The biomarker *TP53* divides patients with neoadjuvantly treated esophageal cancer into 2 subgroups with markedly different outcomes. A p53 Research Group study

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Background: Fluorouracil and cisplatin have been used most frequently as neoadjuvant therapy for esophageal cancer. Both drugs are believed to act via a p53-dependent apoptosis pathway. The *TP53* gene is frequently mutated in esophageal cancer.

Objective: To test the value of *TP53* as a biomarker prognosing outcome in patients with neoadjuvantly treated esophageal cancer.

Patients and Methods: The investigation included 36 patients with primary operable esophageal cancer who were treated neoadjuvantly with cisplatin and fluorouracil. The *TP53* genotype was assessed from paraffin-embedded diagnostic tumor biopsies using a standardized gene-specific *TP53* sequencing protocol (mark53 kit; mark53 Ltd, Vienna, Austria).

Results: Mutations in the *TP53* gene were present in 50% of tumors. Two-year overall survival rates were 55.6% in patients with a normal *TP53* marker status, compared with 16.7% in those with a mutant *TP53* gene. In patients with normal *TP53*, neoadjuvant treatment resulted in significant advantages in terms of tumor-associated survival ($P = .0049$) and overall survival ($P = .0304$) compared with those with mutant *TP53*. The median tumor-associated survival was 34.2 months for patients with normal *TP53*, compared with 8.9 months for those with mutant *TP53*. The latter had a 3-fold higher risk of dying (hazard ratio, 3.01; 95% confidence interval, 1.359-6.86).

Conclusions: The biomarker *TP53* divides esophageal cancer patients into 2 categories with markedly different outcomes: patients with a normal *TP53* marker status may experience notable benefits from neoadjuvant chemotherapy with cisplatin/fluorouracil, whereas those with a mutant *TP53* marker status appear to be at risk for lack of response. (J Thorac Cardiovasc Surg 2014;148:2280-6)

See related commentary on pages 2286-7.

In patients with esophageal cancer, fluorouracil and cisplatin have been used as the standard preoperative chemotherapy regimen. A recent meta-analysis¹ indicated

a marginal survival benefit for preoperative chemotherapy with cisplatin/fluorouracil compared with surgery alone in patients with resectable esophageal cancer. Survival appears to be most significantly improved in patients experiencing complete histopathologic response.^{2,3} However, complete response rarely occurs under this regimen (5%-15%) and currently responders cannot be identified before treatment. The use of more intensive regimens to improve complete response rates appeared to be limited by the concomitant increase in treatment-related morbidity and mortality.⁴

Markers predicting response to chemotherapy would greatly enhance the efficacy of treatment and simultaneously reduce chemotherapy-related risks by permitting individualized preoperative treatment. No such predictive markers have been established for esophageal cancer.

P53 has been suggested to play a crucial role in a patient's response to various chemotherapeutic regimens. Defective *TP53* has been considered a plausible reason for drug resistance, thus permitting response prediction.⁵ Chemotherapy drugs such as cisplatin and fluorouracil act by inducing DNA damage. The latter is the strongest trigger for the

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Disclosures: Martina Mittlböck reports consulting fees from Actelion, equity ownership in Intercell, and lecture fees from Bayer. Johannes Zacherl reports lecture fees from Olympus, Nestle, Covidien, Novartis, and AFS. All other authors have nothing to disclose with regard to commercial support.

Received for publication Sept 5, 2013; revisions received April 14, 2014; accepted for publication June 12, 2014; available ahead of print Aug 16, 2014.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2014.06.079>

Abbreviations and Acronyms

CR	= complete remission
CROSS	= Neoadjuvant Chemoradiation Followed by Surgery versus Surgery Alone for Patients with Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus
PANCHO	= p53-Adjusted Neoadjuvant Chemotherapy for Potentially Resectable Esophageal Cancer
PET	= positron emission tomography

activation of the *TP53* gene. As a result p53 transactivates genes of the apoptotic cascade resulting in programmed cell death. However, because *TP53* is the most frequently mutated gene associated with cancer, this pathway is often disrupted.⁶

We hypothesized that p53 mutation status may be useful for prognosing outcome in patients with resectable esophageal cancer treated with neoadjuvant chemotherapy. The aim of the study was to evaluate the association of response to neoadjuvant cisplatin/fluorouracil in patients with esophageal cancer stratified for the tumor's *TP53* status.

