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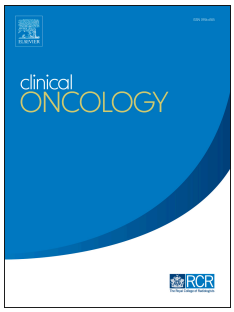

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Radiotherapy plan quality assurance in the ABC-07 trial of stereotactic body radiotherapy (SBRT) for locally advanced biliary tract cancer

Short title: Radiotherapy plan QA in ABC-07 trial of SBRT for biliary tract cancer

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Keywords: SBRT, radiotherapy planning, biliary tract cancer, plan conformity

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Abstract

Purpose: The ABC-07 phase II randomised controlled trial (ISRCTN: 10639376) investigated the addition of stereotactic body radiotherapy (SBRT) to systemic chemotherapy in locally advanced biliary tract cancers. We report the radiotherapy quality assurance (RTQA) of SBRT treatment plans in the trial.

Methods and Materials: RTQA was performed before and during accrual, including benchmark contouring and planning cases, along with prospective independent case review (ICR) of the first three patients from each centre randomised to SBRT. Prescription doses were up to 50Gy in 5 fractions or up to 67.5Gy in 15 fractions. Cases were reviewed for segmentation accuracy and plan quality, including target coverage and organ at risk (OAR) constraints met.

Results: Benchmark cases: 6/17 contouring submissions required revision (35%), and 6/17 planning submissions were revised after feedback on what was achievable by other centres. Prospective ICR: 31/41 cases from all 12 recruiting centres that were randomised to SBRT underwent review in real-time, and the others were reviewed retrospectively. Eight of these prospectively reviewed cases required revisions during the review process (26%, including 7 contouring and 2 planning revisions). 19/41 plans overall (46%) had deviations from trial protocol objectives (even after any revisions), mostly unavoidable target coverage compromise (D95%<90%) because of proximal OARs such as duodenum (17/41) and stomach (6/41).

Conclusions: Despite rigorous plan QA we encountered variability in segmentation, and plan coverage. Revision rate was reduced between pre-trial and on-trial cases. Radiotherapy doses in the

protocol were achievable in many cases, however target coverage was frequently compromised to maintain OAR dose constraints. Such compromises should be prespecified in future studies.

Introduction

The role of RT in locally advanced, inoperable cholangiocarcinoma is uncertain. Standard of care for unresectable biliary tract cancer (BTC) is cisplatin and gemcitabine (CisGem), as established by the ABC-02 trial, which reported median overall survival of 12 months for this combination chemotherapy with no significant increase in toxicity over single agent gemcitabine [1]. Studies of definitive chemoradiation have shown potential for further improved local control and overall survival, especially for the highest biological doses, however the optimum radiation dose has yet to be established [2,3,4]. Technologies to deliver higher doses whilst sparing surrounding normal tissue include brachytherapy, proton beam therapy and stereotactic body radiotherapy (SBRT). SBRT uses advances in image-guidance and radiation delivery technology to give a few high doses of radiation with high conformality of dose, and millimetre accuracy. Recent data suggests that SBRT provides greater local control than conventional fractionated radiotherapy, with overall survival of 11-36 months for selected patients, is easily incorporated into systemic therapy schedules, and is well tolerated with few toxicities [2, 5].

Therefore, the purpose of this multi-centre randomised controlled phase II trial, ABC-07 (https://www.isrctn.com/ISRCTN10639376), is to investigate whether addition of SBRT to chemotherapy improves outcomes for patients with locally advanced, inoperable, biliary tract cancer [6], including larger volumes up to 12 cm diameter.

Radiotherapy quality assurance (RTQA) within clinical trials is essential to monitor protocol compliance and reduce variation in treatment quality between different centres [7]. Robust multi-centre QA programmes are typically managed by regional or national bodies such as the Radiotherapy Trials Quality Assurance group (RTTQA) in the UK [8]. These programmes consist of facility questionnaires, pre-trial benchmark cases for target & organ-at-risk contouring and treatment planning, along with physical dosimetry audits and on-trial individual case reviews (ICR) of recruited patients, which are analysed centrally [9] and hence independently of the treating center.

This work describes the plan RTQA, reviews the adherence to trial protocol, and describes the quality of RT segmentation (tumour and normal tissues) and the dosimetric characteristics of treatment plans for patients who were randomised to receive SBRT.

