Expression of Apoptosis-regulating Proteins and Outcome of Esophageal Cancer Patients Treated by Combined Therapy Modalities

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ABSTRACT
The present study retrospectively examines the correlation between the outcome of patients with locally advanced esophageal squamous cell carcinoma (LAEC) after multimodal treatment (radiochemotherapy ± surgery) and the expression of apoptosis-regulating proteins in pretherapeutic biopsies.

Thirty-eight patients with LAEC who took part in a prospective multicentric trial received radiochemotherapy, optionally followed by surgery. Pretreatment tumor biopsies were immunohistochemically investigated for expression of p53, Bcl-2, Bax (bcl-2-associated X protein), and Bcl-X1, (bcl-2-related X protein).

The overall expression of p53, Bcl-2, Bax, and Bcl-X1 was 52.6, 57.9, 100, and 97.4% respectively. Tumors without p53 expression and tumors with weak Bcl-X1 expression showed response to chemotherapy more frequently (55.6 and 52.6%, respectively) than tumors positive for p53 expression and tumors with strong Bcl-X1 expression (30.0 and 31.6%, respectively); however, these differences did not attain statistical significance. No correlations were found between the expression of Bcl-2 and Bax and the response to chemotherapy. In patients treated by radiochemotherapy and surgery, p53-negative tumors showed a significantly better outcome than p53-positive tumors (mean survival, 31.1 months versus 11.3 months; P = 0.0378). Additionally, a more favorable outcome was observed in tumors positive for Bcl-2 (not significant), whereas no differences in survival were observed in relation to the expression of Bax or Bcl-X1. No differences in survival were observed in patients treated by radiochemotherapy without subsequent resection ther-

 INTRODUCTION
The prognosis of patients with esophageal cancer has only slightly improved during recent years. Even in resectable stages, the results of standard therapy modalities (surgery or radiotherapy) have been poor, with 5-year survival rates of about 20% (1).

The failure of standard therapy has motivated an increasing number of studies that have investigated combined treatment modalities, including chemotherapy and/or radiotherapy and/or surgery, in a variety of schedules. These studies have indicated that preoperative treatment with a combination of chemotherapy and irradiation induces a CR2 in 20–40% of patients. However, only a few trials with combined modality treatment published thus far have shown an advantage over standard therapy, in terms of overall survival and disease-free survival (2, 3). A major problem in this context seems to be that lower rates of cancer-related deaths after combined treatment are counterbalanced by higher rates of treatment-associated mortality (4). It may, therefore, be of great interest to find parameters that may help to identify those patients who will benefit from multimodal treatment modalities and those who will not.

Response or resistance of tumor cells to chemotherapy and/or radiotherapy may be influenced by their propensity to undergo apoptosis (5–7). Among the most important regulators of apoptosis are the tumor suppressor protein p53 and the proteins of the Bcl-2 family. Thus, overexpression of wild-type p53 directly induces growth arrest or apoptosis in response to radiation or exposure to chemotherapeutic drugs (reviewed in Ref. 8). On the other hand, the Bcl-2 family of proteins includes molecules with antiapoptotic effect (e.g., Bcl-2 and Bcl-X1) and molecules with proapoptotic effect (e.g., Bax and Bak). These proteins are highly conserved in four regions, the Bcl-2-homologous domains BH1–BH4, which are required for the formation of homo- and heterodimers (reviewed in Ref. 9). It is accepted that cell susceptibility to apoptosis is determined by competing dimerization of different members of the Bcl-2 family (10, 11).

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2 The abbreviations used are: CR, complete response; LAEC, locally advanced esophageal squamous cell carcinoma; SCC, squamous cell carcinoma; Bax, bcl-2-associated X protein; Bcl-X, bcl-2-related X protein; CT, computed tomography; FLEP, fluorouracil, folinic acid, etoposide, cisplatin.
As a consequence, loss of expression of proteins with proapoptotic action (e.g., p53 and Bax) and/or overexpression of proteins with antiapoptotic action (e.g., Bcl-2 and Bcl-XL) could render tumor cells more resistant to radiochemotherapy.

