



Why aren't we getting consistent results for heart dose and mortality during thoracic radiotherapy?

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Debate on the connection between heart dose and mortality in non-small-cell lung cancer (NSCLC) has been existing for years. In the article that accompanies this editorial, Zhang and colleagues (1) reported the first systemic assessment and intended meta-analysis to evaluate the relevance between cardiac dose and outcomes. Completion of this study is not trivial because an obvious rise in the amount of studies researching the correlation between cardiac dose and outcomes in NSCLC after the publication of RTOCG 0617. In addition, we do not know the strength of connection and the optimal limits of the cardiac dose yet.

Is there a significant effect of cardiac dose on survival in NSCLC?

The systematic review and meta-analysis reported by Zhang and colleagues (1) aimed to make an evaluation on the relevance between heart dose and mortality among the patients with NSCLC, which was based on evidence. This systematic review was carried out in term of PRISMA guidelines. From the beginning to January 31, 2018, information retrieval was conducted in the MEDLINE and Excerpta Medica Databases. Consensus has been reached on that such studies incorporate the concept of carcinoma of lungs, heart disease, and radiation dosage.

This systematic review failed to demonstrate consistent relationships among heart dose parameters, overall survival and heart events. Among 5,614 patients from 22 studies, totally 214 heart dosimetries had been examined

as potential predictors of cardiotoxicity or death, with the broadest analyzed parameters including mean heart dose (MHD), heart V5, and heart V30. For survival, only one of the 11 studies found significant association with heart V5 in multivariable analysis (MVA) and 2 of the 12 studies found significant association with heart V30; in 8 studies, MHD was not statistically significant. For cardiotoxicity, heart V5 was significant by MVA analysis in 1 of 2 studies; heart V30 was significant in 1 of 3 studies, and MHD was significant in 2 of 4 studies.

Is higher heart dose related to poor survival rate in NSCLC? The evidence is controversial; a consensus has not been reached in this area. RTOG 0617 trial (2) suggested that higher heart dose was significantly related with poor survival. Several studies have confirmed this relation (3,4), while others failed to determine such similar correlation (5,6).

Which heart dosimetric parameter is most important? The effect of individual heart dose on survival was controversy. Heart V5 and V30 were remarkably related to poor survival in RTOG 0617 (1). Obvious correlations between heart V5/V30 and overall survival were reported by Stam Group, but not heart V50 (7). One study by Speirs Group reported a significant association between heart V50 and survival (8). On the contrary, although these factors are related to cardiotoxicity, recently, several secondary analyses on random experiments didn't report any significant correlation between heart dosage and overall survival in NSCLC patients (9-12). It was reported by Wang Group

that the MHD, heart V5 and V30 did not correlated with survival (9), and it was reported by Guberina Group that heart V5 hadn't been identified as a prognostic factor for survival (10). A previous study in Michigan also reported that MHD, heart V5, V30 and V50 were not correlated with survival (11). No independent effect of heart dose on the survival of 468 patients with NSCLC was found by Tucker *et al.* (5).

What limit should we set? In practice, heart dosimetry is generally applied in limiting the risks from radiation-related cardiotoxicity, although the reported evidence varies substantially. No clear consensus has been achieved on the surest and safest cut-off level for the dosimetric factors studies, in part since the intense association among the dose parameters (13). There are several studies indicating that certain cardiac dose parameters, for instance, mean heart/pericardial dosage, maximum heart/pericardial dosage, pericardial V30 and total radiation dosage to mediastinum, are significantly related to cardiotoxicities including pericardial effusion (PCE) (14-18). Failure from generating consensus findings from this review makes this task even more challenging.

What are the reasons for the inconsistent effect of cardiac dose factors on survival in NSCLC?