1. Materials and methods

ABC-07 is a multi-centre phase II trial comparing the efficacy of CisGem chemotherapy (6 cycles) & SBRT, compared to CisGem alone (8 cycles), in terms of progression free survival (PFS) [10]. Patients with inoperable, histologically confirmed locally advanced cholangiocarcinoma and WHO performance status 0-1 were eligible for recruitment. Those with stable disease or partial response after initial chemotherapy were randomised 2:1 to SBRT or 2 further cycles of CisGem. SBRT was prescribed in 5 fractions (if lesion size < 6 cm) or moderate hypofractionation in 15 fractions[1] (if >6 and <12 cm) and mean liver dose was used to deescalate the prescription dose if needed to achieve tolerances (Table 1). Extensive radiotherapy guidelines were provided as an appendix to the trial protocol. Ethics approval for the study was acquired from the Hampstead Research Ethics committee (IRAS 173350) and national Health Research Authority.

Comprehensive credentialing of institutions that delivered SBRT included: facility questionnaire and process document with details of techniques and equipment to be used; benchmark outlining and contouring cases with central review and approval before the centre could start recruiting; dosimetry audit of a representative SBRT plan; and prospective case review of at least the first three patients. Radiotherapy planning data for all other SBRT patients was collected and reviewed retrospectively. Further details are given in the supplementary materials.

Treatment delivery using online daily image-guidance and intensity modulated radiotherapy (IMRT) was mandated. As per protocol, patients were simulated supine with arms up in custom

[1] For simplicity both fractionation schemes are referred to as SBRT within the trial and this manuscript. 15 fractions are typically considered moderate hypofractionation, however plans in this study share other characteristics of SBRT such as high conformality and high spatial precision.

immobilisation. Imaging included 4DCT and IV contrast enhanced exhale breath hold (EEBH) 3D scans. The EEBH was used as the primary dataset for contouring and planning. Use of MRI scans to aid tumour delineation was also strongly recommended, co-registered to CT if possible.

Motion management such as abdominal compression or fiducial tracing, was recommended in cases where breathing motion exceeded 5 mm. The 4DCT phases could be used to construct an expanded internal target volume (ITV) for motion up to 20 mm. Gross tumour volume (GTV) included all parenchymal enhancing disease and involved lymph nodes. No margin was added for clinical target volume (CTV), and planning target volume (PTV) was constructed based on observable motion and at least 4mm isotropic margin added for other setup errors.

Guidance was given on normal tissue contouring, and planning dose objectives. Naming conventions were also given to facilitate central analysis, such as target including dose prescription (e.g. *PTV_5000* for 50 Gy, see Table 1), planning organ-at-risk volume (PRV) for spinal canal with 5 mm margin (*SpinalCanal_05*), and normal liver (excluding GTV).

Target dose objectives for dose prescriptions in Table 1 were PTV coverage D95% > 95% (optimal) (i.e. that 95% of the volume should receive at least 95% of the prescription dose), and PTV near-maximum dose D0.1 cm^3 < 120% (optimal) and 130% (mandatory). Objectives were also given for organs-at-risk (OARs) such as duodenum, stomach, bowel, normal liver & kidneys (as listed in supplementary materials), along with instructions to prioritise mandatory OAR constraints over PTV coverage if needed in cases of proximity or overlap.

The following conformity metrics were also calculated, based on those reported by Lee *et al* (2019) [11], modified to use V95% rather than V100%:

$$Prescription\ Dose\ Spillage\ (PDS) = \frac{Body\ V95\%}{PTV\ V95\%}$$

$$Modified\ Gradient\ Index\ (mGI) = \frac{Body\ V50\%}{PTV\ V95\%}$$

$$R50 = \frac{Body\ V50\%}{PTV\ size}$$

Treatment and facility characteristics, and results of case review were summarised as either mean (standard deviation) or median (inter-quartile range, IQR) and frequency (percentage), for continuous and categorical variables respectively.

2. Results

Pre-trial QA

Fifteen centres completed the facility questionnaire in the setup phase of the trial in 2015. Only 5/15 (33%) had treated liver SBRT previously, mostly centres with CyberKnife units (Accuray Inc, Sunnyvale, USA). All centres were able to scan 4DCT and EEBH according to the protocol, although 3/15 centres (20%) initially preferred to use free breathing 3DCT scans for liver SBRT and changed practice to enter to the trial. Only 3/15 were already using abdominal compression devices, but several were looking to introduce these during the time of the trial as they gained experience with liver SBRT. 4/15 centres (27%) were planning to use Cyberknife with fiducial tracking, the rest Varian (6, 40%) or Elekta (5, 33%)) LINACs with either volumetric modulated arc therapy (VMAT) (9, 60%) or intensity-modulated radiotherapy (IMRT) (2, 13%) and 3D-CBCT (9) or 4D-CBCT (2) imaging. A wide range of planning system algorithms were reported: *Cyberknife Multiplan Pencil Beam (PB), Eclipse PB, Eclipse Analytical Anisotropic Algorithm (AAA), Pinnacle Collapsed Cone (CC), OMP CC, Monaco Monte Carlo (MC)*; though several centres changed these during the trial, and all were considered acceptable.

