implementation of advanced techniques [12]. The benefit of a comprehensive clinical trial quality assurance programme extends to the research activities of staff, affects local radiotherapy facilities and ultimately improves treatment for non-clinical trial patients [13–15].

The approach used to minimise OAR contouring variation and the impact on clinical trial end points and the individual patient vary. The RTTQA Group implements a stepwise quality assurance process of benchmark, prospective and retrospective case review, which monitors and captures variation from the clinical trial protocol. Pre-trial benchmark quality assurance identifies major discrepancies or misinterpretation of the trial protocol or radiotherapy guideline document before centres are open to recruitment. On-trial prospective case review monitors variation from the protocol and enables corrective action before radiotherapy delivery. Timely retrospective review monitors on-going adherence to the protocol. This stepwise quality assurance review process, with active feedback to clinical oncologists, radiotherapy physicists and therapy radiographers, aims to limit the impact of variation in OAR contouring on clinical trial end points.

Variation in target volume and OAR delineation is recognised [16–20]. In clinical practice, over- and under-contouring may affect treatment plan optimisation and potentially limit the dose delivered to the target volume or underestimate the dose received by the OAR, respectively [20]. Evaluation of the impact of the variation in organ-specific OAR descriptions is beyond the scope of this study. Imprecise OAR definitions, providing poor contouring guidance, may result in greater interpretation of contouring guidance and subsequently increase contour

Table 5
Examples of variations in superior and inferior organ at risk borders

Structure	Superior border	Inferior border
Brachial plexus	C7	Second rib
	C4	Second rib
	C7	Axilla
Brainstem	Mesencephalon	Foramen magnum
	Bottom of the lateral ventricles	Tip of the dens of C2
	Ponto-medullary junction	Tip of the dens of C2
Heart	Superior aspect of the pulmonary artery	Lowest part of the left ventricle that is indistinguishable from the liver
	The first slice at which the right and left pulmonary arteries separate	Apex of the heart
	Infundibulum of the right ventricle and apex of both atria	Lowest part of the left ventricle that is indistinguishable from the liver
Rectum	Rectosigmoid junction	Anal margin
	Sigmoid colon	Anal sphincter
	Rectosigmoid junction	Bottom of ischial tuberosities

variation. Overall, 40 (9.7%) OAR descriptions referred to a pre-existing clinical trial protocol or radiotherapy guideline document, 38 (9.2%) referred to a contouring atlas and 35 (8.5%) made reference to published contouring guidance. Reference to pre-existing clinical trial protocols should be taken with caution, as normal tissue contouring atlases are constantly refined, so that contouring guidance remains contemporary and clinically relevant [21].

Discrepancies in organ-specific OAR superior and inferior border descriptions exist, seen in brachial plexus, brainstem, heart, and rectum (Table 5). Large variations, such as those seen in bowel descriptions (Table 4) make cross-trial comparisons and extrapolation of dose constraint findings from the trial setting to the non-trial patient population challenging [22].

Pre-trial benchmark quality assurance of heart contouring in the 2008–2013 CONVERT trial [23] (NCT00433563) showed that the heart was not outlined according to protocol in 79.7% of cases [24]. On-trial prospective review was not carried out as part of the quality assurance programme for this trial. Retrospective application of the gold standard heart contours to 50 recruited CONVERT patients revealed that the heart was not outlined according to protocol in 76% of cases [25]. In both the pre-trial and retrospective quality assurance reviews, the superior border of the heart was too low, resulting in a median increase in heart $V_{5\%}$ and $V_{30\%}$ in 77.3% and 82.1% of evaluated plans, respectively [25]. The increase in $V_{5\%}$ and $V_{30\%}$ was reflective of radiation delivery to the uncontoured superior aspect of the organ. The long-term effects of heart irradiation are not clear. Big data analyses imply dose delivered to superior heart substructures may affect patient survival [26] and residual shifts towards the mediastinum have a negative impact on patient outcome [27]. Although translational data are awaited, consistent OAR delineation, accurate OAR dosimetry and retrospective dosimetric analysis will, in part, identify the true long-term effects of heart irradiation. Furthermore, individualised radiotherapy delivered through dose intensification is increasingly incorporated into clinical trial design [28–30]. These radiotherapy plans are often optimised isotoxically; therefore, precise OAR delineation enables optimal dose delivery and avoids inappropriate 'dose-dumping' to anatomical regions that are not defined during the planning process.

Building on prior work from Santanam *et al.* [5], the AAPM [6], and ASTRO [4], this study identified the need for OAR nomenclature and contouring guidance consistency across clinical trials.

In response to this study and in conjunction with the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonisation Group (GHG) (https://rtqaharmonization.com), the RTTQA Group is in collaboration with international partners European Organisation for Research and Treatment of Cancer (EORTC), Imaging and Radiation Oncology Core (IROC), Japan Clinical Oncology Group (JCOG), and Trans-Tasman Radiation Oncology Group (TROG) in reviewing OAR definitions, with a view to providing a comprehensive resource for the delineation of OAR in clinical trials.

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Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.09.054.

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Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group consensus guidelines

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ABSTRACT

Background and purpose: The Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG) is a collaborative group of Radiation Therapy Quality Assurance (RTQA) Groups harmonizing and improving RTQA for multi-institutional clinical trials. The objective of the GHG OAR Working Group was to unify OAR contouring guidance across RTQA groups by compiling a single reference list of OARs in line with AAPM TG 263 and ASTRO, together with peer-reviewed, anatomically defined contouring guidance for integration into clinical trial protocols independent of the radiation therapy delivery technique.

Materials and methods: The GHG OAR Working Group comprised of 22 multi-professional members from 6 international RTQA Groups and affiliated organizations conducted the work in 3 stages: (1) Clinical trial documentation review and identification of structures of interest (2) Review of existing contouring guidance and survey of proposed OAR contouring guidance (3) Review of survey feedback with recommendations for contouring guidance with standardized OAR nomenclature.

Results: 157 clinical trials were examined; 222 OAR structures were identified. Duplicates, non-anatomical, non-specific, structures with more specific alternative nomenclature, and structures identified by one RTQA group were excluded leaving 58 structures of interest. 6 OAR descriptions were accepted with no amendments, 41 required minor amendments, 6 major amendments, 20 developed as a result of feedback, and 5 structures excluded in response to feedback. The final GHG consensus guidance includes 73 OARs with peer-reviewed descriptions (Appendix A).

Conclusion: We provide OAR descriptions with standardized nomenclature for use in clinical trials. A more uniform dataset supports the delivery of clinically relevant and valid conclusions from clinical trials.

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Introduction

Clinical research in radiation therapy is conducted two-fold: through analysis of high-level evidence generated from well-conducted prospective clinical trials, or retrospective evaluation of real-world data extracted from big data repositories [1,2]. The dosimetric, toxicity, and endpoint reporting parameters from these datasets inform the development of normal tissue complication probability (NTCP) models and define organ at risk (OAR) constraints for future radiation therapy planning protocols [3]. In these approaches, variability in the reporting standards of OAR specific metrics reduces the ability to draw robust conclusions and impacts upon the validity of the recommendations [4–6].

Data pooling from institutions is impeded by inconsistencies in nomenclature [1,7–9]. Inconsistency in contouring guidance for OARs may increase contour variability [10]. Consistency and accuracy in structure nomenclature and contouring guidance not only minimizes variation but also improves departmental workflow and safety [9,11–14], with positive impact on clinician peer-review [9]. Miscommunication and lack of well-defined operating procedures have been highlighted as key causative factors in the origin of radiation incidents, particularly during transfers of care [11–16]. Specific target volume (TV) and OAR radiation therapy errors and near misses were seen in 80/1565 incidents voluntarily reported to Public Health England (PHE) from August to November 2019 [16].

Standardization of terminology facilitates data pooling, scripting, and automation of reports; whether that is for departmental quality assurance (QA), data capture in national registries, or wider inter-institutional radiation therapy research. Data pooling and data sharing agreements between investigators and institutions makes research more efficient and increases the value of the initial clinical trial investment [3]. Standardization of data allows robust derivation of dose constraints and the development of dose–response relationship models [1–7].

The transition from two-dimensional radiation therapy (2D RT) treatment planning and delivery to volumetric three-dimensional conformal radiation therapy (3D CRT), inverse-planned intensity-modulated radiation therapy (IMRT) and proton beam radiation therapy (PBT) has enabled dose-intensification to the TV while sparing dose delivered to the OARs [17,18]. Inverse-planned radiation therapy is driven by user-defined planning objectives. Under-contouring of the OAR leads to inferior OAR sparing [19] with potential for increased or unanticipated toxicity; over-contouring could result in unnecessary dose compromises to the TV. In view of the growing use of sequential and multi-modality anti-cancer therapies, inaccuracies in OAR contouring and hence plan optimization risk inappropriate dose delivery to an OAR, with greater potential for "dose-dumping" in normal tissues and subsequent unanticipated toxicity during a patient's treatment pathway.

The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) review proposed OAR tolerances and defined OAR constraints; with the acknowledgement that progress in radiation oncology accelerates only when we understand how treatment decisions impact upon patient outcomes [1,3].

The need for consistent language and terminology has been highlighted, as well as the positive impact of consistency on process improvement and workflow management infrastructure [9]. The international radiation therapy community continually promotes a culture of safety. Organizations including, but not limited to, the Pennsylvania Patient Safety Authority (PSA) [11], Radiation Oncology Safety and Education Information System (ROSEIS) [13], Radiation Oncology Incident Learning System (RO-ILS) [15], PHE [16], and American Society of Radiation Oncology (ASTRO) [14] report inaccurate and incomplete communication as causative themes in the origin of radiation incidents [16].

The American Association of Physicists in Medicine (AAPM) has been a driving force for the implementation of improvements in patient safety. AAPM Task Group (TG) reports 113 [20] and 263 [2] both recommend the use of standardized nomenclature, with the latter publishing standardized TV and OAR nomenclature, reducing variability in naming and enabling multi-vendor platforms to interact easily.

The ASTRO Clinical Affairs and Quality Council provides guidance on which OARs should be contoured per anatomical treatment site, defining those essential OARs that consensus *recommends* regardless of treatment scenario providing a basic minimum standard of care, and those OARs which should be *considered* dependent on the clinical situation for contouring in anatomical site-specific clinical trials [18].

