Epidermal Growth Factor Receptor, p53 Mutation, and Pathological Response Predict Survival in Patients with Locally Advanced Esophageal Cancer Treated with Preoperative Chemoradiotherapy

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ABSTRACT

Purpose: Despite the availability of cellular markers associated with cell cycle, apoptosis, and DNA repair, predictive factors for pathological complete response (CR) and overall survival (OS) are few in patients with locally advanced esophageal cancer. This study evaluates the role of clinical and cellular markers in predicting CR and OS in patients with esophageal cancer.

Experimental Design: Patients were treated with infusional cisplatin and 5-fluorouracil combined with daily radiotherapy followed by esophagectomy. Pretreatment tumors (n = 54) were analyzed for epidermal growth factor receptor (EGF-R), bax, and bcl-2 expression by immunohistochemistry and for p53 mutations by direct DNA sequencing of exons 5–8. Clinical covariates included patients’ age at enrollment; gender; Barrett’s metaplasia; and tumor location, histology, and differentiation. Logistic regression and survival analyses were used to evaluate the predictors.

Results: Age ranged from 32 to 75 years; most patients were male (45 male; 9 female); and tumors were distal (47 distal; 7 mid; 6 proximal). Adenocarcinoma (41 adenocarcinomas; 13 squamous cell carcinomas), and moderately differentiated (33 moderate; 6 well; 15 poor). Female gender predicted CR (odds ratio 7.5; 95% confidence interval, 1.4–41). The OS was 43% at 5 years. Presence of CR (P < 0.001 log rank) and p53 mutation (P = 0.051 log rank) correlated with increased OS, whereas increased EGF-R expression predicted poor OS (P = 0.009 log rank). EGF-R remained significant when adjusted for clinical covariates. There was a trend toward increased OS related to better tumor differentiation and decreased bcl-2.

Conclusions: These data suggest that EGF-R and p53 mutation may be used as both outcome predictors and targets for molecular therapy for esophageal cancer.

INTRODUCTION

Esophageal cancer comprises a small percentage (1.5%) and low incidence (12,300 cases/year) of total cancer cases in the United States; however, the mortality rate remains high (1, 2). In our experience and the experience of others, locally advanced, nonmetastatic disease is curable in up to 40% of patients (3–5). Overall survival with surgery alone ranges between 15% and 25% (6). These rates likely reflect both late stage of disease at diagnosis as well as inadequacy of therapy.

Although survival results in phase II trials using preoperative chemoradiotherapy are promising, randomized trials demonstrate mixed results (7–10). Therefore, the role of this treatment approach remains controversial. Overall, standard preoperative chemoradiotherapy using cisplatin/5-fluorouracil (5-FU)-based regimens results in a pathological complete response (CR) rate of approximately 25%. There is often an apparent improvement in survival and local control compared with results expected with historical controls of surgery alone.

Over the past 10 years, we conducted two phase II trials at Johns Hopkins and Yale that provided intensive regimens of cisplatin and 5-FU chemotherapy combined with radiotherapy before surgical resection (3–5, 11). The second trial also incorporated postoperative chemotherapy with paclitaxel and cisplatin. Combined trial results demonstrated that 93% percent of 92 patients underwent surgery and 87% were completely resected with negative margins. The pathological CR rate was 33%. At median follow-up of 63.5 months, median survival of all enrolled patients was 35 months, and 5-year survival was 40%. Patients with a pathological CR did better (67% survival at 5 years, median not reached), whereas the remainder of the patients had a 5-year survival of 27% (median survival at 21 months; P < 0.001). Survival is promising, but toxicity during therapy and limited tolerance of adjuvant chemotherapy suggest that both novel therapies and better selection of patients for aggressive treatment are warranted.