17 centres completed the benchmark cases. 6/17 contour submissions required revision (35%), mainly deviations such as including normal blood vessels in the GTV contour, variable stomach-duodenum junction or excessive duodenum contoured, pancreas included in small bowel, and either gall bladder, vessels or hilum included in the normal liver contour.

6/17 planning benchmark submissions were also revised after feedback on what was achievable by other centres for this case, for example using a higher nominal prescription dose but allowing lower

coverage on a sub-volume of the PTV or allowing a higher maximum dose to give a steeper dose falloff outside the target. These approaches are preferable to a lower, more homogeneous dose across the whole target and are a hallmark of SBRT planning.

On-trial plan QA

Between March 2016 and August 2022, 47 patients were randomised to receive SBRT, but 6 of these did not proceed to treatment, so overall 41 SBRT plans were produced by 12 treating centres. 2 centres treated 8 patients, 4 centres treated 3-5 patients, 4 centres treated 2 patients, and 2 centres only treated 1 SBRT patient during the trial. The median and most common PTV margin (from ITV) was 5mm (used for 31/41 cases, range otherwise 4-7 mm) and median PTV size was 65cm^3 (IQR 43-121 cm^3, full size distribution is shown in Fig 2).

31/41 cases underwent prospective ICR. 8/31 reviewed plans required revisions (26%), for reasons shown in table 2. There were no clear trends in deviations over the duration of the trial, or number of patients treated, but they were limited to 6 out of 12 centers. The remaining patient plans were analysed retrospectively for protocol compliance. Overall 19/41 plans (46%) had one or more deviations from the radiotherapy protocol, primarily reduction in target coverage (PTV D95% < 90%) because of adjacent duodenum and/or other organs. These deviations are listed in Table 2, and an example case is shown in Fig 1.

A range of planning and delivery systems were used for the 41 SBRT cases: Cyberknife-Multiplan (4), Eclipse-Varian IMRT (3) or VMAT (16), Pinnacle-Elekta IMRT (2) or VMAT (1), and Oncentra-Masterplan (OMP, 1), Monaco (9) or Raystation (5) - Elekta VMAT. Algorithms were as listed above, with the addition of OMP CC and Raystation CC. 30/41 cases used 5 fractions and 11/41 cases 15 fraction regimes. Across both regimes 25/41 cases prescribed the highest dose level, although the target coverage was often compromised as described above and shown in Fig.1. Other planning parameters are shown in Table 3 and Figure 3.

3. Discussion

ABC-07 is the first multicentre randomised phase II trial completed that investigates the role of hypo-fractionated RT in the definitive setting for patients with cholangiocarcinoma who are not surgical candidates. Analysing the quality of RT is critical to understanding the results of the study and guiding future clinical trials in the hepatobiliary setting. We encountered significant variability with respect to simulation, motion management, segmentation and dose planned, despite benchmarking and on trial review.

Robust QA of radiotherapy plans within a clinical trial reduces unwanted variation from protocol non-compliance and gives confidence in final outcomes [7]. Participation can also help centres to implement new techniques in a controlled manner with support from peer review and national groups such as RTTQA [8]. Although the rate of pre-trial benchmark case revisions in this trial was high (35% for both contouring and planning), this was reduced for on-trial cases (to 23% and 6% respectively), suggesting the benefits of the feedback process. There were no clear trends in deviations during the trial accrual period, but this may be a result of low patient numbers per centre. Contouring for abdominal SBRT is challenging, and often requires specialist radiology support, as recommended in the protocol. Provision of an atlas for contouring in the trial materials could also have helped compliance, although collated resources by RTOG [12] and the increasing use of deep learning automated contouring solutions [13] are expected to improve the situation compared to when this trial was initially recruiting.

Use of 4DCT can give wider variability than breath hold imaging and highlights the importance of optimal imaging strategies and motion mitigation for SBRT [14,15]. It was not possible to assess the use of abdominal compression on a per patient basis, although several centres introduced the technique during the trial period and this may have helped to limit motion, PTV size and hence need for compromise of target coverage. Mandating compression or breath hold in future studies may be challenging however, as some patients struggle to comply.

