Pathologic Assessment of Tumor Regression after Preoperative Chemoradiotherapy of Esophageal Carcinoma

Clinicopathologic Correlations

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Background. The benefits of preoperative chemotherapy and radiation for esophageal carcinoma are under investigation. A pilot study was undertaken to determine if pathologic assessment of tumor regression correlated with disease free survival.

Methods. Ninety-three resected specimens from patients treated with cis-dichloro-diamino cisplatin and irradiation before surgery were examined on semiserial sections. Patients selected for surgery were all Status 1 according to the World Health Organization (WHO) classification. Histologic typing was based on the WHO classification. Tumor regression grade (TRG) was quantitated in five grades: TRG 1 (complete regression) showed absence of residual cancer and fibrosis extending through the different layers of the esophageal wall; TRG 2 was characterized by the presence of rare residual cancer cells scattered through the fibrosis; TRG 3 was characterized by an increase in the number of residual cancer cells, but fibrosis still predominated; TRG 4 showed residual cancer outgrowing fibrosis; and TRG 5 was characterized by absence of regressive changes.

Survival curves were estimated according to the Kaplan-Meier method. A quantification of the relationship between treatment failure and confounding variables (age, tumor location, tumor size, esophageal wall involvement by residual cancer and/or regressive changes, histology, treatment, adequacy of surgery, pathologic lymph node status, and tumor regression grade) was done using Cox's proportional hazards model.

Results. Forty-two percent of specimens were TRG 1-2; 20%, TRG 3; and 33%, TRG 4-5. Univariate analysis found that tumor size, pathologic lymph node status, tumor regression grade, and esophageal wall involvement were highly correlated with disease free survival (P < 0.05). After multivariate analysis, only tumor regression (i.e., TRG 1-3 versus TRG 4-5) remained a significant (P < 0.001) predictor of disease free survival.

Conclusions. This study highlights the importance of tumor regression in the survival of patients with esophageal carcinoma treated with preoperative chemoradiotherapy. These findings suggest that tumor regression grade should be considered when evaluating therapeutic results. Cancer 1994; 73:2680-6.

Key words: esophageal carcinoma, preoperative chemoradiotherapy, tumor regression grade, survival, prognostic factors, multivariate analysis.

The benefits of preoperative chemotherapy and radiation for esophageal carcinoma are under investigation.
Those benefits remain to be assessed in prospective randomized trials comparing surgery alone with combined-modality therapy. Several reports on single-arm uncontrolled trials have been published.\textsuperscript{1-3} We present here a detailed pathologic study of the changes of esophageal carcinoma after preoperative chemoradiotherapy.

The current study was performed as part of a pilot study to assess the feasibility and tolerance of a new preoperative regimen and its consequences on the primary tumor in a resected specimen.\textsuperscript{4,5} The aim of the current study was to investigate the features of regression of esophageal cancer after preoperative chemoradiotherapy to assess quantitatively this regression and to determine whether this assessment would correlate with the patient's survival.

**Patients and Methods**

Between October 1985 and March 1989, 93 resected specimens of esophageal carcinoma from patients who had received preoperative chemoradiotherapy were examined in the Department of Pathology of the Centre François Baclesse and the Centre Hospitalo-Universitaire, Caen, France. Eighty-eight of the patients were men and five were women. The age range was 37–74 years (mean age, 58 years).

The tumor was located in the upper third in 14% of the patients, in the middle third in 58%, and in the lower third in 28%. The initial performance status of all patients selected for this treatment was 1 according to the World Health Organization classification.\textsuperscript{6}

The treatment protocol of the current pilot study included radiotherapy delivered in two courses of 18.5 Gy for 5 days (3.7 Gy × 5), with a total dose 37 Gy, separated by a rest period of 15 days. Radiation used were photon beams of 10–25 MV with portals 5 cm above and below the tumor edges and 2 cm laterally by either four oblique fields or one posterior and two oblique posterior fields. Cis-dichloro-diamino-cisplatin (80–100 mg/m\textsuperscript{2}) was given in a single dose 1–5 days before each course of radiation. Surgery was performed 2–3 weeks after the second radiation course. Seventy-two patients (77%) were given the complete treatment as specified in the protocol. The remaining 21 patients (23%) received incomplete treatment: 13 patients were given one cycle of chemotherapy, 3 patients received a total dose of chemotherapy lower than 80 mg/m\textsuperscript{2}, and 5 patients received a total dose of radiation lower than 37 Gy.

