

CORRESPONDENCE



TP53 Mutations in Head and Neck Cancer

TO THE EDITOR: Poeta et al. (Dec. 20 issue)¹ report that a disruptive alteration of the gene for the tumor-suppressor protein p53 (*TP53*), as compared with the absence of a *TP53* mutation, had an independent, significant association with decreased survival in patients with squamous-cell carcinoma of the head and neck. *TP53* mutations were screened with the use of the GeneChip p53 assay (Affymetrix). However, frameshift mutations (from insertions or deletions in the p53 gene) cannot be detected with the GeneChip method.^{2,3} This important limitation biases the study by Poeta and colleagues because such frameshift mutations represent up to 20% of all known p53 mutations in head and neck cancer.⁴

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3. Wikman FP, Lu ML, Thykjaer T, et al. Evaluation of the performance of a p53 sequencing microarray chip using 140 previously sequenced bladder tumor samples. *Clin Chem* 2000;46:1555-61.

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TO THE EDITOR: Poeta et al. conclude that disruptive *TP53* mutations are associated with reduced survival among patients with squamous-cell carcinoma of the head and neck. The authors remark that conclusions with regard to oropharyngeal subsites may not be appropriate, since the presence of the human papillomavirus (HPV), which interacts with *TP53*, was not determined.

We have characterized 90 oropharyngeal squamous-cell carcinomas for HPV and *TP53* status.¹ Independently of the functional properties of the *TP53* mutations, HPV-positive patients had better survival than HPV-negative patients. Among HPV-negative patients, there was no difference in survival between those with mutated *TP53* and those with wild-type *TP53*. Unlike Poeta et al., we did not analyze the entire *TP53* coding region, only exons 5 through 8 and exon 4² in all and most cases, respectively. Moreover, in cases in which there was p53 immunoreactivity of more than 50%, we performed additional sequencing for exons 9 and 10. With the classification of *TP53* status as wild type, disruptive, or nondisruptive in our entire series, no significant prognostic difference was found, nor was there a difference in a separate analysis of HPV-negative patients. This suggests that oropharyngeal squamous-cell carcinoma has biologic prognostic variables that differ from those for other squamous-cell carcinomas of the head and neck.

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THE AUTHORS REPLY: In response to Beutner and colleagues, it is true that the Affymetrix p53 gene chip does not identify all mutations, but the later version of the chip, which we used, does identify single-base deletions and insertions that would account for many of the possible frameshift mutations. In fact, 12 frameshift mutations were included in our cohort (in 12 of 224 patients [5.4%]), 10 of which we scored as “disruptive” in that they resulted in a “stop” sequence later within the gene. The proportion of frameshift mutations that we found in this cohort closely resembles that in our earlier study of 129 head and neck cancers analyzed by direct sequencing of *TP53*,¹ in which 7% of all mutations were frameshifts. The International Agency for Research on Cancer currently reports that 17.2% of *TP53* mutations in head and neck cancer are deletions and insertions.²

The 10 patients with disruptive frameshift mutations in our current cohort had a median survival of 2.2 years — nearly identical to the median survival of 2.0 years for the 75 patients with other disruptive mutations ($P=0.95$). It is logical to ex-

trapolate that the majority of any frameshift mutations we may have missed would also be disruptive, and their identification would therefore serve to reassign some patients with poor outcomes from the wild-type group to the disruptive-mutation group, further enhancing the distinction in outcome based on mutation status that we were able to identify.

We agree with Perrone and colleagues that the evidence indicates a distinctive genetic pathway for tumorigenesis in the setting of HPV-related oropharyngeal tumors. The number of cases in their series and ours is insufficient to comment with statistical confidence regarding the prognostic effect of a *TP53* mutation when it is present with HPV DNA, as compared with either alteration in isolation. Since as many as 70% of tonsil or tongue-base cancers have HPV, and HPV inactivates wild-type p53, a *TP53* mutation would be expected to play a relatively minor role in this subgroup of squamous-cell carcinomas of the head and neck.

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Cetuximab for Colorectal Cancer

TO THE EDITOR: The study by Jonker et al. (Nov. 15 issue)¹ showed that cetuximab improved survival among patients with colorectal cancer, but the authors give no details regarding sites of metastases in the cetuximab group. Were metastatic sites in patients receiving cetuximab correlated with survival? The authors do not mention thromboembolism, which may be associated with poor survival among patients with cancer.² Was cetuximab associated with an increased risk of thromboembolism?

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