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Original article

The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients: a prospective clinical study

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Abstract

Background. **Many studies on postoperative carcinoembryonic antigen (CEA) and/or carbohydrate antigen (CA)19-9 monitoring after operation for gastric cancer have been reported, but most have been retrospective.**

Methods. **A nationwide observational study was implemented in 135 leading institutions in Japan to evaluate the significance of CEA and/or CA19-9 in postoperative monitoring for recurrence in patients with advanced gastric cancer. Three hundred and twenty-one patients examined in this analysis underwent radical gastrectomy at one of Japan's leading institutions between November 1993 and March 1996 and had been followed up for at least 5 years. Serum levels of CEA and CA19-9 were examined preoperatively and every 3 months postoperatively, with diagnostic imagings, such as chest X-ray, computed tomography (CT), and ultrasonography also being performed every 3 months.**

Results. **Recurrence was observed in 120 patients (peritoneum, 48; liver 16; lymph node, 16; multiple sites, 25; and others, 12). Sensitivities of CEA and either CEA or CA19-9, or both, for recurrence were 65.8% and 85.0%, respectively, both of which values were significantly higher than the preoperative positivities (28.3% and 45.0%, respectively). In most patients with high preoperative levels CEA and/or CA19-9, these tumor markers increased again at recurrence. Recurrent diseases were detected between 5 months after detection by diagnostic imagings and 12 months before detection by diagnostic imagings (mean of 3.1 ± 3.6 months before detection by diagnostic imagings) and between 10 months after detection by diagnostic imagings and 13 months before detection by diagnostic imagings (mean of 2.2 ± 3.9 months before detection by diagnostic imagings) by CEA and CA19-9 monitorings, respectively.**

Conclusion. **These results suggest that CEA and/or CA19-9 monitoring after operation was useful to predict the recurrence of gastric cancer, especially in almost all the patients with high preoperative levels of these markers.**

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Key words Gastric cancer · Recurrence · CEA · CA19-9

Introduction

Although there are no specific tumor-associated antigens in gastric cancers, carcinoembryonic antigen (CEA) and carbohydrate antigens of the sialyl-Lewis A group, such as CA19-9, are known to be elevated in the serum of patients with advanced gastric cancer. A combination of CEA and CA19-9 monitoring can extend the possibilities of their use for the early detection for recurrence after operation for advanced gastric cancer. Although many studies of postoperative CEA and/or CA19-9 monitoring for gastric cancer have been reported [1–8], the usefulness of this monitoring is still controversial. Because most of these studies have been retrospective and small-scale and because there were different monitoring periods in the patients, we implemented a nationwide observational study to evaluate the usefulness of CEA and/or CA19-9 in postoperative monitoring for recurrence in patients with advanced gastric cancer. This was a prospective study carried out as an additional study of adjuvant chemotherapy for far-advanced gastric cancer.

Patients and methods

Three hundred and twenty-one patients with advanced gastric cancer of more than stage II, according to the Japanese Research Society for Gastric Cancer [9], examined in this analysis underwent radical gastrectomy at one of 135 leading Japanese institutions between November 1993 and March 1996: they were followed for at least 5 years in the JFMTC (Japanese Foundation for Multidisciplinary Treatment of Cancer) study no. 20 [10], a randomized control study comparing intensive

Table 1. Characteristics of 120 patients with recurrence

Male/Female	77/43	
Age in years (median)	43–75 (59)	
Stage of disease	a	16 (13.3%)
	b	87 (72.5%)
	a	17 (14.2%)
Gross type	0	3 (2.5%)
	1	0 (0.0%)
	2	16 (13.3%)
	3	67 (55.8%)
	4	34 (28.3%)
Histological type	Pap	2 (1.7%)
	Tub1	6 (5.0%)
	Tub2	22 (18.3%)
	Por1	22 (18.3%)
	Por2	47 (39.2%)
	Sig	16 (13.3%)
	Muc	5 (4.2%)
Location	E	1 (0.8%)
	C	20 (16.7%)
	M	51 (42.5%)
	A	48 (40.0%)

E, esophagus; C, cardia; M, middle; A, antrum; Pap, papillary adenocarcinoma; Tub, tubular adenocarcinoma; Por, poorly differentiated adenomcarcinoma; Sig, signet-ring cell adenocarcinoma; Muc, mucinous adenocarcinoma

and standard adjuvant chemotherapy. We obtained informed consent from all patients for this protocol. Serum levels of CEA and CA19-9 were examined preoperatively and every 3 months postoperatively. Diagnostic imagings such as chest X-ray, computed tomography (CT), and ultrasonography were also performed every 3 months, to check for recurrence, for at least 3 years. Recurrence was observed in 120 patients during the 3 years after operation (peritoneum, 48; liver, 16; lymph node, 16; multiple sites, 25; and others, 12). Their whose characteristics are shown in Table 1.