The initial clinical assessment of the esophageal tumor was appraised according to the TNM classification of the International Union Against Cancer for esophageal carcinoma.\textsuperscript{7} According to this classification, 32% of the cases were T1; 52%, T2; and 16%, T3. Initial tumor size was less than 5 cm of the esophageal length in 32 patients (37% of the cases) and more than 5 cm of the esophageal length in 55 patients (63% of the cases). The initial tumor size could not be determined in six patients. The regional lymph node status reported was a postsurgical histopathologic classification (pN): 58% of the cases were pN\textsuperscript{−} and 42% of the cases were pN\textsuperscript{+}.

Histology was performed according to the World Health Organization classification of esophageal carcinoma.\textsuperscript{8} The histologic types were squamous cell carcinoma in 84% of patients, undifferentiated carcinoma in 8%, adenosquamous carcinoma in 3%, and unspecified in 5%.

**Pathologic Examination**

Pathologic examination of all surgical specimens was performed as described previously.\textsuperscript{9} After gross examination and dye test, semiserial sectioning of the entire specimen was performed and sections were numbered on a one-to-one scale diagram showing all the gross lesions. All the sections were examined microscopically, and the lesions identified were recorded on the diagram. Cancer resection was considered adequate when there was no tumor involvement of all surgical margins (upper and lower margins as well as the adventitia). When one surgical margin or more were involved, surgery was considered inadequate. In situ carcinoma, when present, was regarded as distant from the primary tumor only when separated from the latter by at least 0.5 cm of uninvolved tissue.\textsuperscript{10} Lymph nodes were dissected separately, except for periesophageal nodes, the latter being included in the esophageal sections. The lymph nodes identified were the periesophageal nodes, lesser omentum and greater omentum nodes, and those of the mediastinum or other sites, which may have been dissected directly by the surgeon.

**Gross examination.** Specimens were divided into three macroscopic groups. In the first group, there was obvious residual tumor with ulcerating, fungating, or infiltrative features. In the second group, apparent tumor regression had occurred and a scar was found instead. The third group included doubtful cases.

**Histology.** Cases were separated into two histologic groups. In the first group, the tumor showed no regressive changes. The second group included all those cases in which regressive changes were noted. Regressive changes included the following:

1. Cytologically, cancer cells showed cytoplasmic vacuolization and/or eosinophilia, nuclear pyknosis, and necrosis (Fig. 1).
still predominated. Grade 4 showed residual cancer outgrowing fibrosis. Grade 5 was characterized by the absence of regressive changes.

The same grading system was used for assessing tumor regression in metastatic lymph nodes. In the latter, "complete regression" corresponded to the presence of keratin plugs or neoplastic squamous ghost cells scattered in dense fibrosis. The above definition enabled us to confirm the nature of regressed metastatic lymph node.

**Esophageal wall involvement.** Assessment of esophageal wall involvement by residual cancer and/or regressive changes was performed. Esophageal specimens were divided into two groups. In the first group, residual cancer and/or regressive changes extended only in the mucosa and submucosa. In the second group, residual cancer and/or regressive changes ex-
tended within the muscularis propria or beyond, to the adventitia.

**Associated Carcinomas**

Of the 93 patients, 15 (16%) presented an associated carcinoma, which was located in the upper digestive tract for 10 patients. Of these 15 patients, 8 were excluded from the prognostic study on the following grounds: 2 patients had been treated previously for another cancer and 6 patients had associated neoplasm that was diagnosed synchronously (i.e., within 12 months of the esophageal carcinoma).

