Carcinoembryonic Antigen Measurements in the Management of Esophageal Cancer: An Indicator of Subclinical Recurrence

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BACKGROUND: Detection of subclinical recurrence after surgical resection of esophageal cancer would allow earlier treatment of recurrent disease and potentially offer a better outcome for rescue therapy.

METHODS: The utility of serum carcinoembryonic antigen (CEA) assay was evaluated in the management of patients with esophageal cancer.

RESULTS: Serum carcinoembryonic antigen was measured preoperatively in 74 patients. Elevation of the CEA level (>5 ng/mL) was present in 14 patients (19%). There was no relationship between preoperative CEA elevation and the stage of the tumor or the patients' survival. Eighty-three patients had CEA assay at regular follow-up intervals after resection. Objective evidence of recurrent disease was determined at similar intervals by chest radiography and abdominal and thoracic computed tomography scans. During follow-up, 53 of 83 patients developed recurrence. Postoperative elevation of CEA levels occurred in 32 patients, resulting in a sensitivity of 55% for detecting recurrent disease. Twenty-nine of the 32 patients who developed CEA elevation had objective evidence of metastatic disease. In 13 patients, the rise in CEA levels predated objective evidence of recurrence by a median of 4 months (range 3 to 35), and in 16 patients, it occurred concomitantly. The specificity with which an elevated postoperative CEA level indicated recurrence was high, 90%, with a positive predictive value of 91%.

CONCLUSIONS: Postoperative CEA elevation is highly predictive of recurrent disease. In 16% of patients, elevation of CEA was the earliest objective sign of recurrence; such elevation should prompt consideration of adjuvant therapy. Am J Surg. 1995;170:597-601.

Management of patients with esophageal cancer poses a continuing challenge to surgeons. Major predictors of survival are the stage of the tumor at the time of presentation and the extent of the surgical resection performed. Little emphasis has been given to the value of detection of recurrent disease, which has been reliant on crude methods such as development of dysphagia or systemic metastases, both of which herald the patient's rapid decline. The tumor marker, carcinoembryonic antigen (CEA), is often elevated in patients with tumors of the gastrointestinal tract. Elevated CEA levels have been used as a marker for recurrent colorectal cancer, and as a prognostic marker for second-look surgery.

In this setting, the value of serum CEA in the management of patients with esophageal cancer was assessed. The purpose was to answer the following questions: (1) Does an elevated preoperative CEA level correlate with the tumor stage? (2) What is the prognostic influence of an elevated preoperative CEA? (3) And is a postoperative serial estimation of CEA of benefit in the detection of recurrence?

PATIENTS AND METHODS

One hundred patients undergoing surgical resection of esophageal cancer had serum CEA levels measured (Figure 1). There were 83 men and 17 women, with a median age 64 years (range 36 to 82). Eighty patients had adenocarcinoma (48 with Barrett's esophagus); 18 squamous cell carcinoma; and 2 adenosquamous carcinoma.

Carcinoembryonic antigen levels were measured before surgery in 74 of the patients. Seventeen of these patients did not have postoperative CEA measurement. Eighty-three patients had serial CEA levels drawn at 3-month intervals after surgical therapy, including 57 patients whose CEA levels had been measured before surgery.

CEA Measurement

Serum CEA levels were determined by the CEA-Roche enzyme immunoassay (Roche, Montclair, New Jersey), which uses a highly specific monoclonal mouse antibody to CEA. In this process, the patient's sample and CEA standards are incubated with beads coated with monoclonal mouse anti-CEA and with a second monoclonal mouse anti-CEA conjugated to horseradish peroxidase. After the beads are washed, they are incubated with an enzyme-substrate solution to develop a color that is a direct measure of bound anti-CEA peroxidase. The intensity of the color formed is read at 492 nm, and is proportional to the concentration of CEA in the standards. A standard curve is then plotted and the patient's sample value...
read from the curve. In normal subjects, values of 5 ng/mL roughly correspond to the 2.5th percentile in nonsmokers and the 5th percentile in smokers. Levels >5 ng/mL were considered to be elevated for the purpose of this study.

Operative Procedure and Staging
Patients considered to have early tumors on preoperative computed tomography (CT) and endoscopic ultrasound underwent en-bloc esophagectomy if they were physiologically fit, that is, <75 years of age with a left ventricular ejection fraction of >40% and a forced expiratory volume >1.25 L. Patients who were unfit for the en-bloc procedure or who had late-stage disease underwent esophagectomy by the transhiatal route. Tumors were staged pathologically according to the WNM staging system. Tumors were staged early when there was no wall penetration (limited by the muscularis mucosa, W0; beyond the muscularis mucosa but not transmucosal, W1) and <5 metastatic nodes (no involved nodes, N0; <5 involved nodes, N1); intermediate, when either transmural wall penetration (W2) or >4 lymph node metastases (N2) were present; and late, when there was transmural wall penetration with >4 lymph node metastases (W2, N2).

