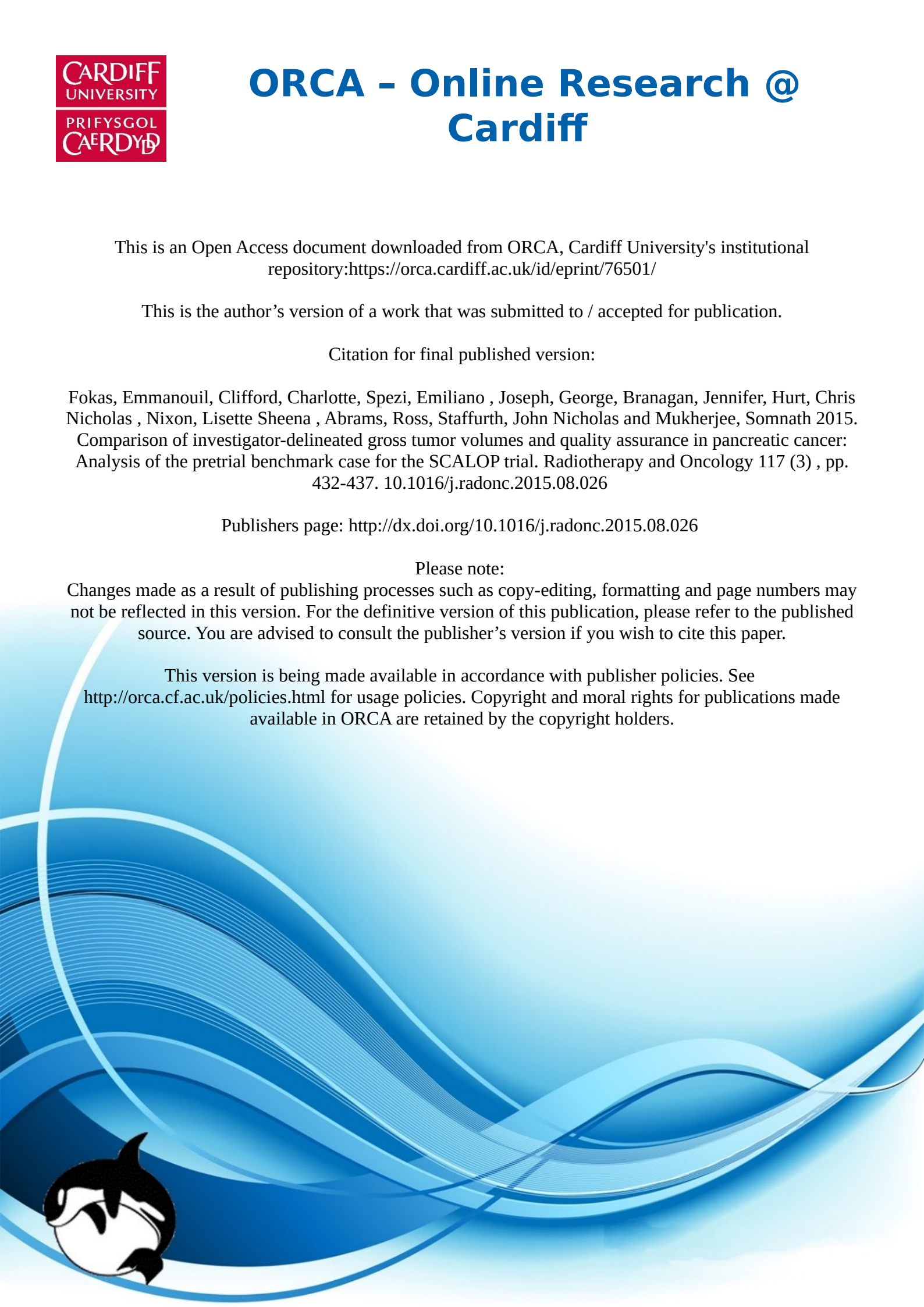


SUPPLEMENTARY DATA

SUPPLEMENTARY METHODS

RTTQA program

The national NCRI Radiotherapy Clinical Trials Quality Assurance (RTTQA) team consisted of the chief investigator, a senior dosimetrist, a radiologist and RT-QA advisors (who were also clinical oncologists), working in conjunction with the Wales Cancer Trials Unit (WCTU) and the RTTQA group. The QA process for RT consisted of:

(A) Pre-trial QA:

1. Questionnaires completed by each centre: a) National QA Baseline questionnaire – detailed questions on available equipment, PTV Definition, Monitor Unit Check, Transfer of Plan to LINAC, DRRs, participant in-vivo dosimetry, and Shielding pre-treatment participant checks; b) National QA staff questionnaire – asked about experience of staff to be involved in RT on the trial. ; c) Trial specific questionnaire – to establish the extent of experience of RT for advanced pancreatic cancer and details of associated RT procedures across the centres. This was administered at the same time as the test cases are done.

2. Radiotherapy section of SCALOP protocol described the process for RT treatment outlining, planning and delivery for pancreatic cancer to aid the delivery of high quality RT. This was developed by a process including review by the SCALOP TMG, within the WCTU, peer-reviewed by UK Clinical Oncologists with a special interest in pancreatic cancer, peer-reviewed by an experienced Radiation Oncologist from the RTOG Trial group and within the NCRI RTTQA group.

3. A planning atlas was included in APPENDIX 8 of the protocol (http://www.wctu.org.uk/trial. php?trial=scalop).

4. One test case (DICOM CT data set along with a clinical summary) was sent to each participating clinician. They were required to provide the GTV, PTV, plan, and a Plan Assessment Form (PAF, supplementary figure 1) that assessed whether or not the plan conforms to the protocol. These were evaluated centrally by the SCALOP QA team and feedback was provided. Each clinical oncologist supervising radiotherapy within the SCALOP trial was required to complete the test case satisfactorily prior to entering participants in the trial. Each centre will be required to submit one plan/PAF prior to entering participants in the trial.

(B) On-trial QA:

For every participant, clinicians at each centre will be asked to complete a detailed PAF which will be an integral part of the trials CRF. These indicate concordance with the radiotherapy protocol, and allow real-time central review, providing an opportunity to identify major deviations prior to start of radiotherapy.

Radiotherapy protocol

The SCALOP trial protocol contained specific instructions on tumour delineation, treatment volumes, dose constraints and planning techniques that were to be followed for patients within the trial. All patients underwent contrast-enhanced planning computer tomography (CT) simulation with 200–300 mL water as oral contrast. The planning computer tomography (CT) scan was acquired in supine position following administration of 100ml of intravenous contrast (3ml/sec) in a Siemens Sensation Open CT scanner (Siemens, Erlangen, Germany) and 3mm slices were obtained using bolus tracking. The gross tumour volume (GTV) consisted of the primary tumour and any node with short axis diameter of 1 cm or more. The planning target volume (PTV) included the GTV with a margin of 2.0 cm in the craniocaudal direction and 1.5 cm in all other directions. Prophylactic irradiation of uninvolved (elective)

regional nodes was not performed. A dose of 50.4Gy in 28 fractions was required to be prescribed to the International Committee on Radiation Units and Measurements (ICRU) 50 reference point, 1.8Gy per fraction, using at least 6MV photons. The exact number of beams, beam energy, beam arrangement and gantry angles were not explicitly defined but a single phase 3D conformal plan was required. The protocol stated that centres should aim to encompass the PTV with the 95% isodose, and that at least 99% of the PTV should receive 95% of the prescription dose (i.e. 47.9Gy). It was recommended that the minimum PTV dose should be >93% of the prescribed dose, but it was not considered to be a deviation if this was not achieved. The dose constraints were specified in the protocol (Supplementary Table 2). Intensity-modulated radiotherapy (IMRT) was allowed if previously developed and established as a departmental technique and the department had previously received credentials for IMRT by the NCRI RTTQA group. Centres were required to follow their local protocols as regards pre-treatment verification. As a minimum on-treatment verification should be carried out on the first 3 days of treatment and thereafter on a weekly basis. Key trial specific recommendations in the protocol included the use of both intravenous contrast and oral contrast/water during CT simulation, the need for advice from a gastrointestinal radiologist for GTV delineation and the compulsory completion and central review of the Plan assessment Form (**PAF**; Supplementary Figure 1) prior to initiation of radiotherapy on patients in the trial.