**Statistical Analysis**

Comparison between proportions was made using the Fisher's exact test. The time at risk for progression or relapse (disease free survival) was computed from the date of first examination to the date of diagnosis of treatment failure, the date of death, the date of last known status, or April 1, 1992, whichever came first. The contribution to the risk of treatment failure of age, tumor location, histologic typing, tumor size, esophageal wall involvement, lymph node metastasis (pN), type of treatment (i.e., complete or incomplete), surgical excision (adequate or inadequate) and grade of tumor regression was estimated by two methods. In the first, univariate analysis selected those parameters that correlated significantly with disease free survival. Survival curves were estimated by the Kaplan–Meier method. The 95% confidence limits (CL) were obtained by the method of Greenwood. Comparisons were made using the log-rank test. In the second method, a quantification of the relationship between the time of occurrence of treatment failure and confounding variables, such as age, tumor location, tumor size, pN, histology, treatment, surgical excision, grade of tumor regression, and esophageal wall involvement was calculated using Cox's proportional hazards model. The Statxact and Stata statistical packages were used.

**Results**

**Pathologic Findings**

The results of tumor regression grading for the 93 patients are shown in Table 1. Tumor regression grades
Table 1. Esophageal Carcinoma: Tumor Regression Grade—93 Patients

<table>
<thead>
<tr>
<th>Grade</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

1 and 2 were seen in 42% of the resected specimens. Correlations between gross findings and tumor regression grade showed that, in some cases, gross examination did not give accurate assessment of the presence of residual cancer. The assessment of esophageal wall involvement by residual cancer and/or regressive changes showed that they remained in the mucosa and submucosa in 13 specimens (14% of the cases). In 77 specimens (86% of the cases), residual cancer and/or regressive changes extended within the muscularis propria or, beyond, to the adventitia. There was a correlation between initial tumor size and esophageal wall involvement by residual cancer and/or regressive changes ($P < 0.001$).

An analysis of relation between tumor regression grade and initial tumor size showed that tumor regression grade decreased with an increase in tumor size ($P = 0.017$) and that tumor regression grade decreased when lymph node metastases were present ($P = 0.009$). These two relations remained significant when made with stratification on pN ($P = 0.007$) or tumor size ($P = 0.012$).

A more detailed analysis of 36 cases with lymph node metastases (pN+) and known tumor regression grade suggested that regression of lymph node metastases paralleled tumor regression ($P < 0.0002$).

Examination of the whole esophageal mucosa showed varying degrees of esophagitis, and distant in situ carcinoma was seen in two specimens (2%).

Surgical excision was considered adequate in 67 cases (72%) and inadequate in 26 cases (28%).

**Survival**

The overall survival rate was 31% (95% CL, 21–41%) at 3 years and 25% (95% CL, 15–35%) at 4 years. Disease free survival was 34% (95% CL, 23–44%) at 3 years and 27% (95% CL, 17–38%) at 4 years. Fifty-nine patients died, of whom 48 died of their cancer, 5 of other causes, and 6 of unknown causes. Fifty-four of the 55 patients who presented with recurrences died.

Table 2. Prognostic Study: Univariate Analysis of Disease Free Survival—85 Eligible Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 60$ yr</td>
<td>47</td>
<td>0.07</td>
</tr>
<tr>
<td>$\geq 60$ yr</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper third</td>
<td>10</td>
<td>0.33</td>
</tr>
<tr>
<td>Middle third</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Lower third</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 5$ cm</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>$\geq 5$ cm</td>
<td>51</td>
<td>0.0007</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>3</td>
<td>0.71</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>67</td>
<td>0.84</td>
</tr>
<tr>
<td>Incomplete</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Surgical excision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>61</td>
<td>0.05</td>
</tr>
<tr>
<td>Inadequate</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>pN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-$</td>
<td>50</td>
<td>0.014</td>
</tr>
<tr>
<td>$+$</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Tumor regression grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Esophageal wall involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosa and submucosa</td>
<td>12</td>
<td>0.02</td>
</tr>
<tr>
<td>Muscularis propria or beyond</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The average interval between the first postoperative recurrence and death was 59 days (0–409 days). Two patients died postoperatively.