The National Radiotherapy Trials Quality Assurance (RTTQA) Group reported on the current provision of OAR specific contouring guidance in United Kingdom (UK) National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio studies [10]. Variation was seen in the OARs contoured across anatomical site-specific clinical trials. The study found that 85.3% of OAR specific descriptions in use within trial documentation provided sub-optimal guidance for contouring [10].

The Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG) (https://rtqaharmonization.com) is a collaborative member group of radiation therapy QA organizations: European Organisation for Research and Treatment of Cancer (EORTC), Imaging and Radiation Oncology Core (IROC), Japan Clinical Oncology Group (JCOG), the National Radiotherapy Trials Quality Assurance (RTTQA) Group, and Trans Tasman Radiation Oncology Group (TROG). The GHG is also associated with the following observer groups: Australian Clinical Dosimetry Service (ACDS), Canadian Cancer Trials Group (CCTG), European Society for Radiotherapy and Oncology (ESTRO), International Atomic Energy Agency (IAEA), National Physical Laboratory (NPL), Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials (QUARTET), and the Radiation Dosimetry Services (RDS).

The objective of the GHG is to enhance the quality of radiation therapy in multi-institutional clinical trials through harmonization of QA in order to reduce ambiguity in trial reporting, interpretation and translation of clinical outcomes. The GHG identified an unmet need for the standardization of OAR nomenclature along with peer-reviewed contouring guidance for use in clinical trials involving adult patients with a radiation therapy component.

The GHG OAR Working Group is a multi-professional collaborative initiative, formed of twenty-two members from six international radiation therapy QA groups and affiliated organizations, assuring broad representation across the radiation therapy community.

The objective of the GHG OAR Working Group was to unify OAR contouring guidance across all the QA groups by compiling a single reference list of OARs, together with peer-reviewed, anatomically defined contouring guidance for integration into future clinical trial protocols independent of the radiation therapy delivery technique.

Materials and methods

The GHG OAR Working Group conducted the work in three stages (Fig. 1).

Stage one

Between August and November 2018 representatives of the EORTC, IROC, RTTQA, and TROG QA groups reviewed documenta-

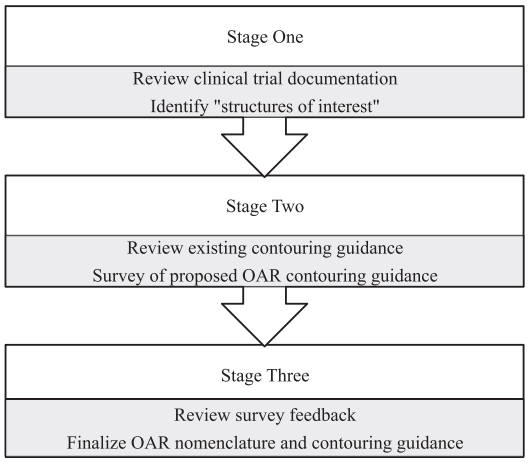

Fig. 1. Work stages one, two, and three.

tion from clinical trials with a radiation therapy QA component, that were either in recruitment or in setup. Data collected included: date of clinical trial opening, radiation therapy technique, anatomical site of radiation therapy delivery, OAR nomenclature, and associated contouring guidance.

Following application of standardized nomenclature [2], OARs in use were collated and combined with those OARs identified as recommended and considered for contouring from the ASTRO Clinical Affairs and Quality Council guidance [18]. Duplicates, non-anatomical, non-specific structures, and structures with more specific alternatives were excluded. Structures identified by two or more radiation therapy QA groups were included, thus creating the "structures of interest".

Stage two

Contouring guidance associated with each structure of interest were collated, whether from the clinical trial protocol, an external reference, or from a pre-existing alternative clinical trial document. The contouring guidance elements were reviewed according to GHG OAR Working Group pre-defined objectives (Fig. 2) and applied to each structure of interest.

Proposed contouring guidance with OAR nomenclature consistent with AAPM TG 263 [2] were created and disseminated to each of the QA groups, who then distributed the proposed nomenclature and contouring guidance to radiation therapy clinical trial investigators within each respective QA network. Investigators participating in the survey were instructed to provide written free-text feedback on the proposed OAR contouring guidance.

Stage three

Anonymized feedback from surveyed individuals was centrally reviewed by the GHG OAR Working Group, reviewed against the pre-defined objectives, and incorporated into consensus OAR contouring guidance. The proposed OAR guidelines were either; accepted, accepted with minor amendment, or accepted with major amendment. Major amendment involved complete revision of the OAR description including modification of borders, whereas minor amendment involved inclusion of omitted landmarks, refinement of borders, or adjustment of sentence structure for user clarity.

1. One name and one description for each OAR[$]
2. OARs are anatomically defined; the same description should be used for all treatment scenarios
3. OAR contouring guidance applies to adults with standard anatomy
4. Laterality is defined on all relevant OARs
5. Contouring guidance incorporates anatomical landmarks and border* definitions. Cranial and caudal terminology used in preference to superior and inferior so guidance is unambiguous regardless of patient positioning
6. Optimal windowing and imaging modality are incorporated into contouring guidance where relevant
7. The clinical trial protocol will define
   a. patient preparation and use of contrast
   b. patient positioning and immobilization
   c. motion management technique(s)
   d. the extent to which the OAR will be delineated beyond the limit of the PTV
8. Consider[$] addition of ~ suffix to denote contouring of a partial structure i.e. SpinalCord~

Fig. 2. Pre-defined objectives for development of the GHG OAR Working Group consensus contouring guidance. [$]consistent with AAPM TG 263 recommendation; *border definitions: cranial, caudal, medial, lateral, anterior, posterior; OAR, Organ at risk; PTV, Planning Target Volume.

The central review process allowed exclusion of OARs and the development of new OAR nomenclature (if not available in AAPM TG 263) and contouring guidance in response to the survey feedback received from the international clinical community.

Ethical approval was not required when producing this consensus report.

Results

One hundred and fifty seven clinical trials including radiation therapy were identified from the QA groups as recruiting or in setup: 14 (8.9%) from EORTC, 38 (24.2%) from IROC, 84 (53.5%) from RTTQA, and 21 (13.4%) from TROG.

The earliest clinical trial included in this analysis opened in November 2004. Overall, 2 clinical trials included 2D RT, 61 included 3D CRT, and 103 included IMRT as the permitted radiation therapy technique(s). Stereotactic Body Radiation Therapy (SBRT), Stereotactic Radiosurgery (SRS), and PBT were included in the randomization(s) in 29, 3, and 7 clinical trials respectively (Table 1).

Two hundred and six instances of OARs were identified from the clinical trial documentation. When combined with the recommended and consider ASTRO structures, 16 additional structures were highlighted as listed within ASTRO guidance, but not identified within clinical trial documentation. Following the exclusion of duplicates (Table 2), 117 distinct structures remained. Exclusion of non-anatomical, non-specific structures, structures with more specific alternatives, and structures specified in clinical trials monitored by one or fewer radiation therapy QA groups resulted in 58 structures of interest.

Table 2
Examples of excluded structures.

Reason for exclusion	Structure	Comment
Non-anatomical	Bag_ostomy Pacemaker	Ostomy bag
Non-specific	Bronchus_Adj RVR	Bronchus adjacent to PTV Remaining volume at risk
More specific alternative nomenclature	Bronchus_Main Bronchus_L/R Reprod^Female	Incorporated into Trachea and Bronchus_Prox Encompassing structure of the ovary, uterus, and vagina
Identified by one radiation therapy QA group	Ear_L/R Liver^Ves	Liver vessels

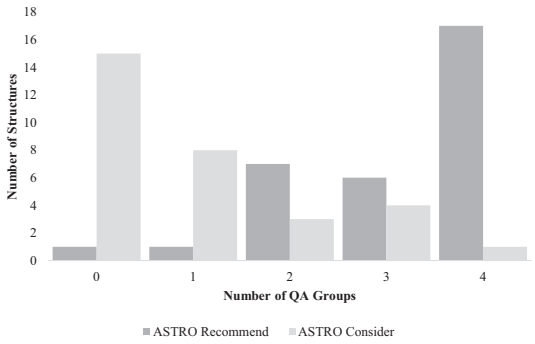

Fig. 3. QA Groups identifying each ASTRO structure.

Structures of interest

Of the 58 structures of interest, 39 (67.2%) were consistent with the ASTRO recommended and consider OAR structures [18]. Sixteen structures were identified for contouring in the ASTRO guidance, but were not included within clinical trial documentation from the QA groups. The cauda equina was the only structure (Fig. 3) listed as recommended for contouring by ASTRO, which was not described in clinical trial documentation across the QA groups.

The brachial plexus was identified by all four radiation therapy QA groups for contouring, but recognized as a structure only to be considered for contouring by ASTRO for treatment involving the cervical spine, nasopharynx, oropharynx, larynx, hypopharynx, cervical esophagus, neck, breast, supra-clavicular fossa, axilla, or lung.

Of the 32 ASTRO recommended structures, 30 (93.8%) were identified in trials monitored by two or more QA groups; 17 structures (53.1%) were identified in trials monitored by all four QA groups (Fig. 3). The ASTRO considered structures of the breast, chest wall, great vessels, and trachea were identified by three QA groups; genitals, hippocampus, and ovary were identified by two QA groups.

Survey

Forty-one radiation oncologists and 6 radiation therapists (RTT) from 38 institutions across 15 countries participated in the survey and commented on the 58 structures of interest. The mean number of responses per OAR was 17.72 (IQR 14–21); the surveyed participants varied by specialist site: 9 gastro-intestinal and head and neck malignancies respectively, 7 lung, 6 breast, central nervous system, and urological malignancies respectively, 5 sarcoma, and 4 gynae-oncology.

On review of survey responses, 6 OAR descriptions were accepted with no amendments, 41 were accepted with minor amendments, and 6 underwent major amendment (Fig. 4). The existing nomenclature choices within AAPM TG 263 did not fulfill requirements for 3 of the surveyed structures, and so new nomen-

Table 1
Anatomical treatment site and permitted radiation therapy delivery technique(s).

