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REDISCOVERING RADIATION MEDICINE AND EXPLORING NEW INDICATIONS

RNA-seq–Derived Radiosensitivity Index for Genomic-Adjusted Radiotherapy

S. Tau PhD[1], S.A. Eschrich PhD[2], J.G. Scott MD,DPhil[3], J.F. Torres-Roca MD[2], D.T. Bergman MD[1,4]

1. Department of Radiation Oncology & Applied Sciences, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
2. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
3. Department of Radiation Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH
4. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Dartmouth Geisel School of Medicine

Moffitt Cancer Center

Cleveland Clinic

INTRODUCTION

- The radiosensitivity index (**RSI**), a tumor gene-expression proxy developed using microarray data, guides clinically meaningful radiotherapy dose adjustment (**GARD**) via the linear–quadratic model.
- **RSI's** translation and applicability in an NGS-dominated era remains unclear.

AIM

- Evaluate concordance between **RSI** from microarray and RNA-sequencing data in matched clinical tumor samples.
- Explore simplified **RSI** models for deployment in future research with improved concordance between microarray and RNA-sequencing **RSI** estimations (**RSI-seq**).
- Apply **RSI-seq** to NGS-based clinical datasets to evaluate the clinical utility of RSI-seq-based GARD.

METHOD

- Affymetrix microarray and RNA-seq data from **637** matching **TCGA** samples were downloaded from the GDC and standard **RSI** was calculated using the previously published 10-gene rank-based linear model.
- We derived a parsimonious RNA-seq–based surrogate for RSI (**RSI-seq**) by systematically evaluating all gene subset linear models using cross-validated log2-TPM input against microarray-derived RSI and tested each model on a 30% held-out test set of TCGA samples.
- We applied the top-performing **RSI-seq** model to **146** radiotherapy-treated head and neck tumors (57% oral cavity, 24% larynx), derived **GARD** as previously described, and evaluated its association with overall survival using a **Cox proportional hazards model** with a **GARD** threshold determined by maximally selected rank statistics.

RESULTS

- **RSI** values from the original 10-gene model showed high concordance between microarray and RNA-seq platforms (**R^2 = 0.65, MAE = 0.159**), but the RNA-seq–derived RSI consistently underpredicted compared to microarray, with a mean error of 0.12 (microarray – RNA-seq) (**Fig. 1B**).
- Simple linear models fit to subsets of RSI gene TPMs (**Fig. 2A**) showed progressively improved estimation of microarray-based RSI, with performance plateauing at 4 genes – ABL1, IRF1, HDAC1, and PRKCB – which yielded a mean absolute error of 0.099 on a held-out test set (**Fig. 2B-C**).
- Head and neck tumors receiving **GARD < 36.75** (derived using 4-gene RSI-seq) had an **85% higher hazard of death** compared to those with **GARD ≥ 36** (HR = 1.85, p = 0.023) (**Fig 3A**).

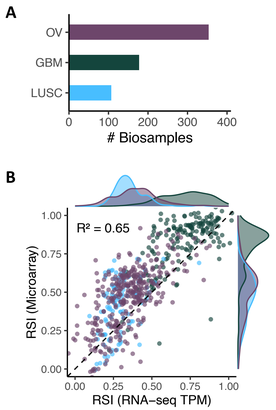

Fig 1 (A) Distribution of TCGA samples – serous ovarian carcinoma (OV), Glioblastoma (GBM), and lung squamous cell carcinoma (LUSC). **(B)** RSI from microarray vs RSI from RNA-seq (original 10-gene rank-based linear model).

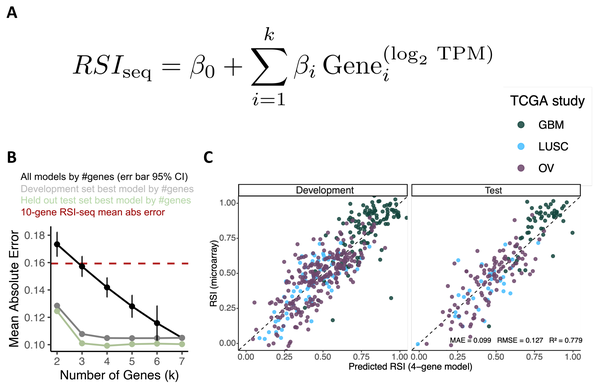

Fig 2 (A) Linear model for RSI-seq, where β_0 is the intercept, β_i is the coefficient for gene *i*, Gene_i is $\log_2$-TPM expression of gene *i*, and *k* is the number of genes. **(B)** Model performance (MAE vs microarray RSI) by *k* genes for all models (black) and top-performing model performance on development (grey) and test (green) sets compared to 10-gene RSI-seq MAE (red line). **(C)** Microarray RSI vs 4-gene RSI-seq for development and test set.

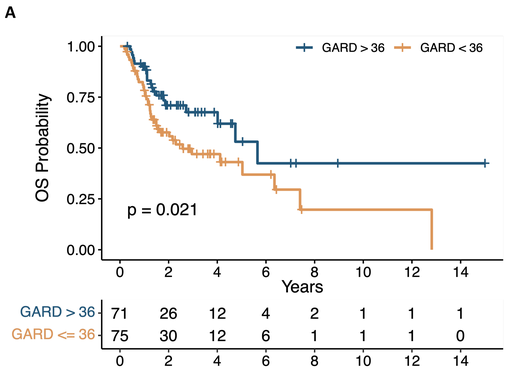

Fig 3 (A) Kaplan–Meier curves for overall survival in the head and neck TCGA cohort by GARD-RSI-seq group, dichotomized at the optimal cutpoint (GARD=36.75) identified using maximally selected rank statistics.

CONCLUSIONS

- **A 4-gene RNA-seq model (RSI-seq) more closely approximated the original 10-gene microarray RSI than the full 10-gene RNA-seq model, which systematically underpredicted.**
- **GARD derived from RSI-seq was significantly associated with overall survival in a TCGA head and neck cohort (HR = 1.85, *p* = 0.023).**
- **RSI-seq provides a practical, NGS-compatible approach for translational radiogenomics and future GARD studies.**

REFERENCES

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CONTACT INFORMATION

Drew T. Bergman, MD
PGY-2, Radiation Oncology, MSKCC
Instructor, Dept. of Radiation Oncology & Applied Sciences, Dartmouth-Hitchcock Medical Center, Dartmouth Cancer Center
Email: bergmand@mskcc.org