**Prognostic Study**

In the analysis of prognostic factors, disease free survival was used as the end point. Univariate analysis of disease free survival was performed with the parameters of age, tumor location, initial tumor size, esophageal wall involvement, pathologic lymph node status (pN), histologic typing, treatment (complete or incomplete), surgical excision (adequate or inadequate), and tumor regression grade. The results are shown in Table 2.
Tumor size and pN, tumor regression grade (tumor regression grade 1–2 and 3 versus tumor regression grade 4 and 5) and esophageal wall involvement correlated highly with disease free survival, whereas adequacy of excision and age were borderline significant. Disease free survival according to tumor regression is shown in Figure 6.

The above parameters that correlated with disease free survival in univariate analysis were included in the multivariate analysis. Using Cox's regression analysis, tumor regression grade correlated highly (relative risk, 2.87; \( P < 0.001 \)) with disease free survival, whereas tumor size (relative risk, 1.93; \( P = 0.07 \)) and age (relative risk, 1.60; \( P = 0.11 \)) were borderline significant.

**Discussion**

We have described the gross and histologic features of tumor regression seen after preoperative chemoradiotherapy in 93 cases of esophageal carcinoma. This regression was assessed by comparing the proportion of residual carcinoma to scarring, and our results were found to correlate with patients' survival. The preliminary assessment was performed using a tumor regression grading of five grades. Multivariate analysis showed two groups of tumor regression grade that were prognostically relevant: Grades 1, 2, and 3 versus Grades 4 and 5.

We believed that our method of assessment was simple and reproducible. We initially used semiserial sections, but this was time consuming in terms of the preparation and study of slides.\(^9\) We found with experience that the procedure could be simplified to facilitate wider application. In the presence of tumor regression corresponding to scarring on gross examination, the esophagectomy specimen could be examined in toto in five to eight longitudinal sections,\(^7\) or the histologic sampling used to assess tumor regression could be limited to sections of the whole scar lesion.

Tumor regression of squamous cell carcinoma of the esophagus after radiotherapy was studied by Akakura et al. in 117 patients.\(^18\) Their gross findings appeared to be identical to ours. However, the microscopic criteria that they used for evaluation of response to radiotherapy were essentially cytologic and did not include an exact quantitative approach. We found that their cytologic criteria correlated with our assessment of tumor regression but were not totally reproducible in our material, possibly due to the difference in preoperative treatment.

Several clinical studies on preoperative chemoradiotherapy of carcinoma of the esophagus\(^2,19-22\) have assessed survival as a function of the presence or absence of residual cancer in the surgical specimen. However, none of those provided a detailed pathologic study of regression of tumor and lymph node metastases.

A quantitative study comparable to ours was conducted by Braun et al.\(^23\) on tumor regression after chemoradiotherapy of head and neck tumors. They reported a statistically significant correlation between grade of tumor regression and survival. Sulfaro et al.\(^24\) presented a study of regression of carcinoma of the head and neck after intraarterial chemotherapy. The cytologic and stromal damage of the carcinoma after treatment were comparable to those we described after chemoradiotherapy. These authors used the TNM classification\(^25\) to assess the different types of regression. We found that the gross diagnosis was not always sufficiently reliable for us to use this classification in our study.

A noteworthy feature in our series was the low incidence of in situ carcinomas distant to the invasive carcinoma. These were found in 14% of cases in a previous study of esophagectomy specimens from patients who had not received preoperative treatment.\(^10\) In the current study, this percentage was only 2%, suggesting a possible regression of in situ carcinoma secondary to the preoperative treatment.

It was not within the scope of the current pilot study to evaluate the benefits of preoperative chemoradiotherapy regarding survival of patients with esophageal carcinoma, because this could only be done in a comparative therapeutic trial. Such a trial is actually in progress (European Organization for Research and Treatment of Cancer protocol No. 40881). However, our results indicate that there is a correlation between response to preoperative treatment and disease free sur-
vival and that this should be considered along with other known prognostic indicators in the evaluation of therapeutic results in esophageal cancer.

Addendum

Since the present study first was submitted, Darnton et al. have shown that in 12 patients with squamous cell carcinoma of the esophagus, quantitative study of tumor regression after chemotherapy, particularly in relation to the proportion of tumor to stroma, is a simple and accurate technique to evaluate objectively the effect of chemotherapy on squamous cell carcinoma of the esophagus.

References