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FULL PAPER

Effect of accurate heart delineation on cardiac dose during the CONVERT trial

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Objective: This study investigated the effect of deviation from protocol in heart delineation for the Concurrent Once-daily *Versus* twice-daily Radiotherapy (CONVERT) Trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00433563) Identifier NCT00433563) quality assurance (QA) programme and the effect of that on mean cardiac dose and percentage of heart volume receiving ≥ 5 Gy ($V_{5\%}$) and percentage of heart volume receiving ≥ 30 Gy ($V_{30\%}$).

Methods: Patients with limited-stage small-cell lung cancer in the CONVERT trial were randomized to receive 45 Gy in 30# twice daily or 66 Gy in 33# once daily radiotherapy, with concurrent chemotherapy in both arms. Of the 100 trial patient cases reviewed by the QA team [for patient selection, disease/organs at risk (OARs) outlining and treatment planning], 50 patient cases were selected, and the heart was reoutlined according to the “gold standard” trial protocol. Dose–volume histogram (DVH) data were extracted. The impact of change in heart volume on cardiac DVH is presented.

Results: For gold standard cardiac outlines, an increase in $V_{5\%}$ and $V_{30\%}$ was seen in 77.3% and 81.8% of cases, respectively, in the control arm (45 Gy) and in 78.6% and 82.1% of cases, respectively, in the experimental arm (66 Gy). The median increase in $V_{5\%}$ was 1.4% and in $V_{30\%}$, it was 3.4%. The average of the mean cardiac dose for the control arm increased by 2.1 Gy (from 15.2 Gy for the centres outline to 17.3 Gy for the gold standard outline) and for the experimental arm by 2.4 Gy (from 16.2 to 18.6 Gy).

Conclusion: This study demonstrates the importance of having a robust QA programme in place to ensure accuracy of cardiac delineation to facilitate future studies investigating the impact of cardiac dose on toxicity.

Advances in knowledge: This study highlights the importance of ensuring accurate delineation of OARs in clinical trials, where conclusions about normal tissue toxicity are to be drawn.

INTRODUCTION

Radiotherapy (RT) plays a major role in the curative treatment of lung cancer. Deviations in RT quality can affect clinical outcomes of patients enrolled in trials. There is a need for strict RT quality assurance (QA) to verify uniformity and to ensure outcome data are useful in the clinic.^{1,2} Dose–volume constraints are used in routine practice to reduce the risk of severe toxicity to organs at risk (OARs). Currently of interest are dose–volume predictors for acute and late radiation-induced heart disease and survival.^{3,4}

Concern regarding radiation-related cardiac and vascular toxicity was raised in the era of two-dimensional RT when patients with breast cancer and Hodgkin’s lymphoma experienced severe complications.^{5–8} In the past two decades, RT treatment techniques have evolved to reduce OAR exposure, and as a result there has been a steady decline in

the risk of RT-related events.^{7–11} Modern treatment techniques such as three-dimensional conformal radiotherapy, volumetric-modulated arc therapy and proton therapy can deliver highly conformal RT and have been found to reduce OAR dose and subsequent radiation-related induced toxicity. For example, Maraldo et al⁹ estimated a significant increase in the risk of stroke, due to carotid artery irradiation, for Hodgkin’s Lymphoma survivors treated with an extensive mantle field as compared with volumetric-modulated arc therapy, three-dimensional conformal radiotherapy and proton therapy.

Furthermore, in the field of lung cancer, the emerging data linking high dose to the heart to poorer survival and increased toxicity suggest that the heart should be considered as a critical OAR.^{3,12,13} RT-associated cardiac events include early events such as pericarditis and late events such as coronary artery disease, myocardial infarction and

dysfunction.¹⁴ Results presented by Huang et al¹² suggest a previously unsuspected role of heart irradiation in the development of radiation pneumonitis.

It is not clear where the minimum dose threshold for risk of cardiac toxicity lies,¹⁵ but there are some data showing that radiation-related heart disease can occur as a result of cardiac doses lower than 3–4 Gy.^{15–19} However, a study investigating the risk of valvular heart disease following mediastinal RT for Hodgkin's lymphoma showed that radiation dose to the heart valves can increase the risk of clinically significant valvular heart disease, especially at doses above 30 Gy.²⁰

In the field of lung cancer, there remains uncertainty of the impact of heart dose on long-term toxicity and survival, particularly in patients who are often elderly and heavy smokers, confounding the interpretation of causality of cardiac adverse events. In order to assess such effect, it is crucial that toxicity and survival data are collected as part of prospective trials and correlated with heart dose–volume histograms (DVHs). However, variation in heart contouring can have a dramatic impact on cardiac dose assessment.

