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# Association between radiation heart dosimetric parameters, myocardial infarct and overall survival in stage 3 non-small cell lung cancer treated with definitive thoracic radiotherapy

Chia Ching Lee[a,b,c,d], Huili Zheng[e], Yu Yang Soon[a,b,c,d,*], Ling Li Foo[e], Wee Yao Koh[a,b,c,d], Cheng Nang Leong[a,b,c,d], Balamurugan Vellayappan[a,b,c,d], Jeremy Chee Seong Tey[a,b,c,d], Ivan Weng Keong Tham[a,b,c,d]

[a] Department of Radiation Oncology, National University Cancer Institute, Singapore
[b] National University Hospital, Singapore
[c] National University Health System, Singapore
[d] National University of Singapore, Singapore
[e] National Registry of Disease Office, Research & Surveillance Division, Health Promotion Board, Singapore

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ABSTRACT

*Objectives:* The aim of this retrospective observational study is to assess the association between various radiation heart dosimetric parameters (RHDPs) and acute myocardial infarct (AMI) and overall survival (OS) outcomes in stage III non-small cell lung cancer (NSCLC) treated with definitive radiotherapy with or without chemotherapy.

*Materials and methods:* We identified eligible patients treated at two institutions from 2007 to 2014. We linked their electronic medical records to the national AMI and death registries. We performed univariable and multivariable Cox regressions analysis to assess the association between various RHDPs, AMI and OS.

*Results:* 120 eligible patients were included with a median follow-up of 17.6 months. Median age was 65.5 years. Median prescription dose was 60 Gy. Median mean heart dose (MHD) was 12.6 Gy. Univariable analysis showed that higher MHD (hazard ratio (HR), 1.03; 95% confidence interval (CI), 1.01–1.06; P = .008) and volume of heart receiving at least 5 Gy (V5) (HR, 1.01; 95% CI, 1.00–1.03; P = .042) were associated with increased hazards for AMI. Univariable analysis showed that higher MHD, V5, V25, V30, V40, V50 and dose to 30% of heart volume were associated with increased hazards for death. Multivariable analysis showed that there was no statistically significant association between various RHDPs and OS.

*Conclusion:* The incidence of AMI is low among stage III NSCLC treated with definitive radiotherapy with or without chemotherapy. There is insufficient evidence to conclude that RHDPs are associated with AMI or OS in our study.

## 1. Introduction

The recently published Radiation Therapy Oncology Group (RTOG) 0617 trial showed an excess of treatment-related deaths associated with radiation dose escalation among patients with unresectable stage III non-small cell lung cancer (NSCLC) treated with concurrent chemoradiation [1]. The investigators reported a worse overall survival (OS) outcome in the intervention arm receiving 74 Gy of thoracic radiotherapy (RT) compared with the standard arm receiving 60 Gy. The secondary analysis suggested that radiation heart dosimetric parameters (RHDPs), for instance, volume of heart receiving at least 5 Gy (heart V5) and 30 Gy (heart V30) were associated with worse OS outcome. However, this trial was unable to clarify whether higher radiation heart doses led to increased incidence of acute myocardial infarction (AMI) resulting in inferior OS outcome.

The findings of RTOG 0617 has sparked off several retrospective studies to investigate the relationship between RHDPs, cardiotoxicity and OS in this population in the modern era [1–4]. Unfortunately, the

* Corresponding author at: 1E Kent Ridge Road NUHS Tower Block, Level 7 Singapore 119228, Singapore.
*E-mail addresses:* chiaching.lee@mohh.com.sg (C.C. Lee), zheng_huili@hpb.gov.sg (H. Zheng), yu_yang_soon@nuhs.edu.sg (Y.Y. Soon), ling_li_foo@hpb.gov.sg (L.L. Foo), wee_yao_koh@nuhs.edu.sg (W.Y. Koh), cheng_nang_leong@nuhs.edu.sg (C.N. Leong), bala_vellayappan@nuhs.edu.sg (B. Vellayappan), jeremy_tey@nuhs.edu.sg (J.C.S. Tey), ivan_wk_tham@nuhs.edu.sg (I.W.K. Tham).

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results of these retrospective studies were conflicting and did not have AMI as a defined end-point. Thus, we performed a retrospective study on patients with stage III NSCLC treated with definitive thoracic RT to clarify the association between RHDPs and the incidence of AMI and OS outcomes using national registry data.

## 2. Materials and methods

### 2.1. Study design

This was an institutional review board-approved retrospective cohort study.

### 2.2. Study population

Patients with histologically-confirmed NSCLC diagnosed between January 2007 and December 2014 were re-staged according to the American Joint Committee of Cancer (AJCC) eight edition criteria [1–4]. Those with stage III NSCLC treated with definitive thoracic radiotherapy in two institutions (National University Hospital and Tan Tock Seng Hospital) were included. All patients were staged with computed tomography (CT) of thorax and abdomen. The use of positron emission tomography (PET)-CT scans or brain imaging (magnetic resonance imaging (MRI) or contrast CT) were not mandated. Those who received palliative, preoperative, postoperative, stereotactic body RT or re-irradiation to the thorax were excluded from this analysis.

