Tobacco-associated mutations and prognosis in laryngeal cancer: an investigation using The Cancer Genome Atlas

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Introduction

- Tobacco smoke causes most laryngeal squamous cell carcinoma and decreases treatment efficacy.[1,2] Genetically, tobacco smoke induces mutations in several important pathways.[3]
- Mutations from direct effects of tobacco smoke carry a particular genetic signature.[4,5]
- This genetic signature can be detected using a publicly-available program through the Wellcome Trust Sanger Insitute, deconstructSig.
- The Cancer Genome Atlas provides whole-genome sequencing of many cancers, including laryngeal squamous cell carcinoma.
- Genomes from TCGA can be analyzed using deconstructSig to determine the relative burden of tobacco-associated mutations.
- Here, we compared tobacco-associated mutations with clinical outcomes in 72 laryngeal squamous cell carcinoma patients from TCGA.

Materials and Methods

- Staging, patient characteristics, and overall survival were collected for 72 laryngeal SCCa from TCGA.
- DeocnstructSig was used to characterize genetic mutations for each patient, generating 30 mutational profiles including one tobacco-induced signature.
- Total mutational burden and tobacco-induced mutations, as well as traditional staging, were used to predict overall survival.
- Univariate and multivariate analysis were performed by cox proportional hazard ratio using R statistics package. Number of pack-years was compared to number of tobacco-associated mutations by linear regression. Significance was defined as $p<0.05$.

Results

- Staging information is presented in Table 1. Most patients had advanced (T3-4) T stage disease.

Larynx SCCa (n=72)			
T stage		N stage	
T1	1	No	33
T2	12	N1	10
T3	23	N2, NOS	5
T4a	29	N2a	3
T4b	0	N2b	6
Unknown	7	N2c	5
		N3	2
		Unknown	7

Table 1. Staging information for 72 TCGA patients. SCCa: squamous cell carcinoma. NOS: not otherwise specified.

Results

- Increasing pack-years was associated with higher number of tobacco-associated mutations (Figure 1, $p=0.0341$).

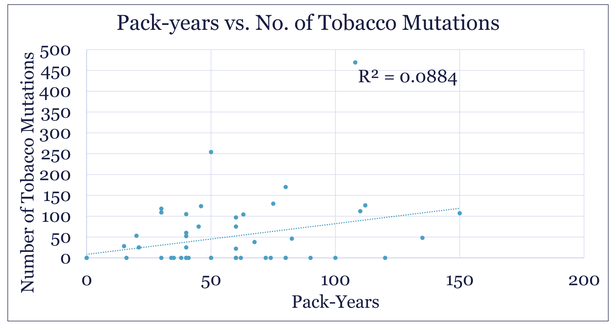

Figure 1. Plot of pack-years (x-axis) vs. number of tobacco-induced mutations (y-axis). There is a significant relationship between number of pack-years and number of tobacco-inducted mutations on linear regression ($p=0.0341$).

- Overall survival for all patients is shown in Figure 2.

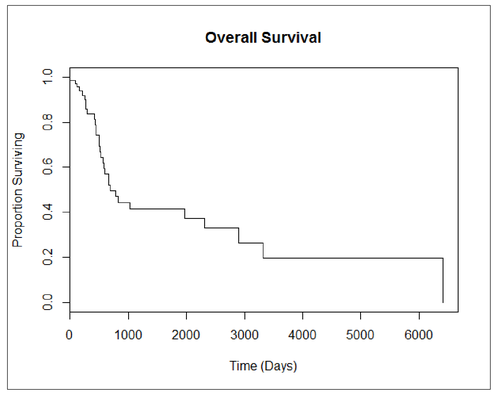

Figure 2. Kaplan-Meier survival curve for overall survival in all 72 patients.

- A receiver operator curve was generated to assess impact of tobacco-induced mutations on overall survival. This suggested that greater than 45 tobacco-induced mutations predicted better overall survival.