First we studied the preoperative positivities and sensitivities of CEA and CA19-9 for the patients with recurrence. Next, we examined the longitudinal changes in CEA and CA19-9 positivities at the preoperative and recurrent stages in individual patients, and we also studied the specificity (true-negatives/true-negatives + false-positives) for recurrent stages in 95 patients who had no recurrence at 5 years after surgery. Lastly, we studied the lead time of CEA or CA19-9 compared with the follow-up findings obtained by using imagings. The lead time was calculated as the time of first detection of elevated markers postoperatively subtracted from the time of first recurrence indicated by chest X-ray, CT, or Echo imagings. A positive lead time indicated that markers were elevated earlier than the recurrence noted by imagings. We also compared the lead time in patients with higher and lower preoperative marker levels (higher CEA group, greater than 10 ng/ml; higher CA19-9 group, greater than 70 IU/ml).

Table 2. Comparative preoperative positivities for CEA and CA19-9 values and their sensitivities for indicating recurrence

	Preoperative positivities	Sensitivities for recurrence
CEA	34 (28.3%)	79 (65.8%)
CA19-9	35 (29.2%)	66 (55.0%)
Either/both	54 (45.0%)	102 (85.0%)

CEA, carcinoembryonic antigen; CA, carbohydrate antigen

Student's *t*-test and the χ^2 test were used to study the differences between positivities for preoperative CEA and/or CA19-9 and their sensitivities for indicating recurrence, differences in the lead time between the higher and lower CEA and CA19-9 groups, and differences between liver and other recurrence sites.

Results

Preoperative positivities for CEA and CA19-9 and their sensitivities and specificities for indicating recurrence

Sensitivities for CEA and CA19-9, and combinations of the two markers, for indicating recurrence were 65.8%, 55.0%, and 85.0%, all of which values were significantly higher than the preoperative positivities (28.3%, 29.2%, and 45.0%, respectively; $P < 0.001$ for all; Table 2). These results suggest that the usefulness of serum CEA and CA19-9 values is much greater for indicating recurrence than for indicating metastases preoperatively. Moreover, the specificities of serum CEA and CA19-9 for recurrence were 81.1% and 93.7%, respectively.

Longitudinal changes in CEA and CA19-9 positivities at the preoperative and recurrent stages in individual patients

Of the 34 patients with elevated preoperative levels of CEA, this marker increased again at recurrence in 32 (94.1%) patients. Similarly, CA19-9 was increased again at recurrence in 32 (91.4%) of the 35 patients with high preoperative levels of this marker. There were also many patients whose CEA and CA19-9 levels increased for the first time at recurrence (54.7% and 40.0%, respectively; Table 3). These data indicate that we can detect elevated levels of serum CEA or CA19-9 at recurrence in more than 90 % of patients with high preoperative levels of these markers.

Lead-time determinations of CEA and CA19-9 levels based on imaging results

The lead times were −5 to 12 months, with a mean of 3.1 ± 3.6 (SD) months, and −10 to 13 months, with

a mean of 2.2 ± 3.9 months for CEA and CA19-9 monitorings, respectively (Table 4). In the higher CEA group, the lead times were 1 to 12 months, with a mean of 5.2 ± 2.2 months, and the values were −5 to 4 months, with a mean of −1.3 ± 2.8 months, in the lower CEA group. In the higher CA19-9 group, these values were −2 to 13 months, with a mean of 4.1 ± 2.7 months, and in the lower CA19-9 group, and the values were −10 to 7 months, with a mean of 0.5 ± 3.1 months. Significant differences in the lead times were observed between the higher groups and lower groups for both markers ($P < 0.001$ for both) (Table 5).

Table 3. Longitudinal changes in CEA and CA19-9 positivities at the preoperative and recurrent stages in individual patients

Preoperative positivities		Sensitivities for recurrence	CEA *n*	CA19-9 *n*
−	→	+	47	34
+	→	+	32	32
−	→	−	39	51
+	→	−	2	3

Table 4. Comparison of the lead times for CEA and CA19-9 levels and the imaging results

	Lead time compared with imagings	Mean ± SD of the lead time
CEA	−5 to 12 Months	3.1 ± 3.6 Months
CA19-9	−10 to 13 Months	2.2 ± 3.9 Months

We next studied the differences in lead times among recurrent sites. The lead times for recurrences in the liver, peritoneum, and lymph nodes were 1.2 ± 4.0, 3.4 ± 3.8, and 3.7 ± 3.5 months, respectively, for CEA; and 2.1 ± 2.6, 1.0 ± 4.3, and 3.6 ± 4.0 months, respectively, for CA19-9. The lead time for CEA for liver recurrence was significantly shorter than those for the peritoneum and lymph node metastases ($P < 0.05$; Table 6).

