Radiomics Improves Prognostication Beyond Clinical Variables and Dose-Volume Metrics for Cardiac Events in Locally Advanced Non-Small Cell Lung Cancer

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Take-home message Whole-heart CT radiomics added prognostic value beyond clinical variables and DVH metrics, achieving the best performance for cardiac-event risk prediction. Its risk-stratification capability remained significant in both the consolidation immunotherapy and non-immunotherapy subgroups.

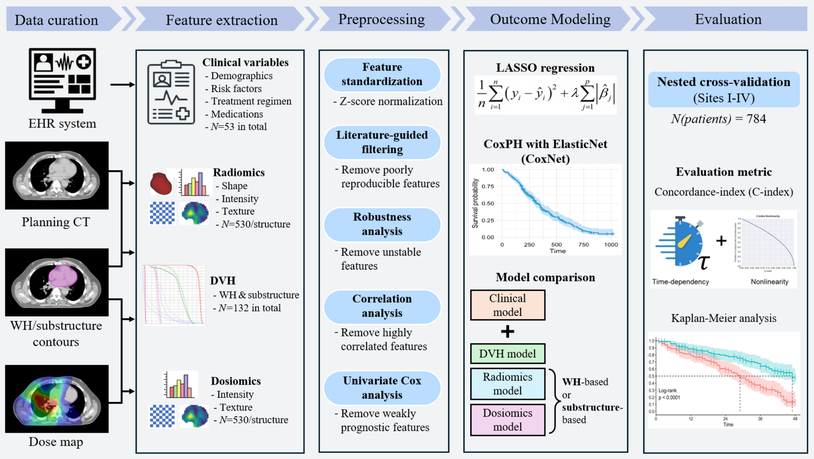
Background and Purpose

- *Cardiac toxicity* is a major late complication for patients receiving *thoracic radiation therapy*.
- Prior studies showed that *whole-heart and cardiac sub-structure DVH metrics* predict cardiac toxicity in *locally advanced non-small cell lung cancer (LA-NSCLC)*.
- However, *modern LA-NSCLC care has evolved*, including consolidation immunotherapy, advanced delivery techniques, and stricter cardiac constraints.
- **Challenge**: *DVH-based predictors may no longer work* for cardiac event prediction in modern LA-NSCLC treatment[1].
- **Key question**: Beyond DVH, *what should we use to predict cardiac events in LA-NSCLC*?

Cohort and Endpoints

- Single-institution, multi-center dataset
  - *N* = 784 total (2010–2021, 4 hospitals)
  - 746 (95%) received IMRT or proton
  - 227 (29%) received consolidation immunotherapy after radiotherapy
- Clinical endpoints
  - *Major adverse cardiac events* post-chemoradiotherapy (CRT), defined as acute coronary syndrome, heart failure hospitalization or urgent visit, coronary revascularization, or cardiac-related death[2].
  - *Grade 3+ cardiac events* post-CRT, defined as "severe or medically significant but not immediately life-threatening" per CTCAE v5.0[3].
  - **96** patients had major adverse cardiac events; **194** patients had grade 3+ cardiac events.

Outcome Modeling Framework



- A standardized pipeline combined *feature selection* with *elastic-net penalized Cox regression*[4].
- Performance was evaluated using *fivefold nested cross-validation*.
- Evaluation metric: *concordance index (C-index)*.

Whole-Heart Radiomics Improved Prognostic Accuracy for Both MACE and Grade 3+ Cardiac Events

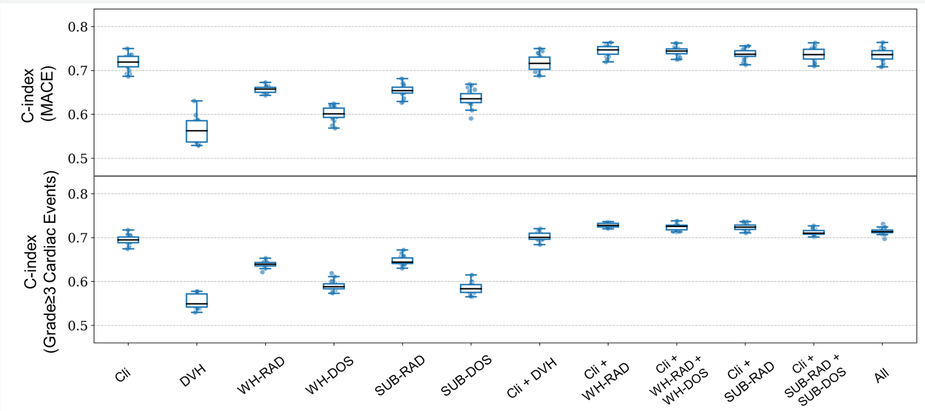


Figure 1. Prognostic performance of outcome models built on different combinations of features, evaluated using the C-index. Cli = Clinical variables; WH-RAD = whole-heart radiomics; WH-DOS = whole-heart dosiomics; SUB-RAD: cardiac substructure (LAD, LV, LA, RA, and RV) radiomics; SUB-DOS = cardiac substructure dosiomics; All = clinical + DVH + whole-heart + cardiac substructure features.