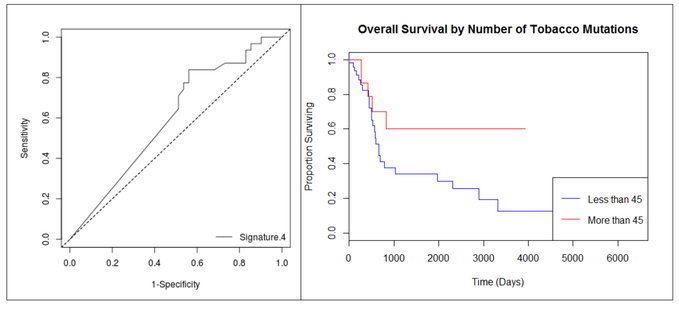

Figure 3. Left: Receiver-operator curve for tobacco-mutations. Cutoff point 45 generates AUC 0.598. Sensitivity 0.839, specificity 0.439. Right: Overall survival by number of tobacco-induced mutations showing trend toward better survival with more tobacco-induced mutations ($p=0.092$).

Results

- Hazard ratios using univariate and multivariate analysis are shown in Table 2.
- On multivariate analysis, only a higher burden (>45 mutations) of tobacco-induced mutations significantly predicted better overall survival. This was independent of a higher percentage of tobacco mutations.

Univariate Analysis				Multivariate Analysis			
	HR	95% CI	p		HR	95% CI	p
Age	0.99	0.95-1.05	0.933	Age	1.01	0.96-1.06	0.684
Female	2.28	0.99-5.26	0.053	Female	2.66	0.99-7.11	0.051
T	0.79	0.50-1.24	0.307	T	0.85	0.51-1.42	0.533
N0 vs. N1	1.11	0.52-2.34	0.79	N0 vs. N1	1.24	0.47-3.29	0.663
ECE	1.46	0.48-4.40	0.507	Tobac >45	0.16	0.03-0.77	0.022
Pack-years	0.99	0.97-1.00	0.127	Tobac >15.8%	2.82	0.64-12.4	0.169
Total mutations	0.99	0.99-1.00	0.227				
Any tobac	0.88	0.42-1.85	0.73				
Tobac >45	0.44	0.17-1.15	0.092				
Tobac >15.8%	0.64	0.27-1.49	0.301				

Table 2. Univariate (left) and multivariate (right) analysis of overall survival using cox proportional hazard ratio. ECE: extracapsular extension.

Discussion

- Increasing burden of tobacco-induced somatic mutations predicts improved overall survival among laryngeal SCCa patients in TCGA, independent of T stage, N stage, or overall number of mutations.
- Improved survival in this setting may indicate increased immune recognition of neo-epitopes generated from tobacco-induced mutations.[6]
- This study is limited by its small number of patients and bias toward advanced-stage laryngeal cancer patient available in TCGA.
- Studies comparing tumor immunity to tobacco-induced mutations in laryngeal cancer are warranted, and may provide insight into risk stratification for laryngeal cancer patients.

References

1. Pezzuto F, Buonaguro L, Caponigro F, Ionna F, Starita N, Annunziata C, et al. Update on Head and Neck Cancer: Current Knowledge on Epidemiology, Risk Factors, Molecular Features and Novel Therapies. Oncology. 2015;89(3):125-36.

2. Browman GP, Wong G, Hodson I, Sathya J, Russell R, McAlpine L, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med. 1993 Jan 21;328(3):159-63.

3. Davidson BJ, Hsu TC, Schantz SP. The genetics of tobacco-induced malignancy. Arch Otolaryngol Head Neck Surg. 1993 Nov;119(11):1198-205.

4. Pfeifer GP. Environmental exposures and mutational patterns of cancer genomes. Genome medicine. 2010;2(8):54.

5. Alexandrov LB, Ju YS, Haase K, Van Loo P, Martincorena I, Nik-Zainal S, et al. Mutational signatures associated with tobacco smoking in human cancer. bioRxiv. 2016:051417.

6. Vormehr M, Diken M, Boegel S, Kreiter S, Türeci Ö, Sahin U. Mutanome directed cancer immunotherapy. Curr Opin Immunol. 2016;39:14-22.