The number of planning protocol deviations was very high at 46%, however almost all of these were unavoidable compromise in target coverage because of adjacent OARs, especially duodenum where toxicity could be very damaging. Although a range of dose calculation algorithms were used, this should not impact deviations, since these were in areas of homogeneous tissue where calculation differences are small. Figure 2 shows no correlation of compromise with target size, except for the few very large lesions which were unaffected. Lee *et al* [11] also found a high level of target compromise for liver SBRT plans (V100%<90%): 43% (albeit for a small number of cases) and pelvic node plans (42%), compared to bone/spine/adrenal (24%) and lung plans (19%). This suggests the objectives for target coverage in the trial were optimistic, although there is some evidence in figure 2 that compromise was more common when the highest nominal prescription dose was retained. Rather than reduce the dose across the whole target to meet the OAR constraints, the other parts of the PTV did receive the full intended prescription dose and only the portion next to or within the OAR was dose de-escalated. With high levels of inhomogeneity within the target, nominal prescription dose (e.g. 50 Gy) is not a good surrogate for received dose. More detailed metrics should be used when analysing trial outcomes, such as covering dose converted to biologically effective dose (BED) [16].

Values for high-dose conformity (quantified in this study by PDS) within the trial were higher than those reported by Lee *et al* [11] for non-lung cases, suggesting the challenges of sparing one side of the target led to spillage of dose elsewhere. However, medium-dose conformity and dose fall-off, as measured by mGI and R50 were similar or slightly lower, so centres were able to produce plans with good conformity at this level regardless of equipment or planning system. Figure 2 shows higher R50 values for smaller targets in keeping with other studies for body or brain stereotactic radiotherapy [17]. Compared to UK SABR consortium guidelines for other body sites [18]: for PDS only 23/41 plans (56%) were within acceptable limits of 1.30 (20-40cm^3) or 1.20 (>40cm^3); for mGI 38/41 plans (93%) were within acceptable limits of 7.5 and 6.5 respectively; which further supports these findings that greater high dose spillage should be expected for BTC SBRT plans.

OAR dose constraints were met in all cases except one, as mentioned in Table 2. In this case the local clinician chose to allow higher volume doses to kidney and duodenum. Mean liver doses were highly variable, but all were within tolerance (13-15.2 Gy for 5 fraction or 22-24 Gy for 15 fraction treatments).

RTQA for this trial was also used to support the *Commissioning through Evaluation* programme in the UK to investigate SBRT for oligometastases [19], and clinical indications are expanding to include primary liver, pancreas and kidney sites [18]. The planning dose constraints from the trial were also used as part of national guidelines for SBRT OAR tolerances [20].

Since the inception of this trial several technologies have become more widespread in radiotherapy practice, including proton therapy [21], MR-LINACs [22] and automation in delineation and planning [23,24,25], with potentially reduced normal liver doses and improved efficiency and consistency. Automation can also be applied to the QA process itself, such as comparing submitted plans to those produced by AI or knowledge-based approaches for rapid screening [23]. However, these interventions have not been tested in clinical trials for cholangiocarcinoma, although one study has reported good tolerance for pancreas SBRT using MR-LINAC [26].

This study is limited to pre-treatment planning data only and so does not reflect the actual dose delivered and received by the patient [27]. Assessment of target volumes and OAR contouring is subjective and can be challenging to quantify. The impact of target dose inhomogeneity on clinical outcomes is not clear, but only through clear reporting from trials can these be investigated [28]. Finally, it is not possible from this study to show a link between protocol compliance achieved by rigorous prospective plan RTQA and clinical outcomes, since any deviations were corrected before the start of treatment. The target volume and normal tissue delineations, which other studies have shown to have considerable variability [29,30], were addressed in our study by radiology support and prospective peer review. Of the cases that did not undergo prospective review, one had a minor deviation of not adjusting nominal prescription dose for mean liver dose (table 1), however delivered

doses were comparable to other patient plans in the trial. Likewise, all but one plan met the OAR constraints, so toxicity variations will depend on individual sensitivities rather than plan RTQA impact. However, the benefits of a "successful" RTQA programme should not be underestimated, since deviations are frequent and can affect trials outcomes [31]. Trial specific plan QA be the standard for all large multi-centre clinical trials.