One strategy to improve the outcome of patients treated with chemoradiotherapy is to select treatment responders for directed therapy. Current knowledge about the molecular mechanisms of cancer-related pathways is facilitating numerous stud-
ies that attempt to identify molecular markers of both response to preoperative therapy and overall survival. Markers of interest include those associated with apoptosis (p53, bax, and bcl-2), cell cycle control (p16, p21, and cyclin D1), growth regulation [epidermal growth factor receptor (EGF-R), transforming growth factor-β, HER-2/neu, Ki-67], and DNA repair (ERCC1), metastatic potential (tissue inhibitor of metalloproteinase, E-cadherin), angiogenesis (vascular endothelial growth factor), and sensitivity to chemotherapy (P-glycoprotein, thymidylate synthase, glutathione S-transferase, and metallothionein; Ref. 12).

Despite extensive study, there remain no clear candidate markers that predict pathological response, and there are only equivocal data for a limited number of markers that might predict survival for patients treated with preoperative multimodality therapy (13–17). Although the study by Harpole et al. (14) contained mostly adenocarcinomas, many of the studies involved only squamous cell histologies, despite the marked increase in the incidence of adenocarcinoma (18, 19). The need for additional information about these mechanisms is becoming more pressing with the recent and ongoing development of drugs that target these markers and pathways.

Given the need for both better predictors of outcome and identification of targets for directed therapy, we examined the role of clinical and cellular markers in predicting pathological response and overall survival in patients with locally advanced esophageal cancer who were treated with combined modality therapy at Johns Hopkins and Yale.

MATERIALS AND METHODS

Study Design. A total of 92 patients with histologically confirmed invasive squamous cell carcinoma or adenocarcinoma of the esophagus, gastroesophageal junction, or gastric cardia were enrolled in two phase II clinical trials (3, 4). All patients were newly diagnosed and had received no prior treatment. Each patient was older than 18 years of age, had a Karnofsky performance status of >60%, and had adequate hepatic, renal, and bone marrow reserve. The disease was limited to the primary and regional nodes, although celiac nodal involvement (M1a) was permitted for primary tumors in the mid, distal, or gastroesophageal junction/cardia. Patients were required to be surgical candidates with disease that could be encompassed in a single radiation port. In study J8908, patients were staged with barium esophagogram and computed tomography scans of the chest, abdomen, and pelvis. In study J9528, staging also included endoscopic ultrasound and exploratory laparoscopy.

Although patients in both trials received preoperative chemoradiotherapy with cisplatin, 5-FU, and radiation, the regimens differed slightly. In both studies, chemotherapy and radiotherapy were administered over 30 calendar days. For study J8908, cisplatin at a dose of 26 mg/m²/day was administered on days 1–5 and 26–30, and 5-FU at a dose of 300 mg/m²/day was given on days 1–30 by continuous i.v. infusion. For study J9528, cisplatin at a dose of 20 mg/m²/day was administered on days 1–5 and 26–30, and 5-FU at a dose of 225 mg/m²/day was given on days 1–30 by continuous i.v. infusion. In each study, radiotherapy was given at a daily dose of 2 Gy to a total dose of 44 Gy. Esophagogastrectomy was carried out approximately 4 weeks after completion of chemoradiation in those patients without disease progression. Study J9528 differed from study J8908 in that patients were subsequently treated i.v. with adjuvant chemotherapy consisting of 135 mg/m² paclitaxel for 24 h on day 1 and 75 mg/m² cisplatin on day 2 repeated every 3 weeks for three cycles.

The NIH CTC criteria were used to measure toxicity, and appropriate dose adjustments and delays were made. All patients provided written informed consent, and the Institutional Review Boards at Yale and Johns Hopkins approved both protocols.

Follow-up after treatment involved medical oncology visits at 4-month intervals for the first year and at 6-month intervals for the 2nd through 5th years. After 5 years, patients were evaluated annually.

The primary outcome was pathological response in the resected specimen. A CR was defined as the histological absence of residual tumor in the resected esophageal specimen and nodal tissue. A partial response was defined as residual malignant cells in the resected specimen. Progressive disease was defined as the presence of metastatic or unresectable disease before surgery. The secondary outcome, survival, was defined as any patient remaining alive within 6 months of the time of final follow-up (October, 2002), regardless of the cause of death.