	CNS	H&N	Thorax	Abdomen	Pelvis	Any*
2D RT						2
BT					1	
3D CRT	11	3	16	9	12	10
IMRT	15	24	20	9	31	4
SBRT			6	6	5	12
SRS	3					
PBT	2	1	2	2		

*Radiation therapy delivery to any anatomical site; BT, Brachytherapy; CNS, Central Nervous System; H&N, Head and Neck; IMRT, Intensity-Modulated Radiation Therapy; PBT, Proton Beam Radiation Therapy; SBRT, Stereotactic Body Radiation Therapy; SRS, Stereotactic Radiosurgery; 2D RT, Two-dimensional Radiation Therapy; 3D CRT, Three-Dimensional Conformal Radiation Therapy.

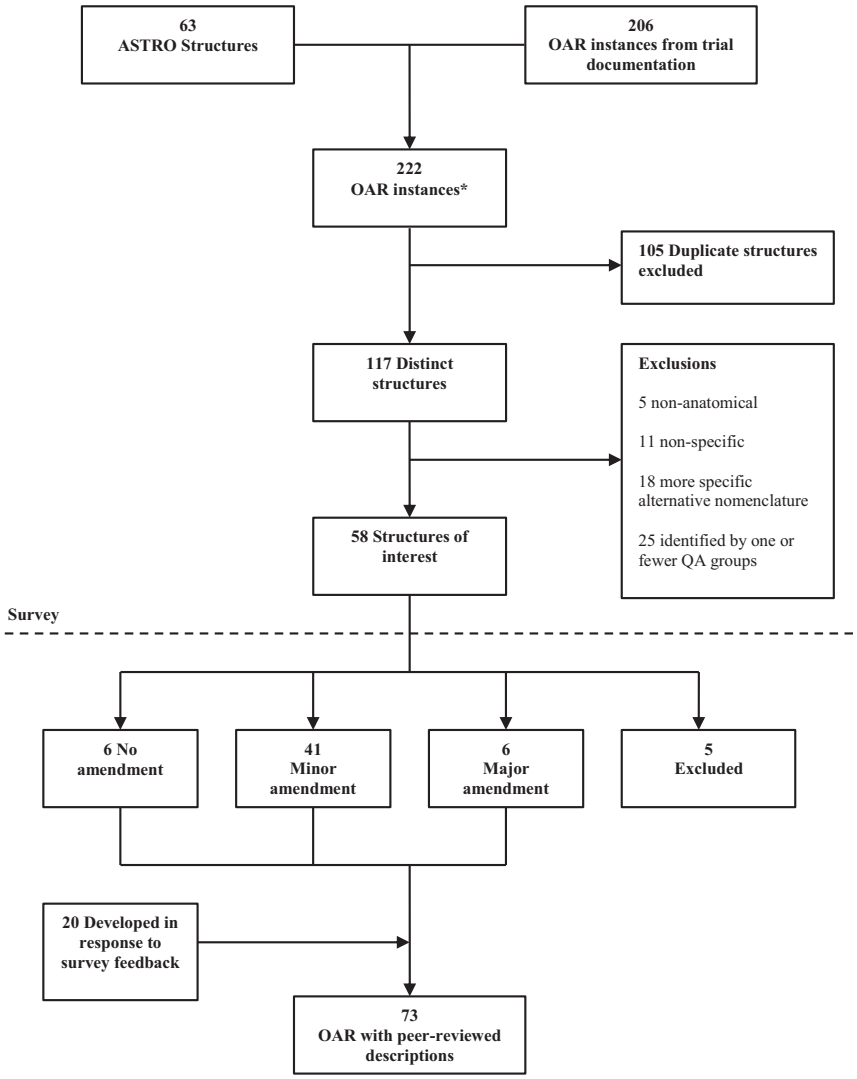

Fig. 4. OAR description survey and feedback responses. *Includes 206 OAR instances and 16 OAR structures listed within ASTRO [18] consensus guidance, which did not appear in clinical trial documentation.

clature were created: *Bronchus_Prox, FemurHeadNeck_L/R,* and *LumbsacPlexs (LumbSacPlex_L/R* with laterality designation). Twenty descriptions were developed in response to survey feedback (Fig. 5), 7 of which did not have standardized nomenclature pre-defined by AAPM TG 263 [2].

Heart

The description for the cranial border of the heart differed between clinical trials. Six landmarks for the cranial border are in use: superior aspect of the pulmonary artery, aorta-pulmonary window, origin of the ascending aorta, inferior to the left pulmonary artery, point at which the pulmonary trunk and right pulmonary artery are seen as separate structures, and the infundibulum of the right ventricle, respectively. The upper most cranial borders were predominantly used in clinical trials pertaining to fractionated radical radiation therapy for lung cancer or SBRT to the lung for either primary lung cancer or oligo-progressive disease, or oligometastatic disease from any primary cancer. The point at which the pulmonary trunk and right pulmonary artery were seen as separate structures was used in clinical trials for lymphoma and primary tumors arising from the breast.

AAPM TG report 101 [21] and UK Consensus on Normal Tissue Dose Constraints [22] recommend the toxicity end-point for heart irradiation in the setting of SBRT is ≥grade 3 pericarditis. To ensure the pericardium is encompassed fully, in the context of SBRT, the cranial heart border is extended to the top of the pulmonary artery to include the attachment of the fibrous pericardium at the adventitia of the great vessels [23].

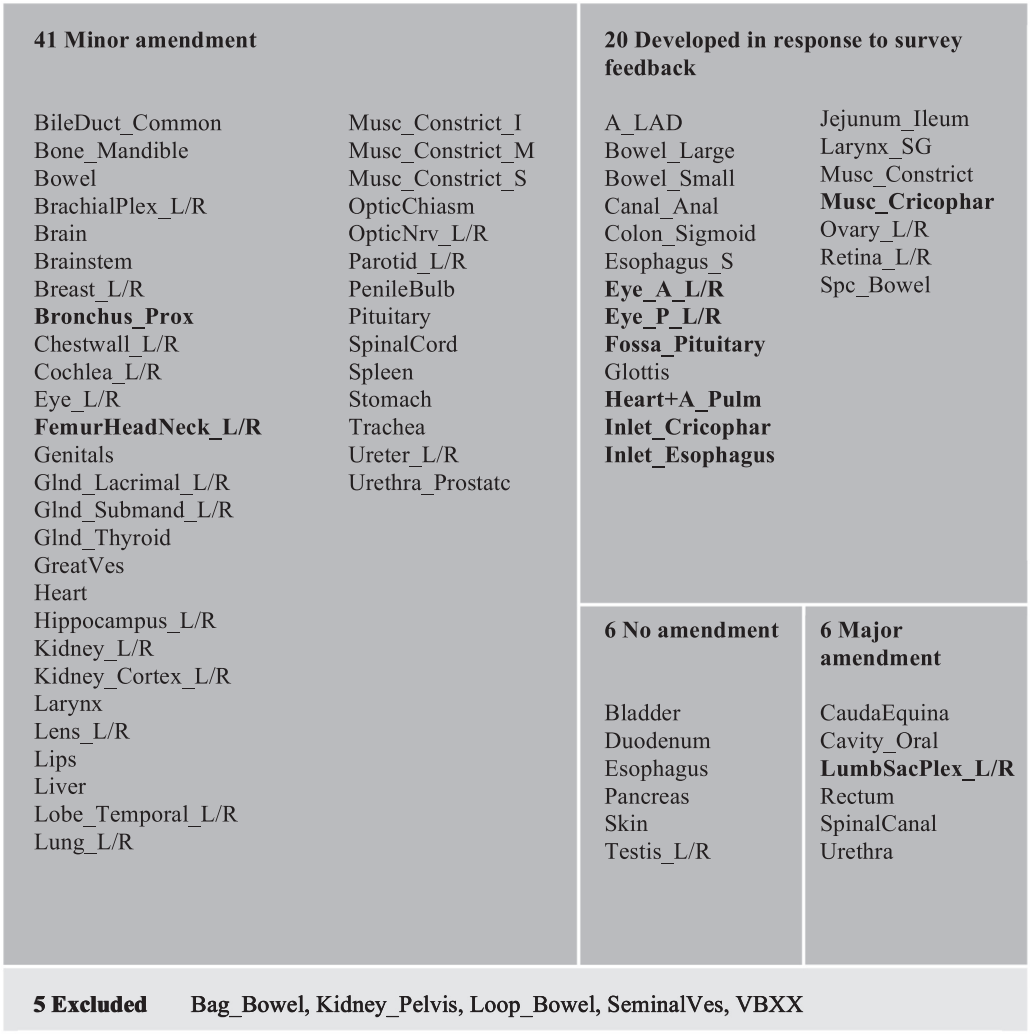

Fig. 5. GHG consensus OAR. Treemap displaying the 73 GHG consensus OAR in dark grey and 5 excluded OAR in light grey, with classifications of no amendment, minor amendment, major amendment, and developed in response to survey feedback. Structures in bold denote nomenclature not pre-existing within AAPM TG 263.

Considering the information above, surveyed investigators had a preference for two of the cranial heart borders described: the superior aspect of the pulmonary artery and the point at which the pulmonary trunk and right pulmonary artery are seen as separate structures. In response to survey feedback and as an exception to the pre-defined objectives (Fig. 2) two distinct heart structures are defined within the GHG OAR consensus guidance, *Heart +A_Pulm* and *Heart*.

Skin

The skin structure was highlighted in clinical trial documentation or external references as "should be outlined", "exclude", or "include"; either in support of the radiation therapy planning and optimization process or as a distinct OAR. This request was seldom accompanied by contouring guidance. Review of clinical and dosimetric evaluation studies demonstrates variation in practice [24–32]. Recommended skin thickness for contouring from clinical trial documentation ranged from 3 to 6 mm; anatomically the thickness of the skin is dependent on the location, ranging from 1.5 to 5 mm [33]. Contouring guidance specifies the skin structure as a 5 mm inner rind automatically created from the external contour [34]; GHG OAR consensus guidance reflects the published contouring guidance, with the caveat that skin thickness will vary dependent on region of interest.