Conclusions

Comprehensive plan RTQA for the ABC-07 randomised controlled trial showed variations in both contour segmentation and planning but also led to improvements in protocol compliance for recruited patients compared to pre-trial benchmark cases. The radiotherapy doses in the protocol were achievable in many cases; however, target coverage was frequently compromised to maintain OAR dose constraints. Such compromises should be prespecified in future studies. To minimise heterogeneity in dose prescription it is essential to report detailed dose metrics such as target coverage, rather than nominal prescription dose alone.

Figure 1. Example of target compromise because of adjacent OAR: in this case (a) an axial (left) and (b) sagittal (right) view of GTV (red), PTV (blue), duodenum (orange) and liver (light green), stomach (green), colon (brown); along with colourwash for 13Gy (33% of prescription dose) and isodose lines for 13 (33%), 25 (63%), 32 (80%), 38 (95%), 40 (100%) and 44 Gy (110%). Note that the sagittal view is reconstructed from planar axial data and reflects uncertainties in the review platform used.

Figure 2. Target coverage (PTV D95%) variation with target volume (PTV size), showing frequency of compromise.

Figure 3. Medium-dose conformity (R50) variation with target volume (PTV size), showing increase in medium-dose spread at lower target volumes.

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Table 1. Radiotherapy dose prescriptions. If the mean liver dose constraint could not be met, the prescription dose was lowered to the next level. Plans with a distant nodal volume were also treated using 15 fractions.

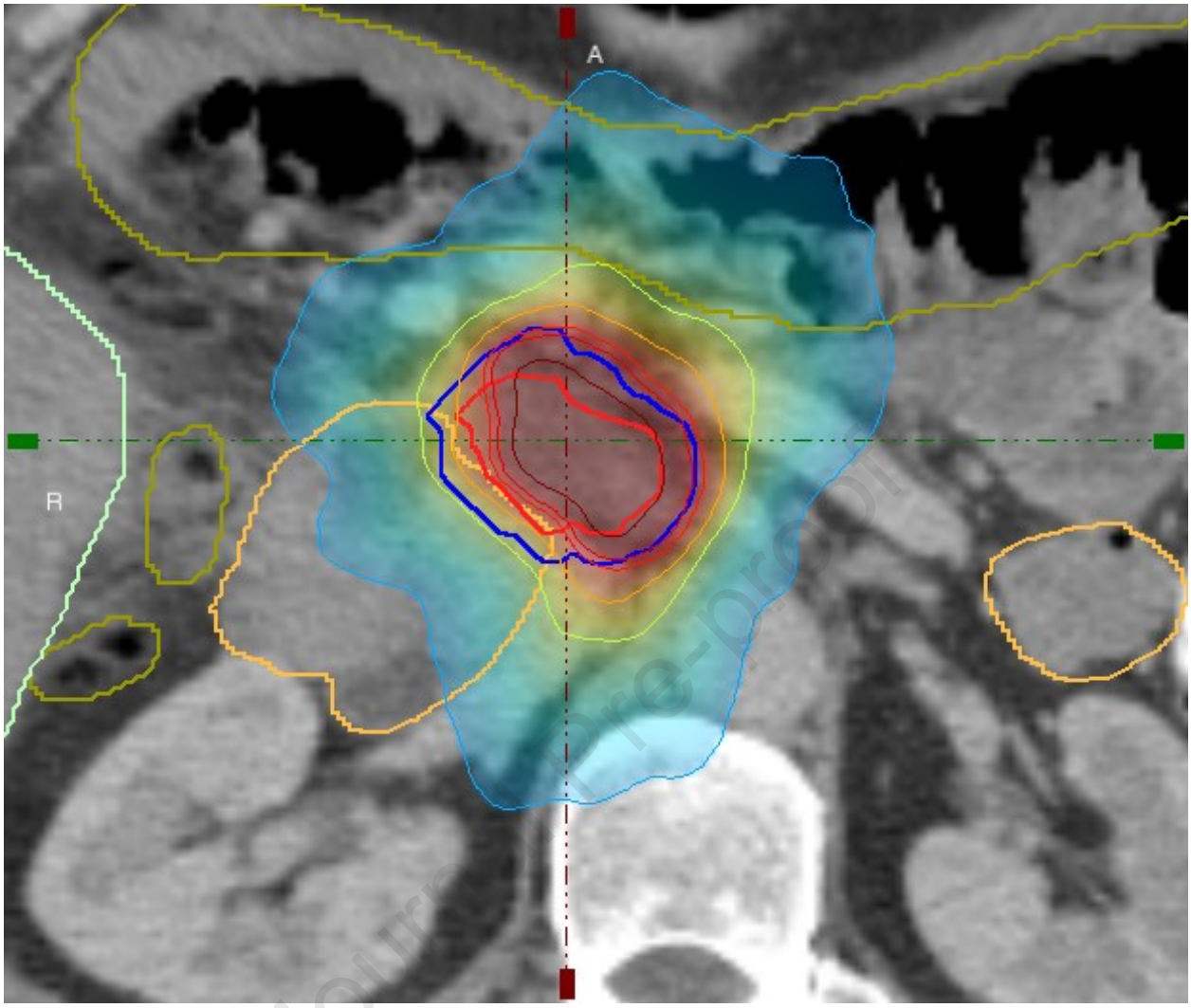
5 fractions (≤ 6cm lesion diameter)		**15 fractions (6-12cm lesion diameter)**	
Mean liver dose (Gy)	**Prescription dose (Gy)**	**Mean liver dose (Gy)**	**Prescription dose (Gy)**
13.0	50	22.0	67.5
15.0	45	22.0	58.1
15.2 (max)	40	24.0 (max)	45