The multicentre Phase III Concurrent Once-daily *Versus* twice-daily Radiotherapy (CONVERT) Trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00433563) Identifier: NCT00433563)^{21,22} was designed to address the question of dose and fractionation for limited-stage small-cell lung cancer (LS SCLC) with the aim of establishing a standard chemoradiotherapy regimen for LS SCLC with good performance status. The trial compared 45 Gy in 30 fractions twice daily (control arm) with 66 Gy in 33 fractions once daily (experimental arm). Outcome data were presented at the American Society of Clinical Oncology annual meeting 2016.²³ It was demonstrated that once daily RT did not result in a superior survival or worse toxicity than twice daily radiotherapy. As the trial was not powered to show equivalence, twice daily RT should be considered the standard of care.

As part of the CONVERT Trial QA programme,²⁴ we decided to investigate the effect of deviations from the heart outlining protocol on mean cardiac dose and percentage of heart volume receiving ≥ 5 Gy ($V_{5\%}$) and percentage of heart volume receiving ≥ 30 Gy ($V_{30\%}$). These parameters were chosen as they were reported in the Radiotherapy Oncology Group (RTOG) 0617³ study as being important predictors of survival, supporting the hypothesis that heart toxicity contributes to poor survival. Our study aims to show the importance of QA within prospective clinical trials with regard to OARs outlining such as the heart.

METHODS AND MATERIALS

CONVERT trial

The CONVERT Trial is a UK-based multicentre Phase III international study which recruited 547 patients with LS SCLC from April 2008 to November 2013.²¹ Patients were recruited from the UK, France, Spain, Canada and European Organisation for Research and Treatment of Cancer centres (Belgium, Netherlands, Poland and Slovenia) and were prospectively randomized to receive twice daily RT (45 Gy in 30 fractions) in the

control arm concurrently with chemotherapy (cisplatin and etoposide) or once daily RT (66 Gy in 33 fractions) in the experimental arm, also concurrently with cisplatin and etoposide. The primary end point was overall survival. The spinal canal, lungs, oesophagus and heart were contoured as OARs for DVHs and constraints were set.²¹

CONVERT trial quality assurance programme

As part of the CONVERT Trial QA programme, 100 trial patient treatment plans were randomly selected for retrospective review by the QA team (a senior radiation oncologist and a medical physicist). As pre-trial QA had been completed by each centre, this was felt to be representative of the 547 patients entered into the trial. At least one treatment plan was requested for review from each centre, and multiple treatment plans were requested from high recruiting centres. The review assessed patient selection, disease and OAR outlining, use of margins and treatment planning technique.

Centres were asked to anonymize and transfer treatment planning data to the QA team, electronically by secure file transfer protocol in either DICOM or RTOG format to be reviewed by the QA team using VODCA, v. 5.4.0.²⁵ A full QA report was issued to each clinician. Any deviations in OAR or disease outlines which did not conform to protocol were communicated to the centre.

Cardiac outlining study

Of the 100 cases submitted for QA review, 50 cases were randomly selected for inclusion in this cardiac outlining study. The CT and structure set for each of the 50 cases was imported into Eclipse™ v. 11 (Varian Medical Systems, Palo Alto, CA), and the heart was reoutlined according to the trial protocol (gold standard cardiac outline) by a medical physicist and reviewed, and amended where necessary, by a radiation oncologist.

The CONVERT Trial protocol²¹ specified that the heart should be contoured along with the pericardial sac surrounding the heart. The superior aspect should begin at the level of the superior aspect of the left atrium and extend inferiorly to the apex of the heart. The pericardial sac should extend superiorly to encompass the main pulmonary artery, the ascending aorta and the superior vena cava. Outlining should extend superiorly to the inferior aspect of the aortic arch and the superior limit of the trunk of the pulmonary artery.

The plan data were exported from Eclipse and imported into VODCA. The dose cube was also imported so that cardiac DVH data could be extracted for comparison between the centres cardiac outline and the gold standard. Heart outline volumes (in cubic centimetre) provided by participating centres were compared with gold standard outline volumes (in cubic centimetre). The impact of the change in heart volume on dose to heart is presented—particularly mean heart dose, $V_{5\%}$ and $V_{30\%}$, respectively.

