

# Are Signatures of Radiosensitivity Ready for Routine Clinical Use? a Pragmatic Comparison of Clinical, Pathological and Gene Signature Predictors of Outcome in Oropharynx Head and Neck Cancers

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To determine abilities and limitations of accepted clinico-pathological predictors of outcome in oropharynx cancer (OPC) in relation to currently-available gene expression signatures, to identify low-risk OPC patients.

Using the Cancer Genome Atlas (TCGA) OPC dataset (N=114), available clinico-pathological parameters were used to translate staging from AJCC version 7 (AJCC 7) to the newly-released AJCC 8, and patients were risk-stratified using a clinical algorithm developed by Ang et al. Literature review identified 15 mRNA expression signatures applicable to OPC encompassing radiosensitivity, HPV status, hypoxia, and microsatellite instability. We quality tested these signatures using the sigQC methodology, and used for signature refinement. We examined signatures and clinico-pathological variables as predictors of survival in univariate and multivariate analyses (including age, stage, and smoking in the model).

AJCC 7 Stage was not predictive of recurrence-free survival (RFS) or overall survival (OS). AJCC 8 more evenly staged cases and significantly predicted RFS and OS. Gene signature quality was highly variable, and refinement improved performance. Among gene signatures and clinico-pathological variables in multivariate analysis, TP53 mutation status remained the strongest predictor of OS, especially for HPV-negative tumors, which showed enrichment for TP53 mutations. Among HPV-positive cases, signatures for radiosensitivity, hypoxia, and microsatellite instability revealed significant biological heterogeneity. Thus, a subset of signatures may apply to stratify patients clinically into 'very low risk' and 'low risk' groups.

Significant heterogeneity exists in OPC, especially among HPV-positive cases. As a result, current prognostic biomarkers may not adequately identify patients for treatment de-escalation. While some gene signatures may be near routine clinical use, our work shows that quality control, refinement, and validation on independent data is paramount to ascertaining their true predictive ability and reproducibility.