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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

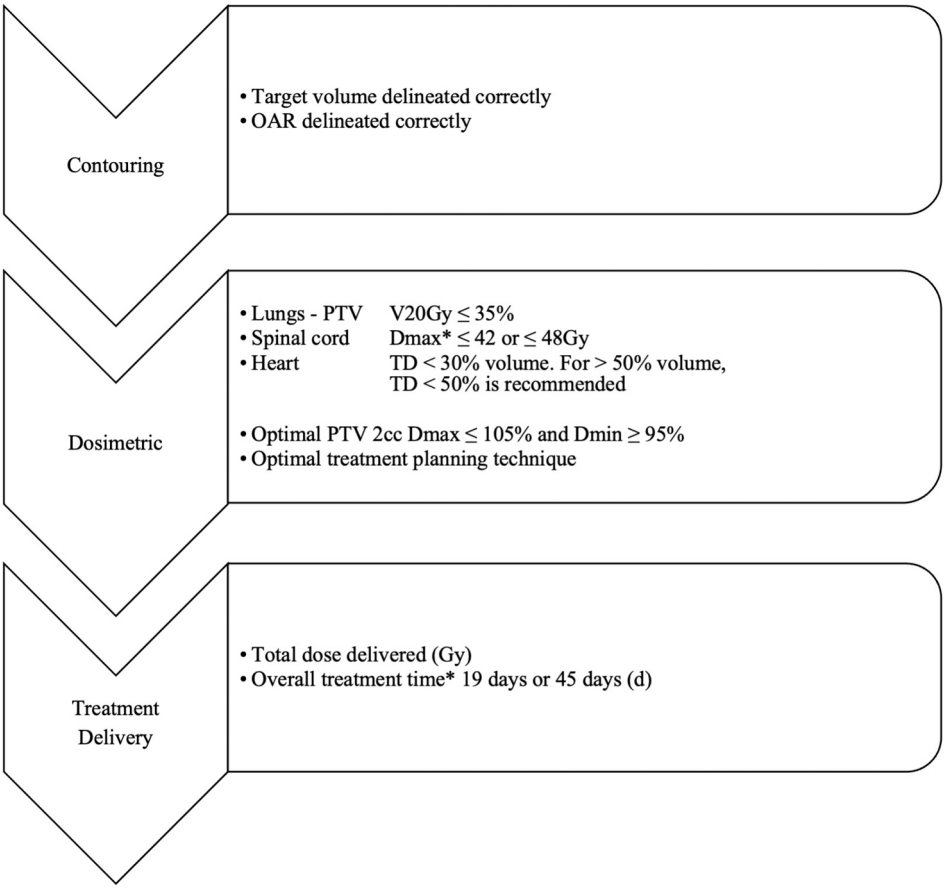


**Fig. 1.** Protocol compliant contouring, dosimetry, and treatment delivery QA parameters. *Dependent on randomisation group; d, days; Dmax, the maximum dose to 2 cc; Gy, Gray; OAR, Organs at risk; PTV, Planning Treatment Volume; TD, Total dose; V20Gy, Volume of organ receiving 20 Gy.

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.<br>• GTV delineated as per protocol according to diagnostic image(s)<br>• OAR contoured as per protocol and the radiotherapy plan meets protocol defined constraint(s)<br>• PTV coverage achieved optimal objective ±5 % prescription dose<br>• 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).<br>• GTV delineated as per protocol according to diagnostic imaging report(s)<br>• OAR contoured not per protocol; with the application of optimal contour(s) and dose cube, the radiotherapy plan meets protocol defined constraint(s)<br>• PTV coverage achieved mandatory objective ±7 % prescription dose<br>• 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.<br>• GTV delineated not as per protocol according to diagnostic imaging report(s)<br>• 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)<br>• PTV coverage does not achieve mandatory dose objective<br>Treatment planning suboptimal – dose not specified at ICRU reference point and not corrected for inhomogeneity<br>• 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)<br>Incorrectly labelled as CTV |
| **Heart** | 19 (20.4) | 74 (79.6)<br>Incorrect cranial heart border<br>Exclusion of pericardial sac<br>Anterior border not encompassing heart |
| **Lung** | 58 (62.4) | 35 (37.6)<br>Incorrectly labelled<br>Incorrect subtraction of lung–target volume<br>Lung contour not delineated |
| **Spinal Cord** | 23 (24.7) | 70 (75.3)<br>Spinal cord contoured instead of spinal canal<br>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.

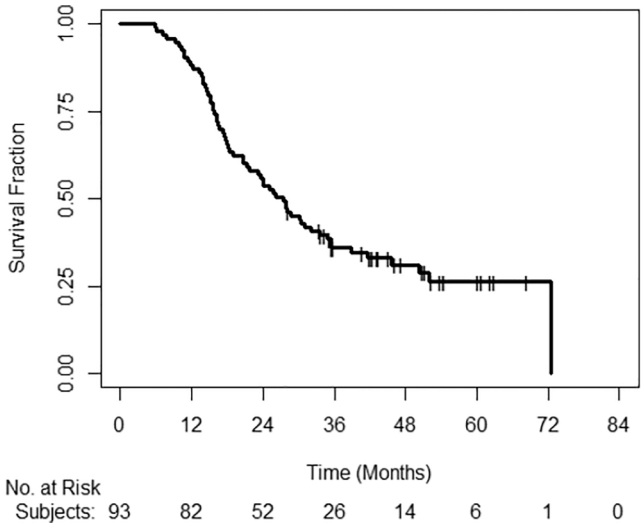


**Fig. 2.** Overall survival in the QA cohort.

**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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