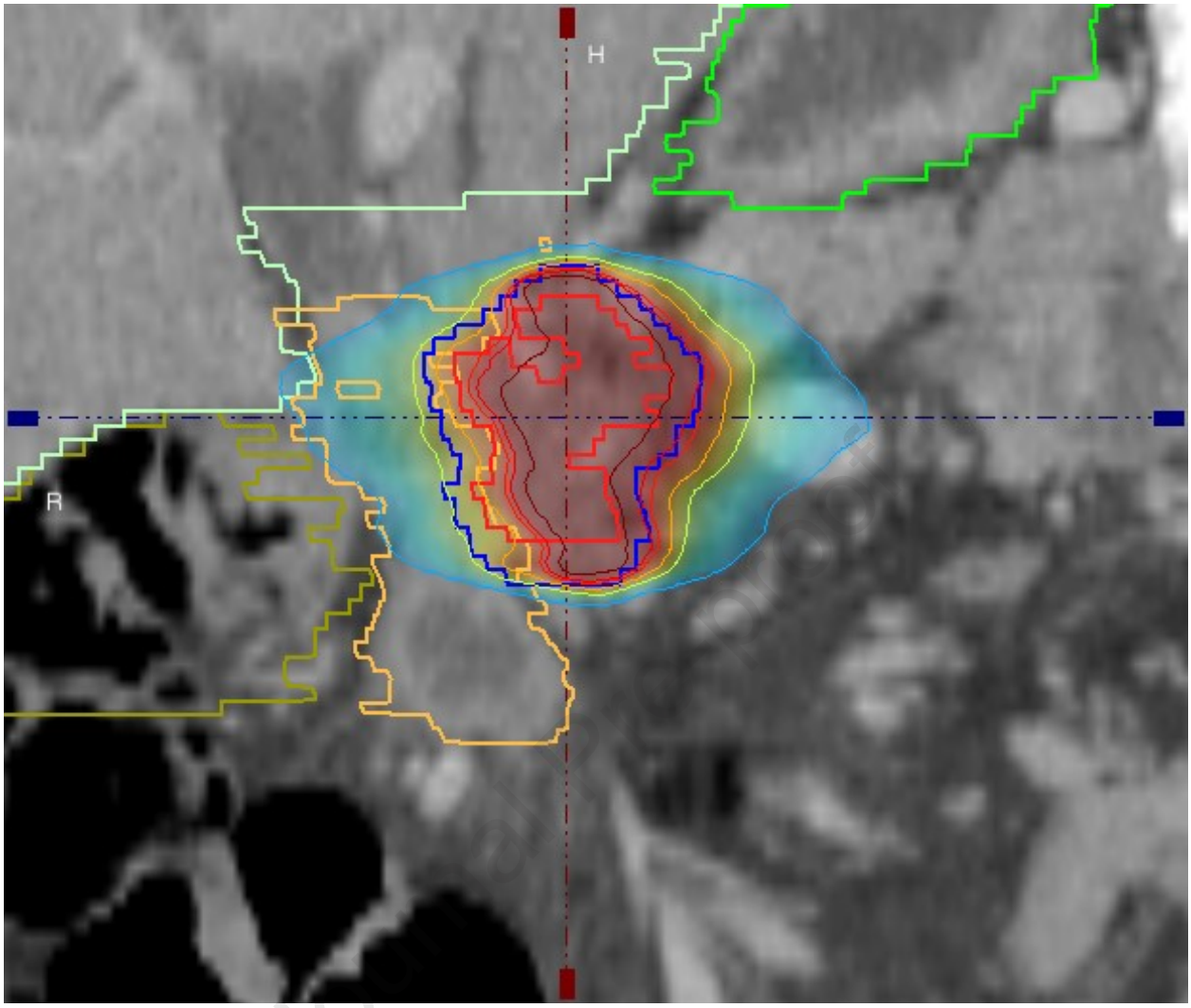
Table 2. Reasons for revisions following prospective review of contours and treatment plans, and accepted radiotherapy plan protocol deviations. Numbers in brackets show number of cases with this issue.