The Dice similarity coefficient (DSC) was calculated for each case.²⁶

$$\text{DSC} = (2 \times \text{UNION of Vol}_{\text{GS}} \text{ and Vol}_{\text{centre}}) / (\text{Vol}_{\text{GS}} + \text{Vol}_{\text{centre}}).$$

DSC values range from 0 to 1, with 1 denoting complete conformity of the outline to the gold standard.

RESULTS

In 38 (76%) out of the 50 cases, the heart was not outlined according to protocol. The average difference in volume between that provided by the centre and the gold standard outline was 79.4 cm³ (range 1.6–248.2 cm³). Median DSC was 0.948 (range 0.841–1.0). In 31 out of 50 cases, the difference in cardiac volume was $\geq 5\%$ (Figure 1).

In 37 (74%) cases, the heart was not outlined superiorly enough (Figure 2). In 1 (2%) case, the outline did not include the pericardial sac on some slices.

Editing the cardiac outline according to protocol (“gold standard”) resulted in a change in mean cardiac dose in 80% of cases (range –1.1–7.8 Gy). The average of the mean cardiac dose for the control arm increased by 2.1 Gy (from 15.2 Gy for the centres outline to 17.3 Gy for the gold standard outline) and for the experimental arm by 2.4 Gy (from 16.2 to 18.6 Gy). In 84% of cases, there was a change in $V_{5\%}$ (range –2.7–14.8%), and in 84% of cases a change in $V_{30\%}$ (range –2.1–15.3%) (Figure 3a,b).

The cardiac volume and dose data for both arms of the trial are presented in Figure 4a–c. In the experimental dose arm (66 Gy), an increase in $V_{5\%}$ and $V_{30\%}$ was seen in 78.6% and 82.1% of the cases, respectively, by using the gold standard cardiac outline rather than that provided by the centre. The increase in $V_{5\%}$ ranged from 0.1% [corresponding to a difference in heart volume of 1.6 cm³ (DSC = 0.88)] to 14.4% [corresponding to a difference in heart volume of 103.9 cm³ (DSC = 0.85)]. The increase in $V_{30\%}$ ranged from 0.1% [corresponding to a difference in heart volume of 1.6 cm³ (DSC = 0.88)] to 15.3% [corresponding to a difference

in heart volume of 233.2 cm³ (DSC = 0.841)]. The median increase in $V_{30\%}$ was 3.4%, and in $V_{5\%}$, it was 1.4%.

In the control arm (45 Gy), an increase in $V_{5\%}$ and $V_{30\%}$ was seen in 77.3% and 81.8% of the cases, respectively, by using the gold standard cardiac outline rather than that provided by the centre. The increase in $V_{5\%}$ ranged from 0.8% [corresponding to a difference in heart volume of 30.3 cm³ (DSC = 0.984)] to 14.8% [corresponding to a difference in heart volume of 248.2 cm³ (DSC = 0.895)]. The increase in $V_{30\%}$ ranged from 0.3% [corresponding to a difference in heart volume of 50.3 cm³ (DSC = 0.96)] to 14.1% [corresponding to a difference in heart volume of 168.2 cm³ (DSC = 0.879)]. The median increase in $V_{30\%}$ was 6.1%, and in $V_{5\%}$, it was 3.7%.

Figure 5a–c show the correlation between the %difference in cardiac volume and DSC and the difference in $V_{5\%}$ and $V_{30\%}$, confirming that cardiac DVH data have been underestimated for most patients (90%).

DISCUSSION

This study shows that in the majority of patients, the heart was not contoured as per protocol, despite the provision of treatment planning guidelines containing an example case, specific instructions for outlining OARs and a thorough pre-trial QA programme (including assessment and written feedback to centres with pictures of OAR delineation non-conformance). This lack of compliance had a significant effect on dose recorded for the heart. This is particularly relevant as data are emerging on the impact of heart dose on excess mortality in patients with lung cancer. In a recent US randomized trial (RTOG 0617), a higher treatment dose led to increased mortality and it was suggested this could be due to higher dose delivered to the heart.³

At the 2016 European Society for Radiotherapy and Oncology conference, two studies showed a correlation between heart dose and outcome. The first study is an analysis of a UK dose escalation

Figure 1. Number of cases showing differences of $\leq 5\%$, 5–10% and $> 10\%$ in cardiac outline volume between that provided by the centre and the gold standard outline.