Bowel

The survey distributed to investigators described the bowel as an encompassing structure from the pylorus to the recto-sigmoid

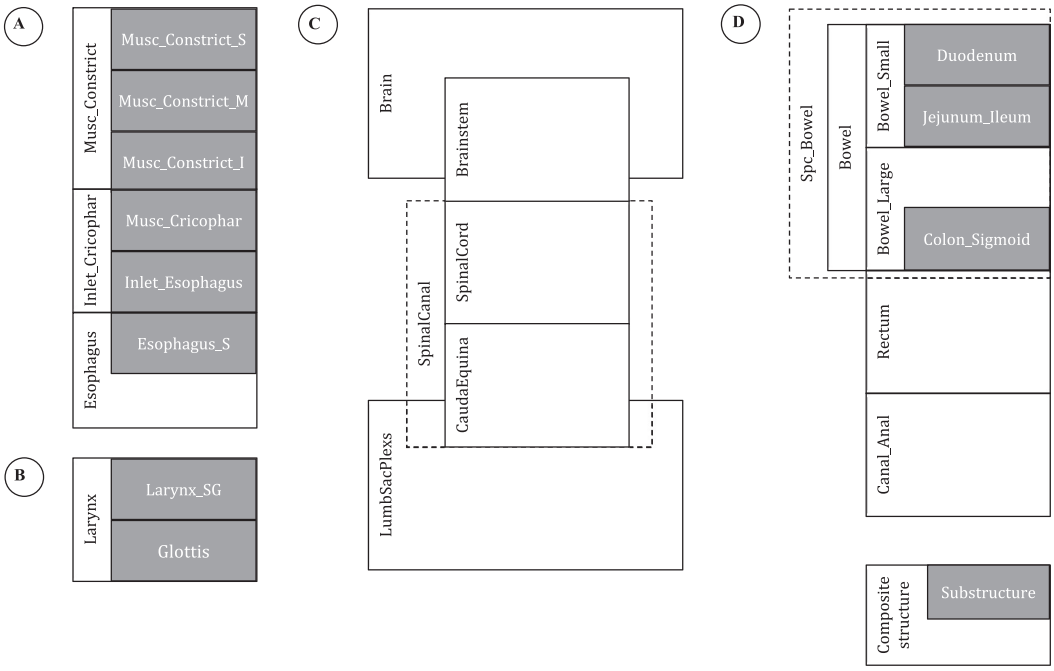

Fig. 6. Relationship between composite and individual substructures. A, swallowing structures of the neck; B, laryngeal structures; C, the central nervous system; D, the sub-diaphragmatic gastro-intestinal tract.

junction; the composite structure was reflective of the current contouring practice [10]. The overwhelming feedback from the radiation therapy community was to allow the bowel to be contoured as individual substructures, and so *Jejunum_Ileum, Bowel_Small, Bowel_Large, Colon_Sigmoid,* and *Canal_Anal* were defined, whilst retaining the original *Duodenum* and *Bowel* structure. Investigators are encouraged to choose the most appropriate structures to contour within a given treatment protocol.

Bag_Bowel nomenclature was excluded in favour of *Spc_Bowel* as the nomenclature for the former was inconsistent with the associated contouring guidance [10,35].

The schematic (Fig. 6) demonstrates the relationship between composite e.g. *Bowel* and individual substructures of the neck, central nervous system, and sub-diaphragmatic gastro-intestinal tract e.g. *Jejunum_Ileum, Colon_Sigmoid*.

New nomenclature

The GHG OAR Working Group adopted AAPM TG 263 [2] recommendations as the nomenclature standard for this work. The existing nomenclature choices did not fulfill requirements for 10 structures; the GHG OAR central reviewers established new nomenclature to align with currently contoured OAR (Table 3).

GHG consensus guidance on 73 OARs with standardized nomenclature and peer-reviewed descriptions are detailed in Appendix A; with an example of implementation of the guidance into a clinical trial protocol.

Table 3
New nomenclature and AAPM TG 263 anatomic group.

	AAPM TG 263 Anatomic Group	New Nomenclature	OAR
1	Eye	Eye_A_L Eye_A_R	Anterior segment of the eye
2	Eye	Eye_P_L Eye_P_R	Posterior segment of the eye
3	Head & Neck	Fossa_Pituitary	Pituitary fossa
4	Head & Neck	Inlet_Cricophar	Cricopharyngeal inlet
5	Head & Neck	Inlet_Esophagus	Esophageal inlet
6	Head & Neck	Musc_Cricophar	Cricopharyngeal muscle
7	Thorax	Bronchus_Prox	Proximal bronchial tree
8	Thorax	Heart+A_Pulm	Heart (extended cranial border)
9	Pelvis	FemurHeadNeck_L FemurHeadNeck_R	Femoral head and neck
10	Pelvis	LumbSacPlex_L LumbSacPlex_R LumbSacPlexs	Lumbar-sacral plexus with laterality, bilateral lumbar-sacral plexus

Discussion

With the advances in the precision and delivery of radiation therapy, the importance of accurate and consistent OAR delineation cannot be understated. This GHG OAR Working Group report from an international collaborative network of radiation therapy QA groups provides consensus guidance on the OAR descriptions and nomenclature for use in clinical trials, with the aim of promoting consistency in OAR contouring and dosimetric reporting.

Seventy-three OARs have been defined the GHG OAR Working Group; 48 (65.8%) are included in the ASTRO Clinical Affairs and Quality Council guidance [18]. Thirty (93.8%) of the ASTRO recommended structures were identified by two or more QA groups; 17 structures (53.1%) were identified by the four QA groups (Fig. 3), thereby validating the consensus guidance and OAR contouring recommendation provided by ASTRO [18].

Six OAR descriptions underwent major amendment following review of survey feedback (Fig. 5); the rectum, a commonly contoured OAR in urological and gynaecological clinical trials, was one such structure. Existing rectal contouring guidance varied in the cranial and caudal border, with use of the ischial tuberosities as a bone surrogate for the caudal border [10]. With the move away from 2D orthogonal radiation therapy planning, it is inaccurate to identify soft tissue structures based on variably positioned bone surrogates, the GHG OAR consensus guidance identifies the levator muscles, the pubo-rectalis sling, and the disappearance of perirectal fat as landmarks for the caudal rectal border.

Five OARs were excluded in response to survey feedback; reasons for exclusion were incorporation of the OAR into alternative nomenclature or survey respondents deeming the structure as a TV as opposed to an OAR.

New OAR nomenclature was created for 10 structures (Table 3). For clarity, the femoral head and neck structure is renamed as *FemurHeadNeck_L/R*, the *Cricopharyngeus* structure is renamed as the encompassing *Inlet_Cricophar* with division to the substructures *Musc_Cricophar* and *Inlet_Esophagus* to discriminate between the muscle and inlet components (Fig. 6). The eye is subdivided into anterior and posterior components with nomenclature consistent with AAPM TG 263 [2] guidance. The *Fossa_Pituitary* defines the inner bony limits of the sella turcica, which in clinical practice is used as an alternative structure for the *Pituitary* gland. The *Bronchus_Prox* describes the proximal bronchial tree, a well-established structure when delivering SBRT to the thorax. *LumbSacPlexs* replaces *SacralPlex* as established contouring guidance is available for the former.

The GHG OAR Working Group pre-specified objectives for the development of consensus OAR descriptions (Fig. 2). One name and one description should be used for each OAR. The GHG OAR Working Group was unable to meet this objective for the heart structure due to the variation in contouring guidance across clinical trials. As an exception, the GHG OAR Working Group has provided two heart OAR descriptions with distinct nomenclature: *Heart+A_Pulm* and *Heart*. Clinical trial protocols and investigators must be clear on which heart contour is used within the respective clinical trial and use the appropriate nomenclature.

The heart as an OAR is of increasing importance. Historical series of Hodgkin's Lymphoma survivors quantify the risk of heart toxicity following large-field mediastinal radiation therapy [36,37]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) review of Surveillance Epidemiology and End Results (SEER) cancer registries identified an excess of cardiac deaths following left sided versus right sided 2D planned tangential breast radiation therapy (cardiac mortality ratio 1.58 95% CI 1.29–1.95 $p = 0.03$) [38]. In the context of contemporary 3D planned radical radiation therapy delivered in the treatment of non-small cell lung cancer and esophageal cancer, big-data analyses imply residual shifts towards the mediastinum [39] and dose to the base of the heart structure [40] negatively impact on overall survival. The GHG OAR Working Group anticipates dose constraints to heart substructures: the ventricles, atria, valves, and conduction pathways [41,42] to be prospectively evaluated in forthcoming clinical trials.

The RTTQA Group identified the lack of OAR laterality in 54.2% of instances of relevant nomenclature within United Kingdom clinical trials, the predominance of these OAR were within the head and neck anatomical site [10]. AAPM TG 263 recognizes the inconsistent approach when designating OAR laterality and recommends the use of the suffix _L or _R following the primary structure name [2]. The GHG OAR Working Group unanimously agrees with AAPM TG 263 with the inclusion of the laterality suffix on paired OAR over contra- or ipsi- prefix, as laterality is unambiguous, avoids non-formalized assumptions, and is logical for all multi-professional members of a radiation oncology department. The application of contra- or ipsi- prefix is uncertain for midline or bilateral TV, and laterality designation provides user clarity in the event of TV re-irradiation.

Automated tools implementing AAPM TG 263 nomenclature, either applied retrospectively or prospectively to institutional datasets improve structure name compliance, with structure naming consistency reported as greater than 99.0% [43,44]. Consistency of the guidance underlying the nomenclature choices was not evaluated; this GHG OAR consensus guidance aims to internationally and prospectively implement a globally agreed standard for OAR contouring.

Auto-segmentation for OAR contouring, particularly based on deep learning algorithms are attractive; as once they have achieved a reliable and consistent quality in OAR contouring these processes may offer time saving efficiencies during the radiation therapy planning process. Deep learning is reliant on consistent expert contours over the normal variation of patient anatomies; this GHG OAR consensus guidance defines OAR anatomically, which could aid the generation of robust auto-segmentation models [45,46].