Tissue Samples and Immunohistochemistry (IHC). Paraffin embedded, pretreatment tumor tissue was available for 54 of the 92 patients treated on protocols J8908 (n = 34) and J9528 (n = 20) at Johns Hopkins and Yale. All tissue was obtained by endoscopic biopsy of the primary esophageal tumor.

Unstained histopathological sections on ChemMate (BioTek Solutions) slides were stained with an automated stainer in the Johns Hopkins Immunopathology Laboratory per methods used in studies of colorectal cancer described previously (20, 21). Tissue was stained with antibodies to the following markers: EGF-R, bax, and bcl-2. Citrate buffer or Pronase (for EGF-R) was used for antigen enhancement, and final detection involved standard avidin-biotin staining methods. The monoclonal antibodies Oncoprotein 124 (DakoCytomation) at a dilution of 1:25 and 31G7 (Zymed, South San Francisco, CA) at a dilution of 1:50 were used for detection of bcl-2 and EGF-R, respectively. Biotinylated rabbit antimouse (DakoCytomation) was used as the secondary antibody. The bax marker was detected using the polyclonal rabbit IgG p19 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) at a dilution of 1:100 with biotinylated swine antirabbit (DakoCytomation) as a secondary antibody. Primary antibodies were replaced with PBS in negative control slides. The positive controls used were lymph node (bcl-2), Paneth cells in small intestine (bax), and basal epithelium (EGF-R).

Slides were reviewed by a single pathologist who had no knowledge of the status of the response to chemoradiation. Grading of immunolabeling for bax, bcl-2, and EGF-R was performed using the immunoreactive score (IRS). The IRS takes

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introduced both the intensity of staining (graded on a scale
of 0 to 3; 0 = no staining, 1 = faint staining, 2 = moderate
staining, 3 = strong staining) and the percentage of positive
tumor cells (graded on a scale of 0 to 4; 0 = none, 1 = <10%,
2 = 10–50%, 3 = >50–80%, 4 = >80%). The final score
ranges from 0 to 12 and was obtained by multiplying the two
parameters.

p53 Gene Mutation Analysis. Four sets of oligonucleo-
tide primers (5′-GACTTTCACTTGTCC-3′ and 5′-
GACGATCAGTGAGGAATC-3′ for exon 5; 5′-TCCCCAG-
GCTTGATTCC-3′ and 5′-TGCAAACCCCTAAACC-3′
for exon 6; 5′-CAAGGCAGCTGGCCTCATC-3′ and 5′-CA-CACGCAGCCATGTGCA-G3′ for exon 7; and 5′-GATTTC-
CTTACTGCCTTGC-3′ and 5′-GTGAATCTGAGGCATA-
CTGC-3′ for exon 8) were used to amplify exons 5–8 of the
p53 gene. PCR was performed under standard conditions in a
50-μl volume using PCR Master (Boehringer Mannheim) and 1
μM of both 5′ and 3′ oligonucleotides with 40 cycles (94°C for
1 min, 58°C for 1 min, and 72°C for 2 min). PCR products
were purified using shrimp alkaline phosphatase and exonuclease I
(Amersham, Buckinghamshire, United Kingdom). Purified PCR
products were sequenced directly with SequiTHERM Excel II
DNA Sequencing kit (Epicenter, Madison, WI) with the same
primers used for DNA amplification. Oligonucleotides were
end-labeled with [γ-32P]ATP (DuPont-New England Nuclear
Research Products, Boston, MA) using T4 polynucleotide ki-

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Protocol no. (patient no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment</td>
<td>mean (SD)</td>
<td>J8908 (34)</td>
</tr>
<tr>
<td>Age category</td>
<td>≤65 years</td>
<td>56 (11)</td>
</tr>
<tr>
<td></td>
<td>&gt;65 years</td>
<td>24</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>Pathologic response</td>
<td>Progressive disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partial response</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Complete response</td>
<td>13</td>
</tr>
<tr>
<td>Location</td>
<td>Mid esophagus</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Distal esophagus</td>
<td>27</td>
</tr>
<tr>
<td>Survival</td>
<td>Alive</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td>21</td>
</tr>
<tr>
<td>Barrett’s histology</td>
<td>Present</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>21</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Well differentiated</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Moderately differentiated</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>12</td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Squamous cell</td>
<td>12</td>
</tr>
</tbody>
</table>

* t test of proportions or χ² test.