Follow-Up
Hospital survivors were followed up with laboratory studies, a chest roentgenogram, and a thoracic and abdominal CT scan at 3-month intervals for the first 3 years, then every 6 months. Objective evidence of recurrence was determined in the presence of biopsy positive findings on endoscopy, enlarging abdominal or thoracic nodes on sequential CT scans, or unequivocal systemic metastases on roentgenogram or CT.

Statistical Analysis
Comparison of proportions was performed using the Fisher's exact test or the chi-square test. Differences in nonparametric data between multiple groups were identified by the Kruskal Wallis test, and comparisons between individual groups were made using the Mann-Whitney U-test. Life tables were calculated using the Kaplan-Meier method, and differences between survival curves were estimated using the log-rank test. Statistical significance was taken at the 5% level (P ≤ 0.05).

RESULTS
Preoperative CEA Measurements
Fourteen of the 74 patients (19%) who had preoperative CEA levels determined had elevated levels of >5 ng/mL. Twelve of 59 patients (20%) with adenocarcinoma had elevated CEA levels, compared to 1 of 13 patients (8%) with squamous cell carcinoma and 1 of 2 patients with adenosquamous tumors (P = 0.29). The prevalence of an elevated CEA level did not correlate with the depth of esophageal wall penetration, the number of lymph node metastases, or the stage of the tumor (Table I). Patients with an elevated CEA level fared no different in their survival compared to patients with normal CEA levels (Figure 2).

Postoperative CEA Measurements
The median follow-up of the 83 patients in the postoperative study was 21 months (range 4 to 81). Fifty-three patients (64%) developed objective evidence of recurrent carcinoma during follow-up, and 30 remained disease free. Thirty-two of 83 patients developed elevated serum CEA levels in their postoperative course. Twenty-nine of these patients went on to develop recurrence, while 3 have remained disease free (significant difference 29/53 versus 3/30, P < 0.01; Fisher's exact test). The sensitivity of an elevated serum CEA level in predicting recurrence was 55%, with a high specificity of 90%, and positive predictive value of 91%. There was significant discordance between the high frequency of false-negative tests and the low frequency of false-positive tests (chi-square = 14.8, P < 0.01). The difference is explainable, since serum CEA levels would not be expected to rise in the presence of recurrence of a tumor that did not express CEA. An elevated

Table I
Preoperative Carcinoembryonic Antigen (CEA) Levels According to Tumor Depth, Nodal Metastasis, and Stage of Disease in Patients With Esophageal Cancer

<table>
<thead>
<tr>
<th>Wall Penetration</th>
<th>No. of CEA &gt;5 ng/mL</th>
<th>Serum CEA</th>
<th>Node Stage</th>
<th>No. of CEA &gt;5 ng/mL</th>
<th>Serum CEA</th>
<th>Stage</th>
<th>No. of CEA &gt;5 ng/mL</th>
<th>Serum CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>W0</td>
<td>2/12 (17%)</td>
<td>2.7</td>
<td>N0</td>
<td>2/22 (9%)</td>
<td>1.6</td>
<td>Early</td>
<td>2/18 (11%)</td>
<td>1.3</td>
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<td></td>
<td>(0.5–7.4)</td>
<td></td>
<td></td>
<td></td>
<td>(0.5–7.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W1</td>
<td>0/9 (0%)</td>
<td>1.0</td>
<td>N1</td>
<td>7/23 (30.4%)</td>
<td>1.8</td>
<td>Intermediate</td>
<td>6/27 (22%)</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>(0.7–3.2)</td>
<td></td>
<td></td>
<td></td>
<td>(0.5–80.1)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>W2</td>
<td>12/52 (23%)</td>
<td>2.1</td>
<td>N2</td>
<td>5/29 (17.2%)</td>
<td>2.4</td>
<td>Late</td>
<td>6/28 (21.4%)</td>
<td>2.4</td>
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<tr>
<td></td>
<td>(0.5–80.1)</td>
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<td>(0.7–80.1)</td>
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Serum CEA values are expressed as median (ng/mL) with ranges. There were no significant associations among variables.

No. of CEA = ratio of numbers of patients with elevated CEA levels to number with normal levels.
CEA level indicated a 1.93 relative risk of developing recurrence compared to the risk for those without an elevated CEA level (confidence interval 1.6 to 2.2).