METHODS

Patients with primary operable esophageal cancer and treated by neoadjuvant chemotherapy were included in this phase II biomarker study. From August 2001 to May 2007, we identified 47 consecutive patients who received neoadjuvant treatment at 2 institutions.

Neoadjuvant treatment consisted of 2 cycles of chemotherapy with cisplatin 80 mg/m² as an intravenous infusion over 4 hours on day 1, and fluorouracil 1000 mg/m² as a continuous infusion on day 1 and day 14 in 36 patients. The neoadjuvant regimen is based on the results of the United Kingdom Medical Research Council esophageal cancer trial.⁷ Eleven patients who received a different treatment were excluded.

The study was approved by the local ethics committee and included informed consent for DNA testing.

Staging was performed before and after neoadjuvant chemotherapy to determine operability. Clinical staging included computed tomography of the abdomen, chest, and neck; endoscopy/biopsy of the upper gastrointestinal tract; as well as a positron emission tomography (PET) scan in some patients and bronchoscopy in patients with squamous cell carcinoma.

Computed tomography scans were used to determine the patients' resectability and the tumor mass at initial staging and preoperative restaging. Data from fluorodeoxyglucose PET scans were available for 10 patients. The remaining patients had either no PET on the day of staging and/or restaging. Thus we did not include this information in our analysis.

At restaging 7 patients had criteria of inoperability after neoadjuvant chemotherapy; local progression was seen in 4 patients who therefore had exploration only. De novo distant metastases were detected in 3 patients who were excluded from surgery. Although these 7 patients had no complete tumor resection, they were not excluded from survival analysis; tumor progression during chemotherapy is a clear indicator of treatment failure. Thus we believe that the exclusion of these patients would have biased the survival comparisons for the assessment of *TP53* as a biomarker predicting response to treatment.

The major outcome measures were response as determined by overall survival, tumor-associated survival, and objective tumor response.

Additionally objective tumor response was measured in terms of a change in the size of the tumor. Computed tomography scans were used to measure tumor mass at initial pretreatment staging and at restaging (before surgery). Complete remission (CR) was defined as complete absence of tumor, confirmed by histologic investigation of the surgical specimen. Partial response was defined as major or obvious response, expressed as a minimum reduction of 30% in tumor mass. Progressive disease was defined as an increase in tumor mass or the appearance of new peripheral lesions.

For analysis of the *TP53* genotype, tumor DNA was extracted from paraffin-embedded tissue of the diagnostic tumor biopsies. The patients' marker status was assessed with a standardized gene-specific sequencing kit for the p53 gene (mark53 kit; mark53 Ltd, Vienna, Austria).

Mutations in the p53 gene were reported according to the recommendations of the Human Genome Variation Society (www.hgvs.org).⁸

Silent mutations were rated normal.

Statistical Analysis

Continuous data are described with mean and standard deviation in cases of normal distribution or by median, minimum, and maximum otherwise. Differences between groups were tested by independent samples *t* test in case of normal distribution and by Wilcoxon rank-sum test otherwise. Categorical data are described with absolute and relative frequencies. A χ^2 test was used to assess for group differences for binary and nominal variables. For ordinal variables a trend χ^2 test was used. In case of sparse data the Fisher exact test or exact χ^2 tests were used.

Surgical mortality included all deaths within 30 days after the operation or during hospitalization.

The primary outcome measure was overall survival, tumor-associated survival, and treatment response. Overall survival and tumor-associated survival are defined from the date of the first cycle of neoadjuvant chemotherapy until death or last time known to be alive. Overall survival included all deaths, independent of the cause. Median follow-up time was calculated by Kaplan-Meier method where deaths are censored for further follow-up. Survival probabilities were estimated by Kaplan-Meier graphs and group differences were assessed by log-rank test. The Cox regression model was used to assess group differences by hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Multiple Cox regression models were fitted to assess the influence of *TP53* on survival additional to standard prognostic factors to evaluate if *TP53* is an independent prognostic factor. However this overfitted model cannot be seen as prognostic model for future patients.