- *Clinical + whole-heart (WH) radiomics* achieved the highest C-index for both endpoints:
  - Major adverse cardiac events (MACE): 0.75 ± 0.01 vs 0.72 ± 0.01 for clinical-only ($P < 0.001$).
  - Grade ≥3 cardiac events: 0.73 ± 0.01 vs 0.70 ± 0.01 for clinical-only ($P < 0.001$).
- *WH or substructure DVH metrics* showed *limited prognostic performance* for cardiac events.
- *Dosiomics features* provided little to no incremental benefit.
- *Cardiac-substructure models* did not outperform *WH-based models*.

Clinical and Whole-Heart Radiomics Model Consistently Separated Low- and High-Risk Patients

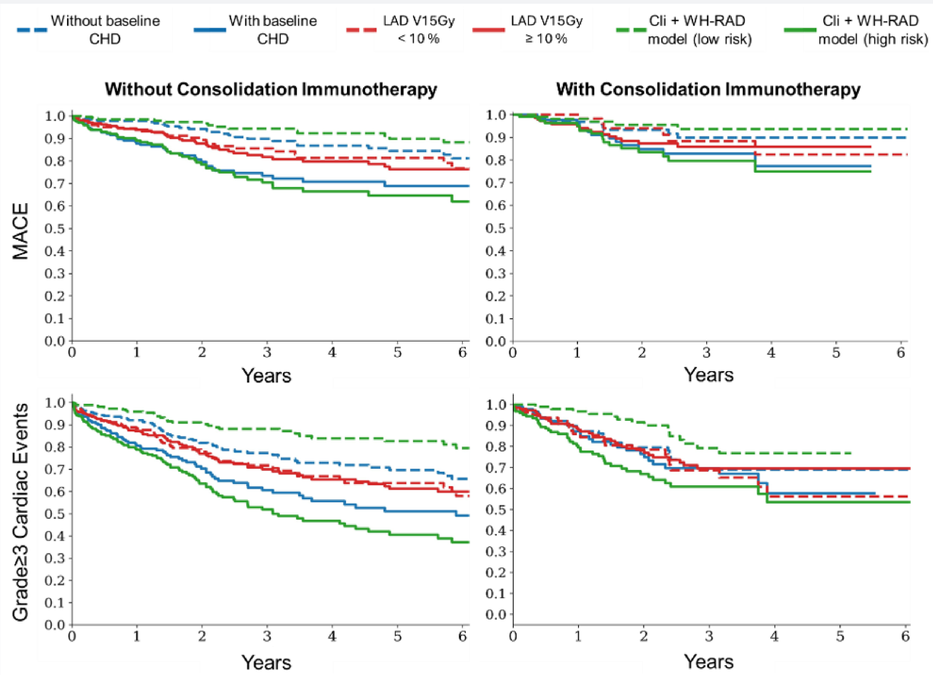


Figure 2. Kaplan-Meier curves comparing cardiac risk stratification using baseline coronary heart disease (CHD, *blue*), left anterior descending artery (LAD) V15Gy ≥10% (*red*), and the clinical (Cli) + whole-heart radiomics (WH-Rad) model (*green*).

- In the *consolidation immunotherapy subgroup* (CIO, modern LA-NSCLC care), risk separation remained significant:
  - MACE: log-rank $P = 0.006$.
  - Grade 3+ cardiac events: $P < 0.001$.
- Left anterior descending artery (LAD) V15Gy ≥10% did not stratify risk in either CIO or non-CIO cohorts.
- Baseline coronary heart disease (CHD) only separated risk in the non-CIO subgroup.

Important Contributors to Predicted Risk

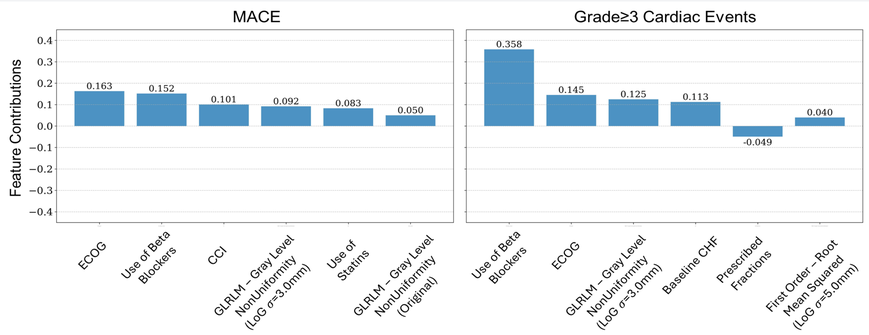


Figure 3. Contributions of individual features in the clinical + whole-heart radiomics models. ECOG: Eastern Cooperative Oncology Group performance status; CCI: Charlson comorbidity index; CHF = congestive heart failure; GLRLM = Gray Level Run Length Matrix; LoG = Laplacian of Gaussian filter (edge enhancement).

- Key predictors included *ECOG performance status*, *beta-blocker use*, *and a WH GLRLM Gray Level Non-Uniformity* feature (reflecting gray-level heterogeneity).

Conclusions

- *Whole-heart radiomics* combined with *clinical risk factors* improved prognostic modeling of cardiac events after definitive CRT for LA-NSCLC.
- *Conventional DVH metrics* and *advanced dosiomics* provided no additional prognostic benefit beyond clinical variables.
- The *whole-heart radiomics model* enabled *individualized* post-treatment cardiac risk assessment.
- The added prognostic value of radiomics *persisted in patients treated with CIO*, supporting the relevance of our findings to *modern LA-NSCLC care*.

References

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