Recent studies indicate that the immunohistochemical analysis of p53 (12), Bcl-2 (13), Bax (14), and Bcl-X (15) in clinical tumor samples may be predictive for response to radio- and/or chemotherapy and for the prognosis of cancer patients treated by multimodal therapy. However, the influence of apoptosis-regulating molecules on the outcome of esophageal cancer patients treated by radiochemotherapy has not yet been determined. In the present study, therefore, we retrospectively investigated the expression of p53, Bcl-2, Bax, and Bcl-XL and the prognostic significance of this in a series of 38 patients with SCC of the esophagus treated by combined modalities (radiochemotherapy ± surgery).

MATERIALS AND METHODS

Patients. All patients of the present investigation were part of a prospective multicentric treatment study. The results of this study, together with the criteria for patient selection and study design, have been extensively described elsewhere (16).

Patient Selection and Study Design. Patients with LAEC [i.e., category T4N0M0 according to the International Union Against Cancer classification (17) or obstructive tumors >5 cm in length in category T2], with or without regional lymph node metastases, were eligible.

Three courses of chemotherapy were administered within 9 weeks, followed by 4 weeks of radiotherapy with concomitant chemotherapy during the first 7 days. After the administration of chemotherapy and a cumulative dose of 40 Gy of radiotherapy, patients were either treated by an additional 20 Gy of radiotherapy (definitive radiochemotherapy) or by transthoracic esophageal resection. Postoperative treatment was not performed.

Preoperative Chemotherapy and Preoperative Radiochemotherapy. Chemotherapy consisted of folinic acid 300 mg/m², etoposide 100 mg/m², fluorouracil 500 mg/m², and cisplatin 30 mg/m² on days 1–3, every 3 weeks (FLEP).

Combined radiochemotherapy was administered on days 22–28 of the last course of chemotherapy. The esophagus was irradiated using parallel-opposed anterior and posterior fields and photons from a 10–15-MV linear accelerator. A total dose of 40 Gy was given in daily fractions of 2 Gy, 5 times/week. During the first days of irradiation, the following chemotherapy was administered: cisplatin 50 mg/m² on days 2 and 8, and etoposide 100 mg/m² on days 4–6.

Surgery. Resection of the esophagus and the proximal stomach was performed by a combined right thoracal and abdominal approach. Resection included excision of the paraesophageal, para cardial, left gastric, and celiac lymph nodes.

Criteria for Response to Chemotherapy. Response to chemotherapy was evaluated clinically after the third course and included barium esophagogram, esophagoscopy, and CT of the chest and abdomen. Response was categorized as follows: CR—normal barium esophagogram, no visible tumor by esophagoscopy, biopsies free of tumor tissue, and normal CT; partial response—>50% tumor regression as evaluated by CT, and >50% reduction of intraesophageal tumor extension as assessed by barium swallow and esophagoscopy; no change—<50% regression of tumor extension, and no evidence of tumor progression; progressive disease—increasing tumor obstruction indicated by barium swallow or esophagoscopy, and increasing tumor diameter assessed by CT.

Pathological Review of Pretherapeutic Tumor Biopsies. Tumor biopsies that had been endoscopically obtained during pretherapeutic staging procedures were retrieved from the files of pathological institutes associated with the medical centers that took part in this study. Tumor biopsies from a total of 50 patients were collected. Of these 50 biopsies, 12 cases had to be excluded for the following reasons: tumor type other than SCC (n = 8; six adenocarcinomas and two adenosquamous carcinomas); patients lost during follow-up (n = 4). This left 38 cases for further investigation.

Of these 38 patients, 31 were male and 7 were female. The median age was 55 years (range, 42–70). Twenty-nine tumors had been clinically categorized as T4, and nine tumors had been categorized as T3; nine cases were in category N0, and 29 cases were in category N1.

Histological slides of the biopsy specimens were stained with H&E for the determination of tumor type and tumor grade (18). Two tumors were graded as G1, 21 tumors were graded as G2, and 15 tumors were graded as G3.

