PROSTOX, a signature of late GU toxicity after SBRT radiotherapy in MIRAGE, a prospective trial

Amar Kishan[1], Kristen McGreevy[2], Luca Valle[1], Michael Steinberg[1], Maria Casado[1], Minsong Cao[1], **Joanne B. Weidhaas**[1], Donatello Telesca[2]
[1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]UCLA Department of Biostatistics, Los Angeles, CA

Abstract

PROSTOX is a previously identified germline genetic signature found to predict late Grade ≥ 2 genitourinary (GU) toxicity after stereotactic body radiotherapy (SBRT)[1] using microRNA-based variants (mirSNPs)[2]. MIRAGE was a prospective clinical trial evaluating toxicity in patients treated with CT or MRI-guided SBRT (Table 1).

We evaluated the ability of PROSTOX to accurately predict late GU toxicity in MIRAGE at the 2-year follow-up point.

We also investigated mirSNP signatures of acute or chronic GU toxicity, as well as performed gene ontology analyses to identify pathways involved in these three radiation-induced toxicities.

Validation Cohort

Table 1. MIRAGE Demographic Information

	Overall (n=147)	MRI (n=76)	CT (n=71)
GU ≥ 2 Toxicity Category			
None	64 (43.5%)	42 (55.3%)	22 (31.0%)
Acute	51 (34.7%)	20 (26.3%)	32 (45.1%)
Late	32 (21.8%)	14 (18.4%)	17 (23.9%)
Age			
Mean (SD)	71.1 (6.73)	70.7 (6.68)	71.5 (6.81)
Race & Ethnicity			
White	118 (80.3%)	61 (80.3%)	57 (80.3%)
Black	9 (6.1%)	5 (6.6%)	4 (5.6%)
Asian	15 (10.2%)	8 (10.5%)	7 (9.9%)
Hispanic	5 (3.4%)	2 (2.6%)	3 (4.2%)

Methods

We evaluated the existing PROSTOX signature's performance in predicting physician-scored late GU toxicity by MIRAGE treatment arm. Model performance was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and AUC (**Table 2, Figure 1**). We used linear regression to assess if PROSTOX score is predictive of toxicity grade overall and within treatment arm (**Figure 2**). We also evaluated the predictive utility of PROSTOX in predicting acute or chronic grade ≥ 2 GU toxicity (**Table 2, 3**).

We performed a gene ontology (GO) analysis[3] to assess biological pathways involved in the PROSTOX signature compared to preliminary acute or chronic GU toxicity mirSNP genetic signatures, using an adjusted p-value cutoff of 0.05 with a universal genomic background **(Figure 3)**.

Genetic Signature Performance

Table 2. PROSTOX Late GU Toxicity Signature Performance Metrics

Data	N	Num Tox	Sensitivity	Specificity	PPV	NPV	AUC
MIRAGE Overall	147	31	0.581	0.940	0.720	0.893	0.760
MIRAGE MRI	76	14	0.571	0.952	0.727	0.908	0.762
MIRAGE CT	71	17	0.588	0.926	0.714	0.877	0.757
Original Signature	93	14	0.714	0.924	0.625	0.948	0.819
MIRAGE Acute	147	50	0.180	0.897	0.474	0.680	0.538
MIRAGE Chronic	147	31	0.032	0.845	0.053	0.766	0.439

Table 3. PROSTOX does not predict Acute GU Toxicity (Grade >= 2)

		Acute GU Tox	Acute GU No Tox
Pred	Tox	9	10
	No Tox	41	87

Fisher's p-value = 0.203

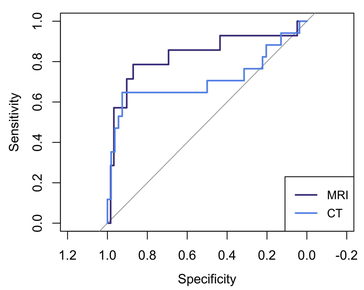

Figure 1. ROC plot displaying PROSTOX accuracy for predicting Late GU toxicity in MIRAGE MRI and CT arms. *This displays numeric output from PROSTOX, not its binary classification. The numeric AUCs are 0.83 and 0.71 for MRI and CT, respectively, which differ from the binary AUC presented in Table 2.*