### 2.3. Thoracic radiation treatment

RT was given with or without chemotherapy, either concurrently or sequentially. RT was delivered at 1.8 Gy to 2.75 Gy per fraction daily, five fractions per week. The total prescribed radiation dose ranged from 55 Gy to 70 Gy. All patients underwent CT simulation-based planning. 4D-CT simulation were utilised based on physicians' discretion, typically for lower lobe tumours, Tumour volumes were delineated using PET-CT diagnostic imaging where available. Elective nodal irradiation was not employed. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) dose constraints were adopted during treatment planning from March 2010 onwards [1–4]. Peer review was performed for all volumes and plans within the first week of starting RT. Radiation was delivered via either 3D-conformal, intensity-modulated radiotherapy (IMRT) or Arc therapy. Individual patient quality assurance was performed for all IMRT plans. Image-guided radiotherapy, first with electronic portal imaging followed by routine cone-beam CT, was used.

### 2.4. Dosimetric analysis

All previous radiation plans underwent dose calculation using Monte Carlo or Analytical Anisotrophic algorithms. To account for variable fractionation schemes, biologically equivalent doses in 2-Gy fractions (EQD2) were calculated using the linear quadratic model (assuming $\alpha/\beta$ ratio = 10 for tumour control, $\alpha/\beta$ ratio = 2.5 for heart and $\alpha/\beta$ ratio = 3.0 for lungs). For the purposes of this study, heart and lung volumes were validated against the RTOG 1106 contouring atlas and edited if necessary. Dose-volume histograms were generated for review. RHDPs for analysis were prespecified based on the previous studies [2–7], including heart mean dose (MHD), heart V5, heart V25, heart V30, heart V40, heart V50, dose to 30% of heart volume (heart D30), lung mean dose, lung V5 as well as lung V20.

### 2.5. Co-variates

Clinical data was collected from the institutional electronic medical records. Gender (male versus (vs) female), Eastern Cooperative Oncology Group (ECOG) performance status (0–1 vs 2), smoking status (current and former vs never), diabetes mellitus (DM) (yes or no), pre-existing ischaemic heart disease (IHD) (yes or no), chronic obstructive pulmonary disease (COPD) (yes or no), use of PET-CT (yes or no), use of brain imaging (yes or no), tumour laterality (left vs right), and use of chemotherapy (yes vs no) were analysed as dichotomous variables. DM was defined as fasting plasma glucose of at least 7.0 mmol/L, a two-hour post oral glucose tolerance test value of at least 11.1 mmol/L, or HbA1c value of at least 6.5% [8]. Pre-existing IHD was defined as the presence of AMI, coronary artery bypass grafting, or coronary angioplasty prior to the start of RT. This data was captured from the national AMI registry as described below [9]. COPD was defined as a forced expiratory volume in one second ($FEV_1$)/forced vital capacity ratio of less than 0.7 or less than the lower limit of normal plus and $FEV_1$ less than 80 percent predicted [10]. Histology was categorised into adenocarcinoma, squamous cell carcinoma and others. Lobar location of tumour was categorised into upper lobe, middle lobe, lower lobe and multiple lobes. Age and RHDPs were analysed as continuous variables.

### 2.6. End-points

The unique national identification number assigned to all Singapore residents was used to link the study's cohort to the national AMI and death registries. The national AMI registry was established in 1988 to collect epidemiological data on AMI cases diagnosed in all the public hospitals [9]. AMI cases diagnosed in private hospitals were included since 2012. The registry receives notifications on AMI cases from all hospitals, Ministry of Health, Ministry of Home Affairs and Health Science Authority. The International Classification of Diseases (ICD)-9 Clinical Modification code 410 was used to identify AMI cases in the data sources from 2007 to 2011, while the ICD-10 American Modification codes I21 and I22 were used from 2012 onwards. The diagnosis of AMI is verified by the registry coordinators by viewing the patients' case notes and electronic medical records, before extracting relevant clinical information at the hospitals. All cases of AMI are diagnosed by any certified doctors, with the evidence of symptoms of AMI, elevation of cardiac enzymes or abnormal electrocardiograms. Death status was obtained from the national death registry which contains information on the date and cause of deaths for all Singapore residents.

### 2.7. Statistical analysis

Frequency with percentage and median with interquartile range were used to describe the baseline characteristics of this study cohort. Time to death was measured from the time of first day of RT treatment to death from any cause. Time to AMI was measured from the time of first day of RT treatment to the first AMI, with non-AMI death accounted for as a competing risk. The univariable Cox proportional hazard model was used to determine the association between AMI events and baseline characteristics. Multivariable Cox regression analysis was not performed due to the small number of AMI events. Univariable Cox regression analysis was used to determine the association between death and baseline characteristics. We also performed several exploratory multivariable Cox regression analyses to investigate the association between various RHDPs and OS. The RHDPs were re-classified into binary variables with cut-offs pre-specified based on the previous studies [2–7], the median values and the receiver operating characteristic (ROC) values in the exploratory multivariate Cox regression analyses. Variables which were statistically significant in the univariate Cox regression analyses were included in multivariable Cox regression analyses. The Akaike Information Criterion (AIC) was used to select the most appropriate multivariable Cox regression model (for instance, the model with lowest AIC). For all analyses, two-sided P values of less than 0.05 were considered statistically significant. Analyses were performed using STATA (version 13.0, StataCorp).