Immunohistochemistry. Expression of p53, Bcl-2, Bax, and Bcl-XL was investigated in consecutive histological sections prepared from the biopsy specimens. After microwave pretreatment in citrate buffer (pH 6.0) three times for 5 min at 750 W (except Bcl-XΔ), slides were incubated overnight at 4°C with monoclonal antibodies against p53 (clone DO-1; dilution, 1:100; Oncogene Science, Uniondale, NY), Bcl-2 (clone 124; dilution, 1:40; DAKO, Copenhagen Denmark), and with polyclonal antibodies against Bax (dilution-1:1000; PharMingen, Hamburg, Germany), and Bcl-XL (dilution, 1:20; Dianova, Hamburg, Germany). After a second incubation with a biotin-conjugated antimouse antibody (p53 and Bcl-2) or with a biotin-conjugated antirabbit antibody (Bax and Bcl-XL), slides were incubated with an avidin-biotin-peroxidase reagent (Vector Laboratories, Inc., Burlingame, CA). Reaction products were visualized by immersing slides in dianaminobenzidine tetrachloride and finally counterstained with hemalun. Negative controls were performed by replacing the primary antibodies with PBS. Positive staining of normal esophageal squamous epithelium provided an internal positive control for immunostaining.

Using light microscopy, the immunohistochemical expression of p53, Bcl-2, Bax, and Bcl-XL was examined by one observer (M. Sa.) without knowledge of the clinical outcome. The percentage of positive tumor cells was determined semiquantitatively by assessing the whole tumor section, and each sample was assigned to one of the following categories: 0 (0–4%), 1 (5–24%), 2 (25–49%), 3 (50–74%), or 4 (75–100%).

Additionally, the intensity of immunostaining was determined as 0 (negative), 1+ (weak), and 2+ (strong) for antigens with cytoplasmical localization (Bcl-2, Bax, and Bcl-XL). Staining intensity was not determined for p53 (nuclear immunostaining) because no significant differences in staining intensity were observed in p53-positive cases. Intensity of Bcl-2 and Bax immunostaining was judged relative to lymphocytes within the sample, which were designated arbitrarily as 2+, whereas...
Esophageal Epithelium

Normal esophageal squamous epithelium was invariably restricted to the basal cell layer. Nuclear immunoreactivity for p53 was occasionally found in the basal cell layer of normal squamous epithelium. Additionally, expression of Bcl-2 was found in lymphocytes and smooth muscle cells; Bax expression was found in lymphocytes, endothelial cells, and smooth muscle cells; and Bcl-X\textsubscript{L} expression was observed in endothelial cells and smooth muscle cells. Immunoreactivity for p53 was not observed in stromal tissues.

Expression of p53, Bcl-2, Bax, and Bcl-X\textsubscript{L} in Carcinomas and Response to Chemotherapy. The 38 patients who received three complete courses of FLEP chemotherapy were subdivided into a group of responders (CR or partial remission) and a group of nonresponders (no change or progressive disease). Tumors without p53 expression were found more frequently in the group of responders than tumors with strong Bcl-X\textsubscript{L} expression (52.6% versus 30.0%). Tumors with p53 expression were found more frequently in the group of responders than tumors without p53 expression (55.6% versus 30.0%). Tumors with weak Bcl-X\textsubscript{L} expression (dichotomized at the mean immunoreactive score) more frequently showed response to chemotherapy than tumors with strong Bcl-X\textsubscript{L} expression (52.6% versus 31.6%). However, these differences did not attain statistical significance. No correlations were found between Bcl-2 and Bax expression and the response to chemotherapy (Table 2).

