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EDITORIAL COMMENTARY

Predicting response to neoadjuvant therapy in esophageal cancer with p53 genotyping: A fortune-teller's crystal ball or a viable prognostic tool?

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See related article on pages 2280-6.

Ideally, predictive biomarkers with associated targeted therapies would be available for individualized treatment of esophageal cancer, optimizing outcome and minimizing

chemotherapy-associated risks. Unfortunately, clinically relevant biomarker identification for esophageal cancer has been elusive, more often resembling predictions from a fortune-teller's crystal ball than proving to be valid, clinically useful prognostic tools. The quest continues, however, and the p53 (*TP53*) gene appears promising. One of the most frequently mutated cancer-associated genes and a critical tumor suppressor gene involved in programmed cell death,¹ multiple studies show a relationship between *TP53* mutation and response to chemotherapy, including that of esophageal cancer. A recent meta-analysis of 28 studies with 1497 patients by Zhang and colleagues² showed high response rates to chemotherapy-based treatment regimens in tumors with low p53 protein expression or wild-type p53. Despite statistically significant findings, however, the conclusions were limited by tremendous heterogeneity across studies with respect to assessment of therapeutic response, chemotherapy regimens (dose and type),

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and use of radiation. Zhang and colleagues² cautioned that immunohistochemistry interpretation is highly susceptible to interobserver differences and may have limited usefulness because of the instability of the wild-type protein. There were also discrepancies between p53 protein levels and p53 gene mutations when assessed with reverse transcription polymerase chain reaction. They concluded that predicting response to chemotherapy in esophageal cancer may be possible by assessing pretreatment p53 status but could not make a definitive statement.

To investigate further the prognostic capabilities of *TP53*, the current study of Kandioler and colleagues, published in this issue of the *Journal of Thoracic and Cardiovascular Surgery*, sought to determine whether mutations in *TP53* were associated with differential survival outcomes after neoadjuvant cisplatin and 5-fluorouracil chemotherapy followed by esophagectomy. *TP53* genotyping identified 18 patients with *TP53* mutations and 18 with normal *TP53* genotype. All patients were evaluated on an intention-to-treat basis, although only 27 patients underwent esophagectomy; 8 patients had disease progression on chemotherapy and 1 had a complete response and declined esophagectomy. Overall and tumor-specific survivals were stratified by *TP53* status and compared; patients with *TP53* mutation had significantly worse survival (median, 8.6 vs 26.2 months) and were twice as likely to be dead at each follow-up interval than patients with normal *TP53*. The study results suggest a lack of response in the population with *TP53* mutation, but Kandioler and colleagues conclude that further validation is needed.

Several study strengths warrant highlighting. First, all patients were treated with cisplatin and 5-fluorouracil. Both agents rely on induction of DNA damage, a potent trigger for activation of the *TP53* gene, for therapeutic effect. In the setting of a *TP53* mutation, DNA damage would not activate *TP53*, providing a biologically plausible explanation for lack of treatment response. Second, p53 status is assessed at a genomic rather than at a protein level, eliminating the potential biases noted by Zhang and colleagues² in their meta-analysis. The analysis is also correctly based on intention-to-treat regardless of esophagectomy, allowing close examination of the relationship between *TP53* mutation and response to treatment. All 8 patients with progression (no esophagectomy) had *TP53* mutations, as did 6 of 7 patients with radiographically stable disease who underwent esophagectomy ($P < .0001$). The 3 patients with complete response had normal *TP53*. Additional strengths include complete patient follow-up of long duration (median, 87.4 months) and appropriately circumspect study conclusions that take into account the study limitations.

The weaknesses of the study of Kandioler and colleagues include small study size, relatively high perioperative

mortality (11%), mixed histologic tumor types (squamous cell and adenocarcinoma), and inadequate clinical staging. The limitations of computed tomographic scanning for depth of tumor invasion and nodal metastasis are well described; tumor-stage misclassification is as high as 58%.³ Misclassification can be either overstaging or understaging, and at a minimum endoscopic ultrasonographic and positron emission tomographic testing should be included in the pretreatment clinical staging assessment. Some surgeons also recommend routine laparoscopic staging before neoadjuvant therapy to lessen the significant rate of misclassification.^{4,5}

In summary, these findings have potentially significant implications for pretreatment decision making for patients with esophageal cancer. If validated, phenotyping of the *TP53* gene with pretreatment tumor biopsies may allow tailored therapy. Whether this means primary esophagectomy, an alternate chemotherapeutic regimen, or palliative definitive chemoradiation, the potential benefit lies in optimizing outcomes while reducing the morbidity and mortality of treatments without measurable, proven benefit to the individual patient. Definitive conclusions regarding the prognostic role of *TP53* remain to be established, but the study of Kandioler and colleagues suggests a potential prognostic role that warrants further study. Toward this end, enrollment of 168 patients in the p53 Adapted Neoadjuvant Chemotherapy for Operable Esophageal Cancer (PANCHO) trial was recently completed. If the study design addresses the weaknesses of the current study of Kandioler and colleagues, particularly with regard to the issues of clinical staging and histologic subtypes, more definitive assessment of the classification accuracy and positive and negative predictive values of p53 for response to chemotherapy may be possible. Although a single crystal ball for predicting response to chemotherapy may not even exist, mutations of the p53 gene may prove to be an important tool for stratifying patients into appropriate treatment regimens.

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