The chronologic relationship between CEA elevation and disease recurrence indicated that 13 patients had CEA elevation prior to the development of any other objective evidence of recurrent tumor (Table II). In this subgroup of patients, the serum CEA measurement provided a "treatment window" of on average 4 months (range 3 to 35). The remaining 16 patients had an elevated serum CEA level recorded synchronously with other objective indicators of recurrent disease. It follows that in 16% of patients (13/83), postoperative elevation of CEA >5 ng/mL was the earliest sign of disease recurrence.

Of the 14 patients whose CEA level was elevated before surgery, postoperative CEA levels were available in 12 patients, while 2 patients died perioperatively. Seven of the 12 patients had their CEA levels return to normal, while in 5, the CEA was still elevated at the first postoperative visit. All of these latter patients developed recurrent disease in 2 to 18 months (median 4). Of the 7 patients whose CEA levels returned to normal, 3 have retained low levels and are free of recurrence at 24, 37, and 45 months. The remaining 4 patients demonstrated a subsequent elevation of their CEA levels, and all went on to develop recurrent disease 8 to 18 months after surgery. It follows that none of the patients with elevated preoperative CEA has developed recurrent disease in the absence of an associated elevation in serum CEA.

**Surgical Rescue Therapy**

Of 53 patients who developed recurrent disease in the postoperative period, 6 were considered suitable for a second surgical operation. In these patients, reoperation was judged appropriate on the basis of findings of objective signs of localized recurrent disease.

Three patients have had a successful outcome from the second procedure: the first had a transhiatal resection, but developed an isolated solitary splenic metastasis on CT after 18 months. A splenectomy was performed and was the sole site of recurrence at laparotomy. The patient remains well and disease free 2 years later. The second patient underwent en-bloc esophagectomy, but 20 months later a solitary hepatic metastasis in the right lobe of the liver was identified on CT. A hemipatectomy was performed, confirming the isolated metastasis, and the patient remains disease free after a further 24 months. The final patient developed an obstruction of his esophagus in the neck from recurrent lymph node disease 39 months after an en-bloc esophagectomy with colonic interposition. The patient underwent a second operation, in which the recurrent nodal disease was resected along with a limited resection of the original esophagocolic anastomosis.

The residual colon graft was mobilized and repositioned sub-externally, restoring gastrointestinal continuity by the refashioning of a new esophagocolic anastomosis. The patient remained well and disease free for a further 26 months, before ultimately dying of pulmonary metastasis 29 months after the latter procedure.

Of the remaining 3 patients, 2 underwent limited pulmonary resections, and 1 underwent a resection of recurrent thoracic nodal disease. Each of these patients developed progressive recurrent disease shortly after surgery.

**Figure 2.** Survival in patients with esophageal cancer according to preoperative carcinoembryonic antigen (CEA) status: negative = CEA -; positive = CEA +. There was no difference in the survival of the two groups of patients: log rank, chi-square = 0.15, P = 0.69. Key box indicates the number of patients present at the beginning of the study and at 12-month intervals.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Time of CEA</th>
<th>Time of Objective</th>
<th>Time of Death</th>
<th>Interval Between Eleva</th>
<th>Eleva and Recurrence</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Elevation</td>
<td>Signs of Recurrence</td>
<td>Death</td>
<td>Eleva and Recurrence</td>
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<tr>
<td>1</td>
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<td>21'</td>
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<tr>
<td>2</td>
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<td>29</td>
<td>31</td>
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<td>4</td>
<td>39</td>
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<td>35</td>
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*All time values are in months.

*Median = 4 months.

*Indicates patients alive at last follow-up.
COMMENTS

Carcinoembryonic antigen was first described by Gold and Freedman in 1965.1 It is an oncofetal antigen that is normally present on the cell surface of embryonic tissues. CEA is often expressed by gastrointestinal malignancies, most notably adenocarcinomas of the sigmoid colon. Since serum CEA levels are also elevated in certain benign conditions such as hepatobiliary disease, pancreatitis, and inflammatory bowel disease, and in heavy smokers, the use of CEA as a screening tool has been discouraged.2 Its most common use has been in the management of patients with established colorectal adenocarcinomas. Preoperative levels have been shown to correlate with pathologic staging of disease and with survival after surgery, but independently it has not been identified as a prognostic factor.3 Elevation in postoperative serum CEA values are highly predictive of recurrent disease, and are sufficiently specific to warrant second-look surgery, even in the absence of other clinical indicators of recurrence.4 With this in mind, the present study was undertaken to evaluate the utility of serum CEA determinations in patients with esophageal cancer.