Results

Clinical Characteristics. Clinical characteristics of the
54 patients who underwent tissue marker analysis are presented
in Table 1. Most patients were male and had adenocarcinoma.
As expected given the preponderance of adenocarcinomas, the
majority of cases (85%) occurred in the distal esophagus. Of the
distal adenocarcinomas (n = 39), 21 were distal esophageal, and
18 were gastroesophageal junction lesions. Significant differ-
ences in distribution between protocols were seen for tumor
location and histology; i.e., patients on protocol J9528 had
essentially only distal adenocarcinomas. The age range was
broad (32–75 years), although most patients (74%) were
younger than 65 years old. Barrett’s histology was identified in
43% of biopsy specimens before initiation of treatment. Histological differentiation was mostly moderate (61%).

Of the 54 studied patients, 50 underwent complete surgical resection of tumor. Of the four patients with progressive disease, three progressed during neoadjuvant therapy (two with liver lesions, one with bone lesions), and one was found to have liver metastases intraoperatively at time of planned resection. Of the remaining 50 patients who underwent potentially curative surgical resection, 20 had no remaining viable tumor for a pathological CR rate of 40%. Using intention-to-treat analysis and including all 54 patients, pathological CR rate was 37%.

Five year follow-up survival data are available for all surviving patients. Death was defined as all-cause (not cancer-specific) mortality. The longest survival follow-up was 11.75 years, and the median survival follow-up was 7.3 years. In nonsurvivors, death occurred anywhere from 4 months to 4.25 years after initial diagnosis. Median survival time of dying patients equaled 1.3 years. The overall survival of approximately 43% did not differ significantly between protocols (P = 0.45 by log-rank test for Kaplan-Meier survival curves).

**IEC and p53 Mutation Analysis.** IEC data and p53 mutation analysis results are shown in Table 2. The IEC IRSs are listed in categorical form. In general, EGF-R and bax scores are evenly distributed, whereas the bcl-2 score is skewed toward the low categories. The mutation analysis results for p53 exons 5–8 show that a mutation is present in 29 of 46 tumors (mutation analysis could not be completed in eight patients because the tumor DNA failed to amplify).

**Correlation of Clinical and Molecular Markers with Patient Outcome.** We next used χ² and regression analysis to determine whether any of the clinical covariates or marker data predicted the presence of pathological CR. Only female gender correlated, but the small number of female patients resulted in a wide confidence interval (1.37–41.4). Furthermore, when adjusted for other covariates, the relation did not persist. Stratification of tumor histology by gender provides a likely explanation. Most males had adenocarcinoma (39 versus 6), whereas most females had squamous cell carcinoma (7 versus 2). In our experience, squamous cell histology tends to be more responsive to chemoradiotherapy.

**Survival Analysis.** Survival analysis (Table 3; Figs. 1–3) revealed several significant predictors of better survival outcome. Patients who attained a pathological CR after preoperative chemoradiotherapy did better than those who did not. Presence of p53 mutation (P = 0.051 by log-rank test) and lower EGF-IRS (P = 0.009 by log-rank test) predicted better survival. In addition, the survival curves were suggestive of better survival in patients with well-differentiated tumors and low bcl-2 scores, but neither reached significance. In the univariate analysis with EGF-IRS coded as a continuous variable, each one-unit increase in EGF-IRS resulted in a 14% decrease in survival (hazard ratio of 1.14; 95% confidence interval, 1.04–1.25). When adjusted for all other clinical covariates using multivariate modeling, only the lower EGF-IRS remained a significant predictor of survival (Table 3). When stratified by tumor histology, however, EGF-IRS was predictive only in patients with adenocarcinoma.