Correlation between Expression of p53, Bcl-2, Bax, and Bcl-X\textsubscript{L} in Carcinomas and Survival. The overall survival of all 38 patients has been followed up every 3 months for the first 3 years after the end of treatment; afterward every 6 months. At the end of the follow-up period (May 31, 1998), 8 of the 38 patients (21.1%) were still alive. The follow-up time for all 38 patients has been followed up every 3 months for the first 3 years after the end of treatment; afterward every 6 months. At the end of the follow-up period (May 31, 1998), 8 of the 38 patients (21.1%) were still alive. The follow-up time for the 8 patients at risk ranged from 24–78 months (median, 46 months). Six of the 38 patients were ex-

### Table 1

Expression of p53, Bcl-2, Bax, and Bcl-X\textsubscript{L} in 38 SCCs of the esophagus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Responder*</th>
<th>Nonresponder*</th>
<th>(P^*)</th>
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<tr>
<td>p53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>18</td>
<td>55.6%</td>
<td>44.4%</td>
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</tr>
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<tr>
<td>Bcl-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16</td>
<td>43.8%</td>
<td>56.2%</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>22</td>
<td>40.9%</td>
<td>59.1%</td>
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<tr>
<td>Bax</td>
<td></td>
<td></td>
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<tr>
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<td>46.7%</td>
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<td>&gt;6</td>
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<td>47.4%</td>
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<tr>
<td>&gt;5</td>
<td>19</td>
<td>31.6%</td>
<td>68.4%</td>
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*Responders, complete remission or partial remission.

*Nonresponders, no change or progressive disease.

*Fisher’s exact test.

*NS, not significant.

### Table 2

Response to polychemotherapy (FLEP protocol) in 38 SCCs of the esophagus in relation to expression of p53, Bcl-2, Bax, and Bcl-X\textsubscript{L} in the tumor cells

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Responder*</th>
<th>Nonresponder*</th>
<th>(P^*)</th>
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</thead>
<tbody>
<tr>
<td>p53</td>
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</tr>
<tr>
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<td>55.6%</td>
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<td>20</td>
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<tr>
<td>Bcl-2</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>16</td>
<td>43.8%</td>
<td>56.2%</td>
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<tr>
<td>Positive</td>
<td>22</td>
<td>40.9%</td>
<td>59.1%</td>
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<tr>
<td>Bax</td>
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<td></td>
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<td></td>
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<tr>
<td>≤6</td>
<td>15</td>
<td>46.7%</td>
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<tr>
<td>&gt;6</td>
<td>23</td>
<td>39.1%</td>
<td>60.9%</td>
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<tr>
<td>Bcl-X\textsubscript{L}</td>
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</tbody>
</table>

*Responders, complete remission or partial remission.

*Nonresponders, no change or progressive disease.

*Fisher’s exact test.

*NS, not significant.

### Statistical Analyses

All statistical analyses were performed using the SAS software package (SAS Institute, Inc., Cary, NC). Statistical analysis of the correlation between expression of p53, Bcl-2, Bax, and Bcl-X\textsubscript{L} and response to chemotherapy was performed by means of two-sided Fisher’s exact test. Survival rates were calculated by the Kaplan-Meier method and were compared by the log-rank test. Statistical analyses were performed using the SAS software package (SAS Institute, Inc., Cary, NC). Statistical analysis of the correlation between expression of p53, Bcl-2, Bax, and Bcl-X\textsubscript{L} and response to chemotherapy was performed by means of two-sided Fisher’s exact test.
cluded from the survival analysis because they received incomplete treatment. Of the remaining 32 patients, 15 received definitive radiochemotherapy and 17 were treated by radiochemotherapy and subsequent esophageal resection. Response to chemotherapy was different in the two treatment groups. Thus, 8 of 17 patients (47.1%) treated by radiochemotherapy and surgery were responders to chemotherapy, and 9 patients (52.9%) were nonresponders. In contrast, only 4 of 15 patients (26.7%) treated by definitive radiochemotherapy were responders, and 11 patients (73.3%) were nonresponders.

Therefore, and to exclude any further impact of treatment modality on the survival analysis, the prognostic significance of p53, Bcl-2, Bax, and Bcl-XL was analyzed separately for these two groups. For the survival analyses, expression of the apoptosis-regulating proteins was either dichotomized at the median immunoreactive score (Bax and Bcl-XL) or positive tumors were compared with negative tumors (p53 and Bcl-2) to avoid further subdivision of the patients into groups with only few members.