Unlike colon cancer, we could identify no correlation between the prevalence of a raised CEA level or the absolute CEA values in patients with esophageal cancer and the pathologic stage of disease. Further, there was no relationship between preoperative serum CEA and survival. Survival after surgery for esophageal cancer is determined by several independent factors, most notably, the pathologic stage of the disease and the patient's physiologic status.5 In patients with limited disease, in particular patients with <5 lymph node metastases, the extent of the nodal dissection positively impacts subsequent survival.6,7,8,9 Despite recent enthusiasm, such an influence has not been demonstrated for adjuvant radiotherapy or chemotherapy. Even with improvements in surgical therapy, the majority of patients with esophageal cancer will eventually die of recurrent disease. Recurrence may be either locoregional (to thoracic, abdominal, or cervical node chains) or systemic (commonly to liver, lung, or bone).10-12 Certain patients may be amenable to salvage surgery, such as those who develop nodal recurrence alone or those with liver metastases restricted to one lobe, while in those with nonresectable disease, early adjuvant therapy may be appropriate.


DISCUSSION

Loren Humphrey, MD (Columbia, Missouri): Dr. Clark, that was a fine presentation of a significant piece of work. The answers to the first two questions are contrary to that published for colorectal cancer. One, does an elevated preoperative carcinoembryonic antigen (CEA) level correlate with stage? The answer, yes. Number two, what is the prognostic influence of an elevated preoperative CEA? The answer, none.

Mehair et al, in Cancer Research, Volume 50, reported results from 30 patients with differentiit and 47 patients with...
undifferentiated gastric adenocarcinoma (GA). In the first postoperative year, increased CEA levels correlated with a decrease in survival in patients with differentiated GA. There is no such correlation in their group with undifferentiated GA.

First question, Sir. Have you correlated CEA levels with the histopathology of the primary? Of the 83 patients in this study, 13 developed increased CEA levels prior to objective evidence of recurrence. Only 6 were resected, 3 for cure. One died, I lived 30 months or is alive, I presume. And the other is alive 36 months after removal of primary; a 2.4% benefit rate. Given the rationing at the VA Health Care System, and that coming rapidly in the form of managed health care, I concluded, so what; 2.4% just won't make it. But then I had the opportunity to read this excellent manuscript. You must read this, for it points out possible use of postoperative CEA levels in prompting adjuvant chemotherapy. Dr. Miedema, Dr. Zhang, and I used enzyme-linked immunocassays to study tissue from 35 colon cancers. CEA was expressed in 71%, CA-19-9 in 72%, and one or the other in 89%. Second question, Sir. Have you or do you plan to study the expression of tumor markers in the primary of these 83 patients? If sensitivity can be increased by studying expression of CEA and CA-19-9 in tissue of the primary along with CEA and CA-19-9 in serum assay, one can save dollars and eliminate CT scans, chest radiography, liver enzymes, et cetera, in following patients by postoperative CEA, CA-19-9 levels.

In addition to prompting perhaps chemotherapy, this could very well select the subpopulation responsive to further salvage therapy. This type of excellent research should be the basis for rationing to cut costs in health care, rather than some specious political system.

Merril Dayton, MD (Salt Lake City, Utah): I have just a brief question. Given the poor survival data even when reexploration for recurrent CEA elevation is done, is there ever a situation clinically where you would explore someone with an elevated CEA level in the absence of other objective findings?

CLOSING
Geoffrey Clark, FRCS(Ed), MD: I would like to thank Dr. Humphrey for his comments and criticisms. First of all, he asked about the histopathology. We did look at histopathology, classifying tumors as well differentiated, and moderately and poorly differentiated. There was no difference in the prevalence of an elevated CEA among the different histologic groups; however, the numbers were really too small to show significant differences with just 14 preoperative patients having elevated serum CEA.

In terms of the low overall productivity of 2.4% of patients in whom reoperation was successful, it is recognized that this isn't a particularly high positive outcome. We do not know what benefits may be obtained following early adjuvant chemotherapy in patients whose recurrence is first identified on the basis of CEA levels.

Tumor markers have been looked at within the tumor itself and have been reported by the Omaha group back in 1990. They found positive CEA markers on the tumor in over 80% of patients.

In answer to the question as to whether blind exploration would be recommended on the basis of an elevated CEA alone, we consider that such action would be premature. In colon cancer, a repeat laparotomy has been advocated on the basis of raised serum CEA levels alone to identify and resect recurrence, however, in patients with esophageal cancer, both a thoracic and abdominal exploration would be required. We would regard such action to be excessive, based on simply a blood test, as we are uncertain what benefit this would provide.