Contour revisions (7 cases)	• Missing structures – not contoured at all, or close to target e.g. bowel loops (4) • GTV contour larger than radiological reports (1) • Overlap between structures e.g. lung and liver (1) • Stomach contour included duodenum; small bowel includes large bowel (1) • GTV mis-identified as post-pancreatitis soft tissue mass (1) • GTV contour jagged on coronal / sagittal views (1) • GTV included gall bladder (1)
Plan revisions (2 cases)	• Changed to 15 fraction regime for greater target coverage and normal tissue sparing (1) • Increased overall prescription dose and allow lower PTV coverage adjacent to duodenum (1)
Protocol deviations (19 cases)	• Target coverage D95% compromised because of adjacent duodenum (16), stomach (4), small bowel (2), heart (1), or kidney (1) • Duodenum D10cm^3 and right kidney V10Gy constraints exceeded (local decision, 1) • Prescription dose not adjusted for mean liver dose (no prospective review, 1) • Maximum PTV dose exceeded 130% to maintain coverage (2)

Table 3. Radiotherapy plan parameters for all 41 SBRT cases, and a cohort of 25 SBRT cases from Lee *et al* (2019) [11].

Parameter	**This study**		**Lee *et al* [11]**	
	Mean ± standard deviation	**Range**	**(non-lung cases 20-40cm^3)**	**(non-lung cases >90cm^3)**
PTV D95%	84 ± 17%	45 – 101%	----	----
PTV D0.1 cm^3	119 ± 8%	103 – 152%	----	----
PDS (95%)	1.24 ± 0.16	1.03 – 1.80	1.13 ± 0.07	1.10 ± 0.06
mGI (95%)	4.5 ± 1.4	3.0 – 9.5	4.7 ± 1.2	4.6 ± 0.9
R50	3.9 ± 1.1	2.5 – 7.7	4.2 ± 0.9	4.2 ± 0.8
Mean normal liver dose (Gy)	7.5 (5 fractions) 15.2 (15 fractions)	1.1 – 14.9 2.6 – 24.0	----	----

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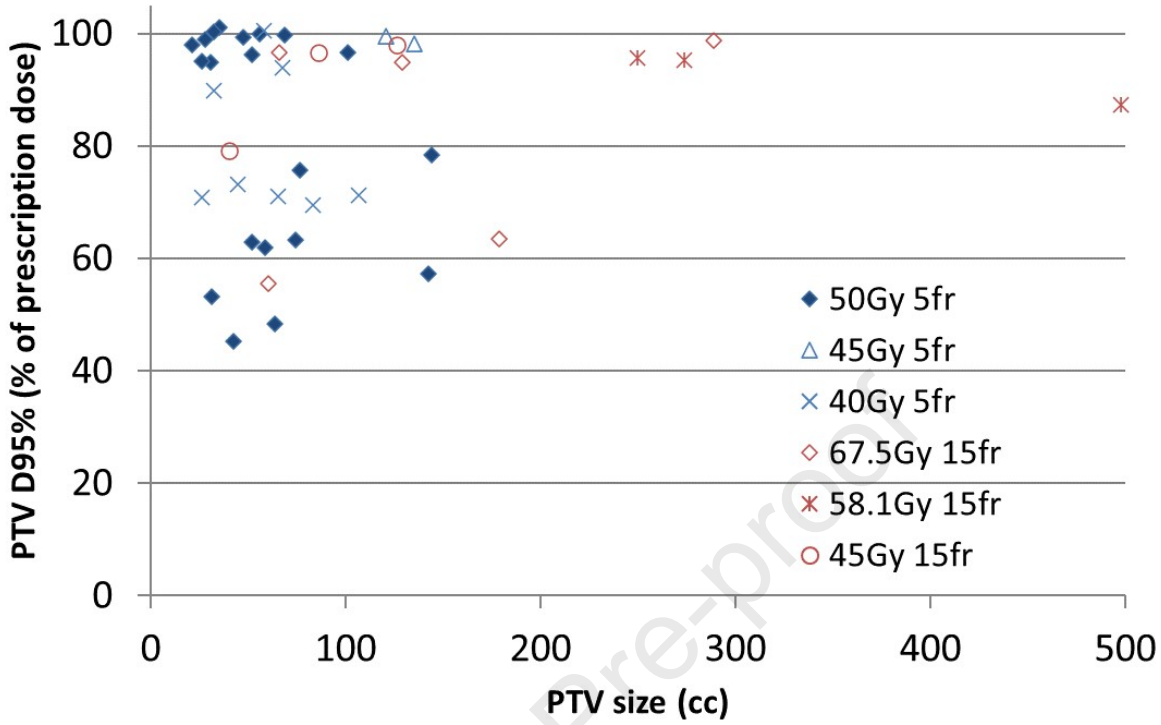