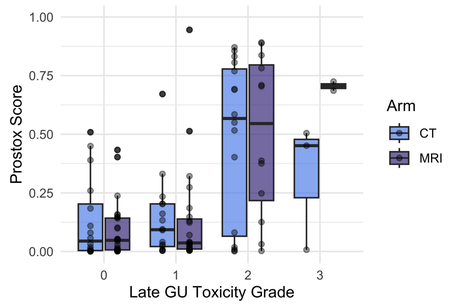

Figure 2. Relationship between Late GU Grade and PROSTOX score predicted value by treatment arm in MIRAGE. PROSTOX is associated to grade overall (p=8.1E-6), in MRI (p=2.1E-5), and in CT arms (p=0.045).

Gene Ontology

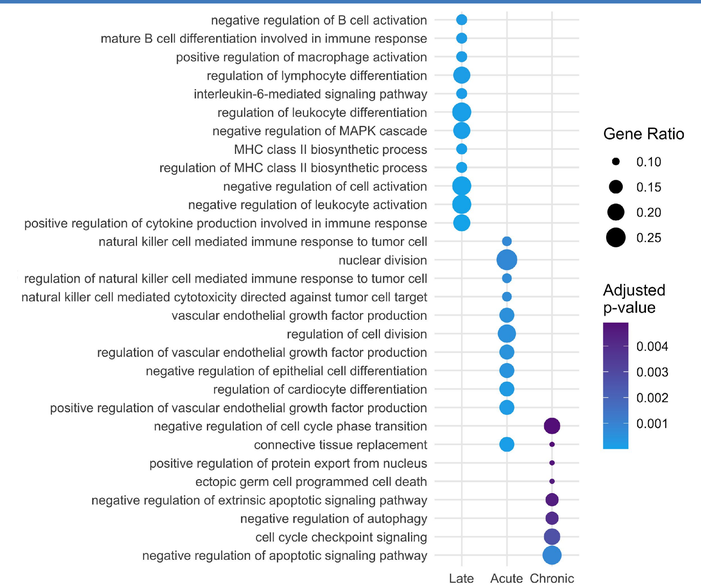

Figure 3. Top Gene Ontology enriched pathways involved in PROSTOX (Late), Acute, and Chronic GU toxicity. PROSTOX is enriched in immune response regulation, cytokine production, and immune cell differentiation and activation, whereas acute and chronic GU toxicities are enriched in natural killer tumor response, immune cell differentiation, and apoptotic processes.

Conclusions

- PROSTOX is confirmed to predict late Grade ≥ 2 GU toxicity in patients treated with SBRT, regardless of delivery method, with high accuracy.
- PROSTOX does not predict acute or chronic Grade ≥ 2 GU toxicity, but we identified preliminary miRSNP signatures for both.
- GO analysis revealed distinct biological pathway involvement in late, acute, and chronic toxicities, suggesting unique molecular mechanisms contributing to these different radiation-induced toxicities.
- These findings could ultimately allow the development of future therapeutic strategies for toxicity prevention.

Contact

Joanne B. Weidhaas, MD, PhD, MSM
Organizations: University of California, Los Angeles
Email: jweidhaas@mednet.ucla.edu

References

1. Kishan AU, Marco N, et al. Germline variants disrupting microRNAs predict long-term genitourinary toxicity after prostate cancer radiation. Radiother Oncol. 2022 Feb;167:226-232.
2. Chen X, Paranjape T, Stahlhut C, McVeigh T, Keane F, Nallur S, et al. Targeted resequencing of the microRNAome and 3'UTRome reveals functional germline DNA variants with altered prevalence in epithelial ovarian cancer. *Oncogene* 2015;34:2125–37.
3. Ashburner M, et al. Gene ontology: tool for the unification of biology. Nat Genet. 2000 May;25(1):25-9