Clinical stage was not included as a clinical covariate, although it is historically the most important predictor of survival. As a result, the impact on survival and on marker expression of potential differences in stage distribution between the two protocols was not assessed. Protocol J8908 used barium esophagogram and computed tomography to determine the local extent of tumor. These techniques are unable to determine T and N stage accurately. In contrast, use of endoscopic ultrasound in protocol J9528 enabled a more precise determination of T and N stage.

Because of inherent limitations, staging with esophagogram and computed tomography only may lead to incorrect inclusion of T1 and exclusion of M1a lesions from the treatment group. However, if these staging errors resulted in marked differences in the stage distribution, one would expect to see a difference in survival between the two protocols. Because a difference does not exist, it is unlikely that the stage, and thus the expression of molecular markers, differs between the two groups.

To determine the relative contribution of each marker to survival, we also carried out a multivariate analysis that included p53 mutation and EGF-IRS in the model simultaneously. When adjusted for each other and all other clinical

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**Table 2** Immunohistochemistry and mutation analysis

<table>
<thead>
<tr>
<th>Marker</th>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 Mutation</td>
<td>Present</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>17</td>
</tr>
<tr>
<td>EGF-R IRS (0–12)</td>
<td>≤1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>2–5</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>6–9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>11</td>
</tr>
<tr>
<td>Bax IRS</td>
<td>≤1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2–5</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>6–9</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>8</td>
</tr>
<tr>
<td>Bcl-2 IRS</td>
<td>≤1</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>2–5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6–9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>0</td>
</tr>
</tbody>
</table>

* Eight missing values.

* EGF-R, epidermal growth factor receptor; IRS, immunoreactive score.

* One missing value.

---

**Table 3** Multivariate Cox proportional hazard model: hazard ratio for not surviving, univariate predictors adjusted for clinical covariates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of p53 mutation (8 values missing)</td>
<td>0.453</td>
<td>0.187 to 1.1</td>
<td>0.079</td>
</tr>
<tr>
<td>EGF-R IRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>1</td>
<td>Baseline hazard</td>
<td></td>
</tr>
<tr>
<td>2 to 5</td>
<td>1.29</td>
<td>0.274 to 6.08</td>
<td>0.747</td>
</tr>
<tr>
<td>6 to 9</td>
<td>3.55</td>
<td>0.944 to 13.4</td>
<td>0.061</td>
</tr>
<tr>
<td>&gt;9</td>
<td>8</td>
<td>1.83 to 35</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Age, gender, protocol, Barrett’s metaplasia, tumor location, tumor histology, tumor differentiation.

* CI, confidence interval; EGF-R, epidermal growth factor receptor; IRS, immunoreactive score.
covariates using multivariate modeling; again, only lower EGF-R score remained a significant predictor of better survival (hazard ratio of 1.26; 95% confidence interval, 1.09–1.45).

**DISCUSSION**

This study reviews the clinical outcomes of pathological response and overall survival in a subset of patients with locally advanced esophageal cancer treated with preoperative chemoradiotherapy in two trials conducted in the 1990s at Johns Hopkins and Yale. In addition, a group of molecular markers thought to be involved in tumorigenesis and response to therapy are evaluated for their correlation with surgically determined response to induction therapy and overall 5-year survival.

The clinical outcomes of pathological response and survival in these patients compare favorably with those seen in previous studies both at Johns Hopkins and elsewhere that used induction regimens containing 5-FU and cisplatin (23, 24). In study J8908, 40% of patients had a pathological CR, 58% of patients had 2-year survival, and pathological CR predicted a more favorable outcome. In study J9528, 28% of patients had a
CR, 62% of patients had 2-year survival, and again CR predicted better outcome. Median survival follow-up was 43 months in the earlier trial and 30 months in the later trial.