In the group treated by radiochemotherapy and surgery, mean survival times markedly differed between p53-negative tumors (31.1 months) and p53-positive tumors (11.3 months; Fig. 1). This difference was statistically significant according to the Wilcoxon test ($P=0.0378$), whereas according to the log-rank test it marginally failed to attain statistical significance ($P=0.0771$). Differences in survival between patients with p53-negative tumors and p53-positive tumors were not attributable to differences in tumor stage before the beginning of therapy because patients with p53-positive tumors tended to be in a lower stage than patients with p53-negative tumors. Thus, two of nine patients (22.2%) with p53-negative tumors, but three of eight patients (37.5%) with p53-positive tumors, were in category N0 at the beginning of therapy. Similarly, of the p53-negative cases six tumors (66.7%) were in category T4 and three tumors (33.3%) were in category T3, whereas among p53-positive cases seven tumors (87.5%) were in category T4 and only one tumor (12.5%) was in category T3.

Additionally, longer survival was observed in tumors positive for Bcl-2 than in tumors negative for Bcl-2 (26.7 months versus 13.3 months; not significant), whereas no differences in survival were observed in relation to the expression of Bax or Bcl-XL (Table 3).

No significant differences in survival in relation to the expression of apoptosis-regulating proteins were observed in the group of patients treated by definitive radiochemotherapy (Table 4).

Testing the prognostic impact of apoptosis-regulating proteins in all 38 patients of this study as a whole, patients with p53-negative tumors again showed longer survival (mean survival time, 21.2 months) than patients with p53-positive tumors (14.4 months); however, this difference was not statistically significant. In this analysis, no significant prognostic impact was found testing Bcl-2, Bax, and Bcl-XL (data not shown).

**DISCUSSION**

The present study shows that positive p53 immunostaining in preoperative biopsy specimens predicts poor outcome of patients with LAEC treated with neoadjuvant radiochemotherapy and subsequent esophageal resection. Additionally, p53-positive carcinomas show lower response rates to chemotherapy than p53-negative carcinomas. This result is not unexpected, given that the presence of immunohistochemically detectable p53 protein is frequently due to p53 gene mutations in esophageal SCCs (21, 22). Because the induction of apoptosis due to genotoxic stress (e.g., by radiation or chemotherapeutic agents) in many experimental systems relies on the presence of wild-type p53 (23, 24), it is reasonable to expect tumors with mutated p53 to be poorly sensitive to chemoradiation (8). In the context of clinical studies, the correlation between p53 and multimodal therapy has been most extensively studied in breast cancer.

Thus, Bergh et al. (25) found a significant correlation between deteriorated outcome of breast cancer patients and p53 mutation, as determined by direct sequencing. In contrast, Elledge et al. (26) and Makris et al. (27) found no such correlation using p53 immunohistochemistry. In ovarian cancer, tumors with immunohistochemically detectable p53 protein showed poor response to chemotherapy (12), whereas in SCCs of the head and neck the...
presence of p53 mutation was correlated with locoregional treatment failure, but not with overall survival (28). Conflicting results for the prognostic significance of p53 in carcinomas treated by multimodal therapy may be due to differences inherent in diverse tumor types. In this regard, it may be of importance that the correlation between p53 overexpression as determined by immunohistochemistry and the presence of p53 mutations evidently varies from tumor type to tumor type. Although in non-Hodgkin’s lymphomas p53 protein overexpression only poorly correlates with the presence of p53 mutations, there is a reasonable correlation in gastrointestinal carcinomas and breast carcinomas (reviewed in Ref. 29). The potential influence of p53 may also be substantially influenced by the type of therapy that has been applied. This suggestion is supported by our finding that, in contrast to the influence of p53 in patients who received radiochemotherapy and surgery, p53 did not influence the survival of patients treated by definitive radiochemotherapy. This result may be explained by the existence of substantial differences in outcome between the two groups. Thus, as outlined in “Results,” response to chemotherapy was less effective among tumors that had been subsequently treated by definitive radiochemotherapy than among tumors treated by radiochemotherapy and surgery. This suggests a bias toward unfavorable outcome for the former group of patients because chemotherapy had been equal for all patients under investigation. Consequently, the mean survival time of the patients with definitive radiochemotherapy was only 14.9 months compared with 24.5 months in patients treated by radiochemotherapy and subsequent esophageal resection. We, therefore, assume that the unusually poor outcome of the group treated with definitive radiochemotherapy may have masked the prognostic impact of p53.