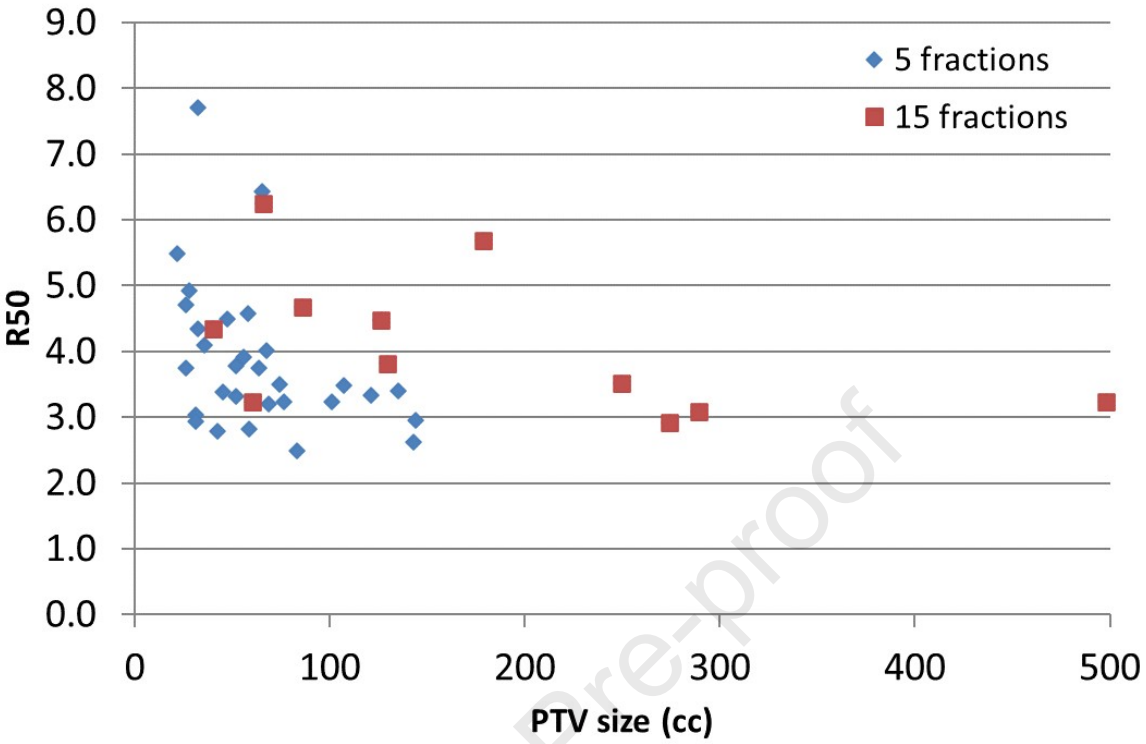

Radiotherapy plan quality assurance in the XXXX trial of stereotactic body radiotherapy (SBRT) for locally advanced biliary tract cancer

Research highlights

- Radiotherapy quality assurance of treatment plans within the XXXX trial showed reduced deviations between pre-trial and on-trial cases.
- Protocol radiation doses were achievable in many cases.
- Target coverage was frequently compromised to maintain adjacent normal tissue dose constraints.

Author Contributions

1 guarantor of integrity of the entire study MAH
2 study concepts and design DE, MAH
3 literature research n/a
4 clinical studies DE/MH/AL/PM/RG/NH/SS/MAH
5 experimental studies / data analysis DE/MAH/DB/AL/PM/GR
6 statistical analysis DE/AL/MAH
7 manuscript preparation DE/MAH
8 manuscript editing DE/MH/AL/PM/RG/NH/SS/MAH

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Declaration of interests

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

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

GR is on the editorial board for this journal, however they had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.