RT planning comparison between VODCA and PAF

From the n=25 cases, only 22 plans were evaluable because of technical issues in opening the data. Regarding the assessment of target volume contouring, the CT slice thickness for the benchmark case was 0.3cm and therefore a 2.1cm expansion of the iGTV to iPTV expansion in the sup-inf direction to generate the 2.0cm margin was the correct interpretation of the

protocol. Sixteen centres applied this correctly and 4 applied a 1.8cm margin. All applied the 1.5cm radical iGTV to iPTV margin correctly. A spinal cord margin of 0.5cm was recommended in the protocol, but sites were allowed to use a 0.3cm margin if this was their standard practice. 14 sites used a margin of 0.5cm, 5 used a margin of 0.3 cm and 1 added no margin. The site that did not apply a margin was advised that this was not according to the protocol and a note made to check the first patient case from this site.

SUPPLEMENTARY RESULTS

Analysis of slice-by-slice conformity

The slice by slice analysis of conformity between each iGTV and the gsGTV performed in CERR is shown in Supplementary Figure 2 for JCI ***(A)***, GMI ***(B)*** and MDC ***(C)***. The proportion of iGTVs achieving different cutoff levels for each index is shown. The figure shows that the greatest variation is at the cranial and caudal limits of the volume (slices 579 and 612). Less than 15% of investigators achieved a local JCI of ≥0.6 for both slices and <10% of investigators achieved a slice GMI of ≤0.3 for slice 612. In addition, two of the central slices (597 and 600) also had lower levels of conformity, shown most clearly with MDC (<15% investigators achieved an MDC of ≤0.20mm on both slices). This would support a concept of using slice by slice geometric review to aid assessment of benchmark case outlining.

Supplementary Figure 1

WCTU WALES CANCER TRIALS UNIT / UNED YMCHWIL CANSER CYMRU

Participant Trial No. ☐☐☐☐☐ Participant Initials ☐☐☐ Participant Date of Birth ☐☐ ☐☐ ☐☐☐☐ (dd mm yyyy)

Induction Chemotherapy Treatment Form (cycle 3) - Week 13

7 Radiotherapy Plan Assessment Form

Target Volume Delineation

7.1 IV contrast solution used Contrast ☐ Water ☐ Neither ☐

7.2 Radiologist delineated/assisted? Yes ☐ No ☐

Renal function	*Protocol*	*Participant*
7.3 Corrected GFR (ml/min)	> 50	☐☐

7.4 Was this GFR calculated or EDTA? Calculated ☐ EDTA ☐

7.5 If MAG3 renogram done, please enter result Right ☐☐ % Left ☐☐ %

Margins applied	*Protocol*	*Participant*
7.6 GTV to PTV S-I (cm)	2.0	☐.☐
7.7 GTV to PTV R-L (cm)*	1.5	☐.☐
7.8 GTV to PTV A-P (cm)	1.5	☐.☐

7.9 PTV post margin modified? Yes ☐ No ☐

7.10 If YES, on slices (z positions): ☐☐☐ to ☐☐☐

Dose volume constraints

NORMAL TISSUES	PROTOCOL	PARTICIPANT	
Organs At Risk (OAR)	Dose Volume Criteria *	Vol. of OAR achieved %	Comment
Spinal cord	No part of cord PRV to receive 40Gy*	☐☐☐ %	
Liver	No more than 40% of liver to receive 30Gy*	☐☐☐ %	
Ipsilateral kidney (right/left)	No more than 40% of kidney to receive 20Gy*	☐☐☐ %	
Combined kidneys	No more than 30% of total kidney to receive 20Gy*	☐☐☐ %	

** If limits exceed please contact the WCTU for discussion*

TARGET COVERAGE	PROTOCOL	PARTICIPANT	
Region of Interest	Dose Volume Criteria	Achieved	Comment
PTV volume (cc)	N/A	☐☐☐ %	
PTV D95 (47.9Gy)	99% of PTV to receive 95% prescription dose	☐☐☐ %	
PTV minimum dose	N/A	☐☐☐ %	
ICRU defined plan maximum dose	Should be no more than 107%	☐☐☐ %	

Prescribed dose Gy in ☐☐.☐ Fractions ☐☐ [N.B: Protocol 50.4Gy in

Is there any deviation from the SCALP protocol? Yes ☐ No ☐ Comments.....