The impact of standardized nomenclature on treatment planning systems (TPS) and end-to-end accuracy has been estimated. AAPM TG 263 limit OAR nomenclature to 16 characters to ensure compatibility with the majority of TPS [2]. Three TPS compatible special characters have been included in this consensus report: plus, included in *Heart+A_Pulm* nomenclature; underscore, distinguishing OAR laterality from the primary or root name; and tilde, designating where a structure has not been contoured in entirety (Fig. 2). User uptake of these special characters and the impact on compatibility between multi-vendor platforms and end-to-end accuracy will be recorded with ongoing audit.

There are limitations to this work. The GHG OAR Working Group elected to exclude structures which were not listed within ASTRO contouring consensus guidance and were identified by one or fewer radiation therapy QA groups; structures not frequently contoured such as the *Ear_L/R* and the *Liver^Ves* were excluded from the stage two investigator survey. The consensus OAR are defined in entirety; the consensus guidance may not be suitable when overarching structures are used for optimization and dose-reporting of substructures of variable radio-sensitivities e.g. optimizing to the *SpinalCanal* structure using the dose-constraint of either the underlying *SpinalCord* or *CaudaEquina*. In these circumstances, the GHG OAR Working Group recommend either use of the GHG consensus contouring guidance and nomenclature or development of situation-specific clinical trial nomenclature.

The GHG OAR Working Group consensus guideline provides peer-reviewed contouring guidance alongside standardized nomenclature for implementation in clinical trials. In addition to this consensus guidance, users should employ good practice and confirm the structure contour on all viewing planes. Image co-registration inaccuracies and artefacts affecting image quality impact upon contouring accuracy and precision; users should be aware of these potential sources of error and review the final contours on the primary dataset. This consensus guidance describes each OAR in entirety; in practice, clinical trial protocols may either specify partial OAR contouring or define the extent to which the OAR will be contoured beyond the planning target volume (PTV). The tilde suffix discriminates between a complete and partially contoured OAR and on data analysis identifies the contour to researchers as suitable for point dose measurement reporting, and not suitable for volumetric dose reporting.

The OAR structures within this report are anatomically defined; the GHG OAR consensus contouring guidance of whole organs is unlikely to change. Further work and dosimetric research will

identify radiosensitive OAR substructures with respective dose constraints; contouring guidance for these newly identified substructures should be developed with the engagement of the international radiation therapy community.

Conflict of interest

Authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.05.038.

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Association between radiotherapy protocol variations and outcome in the CONVERT trial

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ABSTRACT

Background: Radiotherapy quality assurance (QA) is integral to radiotherapy delivery. Here we report comprehensive contouring, dosimetry, and treatment delivery QA, describe protocol compliance, and detail the impact of protocol variations on acute grade ≥3 toxicity, progression free survival (PFS), and overall survival (OS) in the phase III CONVERT trial.

Materials/Methods: Radiotherapy planning data from one hundred randomly selected patients were requested. Members of the CONVERT Trial Management Group (TMG) recontoured the heart, lung, and spinal cord organs at risk (OAR) according to the trial guideline. The existing radiotherapy plan were re-applied to the new structures and the new dosimetric data were recollected. Compliance with radiotherapy QA components were recorded and radiotherapy QA components were pooled into protocol variations: acceptable, acceptable variation, and unacceptable variation. Univariable analysis with a Cox proportional hazards model established the relationship between protocol variations and patient outcome.

Results: Ninety-three cases were submitted for retrospective radiotherapy QA review. Demographics of the radiotherapy QA cohort (n=93) matched the non-QA (n=450) cohort. 97.8% of gross tumour volume (GTV) contours were protocol compliant. OAR contours were non-compliant in 79.6% instances of the heart, 37.6% lung, and 75.3% spinal cord. Of the non-compliant heart contours, 86.5% and 2.7% had contours caudal and cranial to the protocol-defined heart borders. 10.8% did not include the pericardial sac and 2.7% did not include the anterior aspect of the pericardium. Eleven (11.8%) submissions exceeded protocol-defined dosimetric heart constraints; six of which were only noted on the application of protocol-compliant contours. Unacceptable variations were not associated with an increase in grade 3 toxicity (p=0.808), PFS (p=0.232), or OS (p=0.743).

Conclusion: Non-protocol compliant heart contours were associated with increased dose delivered to the heart OAR, with 11.8 % of submitted heart structures exceeding protocol-defined constraints. In this QA cohort of patients with small cell lung cancer, unacceptable variations were not associated with acute grade ≥3 toxicity, PFS, or OS. Radiotherapy QA remains the cornerstone of high-quality radiotherapy delivery and should be embedded into clinical trial and non-clinical trial practice; clinical trials should report standardised radiotherapy QA parameters alongside trial outcomes.

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Introduction

The non-surgical, radical management of lung cancer is rapidly evolving [1]. High-quality diagnostic imaging and highly conformal treatment techniques fuel advanced radiotherapy planning and delivery [1–3]. International consensus guidance standardises the processes underlying optimal target volume delineation (TVD), plan dosimetry, and treatment delivery [2,3]. Consequently, the radiotherapy quality assurance (QA) process has become increasingly complex and the impact of the individual processes within the chain of tumour site-specific QA parameters should be understood [4].

The quality of radiotherapy delivered directly impacts patient outcomes [5]. The QA parameters for radical lung radiotherapy are described; to date, CHART, GFPC-IFCT 02.01, PET-Plan, and PROCLAIM have formally reported radiotherapy QA in the radical treatment of lung cancer [6–9]. The radiotherapy QA parameters differ between these clinical trials with a variable focus on TV and OAR delineation, dosimetry, and treatment delivery; the radiotherapy QA parameters are reported as isolated components.

Radiotherapy QA is a multi-faceted process; from the verification of linear accelerator output to retrospective review of the final radiotherapy treatment plan, consequently, radiotherapy QA parameters should be reported as a continuum rather than isolated components as each component is likely to impact the reporting of the subsequent component.

This study reports contour variation, the dosimetric impact of contour variation, and treatment delivery radiotherapy QA for the randomised phase III CONVERT trial and describes protocol compliance and the impact of the protocol variations on acute toxicity, progression free survival (PFS), and overall survival (OS).

Materials and methods

The CONVERT trial was an international, multicentre, phase III randomised controlled trial establishing the standard chemo-radiotherapy regimen in limited-stage small-cell lung cancer. Details of the trial design have been published previously [10].

Patients were randomised to receive either twice-daily radiotherapy (45 Gy in 30 fractions over 19 days) or once-daily radiotherapy (66 Gy in 33 fractions over 45 days) concurrent with cisplatin-etoposide chemotherapy. Radiotherapy commenced on day twenty-two of the first cycle of chemotherapy.

All participants gave written informed consent to participate. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines. The institutional review board or the research ethics committee at each study centre approved the protocol.

The CONVERT QA programme

The CONVERT radiotherapy QA programme was developed by the CONVERT Trial Management Group (TMG) in conjunction with the National RTTQA Group and consisted of two components [10] i) pre-trial facility questionnaire recording radiotherapy facilities at each centre, followed by submission of tumour and organs at risk (OAR) contours and a radiotherapy plan of a patient who satisfied the eligibility criteria for the CONVERT trial and ii) retrospective review of 100 randomly selected recruited participants evaluating contouring, dosimetric, and treatment delivery QA (Fig. 1).

In advance of recruitment, all participating centres were provided with the CONVERT radiotherapy planning guidelines including an atlas of protocol-compliant OAR delineation [10]. Patients were treated on a

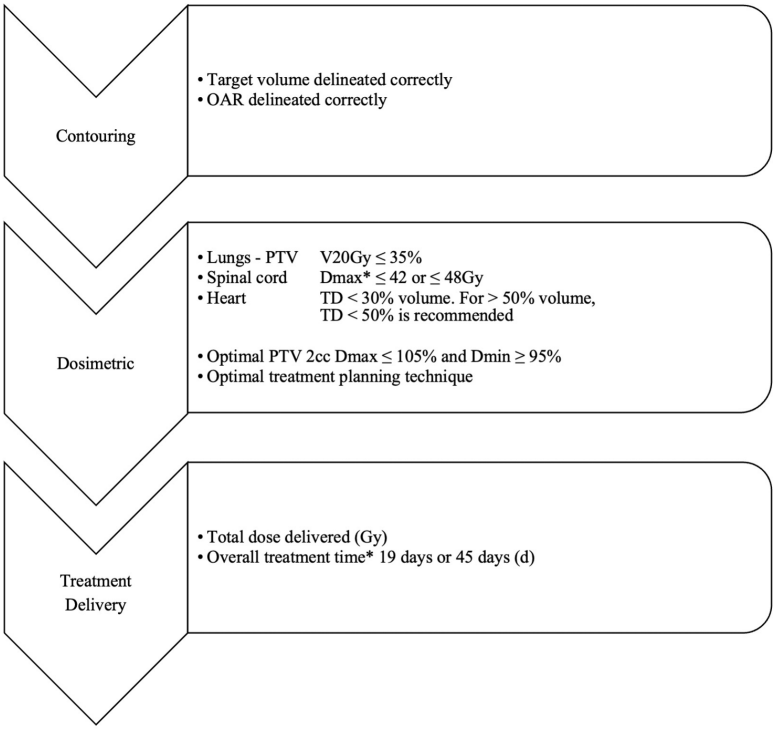

Fig. 1. Protocol compliant contouring, dosimetry, and treatment delivery QA parameters. *Dependent on randomisation group; d, days; Dmax, the maximum dose to 2 cc; Gy, Gray; OAR, Organs at risk; PTV, Planning Treatment Volume; TD, Total dose; V20Gy, Volume of organ receiving 20 Gy.

linear accelerator operating at 4–10MV. Three-dimensional conformal radiotherapy was mandatory; intensity-modulated radiotherapy (IMRT) was permitted for centres routinely using the technique. Elective nodal irradiation was not permitted; participants were followed up until death.

The radiotherapy total dose (TD) was dependent on the randomisation arm: 45 Gy in 30 fractions over 19 days or 66 Gy in 33 fractions over 45 days. The radiotherapy dose was specified at the ICRU reference point and corrected for heterogeneity. The optimal PTV planning objective was within ±5 % of the TD; the mandatory PTV planning objective was ±7 % of the TD. Normal tissue constraints are described in Fig. 1; the optimal overall treatment time (OTT) was 19 days and 45 days.

