The Value of Acute-Phase Protein Measurements After Curative Gastric Cancer Surgery

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Objective: To determine whether acute-phase protein measurement provides clinically useful information about tumor recurrence.

Patients and Methods: Acute-phase serum protein levels were measured at regular intervals in 43 patients who underwent curative gastrectomy for gastric cancer. At 12 months after surgery, patients were grouped according to the presence or absence of a C-reactive protein response, and were followed up for a minimum of 12 months or until death.

Results: There was a significant difference ($P = .02$) in a recurrence rate between patients with a C-reactive protein response (3 of 4 patients) and those without such a response (4 of 39 patients). Moreover, serum levels of C4 and $\alpha_1$-antitrypsin 12 months after surgery in patients who eventually recurred were significantly ($P < .05$) higher than those in a group without recurrence.

Conclusion: An acute-phase protein response may be a predictive factor in the early stages of tumor recurrence. Acute-phase protein measurement provided clinically useful information about tumor recurrence after curative gastric cancer surgery.

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Because of the advances in diagnostic methods and the progress of surgical treatment, the 5-year survival rate of patients with gastric cancer has steadily increased, reaching more than 60% in Japan$^1,2$; however, approximately a quarter of patients who underwent curative resection of gastric cancer had tumor recurrence. $^3$ It is known that a proportion of patients develop an acute-phase protein response following tumor recurrence or progression. $^3$ Although a recent study$^4$ showed a higher recurrence rate of colorectal cancer for patients with ongoing, acute-phase protein response compared with patients without such a response, there is little evidence that an acute-phase protein response indicates the early phase of tumor recurrence after curative cancer surgery.

We wanted to determine whether acute-phase protein measurement provides clinically useful information about tumor recurrence after curative gastric cancer surgery.

RESULTS

Of the 43 patients studied, 4 had a CRP response at 12 months after gastrectomy. Although radiological examinations did not show definitive evidence of tumor recurrence, peritoneal or lymph node metastases were highly suspected during physical examinations in 2 patients. One had a CRP response and died of massive metastases to the peritoneum 1 month later and another died of metastases to systemic lymph nodes 13 months later. In other 5 patients in whom tumor eventually recurred, a relapse could be detected at 16, 22, 29, 30, and 38 months after surgery. There was a significant difference ($P = .02$) in a recurrence rate between patients with a CRP response (3 of 4 patients) and those without such a response (4 of 39 patients) (Table 2). Serum levels of $\alpha_1$-AT and C4 in patients with subsequent clinical recurrence were significantly higher than those without recurrence ($\alpha_1$-AT: 2.37 ± 0.49 g/L [236.86 ± 49.01 mg/dL] vs 1.96 ± 0.32 g/L; C4: 0.31 ± 0.01 g/L vs 0.23 ± 0.08 g/L) at 12 months after surgery (Figure 1 and Figure 2). No statistical difference was found between the 2 groups in preoperative and postoperative serum levels of total protein, albumin, prealbumin, transferrin, immunoglobulins, C3, and ceruloplasmin.
PATIENTS AND METHODS

PATIENTS

Forty-three patients who underwent curative resection of gastric cancer between January 7, 1991 and June 30, 1994 were enrolled in our prospective study after informed consent was obtained. All operations were performed by one of us (T.F.). Curative resections were defined as patients with no residual macroscopic disease after surgery. Distal (subtotal) gastrectomy was carried out in 26 patients, total gastrectomy in 12, and total gastrectomy with splenectomy in 5 (Table 1). The new Japanese classification of gastric cancer7 was used for clinical staging of the tumors. Blood samples were obtained from each patient before surgery to measure serum levels of total protein, albumin, negative acute-phase proteins (prealbumin and transferrin), immunoglobulins, and positive acute-phase proteins (C3 and C4, α1-antitrypsin [α1-AT], ceruloplasmin, and C-reactive protein). These protein levels were also measured at 3, 6, and 12 months after surgery. Following an annual computed tomographic scan and ultrasound examination of the upper abdomen, patients were divided into 2 groups according to serum C-reactive protein (CRP) levels at 12 months after surgery (CRP<0.3 mg/dL or CRP ≥0.3 mg/dL). At this time, none of the patients showed any evidence of infections or liver dysfunction. They were then followed up once a month for a minimum of 12 months or until death.

PROTEIN ASSAYS

Serum albumin levels were measured using the bromocresol green method.8 Nephelometric assays were used to determine serum levels of both negative and positive acute-phase proteins. Goat antiserum to human CRP was purchased from the Yatoron Corporation (Tokyo, Japan), rabbit antiserum to human prealbumin, transferrin, C3 and C4, α1-AT, and ceruloplasmin were purchased from Behringwerke Corporation (Marburg, Germany). Light scattering intensity was measured by a nephelometer analyzer (Behring Corporation, Marburg, Germany). The detection limit of CRP concentration in this assay was 0.003 g/L.

STATISTICAL ANALYSIS

Data are presented as mean ±SD, or as means and ranges. Differences in serum protein levels between the 2 groups were statistically analyzed using the Mann-Whitney U test. The comparison of a recurrence rate was made with the 2-sided Fisher exact test. Differences were considered significant at P<.05.

COMMENT

In general, the acute-phase proteins are defined as serum proteins that increase in concentration by 25% or more in the first 7 days following tissue damage.5 Some serum proteins, however, consistently demonstrate reduction in serum concentration during the acute-phase response, and are often referred to as negative acute-phase proteins.9 Of these proteins, CRP is the best-studied major acute-phase proteins in human. At 12 months following surgery, a CRP response (CRP level was ≥0.003 g/L) was identified in 4 of 43 patients. This low incidence of a CRP response is in contrast to a high incidence of a CRP response (15 of 36 patients)4 at 4 months following surgery, a CRP response (CRP level was >0.3 mg/dL). Differences were considered significant at P<.05.
cancer in patients with an ongoing CRP response compared with those without such a response. Moreover, high levels of serum α1-AT and C4 in patients who eventually recurred were also compared with those in patients without recurrence, and suggest that the presence of an acute-phase protein response is a predictive factor in the early phase of tumor recurrence in patients who undergo curative surgery for gastric cancer.

CONCLUSION

There was a significant difference in the gastric cancer recurrence rate between patients with a CRP response and those without such a response following curative gastric cancer surgery. Higher serum levels of α1-AT and C4 in patients who eventually recurred were also compared with those in patients without recurrence, and suggest that the presence of an acute-phase protein response is a predictive factor in the early phase of tumor recurrence in patients who undergo curative surgery for gastric cancer.

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REFERENCES