On the other hand, one has to take into account that p53 is not the only protein that influences the radio- and chemosensitivity of tumor cells. In this context, the proteins of the Bcl-2 family may play an important role. The analysis of the influence of these proteins is even more complicated than the analysis of the influence of p53, because this group contains molecules with proapoptotic action (e.g., Bax) and molecules with antiapoptotic action (e.g., Bcl-2 and Bcl-XL). Experimental data indicate that the relative ratio between proapoptotic and antiapoptotic molecules (e.g., Bcl-2 and Bax) actually determines the susceptibility of cells for apoptosis (10, 30). However, the quantity of functionally active protein is difficult to determine by means of immunohistochemistry, even if a score system taking account of the proportion and staining intensity of immunoreactive cells is applied. Therefore, we did not correlate combinations of Bcl-2 type proteins with the patients’ outcome. However, the impact of Bcl-2 type proteins seems to be less important than that of p53 for esophageal cancer patients, as we did not find any significant correlations, either with response to chemotherapy or with overall survival. Nevertheless, we observed that tumors with low Bcl-XL expression more frequently showed response to chemotherapy than tumors with strong Bcl-XL expression. This seems logical because a loss of the antiapoptotic Bcl-XL protein is likely to render tumor cells more sensitive to radiochemotherapy. On the other hand, we found an unexpected, though not significant, association between relatively favorable survival and expression of the antiapoptotic protein Bcl-2. In looking for an explanation of this finding one has to take into account the possibility of complex interactions between the different members of the Bcl-2 family. Thus, in acute lymphoblastic leukemia cell lines with wild-type p53, it has been shown that apoptosis after irradiation is dependent on down-regulation of Bcl-2 and up-regulation of Bax. High-level expression of Bcl-XL, on the other hand, predominantly occurred in the absence of functionally active p53 and was associated with resistance to irradiation-induced apoptosis (31). The interactions of Bcl-2 family proteins in esophageal carcinoma cells have not yet been determined. However, in previous studies on the expression of Bcl-2, Bax, and Bcl-XL in 172 surgically treated SCCs of the esophagus, we were able to show that expression of Bax and Bcl-2 is correlated inversely (32). Additionally, we found an inverse correlation between the expression of Bcl-2 and Bcl-XL (33), giving rise to the suggestion that these two molecules with antiapoptotic action may be regulated in a reciprocal manner (15, 34).

Our observation that p53 may be of prognostic influence in esophageal cancer patients treated by combined therapy modalities may be of great clinical interest. Thus, combined modality treatment probably improves the prospect for cure.
of esophageal cancer patients, even in locally advanced stages of disease, in comparison with standard therapy modalities (surgery and radiotherapy). On the other hand, multimodal therapy causes increased therapy-associated morbidity and mortality (4). Tumor biological factors that predict response to radio- and/or chemotherapy could identify patients most likely to benefit from treatment while avoiding toxic effects in those patients who are unlikely to respond. Of course, our data are only preliminary because we were unable to perform multivariate survival analysis due to the small number of patients in our study. However, the present results provides encouragement for further studies on this topic. Thus, if the predictive value of p53 is confirmed by future trials on a larger number of patients, a simple immunohistochemical investigation using endoscopically obtained tumor samples may provide information to the oncologist for the selection of patients for intensive combined therapy modalities with curative intention or for palliative therapy.

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REFERENCES


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