Data collection

For both the pre-trial and retrospective QA component, centres were required to anonymise and transfer treatment-planning data to the RTTQA Group electronically. Data were reviewed and analysed with Visualization and Organization of Data for Cancer Analysis (VODCA) version 3.2.7 (Medical Software Solutions GmbH, Hagendorn, Switzerland).

Gross Tumour Volume (GTV) delineation was evaluated by members of the CONVERT TMG and the RTTQA Group in conjunction with the diagnostic imaging report(s) and, where available, the original diagnostic image(s). Expert members of the CONVERT TMG recontoured the heart, the lung, and the spinal cord OARs according to the guideline. The existing dose cube and radiotherapy plan were re-applied. Dosimetric data were collected and compliance with the trial specified normal tissue constraints (Fig. 1) were recorded; protocol variations were noted (Table 1).

Protocol variation definition

Individual protocol compliance QA parameters were combined and classified as per the 2015 Global Quality Assurance of Radiotherapy Clinical Trials Harmonization Group (GHG) Protocol Variation Definition version 1.0 (www.RTQAHarmonization.com) recommendation and modified to a) acceptable, b) acceptable variation, c) unacceptable variation – treatment delivered categories [11]. The CONVERT TMG and the RTTQA Group tailored the protocol variation definition criteria for radical lung radiotherapy (Table 1).

Statistical analysis

The CONVERT TMG and the RTTQA Group combined the trial-specific protocol compliance QA parameters (Fig. 1), into acceptable, acceptable variation, and unacceptable variation – treatment delivered protocol variation categories (Table 1). Acceptable and acceptable variation categories were combined for analysis.

Univariable PFS and OS complete case analysis was performed for selected protocol compliance QA parameters and acceptable and unacceptable variation, using the Cox proportional hazards model with and without adjusting for the clinical prognostic model (CPM), which accounted for Eastern Cooperative Oncology Group Performance Status, GTV, and tumour laterality.

Due to the sample size in the QA cohort multivariable analysis was not conducted following advice from the study statistician. Hazard ratios (HR) with 95% confidence intervals and p-values are reported.

A univariable logistic regression analysis was conducted for correlating QA variables to any grade 3 or above toxicity. Odds ratios (OR) with 95% confidence intervals and p-values are reported.

All analyses were conducted in R v 3.5.1.

Results

Between April 2008 and November 2013 547 patients from 73 centres in 8 countries were recruited to the CONVERT trial. Two hundred and seventy-four were randomly assigned to receive twice-daily radiotherapy, and 273 to receive once-daily radiotherapy. Four patients were lost to follow-up; the modified intention to treat analysis included 543 patients.

The pre-trial QA component has been reported [10,12]. For the retrospective QA component, the CONVERT TMG retrospectively requested treatment-planning data for 100 randomly selected patients. Ninety-three complete cases were returned: 62 (66.7%) from 25 centres within the United Kingdom, 25 (26.9%) from 18 European centres across 5 countries, and 6 (6.4%) from 6 centres in the Canadian Provinces.

The baseline characteristics of the QA cohort were well matched to the non-QA cohort (Table 2).

Contouring compliance

The GTV contours were deemed as protocol compliant in 90/92 (97.8%) (Table 3). One case was not evaluable due to a complete radiological response to cycle one cisplatin-etoposide chemotherapy. Two GTV contours were incorrectly labelled as clinical target volumes (CTV).

Table 1
CONVERT protocol variation.

A) Acceptable	Radiotherapy was delivered to the patient according to the protocol specifications and meets all the criteria as defined by the protocol. • GTV delineated as per protocol according to diagnostic image(s) • OAR contoured as per protocol and the radiotherapy plan meets protocol defined constraint(s) • PTV coverage achieved optimal objective ±5 % prescription dose • Overall treatment time* 19 days (BD arm) or 45 days (OD arm)
B) Acceptable variation	Radiotherapy was not delivered to the patient according to all of the protocol specifications; no major clinical impact is expected due to the variation(s). • GTV delineated as per protocol according to diagnostic imaging report(s) • OAR contoured not per protocol; with the application of optimal contour(s) and dose cube, the radiotherapy plan meets protocol defined constraint(s) • PTV coverage achieved mandatory objective ±7 % prescription dose • Overall treatment time* 20–21 days (BD arm) or 46–47 days (OD arm)
C) Unacceptable variation – treatment delivered	Radiotherapy delivered to the patient did not meet all the protocol specifications; the variation(s) may impact upon the trial outcome. Radiotherapy is delivered due to clinical necessity as perceived by the treating physician. • GTV delineated not as per protocol according to diagnostic imaging report(s) • OAR contoured not as per protocol; with the application of optimal contour(s) and dose cube, the radiotherapy plan does not meet protocol defined constraint(s) • PTV coverage does not achieve mandatory dose objective Treatment planning suboptimal – dose not specified at ICRU reference point and not corrected for inhomogeneity • Overall treatment time* ≥22 days (BD arm) or ≥48 days (OD arm)

*dependent on randomisation group; BD, twice daily; GTV, Gross Tumour Volume; OAR, Organs at risk; OD, once daily; Dmax, the maximum dose to 2 cc; QA, Quality Assurance; ICRU, International Commission of Radiation Units and Measurements; PTV, Planning Treatment Volume.

Table 2
Baseline and treatment characteristics of the QA and non-QA cohort.

	QA Cohort (n = 93)	Non-QA Cohort (n = 450)
Age (y, range)	63 (34–79)	62 (29–84)
Sex (n, %)		
M	59 (63)	235 (52)
F	34 (37)	215 (48)
Ethnicity (n, %)		
White	91 (98)	433 (96)
African	0 (0)	2 (less than1)
Asian	0 (0)	5 (1)
Other	2 (2)	7 (2)
Not known	0 (0)	3 (1)
ECOG PS (n, %)		
0	43 (46)	205 (46)
1	48 (52)	228 (51)
2	2 (2)	15 (3)
Smoking history (n, %)		
Never smoker	1 (1)	6 (1)
Former smoker	53 (57)	284 (63)
Current smoker	39 (42)	158 (35)
Adverse biochemical factors (n, %)		
LDH > ULN	20 (22)	109 (24)
Hyponatraemia	22 (24)	87 (19)
ALP greater than 1.5 ULN	1 (1)	10 (2)
Radiotherapy (n, %)		
66 Gy, 33 fractions once daily	53 (57)	217 (48)
45 Gy, 30 fractions twice daily	40 (43)	233 (52)
UICC/AJCC Stage (n, %)		
I	1 (1)	3 (1)
II	13 (14)	69 (15)
III	72 (77)	351 (78)
Median gross tumour volume (cc, range)	79.9 (0.5–593.0)	83.9 (1.6–635.1)
Planned chemotherapy cycles (n, %)	61 (66)	308 (68)
Four	32 (34)	142 (32)
Six		
PET-CT Staging		
Yes	44 (47)	265 (59)
No	48 (52)	183 (41)
IMRT		
Yes	12 (13)	71 (16)
No	81 (87)	331 (74)
Unknown	0 (0)	48 (11)

QA, Quality Assurance; y, years; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate Dehydrogenase; ULN, Upper Limit of Normal; UICC, Union for International Cancer Control; AJCC, American Joint Committee on Cancer; IMRT, Intensity Modulated Radiotherapy.

Table 3
Protocol compliant and non-compliant contours.

Structure	Protocol compliant (n, %)	Protocol non-compliant (n, %)
GTV	90 (97.8)	2 (2.2) Incorrectly labelled as CTV
Heart	19 (20.4)	74 (79.6) Incorrect cranial heart border Exclusion of pericardial sac Anterior border not encompassing heart
Lung	58 (62.4)	35 (37.6) Incorrectly labelled Incorrect subtraction of lung–target volume Lung contour not delineated
Spinal Cord	23 (24.7)	70 (75.3) Spinal cord contoured instead of spinal canal Structure insufficiently contoured superior and/or inferior to the PTV

The quality of heart contours varied across the submitted cases; 19/93 (20.4%) contours were protocol compliant; the remaining 74 (79.6%) heart contour variations were classified as; i) heart contour either caudal (86.5%) or cranial (2.7%) to the protocol defined upper heart border, ii) heart contour not including the pericardial sac (10.8%), or iii) anterior border not encompassing the most anterior aspect of the pericardium (2.7%).

Thirty-five (37.6%) lung contours were protocol non-compliant. The right and left lung contours were submitted as individual structures in 27 submissions; the planning target volume (PTV) were excluded from either the right or left lung as opposed to the combined lung contour in 2 case submissions. One case submission excluded the GTV from the combined lung volume; 5 submissions did not include the lung contours.

The contouring guidance specified that the spinal cord structure was based on the inner bony limits of the spinal canal, with the contour extending 10 cm superior and inferior to the PTV. In 67 (72.0%) instances, the structure was not contoured sufficiently superior or inferior to the PTV.

Dosimetric compliance

Following the application of protocol-compliant lung, spinal cord, and heart contours by the QA team, there were 16 instances of OAR dosimetric non-compliance; 4 in lungs–PTV, where V20Gy exceeded 35% (range 35.1–38%), 11 in D50% delivered to the heart (range 45Gy arm: 25.7–33.3Gy, range 66Gy arm: 35.2–48.3Gy), and 1 in spinal cord Dmax (48.1Gy). The protocol specified spinal cord Dmax was 48Gy.

Of the 11 instances of heart dosimetric non-compliance, 6 (55%) heart structures were found to exceed protocol-defined constraints after application of protocol-compliant contours. In comparison of submitted heart contours and protocol-defined contours, the mean heart V5Gy and V30Gy increased by 4.89% (IQR 0–9.56) and 5.24% (IQR 0–9.08) in the 45Gy arm and 3.56% (IQR 0–6.81) and 4.49% (IQR 0–8.97) in the 66Gy arm. The mean D50% increased by 1.89Gy (IQR 0–1.2) and 1.44Gy (IQR 0–1.58) (Table 4). The mean Dmax increased by 2.10Gy (0–1.3) and 1.36Gy (0–1.36).