If yes please discuss with PI

Planned by:..... ☐☐ ☐☐ ☐☐ (dd mm yy) Checked by:

Checked by:..... ☐☐ ☐☐ ☐☐ (dd mm yy) Checked by: ☐☐ ☐☐ ☐☐ (dd mm yy)

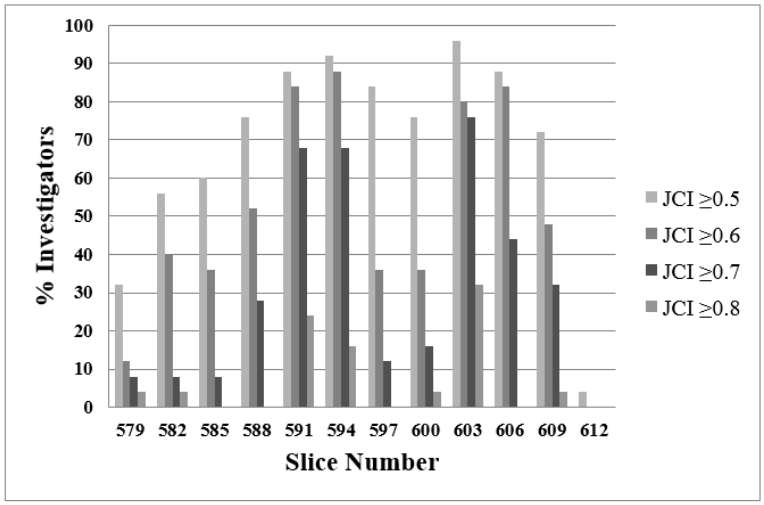
Has the CD-ROM of the RT plan been sent to WCTU?..... Yes ☐ No ☐

Completed by..... Date ☐☐ ☐☐ ☐☐ (dd mm yy)

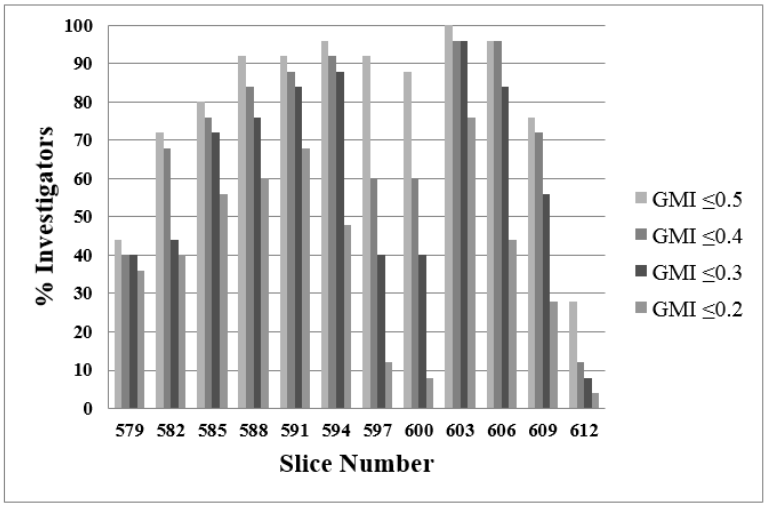
WCTU USE ONLY: Data input on MACRO by: _____ ____/____/____