This study extends the results seen in each of these individual trials by adding longer follow-up using the combined data. After 4 years and 3 months, the survival curve reached a plateau of 43%, with no additional deaths seen at a median of 7.3 years and a maximum follow-up of 11 years and 9 months. Overall survival in this combined group is lower than the 2-year survival in either single study, because a number of deaths occurred after 2 years of follow-up. This suggests that patients remaining alive after approximately 4 years are cured and that at least 4 years of follow-up is required for accurate survival data in this patient population.

Although we were unable to identify any variables that predicted response to therapy, we did confirm that patients who attain a pathological CR do better. Several molecular markers that correlate with survival were also found. Patients whose tumors possess a p53 mutation had better survival. Many studies have evaluated the role of p53 in the prediction of both pathological CR and survival in patients treated with chemoradiotherapy, but the results are mixed. Ribeiro et al. (15) showed by sequence analysis that the presence of a p53 mutation in either squamous or adenocarcinoma correlated with worse survival. A study by Eto et al. (25), however, demonstrated no predictive role of p53 mutation in squamous cell cancers.

Consideration of the role of p53 in tumorigenesis and response to treatment could support any of the above results. Given that p53 mutation is so frequent in human tumors, loss of normal functioning for DNA damage sensing, cell cycle arrest, and apoptosis is thought to be a hallmark of cancer (12, 26). Despite its clear contribution to the molecular pathogenesis of tumors, however, the roles of p53 in the response of tumors to therapy and survival are variable (27).

Although the impact of p53 mutations on survival in esophageal cancer remains unclear, recent work with the p53 codon 72 polymorphism may provide some insight. The Arg variant of this codon, located in exon 4 of the p53 gene, seems to enhance the apoptotic ability of the protein (28). Perhaps the patients in this study sustained this or a similar activating mutation. Other effectors of the intrinsic apoptosis pathway, bax and bcl-2, were also analyzed. Although the effect of neither reached statistical significance, it is intriguing that the absence of the antiapoptotic bcl-2 suggested better survival.

An additional strong predictor of poor outcome was increased EGF-R expression. This transmembrane protein tyrosine kinase growth factor receptor is abnormal or overexpressed in many human tumors of epithelial origin, including head and neck, colorectal, pancreatic, lung, and esophageal cancers (29–32). In these tumors, overexpression is associated with more aggressive behavior and poor prognosis (33).

The findings in this study are consistent with the EGF-R expression of approximately 30–70% in esophageal cancers documented previously. Our data are also in agreement with numerous prior studies, mostly in the squamous cell cancer, that demonstrate that EGF-R expression is associated with poor prognosis (17, 34–40).

Our findings expand on these prior studies by evaluating a greater number of patients, of whom a significant number have adenocarcinoma (41 versus 13). Interestingly, differing from earlier studies involving squamous cell carcinomas, our data suggest that the predictive effect of EGF-R is limited to patients with adenocarcinoma. These findings are intriguing in that they suggest that adenocarcinoma, the histological type that is most rapidly increasing, is also a target for EGF-R directed therapies (18, 19). Recently available drugs include the small molecules ZD1839 (Iressa) and OSI-774 (Tarceva) as well as the monoclonal antibody C225 (Erbitux).

This demonstration of a measurable tumor marker to which a selective therapy is directed creates the possibility of individ-
ual tumor profiling for selection of therapy and prognosis. To this end, we are currently designing an intervention trial to further evaluate (a) if patterns of EGF-R pathway component expression and activation generated with IHC will predict response to therapy and survival outcome in patients with resectable esophageal cancer treated with preoperative chemoradiotherapy and ZD1839 followed by surgery and (b) if the EGF-R inhibitor ZD1839 combined with preoperative chemoradiotherapy followed by postoperative ZD1839 improves outcome in patients with resectable esophageal cancer. Perhaps additional targeted therapy will improve the outcome for patients with this aggressive tumor, the incidence of which is increasing.

REFERENCES


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