87% of the QA cohort were treated with three-dimensional conformal radiotherapy. The maximum and minimum dose to 2cc of the PTV were recorded as a parameter of plan quality with the optimal and mandatory objectives of ± 5% and ± 7% prescription dose. The optimal objective was achieved in 14/40 (35%) of the 45Gy arm and 30/53 (56.7%) of the 66Gy arm. The mandatory objectives of ≤ 107% and >93% were not met in 6/40 (15%) and 24/40 (60%) of the 45Gy arm. Similarly, in the 66Gy arm, the maximum dose objective of 2cc PTV was more likely to be achieved compared to the minimum dose objective; 73.5% vs 22.6%.

Treatment plans were deemed optimal in 71/93 (81%). Examples of sub-optimal planning included variation in beam arrangement resulting in hotspots outside of the PTV and poor beam arrangement resulting in delivery of avoidable radiotherapy dose to the heart. Seven radiotherapy treatment plans were subjectively deemed "too generous" with excessive 90% isodose coverage outside of the PTV.

Table 4
Dosimetric impact of the application of protocol non-compliant heart contours.

Dosimetric increase from institution supplied and protocol compliant heart contours	45 Gy twice daily (n = 40)	66 Gy once daily (n = 53)
V5Gy (%)	4.89, 1.42,	3.56, 1.85,
(Mean, median, IQR)	0–9.56	0–6.81
V30Gy (%)	5.24, 2.73,	4.49, 3.8,
(Mean, median, IQR)	0–9.08	0–8.97
D50% (Gy)	1.89, 0.2,	1.44, 0.55,
(Mean, median, IQR)	0–1.2	0–1.58
Dmax (Gy)	2.10, 0,	1.36, 0,
(Mean, median, IQR)	0–1.3	0–1.36

V5Gy, Volume of heart receiving 5 Gy; V30Gy, Volume of heart receiving 30 Gy; D50%, Dose to 50 % of the heart; Dmax, Maximum dose to 2 cc.

Treatment delivery compliance

All patients within the QA cohort received the planned radiotherapy dose. The optimal OTT was exceeded in 18/93 (19.4%) of the QA cohort; 9 (17.0%) in the 66Gy arm and 9 (22.5%) in the 45Gy arm.

Impact of protocol variation on outcome

The unacceptable variation rate was 21.1% across all QA parameters.

Sixty-five (69.9%) patients in the QA cohort had any form of Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grade ≥3 toxicity occurring up to 3 months following completion of treatment. Univariable analysis of instances of grade ≥3 toxicity demonstrated no significant increase in toxicity in instances of heart, lung, and spinal cord dosimetric non-compliance (Table 5). Extension of OTT beyond 22 days or 48 days was not associated with grade ≥3 toxicity (OR 2.30 (95% CI 0.68–10.63) p=0.221). Similarly, pooled acceptable variations compared with unacceptable variations (OR 1.26 (95 % CI 0.16–7.43) p=0.808) were not associated with grade ≥3 toxicity.

Univariable and CPM-adjusted PFS analysis revealed no detriment with dosimetric non-compliance of the heart, lung, or spinal cord (Table 6). OTT over protocol recommendation were not associated with prolonged PFS (HR 1.28 (95% CI 0.69–2.35) p=0.431). Pooled acceptable variations compared with unacceptable variations (HR 0.57 (95% CI 0.23–1.43) p=0.232) were not associated with prolonged PFS.

Median OS of the QA cohort was 28 months (95% CI 21–35; Fig. 2) and matched the trial cohort of 30 months (95% CI 24–34) in the twice-daily group and 25 months (95% CI 21–31) in the once-daily group (HR 1.18 (95% CI 0.95–1.45) p=0.14). Univariable and CPM adjusted OS analysis revealed no detriment with dosimetric non-compliance of the heart, lung, or spinal cord (Table 7). OTT over protocol recommendation were not associated with reduced OS (HR 1.01 (95% CI 0.99–1.03) p=0.240). Pooled acceptable variations compared with unacceptable variations (HR 0.86 (95% CI 0.34–2.16) p=0.743) were not associated with reduced OS.

Discussion

This study reporting radiotherapy QA for the international randomised controlled CONVERT trial reports radiotherapy QA parameters and relates the dosimetric impact of contour variation, with treatment delivery compliance against patient outcome [6,7,10,12].

Of 543 recruited patients, 93 cases were submitted for retrospective radiotherapy QA. The baseline characteristics of the QA cohort were well matched to the non-QA cohort. The GTV contours were more likely to be protocol compliant than OARs contours for the heart (20.4%), the lungs (62.4%), and the spinal cord (24.7%). In 11 (11.8%) instances the heart structure received radiation dose exceeding protocol-defined constraints; half (54.5%) of these protocol variations were detected after the participant had completed treatment.

Of the 74 non-protocol compliant heart contours, 89.2% had contours terminating either cranial or caudal to the protocol-defined upper heart border, the remainder did not encompass the anterior-most aspect of the pericardium, which may be reflective of the individual not

Table 5
Univariable any grade 3 toxicity analysis and variation from protocol.

	OR (95% CI)	p-value
Dosimetric non-compliance		
Heart	0.72 (0.20–2.97)	0.631
Lung	1.00 (0.01–99.99)	0.990
Spinal cord	1.00 (0.01–99.99)	0.991
Treatment delivery non-compliance		
OTT	2.30 (0.68–10.63)	0.221
Acceptable vs unacceptable variation	1.26 (0.16–7.43)	0.808

OTT: Overall treatment time.

Table 6
Univariable and CPM adjusted progression free survival analysis with variation from protocol.

	Univariable analysis		CPM Adjustment	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Dosimetric non-compliance				
Heart	1.12 (0.57–2.20)	0.743 0.635	1.05 (0.51–2.14)	0.899 0.672
Lung	1.28 (0.46–3.52)	0.626	1.25 (0.45–3.43)	0.791
Spinal cord	1.64 (0.23–11.92)		1.31 (0.18–9.82)	
Treatment delivery non-compliance				
OTT	1.13 (0.62–2.03)	0.691	1.28 (0.69–2.35)	0.431
Acceptable vs unacceptable variation	0.63 (0.25–1.57)	0.321	0.57 (0.23–1.43)	0.232

OTT: Overall treatment time.

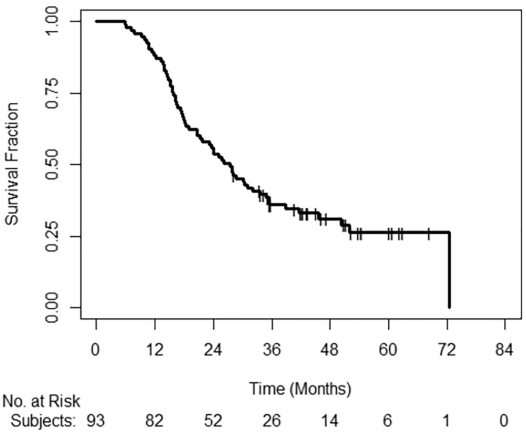

Fig. 2. Overall survival in the QA cohort.

Table 7
Univariable and CPM adjusted overall survival analysis with variation from protocol.

	Univariable analysis		CPM Adjustment	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Dosimetric non-compliance				
Heart	1.02 (0.50–2.06)	0.962 0.296	0.91 (0.43–1.93)	0.800 0.303
Lung	1.72 (0.62–4.76)	0.907	1.71 (0.62–4.74)	0.946
Spinal cord	1.13 (0.16–8.15)		0.93 (0.12–6.99)	
Treatment delivery non-compliance				
OTT	1.01 (0.99–1.03)	0.259	1.01 (0.99–1.03)	0.240
Acceptable vs unacceptable variation	0.82 (0.33–2.04)	0.674	0.86 (0.34–2.16)	0.743

OTT: Overall treatment time.

contouring the heart structure with the optimal window or level. The CONVERT trial protocol provided each participating institution with radiotherapy planning guidelines including atlas of protocol-compliant OAR delineation detailing the heart contours [10]. Despite centres possessing OAR contouring guidance and submitting contours and radiotherapy plan of a previously treated patient who satisfied the eligibility criteria for the CONVERT trial, timelier on-trial QA review may have highlighted heart structure contouring non-compliance to centres during recruitment and reduced the incidence of non-compliant heart contours.

Reported heart dosimetry increased following application of protocol-compliant heart contours, with the greatest increase seen in mean V5Gy (Table 4). This dosimetric difference is consistent with that seen in RTOG 0617 when auto-segmented heart contours were applied to trial data [13]. The proportion of heart structure dosimetric non-compliance was 11.8% and too small to proceed with robust statistical analysis to compare radiotherapy dose to the heart structure against participant outcome.

The evidence base surrounding heart irradiation in lung cancer is building. Single centre pooled analysis of 112 patients with stage III non-small cell lung cancer (NSCLC) treated with dose-escalated radiotherapy implied cardiac events are independently related to both baseline cardiac risk and dose delivered to the heart structure, with threshold mean heart dose in patients with cardiologist determined cardiac events as 20Gy and V30Gy of 29% [14]. Meta-analysis of cardiac dosimetric parameters in 5614 NSCLC clinical trial patients determined heart dose should not be prioritised over lung dose given the weaker strength of association between heart dose-volume parameters, toxicity, or mortality, with insufficient evidence to justify compromising tumour dose or coverage [15]. The *meta*-analysis did not consider the impact of radiotherapy QA, the variation in heart contouring in and across clinical trials, disease-related and cardiac-specific mortality, nor the impact of fraction size, radiotherapy delivery technique, or TD delivered.

The CONVERT trial specified the heart dose constraint as TD less than 30% volume, and TD less than 50% if greater than 50% of the heart structure was irradiated [10]. These constraints are more generous than the constraints proposed by Wang et al. but consistent with radiotherapy lung cancer clinical trials which recruited at a similar time to the CONVERT trial at a time when the literature on risk of cardiac toxicity in patients treated with thoracic radiotherapy was more limited [14] and the when the results from RTOG 0617 were not known [16].

Radiation induced heart disease following treatment for lung cancer are multifactorial; patients with lung cancer are older, often with established co-morbidities. Prognostic scales aim to quantify the impact of these individual patient baseline risk factors on outcome [17,18]. Further work will include the prospective collection of patient baseline risk factors, with quality assured dosimetric data collected from the heart substructures aided by OAR atlases to establish the true impact of radiotherapy dose to the heart [18,19]. Considering such limitations, it is not surprising that this study reporting the CONVERT radiotherapy QA parameters did not demonstrate an advantage for those trial participants with pooled acceptable protocol variations.