First, the above conflicting results can be partially explained by changes in the contours of the heart. Actually, there is no uniform and strict definition for contour of the heart, and most researches haven't specified the definition of the heart. This review did not mention the potential confounding effect of variations of the confounding effect. But the editorial comment from Banfill and colleagues made a great discussion on this issue and the various substructure of the heart (19). Our experience of the reviewed patients enrolled in RTOG1106 (FM Kong, unpublished experience) showed there are big differences in the definition of heart among institutions. Heart is one of the organs with remarkable variations from Center to Center, particularly regarding superior border in terms of inclusion of the full pericardium or not, despite the fact that the protocol atlas specified clearly for the contour of heart, with starting superiorly at one slide below the pulmonary trunk passing the midline. Some centers include the whole pericardium within big vessels in superior mediastinum, but others include nothing but the heart cavities. The heart can't be separated from the lower pericardium, and the dose parameters of the pericardium are remarkably related to the heart, thus

determining the function of the individual structure is becoming challenging (14). Using guideline of Kong Group (13) (which was also used as RTOG atlas, <http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx>), Xue and colleagues (20) found that the risks of PCE were related to multiple cardiac parameters (such as heart/pericardial mean dose, V5, V55 and pericardial V30). These associations were also confirmed by the DVH atlas analysis, which illustrated the high-risk area for toxicity. Should the heart structure be consistently contoured, more consistent dosimetric correlates be likely generated in future studies.

Second, most reports were retrospective studies from single institutional data with inclusions of heterogeneous patients with poorly defined cardiac toxicity endpoints. Particularly for cardiac toxicity events, some include arrhythmia or pericardial effusion as toxicity, while others may only include ischemic event. For retrospective study, record of the toxicity often depends on the thoroughness of the medical record generated by the treating physicians. Furthermore, studies rarely proposed a priori assumption to testify the included events in analysis.

Third, the inconsistencies of the cardiac dosimetric parameters included in different studies made the comparison difficult. As most of dosimetric factors are DVH generated point parameters which are sensitive to the shape of the DVH, the field arrangement and radiation technique. These point parameters may not represent the dose and damage of the whole organ. It may still be related to other untested cardiac dosimetric factors that we can't totally determine. Furthermore, researches with smaller-size samples may not prove their association with overall survival. Finally, most studies have not adjusted for the dose parameters, causing the increased error rates of type I.

The last, not the least, heterogeneous treatments including radiotherapy itself may have an impact on overall survival. It was found that concurrent or induced chemotherapy may increase the occurrence of cardiac events, while in Ning's study (21) by multivariate analysis, adjuvant chemotherapy was the most relevant factor for PCE, but not concurrent or induced chemotherapy. Chun and colleagues (2) found that IMRT technique is related to decrease of severe pneumonia and cardiac doses in the NRG clinical trial RTOG 0617, and this study provided supports for the routine use of IMRT for locally advanced NSCLC. Cardiotoxicity is also related to some chemotherapeutic drugs in treating NSCLC, for example, platinum-based agents (22), taxanes (23), vinorelbine (24) and gemcitabine (25).

Cardiotoxicity is also occurred after targeted therapy (26), and severely with high mortality after using of immune checkpoint inhibitors (27-31).

In summary, this systemic review shows that no consistent heart dose factors are found to associate with survival and cardiotoxicity in NSCLC patients receiving radiotherapy. This finding challenges some part of assumption regarding the association between heart dose and inferior survival under current practice. However, as discussed above, we agree with the comments from Banfill (19) and Badiyan (32) that many factors may have contributed to this inclusive conclusion. Unless there are some studies with large-size samples with consistent structure delineation, the debate will continue, and the physicians will continue to be challenged with the decision of appropriate cardiac dose and parameters in NSCLC.

Learning from the review (1) of many published studies, we strongly propose the following for current practice and future research: (I) contour the heart structure consistently (reviewers shall also at least ask all the investigators to provide the information so we know what structure we are studying at), RTOG atlas (13) shall be used until a better atlas becomes available; (II) study this question in a prospective manner and define the cardiac toxicity endpoint consistently according to updated CTCAE criteria which is the criteria used by all clinical trials around the world and is available online for investigators all over the world; (III) consider the co-linearity of the various dosimetric factors and avoid testing the significance of multiple correlated dosimetric variables; (IV) build and test novel predictive models by considering all the DVH parameters like biologically representative parameters (like effective dose or effective volume) based or atlas based model prediction. Additionally, baseline heart disease also should be recorded and integrated in risks prediction models. It's necessary that studies in the future pay more attention to injury to the immune substructures included in the conventionally defined "heart" and possibly differentiate them from the true cardiac structural damage. Finally, long-term follow up is necessary to further identify the effect of cardiac dose parameters on cardiac toxicities and survival.

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