Statistical calculations are performed with SAS (SAS Institute Inc, Cary, NC) and SPSS (IBM-SPSS Inc, Armonk, NY). All *P* values are 2-sided and *P* ≤ .05 was considered significant.

RESULTS**Patients**

Thirty-six patients with primary operable esophageal cancer who had received neoadjuvant treatment with fluorouracil and cisplatin were evaluated for their *TP53* status. The *TP53* mutation rate in the study cohort was 50% (18 out of 36). *TP53* mutations are described in Table 1. Pre-treatment patient characteristics are shown in Table 2.

At the time of evaluation, after a median follow-up of 87.4 months (7.3 years), 33 of 36 patients were dead (91.7%) (Figure 1). Seven patients died from nontumor-related causes: of these 3 died perioperatively due to acute respiratory distress syndrome, pneumonia, or anastomosis failure; 2 patients died as a result of stroke; 1 died due to sepsis; and in 1 patient the cause of death was unknown. Three patients are still alive and were censored between 79 and 96 months. One half of patients survived for longer than 13.9 months.

TABLE 1. *TP53* mutations in patients with esophageal cancer

Patient no.	Exon	<i>TP53</i> mutation*
1807	5	c.422G>A (p.Cys141Tyr)
1789	5	c.452C>G (p.Pro151Arg)
1794	5	c.469G>T (p.Val157Phe)
2047	5	c.514G>T (p.Val172Phe)
1916	6	c.569dupC (p.Pro191SerfsX18)
1811	6	c.635_636delTT (p.Phe212SerfsX3)
1804	6	c.659A>G (p.Tyr220Cys)
1797	7	c.707A>G (p.Tyr236Cys)
1837	7	c.713delG (p.Cys238LeufsX9)
1809	7	c.743G>A (p.Arg248Gln)
1833	7	c.742C>T (p.Arg248Trp)
1798	8	c.811G>A (p.Glu271Lys)
1800	8	c.818G>A (p.Arg273His)
1579	8	c.818G>A (p.Arg273His)
1805	8	c.824G>A (p.Cys275Tyr)
2048	8	c.833C>G (p.Pro278Arg)
1810	8	c.844C>T (p.Arg282Trp)
1802	8	c.916C>T (p.Arg306X)

*Reported according to Recommendations of the Human Genome Variation Society (www.hgvs.org).⁸

Complete Remission After Neoadjuvant Chemotherapy

CR (2 pathologic and 1 clinical) occurred in 9% of patients (3 out of 36). The patient with clinical CR at restaging refused to undergo surgery (Table 3). Pathologic CR

TABLE 2. Pretreatment patient characteristics

Characteristic	<i>TP53</i> normal	<i>TP53</i> mutated	Total	<i>P</i> value
<i>TP53</i> genotype	18	18	36	
Sex				
Male	15	15	30	
Female	3	3	6	1.000
Age, y (mean $\pm$ SD)	60.4 $\pm$ 8.0	64.2 $\pm$ 7.9	62.3 $\pm$ 8.1	.1619
Tumor type				
Adenocarcinoma	11	9	20	
Squamous cell carcinoma	7	9	16	.5023
Clinical tumor staging				
T0/carcinoma in situ	0	0	0	
T1	0	2	2	
T2	6	5	11	
T3	9	9	18	.7994
T4	0	1	1	
Missing*	3	1	4	
N0	7	3	10	
N1	8	14	22	.1283
Missing*	3	1	4	
Gx			0	
G1	1	1	2	
G2	6	10	16	
G3	6	7	13	1.000
Missing*	5	0	5	

SD, Standard deviation. *Missing values in TN staging are due to stent implantation before computed tomography.

FIGURE 1. Overall survival in patients with normal *TP53* versus mutant *TP53*.

includes 1 patient with yT0 and 1 patient with carcinoma in situ. All CRs occurred in patients with *TP53* normal tumors, whereas there was no CR observed in patients with *TP53* mutant tumors (Table 3).

