Genetic diversity within tumors predicts outcome in head and neck cancer

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A new measure of the heterogeneity – the variety of genetic mutations – of cells within a tumor appears to predict treatment outcomes of patients with the most common type of head and neck cancer. In the May 20 issue of the journal *Cancer*, investigators at Massachusetts General Hospital (MGH) and Massachusetts Eye and Ear Infirmary describe how their measure was a better predictor of survival than most traditional risk factors in a small group of patients with squamous cell carcinoma of the head and neck.

"Our findings will eventually allow better matching of treatments to individual patients, based on this characteristic of their tumors," says Edmund Mroz, PhD, of the MGH Center for Cancer Research, lead author of the *Cancer* report. "This method of measuring heterogeneity can be applied to most types of cancer, so our work should help researchers determine whether a similar relationship between heterogeneity and outcome occurs in other tumors."

For decades investigators have hypothesized that tumors with a high degree of genetic heterogeneity – the result of different subgroups of cells undergoing different mutations at different DNA sites – would be more difficult to treat because particular subgroups might be more likely to survive a particular drug or radiation or to have spread before diagnosis. While recent studies have identified specific genes and proteins that can confer treatment resistance in tumors, there previously has been no way of conveniently measuring tumor heterogeneity.

Working in the laboratory of James Rocco, MD, PhD – director of the Mass. Eye and Ear /MGH Head and Neck Molecular Oncology Research Laboratory, principal investigator at the MGH Center for Cancer Research and senior author of the *Cancer* report – Mroz and his colleagues developed their new measure by analyzing advanced gene sequencing data to produce a value reflecting the genetic diversity within a tumor – not only the number of genetic mutations but how broadly particular mutations are shared within different subgroups of tumor cells. They first described this measure, called mutant-allele tumor heterogeneity (MATH), in the March 2013 issue of Oral Oncology. But that paper was only able to show that patients with known factors predicting poor outcomes – including specific mutations in the TP53 gene or a lack of infection with the human papillomavirus (HPV) – were likely to have higher MATH values.

In the current study, the investigators used MATH to analyze genetic data from the tumors of 74 patients with squamous cell head and neck carcinoma for whom they had complete treatment and outcome information. Not only did they find that higher MATH values were strongly associated with shorter overall survival – with each unit of increase reflecting a 5 percent increase in the risk of death – but that relationship was also seen within groups of patients already at risk for poor outcome. For example, among patients with HPV-negative tumors, those with higher MATH values were less likely to survive than those with lower MATH values. Overall, MATH values were more strongly related to outcomes than most previously identified risk factors and improved outcome predictions based on all other risk factors the researchers examined.

The impact of MATH value on outcome appeared strongest among patients treated with chemotherapy, which may reflect a greater likelihood that highly heterogeneous tumors contain treatment-resistant cells, Mroz says. He also notes that what reduces the chance of survival

appears to be the subgroups of cells with different mutations within a tumor, not the process of mutation itself. "If all the tumor cells have gone through the same series of mutations, a single treatment might still be able to kill all of them. But if there are subgroups with different sets of mutations, one subgroup might be resistant to one type of treatment, while another subgroup might resist a different therapy."

In addition to combining MATH values with clinical characteristics to better predict a patient's chance of successful treatment, Mroz notes that MATH could someday help determine treatment choice – directing the use of more aggressive therapies against tumors with higher values, while allowing patients with lower values to receive less intense standard treatment. While MATH will probably be just as useful at predicting outcomes for other solid tumors, the investigators note, that will need to be shown in future studies.

"Our results have important implications for the future of oncology care," says Rocco, the Daniel Miller Associate Professor of Otology and Laryngology at Harvard Medical School. "MATH offers a simple, quantitative way to test hypotheses about intratumor genetic heterogeneity, including the likelihood that targeted therapy will succeed. They also raise important questions about how genetic heterogeneity develops within a tumor and whether heterogeneity can be exploited therapeutically."

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