Discussion

The usefulness of serum tumor markers is still controversial. According to the guidelines of the American Society of Clinical Oncology [11], the serum CEA level is not recommended for screening or for use as a surrogate marker of chemotherapy, but it is recommended for the preoperative prediction of disease staging and for monitoring recurrence after surgery in colon cancer. However, it is not recommended for the screening, diagnosis, staging, or routine surveillance of breast cancer patients after operation. In the present prospective study, we examined whether the serum CEA level could be recommended for monitoring the recurrence of gastric cancer after surgery.

Many tumor markers, such as CEA, CA19-9, CA72-4, CA12-5, and CA-50, have been studied in the monitoring of gastric cancer [1–8], but the sensitivity of any one of them is not sufficient. Our study showed that preoperative positivities for CEA, and CA19-9, and their combination were 28.3%, 29.2%, and 45.0%, respectively, in 321 patients with moderately advanced gastric cancers. However, the sensitivities for recur-

Table 5. Lead times for higher and lower CEA and CA19-9 groups

	Lead time compared with imagings	Mean ± SD of the lead time	
CEA			
higher group ($n = 43$)	1 to 12 Months	5.2 ± 2.2 Months	$P < 0.001$
Lower group ($n = 36$)	−5 to 4 Months	−1.3 ± 2.8 Months	
CA19-9			
Higher group ($n = 38$)	−2 to 13 Months	4.1 ± 2.7 Months	$P < 0.001$
Lower group ($n = 28$)	−10 to 7 Months	0.5 ± 3.1 Months	

Table 6. Differences in lead times among recurrent sites

	CEA		CA19-9
Liver ($n = 16$)	1.2 ± 4.0 Months	*	2.1 ± 2.6 Months
Peritoneum ($n = 48$)	3.4 ± 3.8 Months		1.0 ± 4.3 Months
		*	
Lymph node ($n = 16$)	3.7 ± 3.5 Months		3.6 ± 4.0 Months

* $P < 0.05$

rence were 65.8%, 55.0%, and 85.0%, respectively, in 120 patients with recurrence. These significant increases in sensitivity suggest that the serum levels of these markers would be highly suitable for monitoring for recurrence after operation. Moreover, in more than 90% of patients with high preoperative levels of CEA or CA19-9, these markers increased again at recurrence. In other words, we can follow up on recurrence by monitoring these tumor markers in patients with high preoperative levels of these markers.

We also examined whether or not we could detect recurrence earlier by the monitoring of the tumor markers than by imagings. If we cannot detect recurrences when they are of a smaller size than recurrences detected by imagings, monitoring by tumor markers is not very useful. When we perform imagings after the elevation of tumor marker levels, we may detect large-size recurrences. Therefore, we determined which was the earlier event, detection of recurrence by imaging, or the elevation of tumor markers, by studying the lead time of tumor markers based on imaging. Recurrent diseases were detected at -5 to 12 months (mean, 3.1 ± 3.6 (SD) months) for CEA monitoring and at -10 to 13 months (mean, 2.2 ± 3.9 months) for CA19-9 monitoring before detection by imaging. These results indicate that monitoring for recurrence by tumor markers is useful but not sufficient. We need to recognize that elevation of tumor marker levels is seen much later than detection of recurrence by imaging in some cases.

We finally analyzed in which patients the tumor markers were elevated earlier. In the patients with higher preoperative levels of tumor markers, these markers were elevated earlier. We studied the lead times in relation to other factors, such as recurrent sites and pathological classification; the lead time for CEA in liver recurrence was significantly shorter than those for peritoneum and lymph node metastasis ($P < 0.05$), and this was the only significant difference in lead time in relation to other factors.

In summary, monitoring for recurrence by serum CEA and/or CA19-9 levels is useful in most patients with gastric cancers. In particular, in almost all of the patients with high preoperative levels of of the tumor markers, levels of these markers were elevated earlier than the detection of recurrence by some imagings. However, suggest that we should monitor imagings mainly, rather than monitoring these markers, in the remaining patients with low preoperative levels of these markers.

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