Survival by *TP53* Mutation

Neoadjuvant treatment with cisplatin/fluorouracil resulted in a significant benefit for overall survival ($P = .0304$) and tumor-associated survival ($P = .0049$) in patients with a normal *TP53* status compared with those with a mutant *TP53* status (Figures 1 and 2).

Overall survival is shown in Figure 1. Median overall survival was 8.6 months for patients with mutated *TP53* and 26.2 months for patients with nonmutated *TP53*, which corresponds to an HR of 2.15 (95% CI, 1.06-4.38).

Tumor-associated survival is shown in Figure 2. Median tumor-associated survival was 8.9 months for patients with mutated *TP53* and 34.2 months for nonmutated patients, which corresponds to an HR of 3.01 (95% CI, 1.36-6.86).

Multiple Cox regression models were fitted to assess the influence of *TP53* on survival additional to the standard prognostic factors shown in Table 2 to evaluate if *TP53* is an independent prognostic factor. Despite the overfit of the model, patients with *TP53* mutations still showed a significantly higher risk for shorter overall survival (HR, 4.075; 95% CI, 1.209-13.737; $P = .0235$) and tumor-associated survival (HR, 7.417; 95% CI, 1.974-27.876; $P = .0030$) additional to the standard prognostic factors.

Adenocarcinoma Versus Squamous Cell Carcinoma

Sixteen cases of squamous cell carcinoma and 20 cases of adenocarcinoma were included in our investigation. Of the

TABLE 3. Posttreatment patient characteristics

Characteristic	TP53 normal	TP53 mutated	Total	P value
Pathologic tumor staging				
yT0	1	0	1	
Carcinoma in situ	1	0	1	
yT1	3	2	5	
yT2	3	4	7	
yT3	9	4	13	
yT4	0	0	0	.8471
Missing	1	8	9	
N0	7	3	10	
N1	10	7	17	.6919
Missing	1	8	9	
Gx	1	0	1	
G1	2	3	5	
G2	8	5	13	
G3	6	2	8	.6282
Missing	1	8	9	
Adapted pathologic tumor staging*				
Carcinoma in situ	2	0		
yTIS	1	0		
yT1	3	2		
yT2	3	4		
yT3	9	4		
Adapted T4	0	8		
Adapted missing	0	0		.0191
Surgery				
Mean number (range) of resected lymph nodes	17 (10-43)	16 (5-28)	16 (5-43)	.4598
Resection				
Radical	15	9	24	
R1	2	1	3	
No resection	1	8	9	.0236
Reasons for no resection				
Complete tumor remission/refused surgery	1	0	1	
Clinical progression, poor condition	0	1	1	
Inoperability due to local progression	0	4	4	
Inoperable due to systemic progression	0	3	3	
Nontumor-related deaths				
Pneumonia	2	1	3	
Other	3	1	4	
Response				
Complete remission†	3	0	3	
Partial remission	14	4	18	
Stable disease	1	6	7	
Progressive disease	0	8	8	<.0001

*For the adapted tumor staging the missing values were adapted in that the 8 patients who were nonoperable due to disease progression (all TP53 mutated) were added to pT4 (worst case) and the 1 patient who refused surgery due to clinical complete remission was added to pT0 (best case). †Complete remission included 2 pathologic and 1 clinical complete remission: 1 patient refused to undergo surgery after experiencing clinical complete remission at restaging. Pathologic complete remission occurred in 2 patients. One had stage yT0 and 1 showed circumscribed high grade dysplasia with focal transition to carcinoma in situ in the pathologic specimen. Both patients had negative lymph nodes.

3 patients with CR, 2 had squamous cell carcinoma and 1 had adenocarcinoma. There was no difference in the frequency of TP53 mutation between the 2 histologic types (Table 2). Tumor-associated overall survival did not differ in the 2 histologic types ($P = .4102$). For both histologic types, tumor-associated survival was improved in patients with normal TP53 (adenocarcinoma $P = .0042$; squamous cell carcinoma $P = .0615$).