CHART, GFPC-IFCT 02.01, PET-Plan, and PROCLAIM have formally reported radiotherapy QA [6–9]. The QA parameters differ between these clinical trials and are reported as isolated components. A comprehensive radiotherapy QA programme should report these parameters as a continuum. This allows, as we did with the CONVERT QA study, to demonstrate the impact of contour compliance upon reported dosimetry.

Radiotherapy QA within the PROCLAIM and PET-Plan studies mandated a prospective review of the first radiotherapy plan from each centre followed by mandatory and selective on-trial review; all remaining data were reviewed retrospectively [6,7]. PROCLAIM QA was based on 4 trial-specific QA parameters: PTV coverage, hot spots within and outside the PTV, spinal cord dose, and V20Gy lung. 7.2% (40/554) of cases within PROCLAIM had major radiotherapy QA violations [6]. PET-Plan employed extensive radiotherapy QA (EORTC-radiotherapy QA level 4) and reported an overall 25% minor, 59% intermediate, and 15% major deviation incidence [7]. Twenty-six of the 204 evaluated radiotherapy records had more than one major deviation. Neither study reported the impact of contouring variations on reported dosimetry. As there is variation in QA reporting, there is an unmet need to systematically define the radiotherapy QA parameters in the radical treatment of lung cancer.

The QA analysis of the CONVERT trial reports an unacceptable variation rate of 21.1%, this is greater than that reported in PET-Plan and PROCLAIM [6,7]. In both trials QA parameters were reported in isolation, indicating the true major QA violation or unacceptable deviation incidence are only appreciated when the processes within the chain of QA parameters are evaluated as a continuum. Radiotherapy treatment planning was deemed optimal in 81% of submitted cases; despite most plans being optimal, optimal radiotherapy treatment planning does not mitigate the impact of non-compliant OAR contouring.

In contrast to this analysis of the CONVERT QA data, secondary QA analysis of the 2002–2005 TROG 02.02 HeadSTART trial and radiotherapy QA of the PET-Plan and PROCLAIM trials reveal the negative impact of protocol violation on patient outcome [5]. Violations of the pre-defined QA parameters as described within TROG 02.02 HeadSTART trial are not likely to be seen in either usual clinical practice or contemporary clinical trials due to robust governance processes: departmental peer-review, prospective QA review, or on-trial correction of protocol non-compliance. With present-day governance and stringent treatment delivery guidance the magnitude of the impact of radiotherapy QA as reported in the TROG 02.02 HeadSTART trial is not likely to be seen again [5].

There are limitations to this work. This QA analysis was conducted retrospectively, 17.1% of cases were reviewed having been selected randomly from the total participant cohort; stratified selection of cases submitted for QA review would have overcome the bias of case selection. 87% of the QA cohort were treated with 3D conformal radiotherapy with the majority planned with type b dose calculation algorithms.

With the drive to deliver modern radiotherapy with IMRT the treatment delivery process is increasingly complex and the impact of radiotherapy QA is even more important. Artificial intelligence and automated segmentation tools provide opportunities to standardise the radiotherapy QA workflow and improve contour accuracy and consistency; such tools may streamline the radiotherapy QA process and render the process less resource intensive [20].

Conclusion

Radiotherapy QA remains the cornerstone of high-quality radiotherapy delivery and should be embedded into clinical trial and non-clinical trial practice; radiotherapy QA likely impacts on the quality of radiotherapy delivered in the routine setting in participating centres. Clinical trials should report standardised radiotherapy QA parameters alongside trial outcomes.

Declaration of Competing Interest

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.

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Portfolio

1. Membership

The Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group

NCRI CSG Clinical and Translational Radiotherapy

EORTC Development of a Health-Related Quality of Life (HRQOL) Module for Keratinocyte Carcinoma

2. NIHR RTTQA Research Fellow: Protocol development

ALL-RIC
ATNEC
BRIOChe
NICO
Primus-002
TORPEdO

3. Publications

Automatic Evaluation of Contours Utilizing Conformity Indices and Machine Learning

Sami Terparia, Romaana Mir, Yat M Tsang, Catharine H Clark, Rushil Patel
phiRO 2020; 16: 149-55
doi.org/10.1016/j.phro.2020.10.008

Sacral insufficiency fracture following pelvic radiotherapy in gynaecologic malignancies: development of a predictive model

Romaana Mir, Alina D Dragan, Hitesh B Mistry, Yat M Tsang, Anwar R Padhani, Peter Hoskin
Clin Oncol 2021; 33: e101-9
doi.org/10.1016/j.clon.2020.10.013

A Real Pain In The Neck: Return to first principles

Romaana Mir, Agata Rembielak
IJROBP 2022; 113: 892
doi.org/10.1016/j.ijrobp.2022.05.007

Management of Bone Pain in Palliative Care. Pain in Palliative Care OUP

Romaana Mir, Peter Hoskin

IMAT: Quality Assurance of benchmark submissions – in progress

Sarah Kelly, Romaana Mir, Chris Stacey, Greg Smyth, Emma Pond, Jenny Gains, Henry Mandeville, Mark Gaze

4. Engagement with Industry

Clinical support or the Elekta ProKnow Working Group
Aim: Integrate GHG Paper 3 into ProKnow and to develop Python scripting solutions

5. Oral & Poster Presentations

National Cancer Research Institute Annual Conference
Berner AM, Skyllberg E, Mir R, Shamash J
Poster: VAPS (VATS, Anaemia, Performance Status and Sarcomatoid histology) prognostic index in malignant pleural mesothelioma

Radiological Society of North America
Dragan AD, Padhani AR, Mir R, Hoskin P
SSE25-03 Bone Fragility After Pelvic Chemoradiotherapy Cervix Cancer

United Kingdom Lymphoma Radiotherapy Group
Diez P, Mir R, Thomas E, Stacey C, Miles E, Mikhaeel G, Marks D
National TBI Survey

San Antonio Breast Cancer Virtual Symposium; 2020 Dec 8-11; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2021; 81 (4 Suppl):Abstract nr OT-04-01
Goyal A, Cramp S, Wheatley D, Marshall A, Puri S, Homer T, Vale L, Mir R, Nabi Z, Rose J, Edwards HT, Ahmed S, Shaaban A, Elsberger B, Bruce J, Gasson S, Speirs V, Shaw J, Higgins H, Dunn J
Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation after neoadjuvant chemotherapy - ATNEC

European Society for Therapeutic Radiology and Oncology Annual Meeting
Terparia S, Mir R, Tsang YM, Patel R, Clark CH
OC-0348 Automatic Evaluation of Contours Utilising Conformity Indices and Machine Learning

European Society for Therapeutic Radiology and Oncology Annual Meeting
Mir R, Dragan AD, Tsang YM, Padhani AR, Hoskin P
Oral: PH-0653 Sacrum D30% >38.3Gy_3 predicts for insufficiency fracture following pelvic chemo-radiotherapy

European Society for Therapeutic Radiology and Oncology Annual Meeting
Mir R, Kelly S, Xiao Y, Moore A, Clark CH, Clementel E, Corning C, Ebert M, Hoskin P, Hurkmans C, Ishikura S, Kristensen I, Kry SF, Lehmann J, Michalski J, Monti A, Nakamura M, Thompson K, Yang H, Zubizarreta E, Andratschke N, Miles E
PO-1294 Consistency of OAR delineation for clinical trials: A Global Harmonzation Group Consensus

European Society for Therapeutic Radiology and Oncology Annual Meeting
Diez P, Mir R, Stacey C, Thomas E, Miles A, Hodgkinson A, Marks DI
PO-1767 A national survey of total body irradiation to define best practice for the ALL-RIC trial

European Society for Therapeutic Radiology and Oncology Annual Meeting
Lopes Simoes AR, Mir R, Lawless C, Shaw A, Peedell C, Pope T, Lester J, Landau D, Faivre-Finn C, Hatton M
PO-1879 A novel and objective plan evaluation tool for dose escalation in NSCLC with the ADSCaN trial

2021 World Conference on Lung Cancer, Singapore: Worldwide Virtual Event
Mir R, Faivre-Finn C, Lawless C, McCartney E, Peedell C, Pope T, Shaw A, Simoes R,
Hatton M
Oral: FP-04 #1884 Feasibility of Radiotherapy Planning in the First 50 Patients Recruited to the ADSCaN Clinical Trial

2021 American Society of Clinical Oncology

Goyal A, Cramp S, Wheatley D, Marshall A, Puri S, Hammonds N, Homer T, Vale L, Mir R, Rose J, Edwards HT, Ahmed S, Shaaban A, Eisberger B, Bruce J, Gasson S, Speirs V, Shaw J, Higgins H, Dunn J

TPS600 Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation after neoadjuvant chemotherapy (ATNEC)

2021 5th Annual Christie Advanced Radiotherapy Summer School

Mir R

Oral: Organs at risk: Do we know what we are talking about?

European Society for Therapeutic Radiology and Oncology Annual Meeting

Butt R, Nabi Z, Mir R, Hills J, Wheatley D, Bhattacharya I, Ranger A, Cramp S, Hammond N, Goyal A, Tsang Y. MO-0644 Practice patterns for outlining the axilla and IMC, findings of the RTQA for the ATNEC trial.

European Society for Therapeutic Radiology and Oncology Annual Meeting

Nabi Z, Butt R, Mir R, Hills J, Tsang YM, Wheatley D, Bhattacharya I, Ranger A, Cramp S, Hammonds N, Goyal A

PO-1835 A glimpse at breast internal mammary chain radiotherapy in the United Kingdom.

European Society for Therapeutic Radiology and Oncology Annual Meeting

Price H, Nabi Z, Butt R, Mir R, Diez P, Dodwell D, Sadiq S, Lewis M, Goyal A.

PD-0335 Dosimetric differences between field and volume-based regional nodal RT in the POSNOC breast trial.

2022 6th Annual Christie Advanced Radiotherapy Summer School

Mir R

Oral: Organs at risk: Do we know what we are talking about Part II?