Supplementary Figure 2

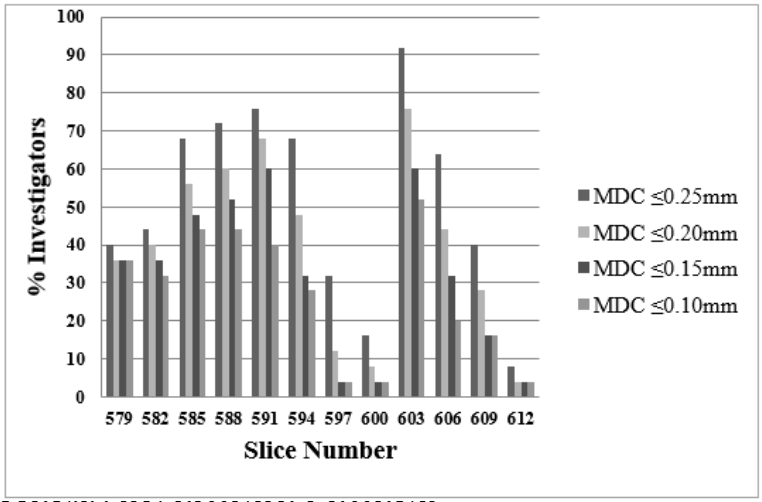
A



B



C



SUPPLEMENTARY FIGURE LEGEND

Supplementary Figure 2. Bar charts showing the percentage of investigators achieving different cutoff levels for ***A)*** the Jaccard Conformity Index (JCI), ***B)*** the Geographical Miss Index (GMI) and ***C)*** the mean distance to conformity (MDC).

Supplementary Table 1. Formulas and descriptions of different metrics used for contour comparisons.

Conformity Index	Equation / Description
Jaccard Conformity Index JCI *Range: 0 – 1; Ideal: 1*	$\frac{A \cap B}{A \cup B}$ Amount of the gold standard contour covered by the investigating contour as a fraction of their encompassing volumes.
Geographical Miss Index GMI *Range: 0 – 1; Ideal: 0*	$\frac{B - (A \cap B)}{B}$ Amount of the gold standard contour missed by the investigating contour as a fraction of the gold standard contour.
Mean Distance to Conformity MDC [mm] *Range: 0 – ∞ ; Ideal: 0*	Average distance that all outlying points in the investigating contour must be moved in order to achieve perfect conformity with the gold standard contour
Abbreviations: A = investigator contour; B = gold standard contour; $A \cap B$ = intersection of A and B; $A \cup B$ = union of A and B.	

Supplementary Table 2. Dose-Volume constraints and trial deviations for the SCALOP trial

Region of interest / organ at risk	Dose Constraint	Further detail	Minor variation	Major Deviation (acceptable)	Major Deviation (unacceptable)
PTV	V95% (47.9Gy)> 99.0%	More than 99% of the PTV volume to receive 95% of the prescribed dose	≥95%	≥90%	< 90%
PTV Dmin	N/A	Recommended to be >93%	<93%	<90%	
PTV Dmin	≤107%	Region considered clinically meaningful if minimum diameter exceeds 15mm	≤110%	≤113%	>113%
Spinal Cord planning risk volume	V40 Gy <0%	Maximum dose to any part of the spinal cord PRV is 40Gy	V42Gy <0%	V45Gy <0%	Any cord receiving >45Gy
Liver	V30 Gy < 40%	No more than 40% of the liver to receive 30Gy	V30Gy ≤ 45%	V30Gy ≤ 50%	V30 > 50%
Ipsilateral Kidney (or for central tumours, kidney receiving the higher dose)	V20 Gy < 40%	No more than 40% of the kidney receiving the highest dose to receive 20Gy	V20Gy ≤ 45%	V20Gy ≤ 50%	V20 > 50%
Combined Kidneys	V20Gy < 30%	No more than 30% of the combined kidney to receive 20Gy.	V20Gy ≤ 35%	V20Gy ≤ 40%	V20 > 40%

Supplementary Table 3. Volume (cm^3) of outlined structures in benchmark case from VODCA

	Gold standard outline	Investigator outlines			
		Mean	**SD**	**Min**	**Max**
GTV	26.2	25.4	10.8	11.7	47.3
PTV	223.3	210.1	38.9	151.5	289.1
Liver	1905	2021	104	1811	2367
Left Kidney	120	116	5	106	124
Right Kidney	111	109	5	100	119