Surgery

A transthoracic resection was performed in 13 patients, a transhiatal resection was performed in 12 patients, and 2 patients underwent extended gastrectomy. Posttreatment patient characteristics are shown in Table 3. Nine patients had no curative resection. Therefore we had 9 missing values for pathologic staging. With 9 missing values in the calculation no statistically significant

FIGURE 2. Tumor-associated survival in patients with normal *TP53* versus mutant *TP53*.

associations were observed between pathologic T stage and *TP53* status (Table 3).

Regarding the reasons for not performing curative resection, they could be considered as informative for treatment response: One patient refused to undergo surgery after experiencing clinical CR at restaging. Eight patients presented with disease progression after neoadjuvant chemotherapy: 4 were inoperable due to local progression (confirmed by surgical exploration), 3 were inoperable due de novo distant metastases, and 1 had progressive disease and deemed unfit for surgery.

When we take the missing values as clinically informative and adapt them in that we considered the 8 patients without surgery due to disease progression as T4 (worst case), and the 1 patient who refused surgery due to clinical CR as T0 (best case), the statistical test shows a significant association between pathologic tumor stage and *TP53* mutation status ($P = .0191$).

DISCUSSION

A markedly different survival after neoadjuvant chemotherapy was observed comparing patients with *TP53* normal and *TP53* mutant esophageal cancer, suggesting a lack of response to neoadjuvant cisplatin/fluorouracil in the population with mutant *TP53*.

Overall the observed median survival (13.9 months) and 2-year survival rate (36.1%) conformed with results from 2 published clinical trials,^{7,9} namely the US Intergroup trial and the British Medical Research Council trial, which had applied comparable neoadjuvant regimens and patient selection criteria.

Stratification by *TP53* marker status revealed a markedly different survival in the 2 marker groups: *TP53* normal patients showed a median overall survival of 26.2 months and

a 2-year overall survival rate of 55.6%, compared with 8.6 months and 16.7% in patients with mutant *TP53*.

There are several studies evaluating the correlation of *TP53* status and response to chemo/radio therapy in esophageal cancer: A recent meta-analysis comprising 1497 cases from 28 studies concluded that normal *TP53* was associated with high response to chemotherapy-based treatment in esophageal cancer.¹⁰ By its nature a meta-analysis is not homogenous for treatments, patient selection, and particularly for the p53 assays (several studies used p53 immunohistochemistry). Nevertheless the HR for pathologic major response was reported to be 1.15 (95% CI, 1.06-1.25; $P = .001$). Our study, which is unique in that it uses for the first time a standardized, p53-specific sequencing analysis, and thereby avoids the possibility of missing of mutations, showed an HR for tumor-associated survival of 3.01 (95% CI, 1.36-6.86).

Other published reports addressing the clinical significance of p53 have been inconsistent.^{11,12} Methodologic limitations such as the use of p53 immunohistochemistry or incomplete sequencing may account for these conflicting results. For esophageal cancer it has been explicitly shown that p53 immunohistochemistry does not correlate with response to chemotherapy, curative resection rate, or prognosis, whereas data from *TP53* mutation analyses are more consistent concerning the association of *TP53* mutation and poor survival.¹³⁻¹⁵ To date it is not clear if poorer prognosis or poorer response to chemotherapy is the reason for the survival disadvantage in patients with mutant *TP53*.

The objective tumor response observed in our study suggests a lack of response to neoadjuvant therapy in the population with mutant *TP53*. Fourteen of 18 patients with *TP53* mutations had stable or progressive disease. On the other hand, CR was observed only in patients with normal *TP53*.

The multiple Cox model indicated that *TP53* prognosed survival independently from established prognostic markers. However this model is based on a small sample size and model instability cannot be excluded. Because *TP53* showed significant effects despite these heavily overfitted models, this is an indicator that *TP53* might be an independent prognostic factor.

Study Limitations

It should be noted that our study lacked a surgery-only arm. Therefore we can only speculate that *TP53* may be useful as a predictor of response to neoadjuvant therapy.

Assessment of objective tumor response in cancer therapy is a difficult issue. Comparisons of pretreatment with posttreatment staging bear limitations that need to be considered. The neoadjuvant setting of our study is advantageous in that it permits determination of pathologic response in resected specimens, which is considered more accurate than imaging. But as demonstrated, patients who cannot undergo resection due to disease progression during chemotherapy create missing values for pathologic staging.

