**Is the Importance of Heart Dose Overstated in Non-Small Cell Lung Cancer? A Systematic Review of the Literature**

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**Purpose/Objective(s):** Thoracic radiation has been associated with increased cardiac toxicity and mortality in studies of patients with breast cancer and Hodgkin Lymphoma. However, this impact is not well studied in patients with non-small cell lung cancer (NSCLC). Recent studies have suggested a relationship between cardiac dose and mortality, but the strength of the relationship and the optimal dosimetric predictors are unknown. The goal of this study was to conduct a systematic review and meta-analysis to provide an evidence-based estimate of the relationship between cardiac dose and mortality in patients with NSCLC.

**Materials/Methods:** A systematic review of MEDLINE (PubMed) and Embase databases (inception to January 2018) according to PRISMA guidelines was performed. Studies which evaluated cardiac dosimetric factors in patients with NSCLC and which include outcomes of cardiac events, cardiac mortality and overall survival were identified. After the initial search (n= 461), studies were screened by title (n= 78), then by abstract (n= 33), and then included for full text review (n=22).

**Results:** From 6240 patients across 22 studies, a total of 214 cardiac dosimetric parameters (84 unique parameters) were assessed as possible predictors of cardiac toxicity or death, with a mean of 10 dosimetric factors assessed per study. Predictors assessed included general dosimetric factors (e.g. mean and maximum heart doses), factors based on threshold doses (e.g. heart V5), and factors based on doses to anatomic structures or sub-volumes (e.g. atria, ventricles). The most commonly analyzed parameters were mean heart dose (MHD), heart V5 and V30. Most studies did not make corrections for multiplicity of testing. For the endpoint of overall survival, V5 was found to be significant on multivariable analysis (MVA) in 1 of 11 studies, V30 significant in 2 of 12 studies and MHD was not significant in any of 8 studies. For the endpoint of cardiac events, V5 was found to be significant on MVA in 2 of 4 studies, V30 in 1 of 3 studies, and MHD in 2 of 4 studies. There was little overlap in the sub-volume parameters included in multivariable models across studies. A meta-analysis of the data could not be performed, as most negative studies did not report effect estimates (e.g. hazard ratios) and could not be meta-analyzed.

**Conclusion:** Heart dose-volume constraints are not consistently associated with overall survival of NSCLC patients. Multiplicity of testing is a major issue and likely inflates the overall rate of type I error in the literature. Future studies should specify predictors a priori, correct for multiplicity of testing, and report effect estimates for non-significant variables.