Figure 2. Example of a non-compliant cardiac outline: the outline in red is the “gold standard” and the one in cyan is the outline provided by the centre.

trial (IDEAL conformal radiotherapy) in Stage III non-small-cell lung cancer reporting a correlation between heart dose volume and lower survival.²⁷ The second study is an analysis of a large lung stereotactic ablative radiotherapy (high-dose, high-precision treatment in Stage I non-small-cell lung cancer) cohort showing a correlation between non-cancer death and dose to anatomical structures located at the base of the heart.²⁸ In nearly half (22) of the cases in our study, there was a difference in cardiac volume of >10% when comparing centres outlines with the gold standard. The resulting effect on mean cardiac dose, heart $V_{5\%}$ and $V_{30\%}$ depends on the position of the planning target volume relative to the areas of the heart which had not been contoured by centres. This explains the presence of some of the outlying points in Figure 5a–c. As expected, the trend lines in Figure 5c show a general decrease in %change in heart $V_{5\%}$ and $V_{30\%}$ as DSC approaches unity. Heart $V_{5\%}$ and $V_{30\%}$ are important predictors of survival as demonstrated in RTOG 0617³ and of the likelihood of developing radiation pneumonitis,^{12,29} highlighting the importance of developing an appropriate cardiac outlining protocol for use in the clinic. Veerle *et al*³⁰ also investigated dose distribution parameters as predictors for acute coronary events and stressed the importance of replacing mean heart dose with heart $V_{5\%}$.

In most cases in this study (74%), the superior vena cava was omitted from the outline provided by the centres. The importance of this is highlighted by data from the Dutch group,²⁸ suggesting that there may be an association between higher radiation dose to the left atrium and superior vena cava and a small, but increased, risk of death from causes other than cancer.

Feng *et al*³¹ developed a cardiac CT atlas for use as a tool to improve the accuracy of contouring and to assess the relationship between dose to cardiac structures and subsequent toxicity. Similarly, they highlight the issue of variation in substructure delineation which can lead to inconsistent dose

Figure 3. Number of cases showing percentage differences of $\leq 5\%$, 5–10% and >10% in percentage of heart volume receiving ≥ 5 Gy ($V_{5\%}$) between that provided by the centre and the gold standard outline. (b) Number of cases showing percentage differences of $\leq 5\%$, 5–10% and >10% in percentage of heart volume receiving ≥ 30 Gy ($V_{30\%}$) between that provided by the centre and the gold standard outline.

reporting. Veerle *et al*³⁰ also investigated dose distribution parameters for the whole heart and substructures for patients treated for breast cancer. The Feng atlas was not used in the CONVERT trial, as it was published after the start of recruitment. Automatic segmentation tools for delineation of OAR, including the heart, are the best way forward to avoid interobserver variability, but current commercial software need refining.³²

Many trials, including the CONVERT trial, do not mandate dose constraints for the heart as such constraints have not been well defined.¹⁴ Prospective trials are required to correlate heart dose to cardiac toxicity and survival. Such work is currently ongoing based on the CONVERT data set. Furthermore, there is therefore an unmet need to identify substructures of the heart that are sensitive to radiation and could be avoided and also to investigate prospectively the effects of RT on the

Figure 4. (a) Box plot of cardiac volume data. (b) Box plot of percentage of heart volume receiving ≥ 5 Gy ($V_{5\%}$) data. (c) Box plot of percentage of heart volume receiving ≥ 30 Gy ($V_{30\%}$) data.

heart in patients with lung cancer. There may be some benefit in investigating the effect of heart-sparing RT on survival, but this should not be at the expense of dose delivered to the tumour.

In conclusion, our study highlights the importance of a QA programme that includes verification of OAR contours, such as the heart, in order to ensure the consistent reporting of doses and RT planning.

Figure 5. (a) Correlation between % difference in cardiac volume between the centres outline and the gold standard outline and difference in percentage of heart volume receiving ≥ 5 Gy ($V_{5\%}$). (b) Correlation between % difference in cardiac volume between the centres outline and the gold standard outline and difference in percentage of heart volume receiving ≥ 30 Gy ($V_{30\%}$). (c) Dependence of % difference in $V_{5\%}$ and $V_{30\%}$ on Dice similarity coefficient (DSC).

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