However from the clinical point of view progression during chemotherapy resulting in inoperability is very informative, because it indicates treatment failure. Thus ignorance of this information can bias the results because patients with treatment failure are excluded from analysis. Therefore, we adapted the missing values for an additional calculation in Table 3 (adapted pathologic tumor staging), and could demonstrate that posttreatment staging was significantly worse for the populations with mutated *TP53*.

Another problem when dealing with objective tumor response is the inaccuracy of imaging, a problem that may be aggravated by chemotherapy.¹⁶ The Response Evaluation Criteria In Solid Tumors criteria aimed to standardize tumor measurements and response reporting.¹⁷

Availability of pathologic tumor staging in neoadjuvant therapy studies reveals that the inaccuracy of clinical staging is still a problem and cannot be eliminated completely even with the integration of advanced technology like endoscopic ultrasound and fluorodeoxyglucose PET or (better still) PET-computed tomography.

Many anticancer treatments fail to induce substantial benefits. It has been said that “over the last decade, the use of overall survival as primary endpoint has decreased significantly in clinical trials, as has the magnitude of benefit deemed clinically relevant.”¹⁸ Molecular markers are expected to generate significant survival differences. Our results seem to be consistent with these expectations. In contrast to tumor response, survival can be assessed accurately and calculated to the day.¹⁹⁻²¹ Today we notice that with the implementation of molecular markers overall survival regains importance for demonstrating a benefit from treatment.²⁰ As a consequence molecular markers are expected to raise the bar for clinical trials.

FUTURE ANALYSES

The Neoadjuvant Chemoradiation Followed by Surgery versus Surgery Alone for Patients with Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus (CROSS) trial probably addresses the most effective treatment for esophageal cancer to date, but the data may not be useful for retrospective evaluation of a biomarker like *TP53*. In the CROSS trial, neoadjuvant treatment consisted of weekly carboplatin plus paclitaxel and concurrent radiotherapy.²² Carboplatin and radiation are likely to act via a p53-controlled pathway—a hypothesis that we were able to validate in a number of clinical studies.²³⁻²⁶ But docetaxel acts differently and it is not clear if and how it interacts with *TP53*.^{27,28} Thus, due to the combination of these differential acting treatments in the CROSS trial, findings may be difficult to interpret when the population is stratified by *TP53* status.²⁹

To answer the question if and how *TP53* interacts with different classes of chemotherapy drugs in esophageal cancer, we conducted a prospective randomized trial, the

p53-Adjusted Neoadjuvant Chemotherapy for Potentially Resectable Esophageal Cancer (PANCHO) trial.* The trial was designed according to the “marker by treatment interaction design” recommended by Sargent and colleagues³⁰ as a suitable design to answer a predictive biomarker question. In the PANCHO trial, patients with resectable esophageal cancer were stratified on the basis of the biomarker *TP53* and subsequently randomized to different neoadjuvant treatments (cisplatin/fluorouracil vs docetaxel monotherapy). Recruitment for the PANCHO trial was recently completed; the data are awaited.

CONCLUSIONS

In patients with esophageal cancer a markedly differential survival after neoadjuvant chemotherapy could be demonstrated for the first time when comparing tumors with normal *TP53* and tumors with mutant *TP53*. Our results suggest a lack of response to neoadjuvant cisplatin/fluorouracil in the population with mutant *TP53*. Further studies are needed to validate our findings.

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*The P53 Adapted Neoadjuvant Chemotherapy for Operable Esophageal Cancer (PANCHO) trial (www.clinicaltrials.gov identifier: NCT00525200; www.p53.at) is being conducted by the p53 Research Group and has successfully recruited 168 patients with primarily resectable esophageal cancer from 2007 to 2012 at 13 centers in Austria.

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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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Dr Nason's work is supported by Grant K07CA151613 from the National Cancer Institute.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Sept 14, 2014; accepted for publication Sept 15, 2014

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J Thorac Cardiovasc Surg 2014;148:2286-7

0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2014.09.036>