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Synchronous Elevation of Soluble Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) Correlates with Gastric Cancer Progression

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Soluble forms of ICAM-1 (sICAM-1) and VCAM-1 (sVCAM-1) have been reported from the supernatant of cytokine-activated endothelial cells, cancer cells and from sera of cancer patients. We measured sICAM-1 and sVCAM-1 from the serum of 20 healthy volunteers and 142 gastric cancer patients by ELISA assay. Ninety-five patients were operable and 47 patients were inoperable at the time of this study. Particularly in the 28 operable patients, we sampled both portal and peripheral blood simultaneously and measured the levels of the soluble forms of cell adhesion molecules (sCAMs). The sCAMs level and sero-positivity rate increased with cancer progression in order of the healthy controls, operable patients, and inoperable patients. In inoperable cancer, the sICAM-1 level increased more with liver metastasis. sICAM-1 and sVCAM-1 did not correlate with each other in either portal or peripheral blood. A total of 58.3% of patients with liver metastasis and 22.9% of patients without liver metastasis showed synchronous expression of both sCAMs ($p=0.03$). Synchronous sero-positivity of sCAMs and αFP was higher with liver metastasis ($p=0.01$). The median overall survival duration which co-expressed both sCAMs was 9 months. This showed a significant difference compared with the sICAMs non-expressing group, where the median survival was not reached until 24 months follow-up ($p=0.002$). The synchronous expression of sCAMs was an independent risk factor in gastric cancer patients. We raise the possibility that synchronous sICAM-1 and sVCAM-1 elevation may be a useful monitor to determine tumor burden in gastric cancer.

Key Words: Synchronous, sICAM-1, sVCAM-1, gastric cancer, liver metastasis

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The intercellular adhesion molecule-1 (ICAM-1) is a glycoprotein belonging to the immunoglobulin superfamily and a ligand for leukocyte-function associated antigen-1 (LFA-1) (Marlin and Springer, 1987). It shows a rather broad distribution, such as on endothelial cells, keratinocytes, fibroblasts, leukocytes and many tumor cells (Smith and Thomas, 1990). Vascular cell adhesion molecule-1 (VCAM-1, CD106), also a member of the immunoglobulin superfamily, is a 90 kD cell surface glycoprotein. VCAM-1 will bind to cells expressing the integrin VLA4, including lymphocytes, monocytes and eosinophils. VCAM-1 has a more restricted distribution than ICAM-1, being expressed on vascular endothelium, lymphoid dendritic cells, some tissue macrophages and renal parietal epithelium (Norris *et al.* 1991). Recent evidence has implicated the possible roles of these adhesins in cancer metastasis, i.e. VCAM-1-mediated melanoma cell adhesion (Rice and Bevilacqua, 1989) and E-selectin-mediated colon cancer cell adhesion to endothelium (Lauri *et al.* 1991).

Soluble forms of ICAM-1 and VCAM-1 had been reported from the supernatant of cytokine-activated endothelial cells, cancer cells and from sera of normal individuals (Rothlein *et al.* 1991; Seth *et al.* 1991; Pigott *et al.* 1992). Later, the soluble forms of cell adhesion molecules (sCAMs) were also found in the serum of cancer patients (Gearing *et al.* 1992; Banks *et al.* 1993; Gardner *et al.* 1995; Klein *et al.* 1995). This release of cell surface adhesins can be an active mechanism for breaking interactions between cells and clearing surface adhesins for movement. They may allow tumor escape from immunological surveillance of the host cytotoxic T cells and thus promote cancer metastasis. In diametric contradiction, they may also block the receptors on the surface of tumor cells or endothelium and thus prevent the adhesion of cancer cells to the metastatic focus. Moreover, existence of sCAMs can be interpreted as predictively favorable, meaning an enhanced immune recognition function in the host (Webb *et al.* 1991).

The elevated level of sICAM-1 has correlated with the disease state and treatment response (Johnson *et al.* 1989; Pizzolo *et al.* 1993; Fortis *et al.* 1995). Also reduced survival duration was found in patients with high sICAM-1 levels. We report that elevation of both sICAM-1 and sVCAM-1 could be a biomarker to monitor tumor burden, especially for hepatic metastasis in gastric cancer.

MATERIALS AND METHODS

Patients population

A total of 142 gastric cancer patients who had been treated at Yonsei Cancer Center, Yonsei Medical Center from January 1995 to May 1996 were enrolled for study. Ninety-five patients were operable and 47 patients were inoperable (in advanced or relapsed states) at the time of study. All patients were pathologically-proven adenocarcinomas. Pathological staging was done based on AJCC classification. Male to female ratio was 100 to 42 and median age was 61 years (range 25~80 years). Among operable patients, there were 11 patients in the T1 classification, 12 in T2, 67 in T3, and 5 in T4. There were 28 patients in the N0 classification, 29 in N1, and 85 in N2. There were 19 patients in stage I, 21 patients in stage II, 51 patients in stage III, and 50 patients in stage IV. Median follow-up duration was 12.5 months (range 2~24 months). Twenty healthy volunteers participated in the study after the following routine examinations; physical examination, chest X-ray, blood chemistry, routine blood and urine analysis. The study was performed after approval of the hospital ethical committee and informed consent was obtained from each patient and healthy volunteer before blood sampling.

Blood sampling and storage

In 95 patients, peripheral blood was sampled just before tumor resection during the operation. Particularly from 28 patients, both portal and peripheral blood were sampled. Among those 28 patients, 4 were in pathological stage IV (2 with N3 group lymph node metastasis and 2 with peritonectomy from peritoneal metastasis). Portal blood was sampled twice; just before and after stomach resection during surgery. In inoperable patients, blood was sampled on the starting day of chemotherapy. After centrifugation, sera were kept frozen at $-80°C$ until study.

Determination of serum ICAM-1 and VCAM-1

Quantitative determination of sICAM-1 (R&D, MN, USA), sVCAM-1 (R&D), soluble form of vascular endothelial cell growth factor (sVEGF) (R&D), and αFP (Abbot, Abbotpark, IL, USA) was performed employing commercially available ELISA kits according to the procedures recommended by the manufacturer. Each serum sample was tested in duplication. The detection limit of the assay was 7 ng/ml, 100 ng/ml, 5 pg/ml, 0.4 ng/ml in an order of ICAM-1, VCAM-1, VEGF and αFP, respectively. Optical density was measured at 450 nm with a correction wavelength of 570 nm using a microtiter plate reader (Co-star, Boston, MA, USA).

Statistics

Statistical analysis was done using non-parametric statistics. When clinical parameters were divided into groups and compared, the Mann-Whitney rank test was applied. Correlation was examined by the Spearman rank correlation coefficient. Survival curves were estimated by the Kaplan-Meier product-limit method and compared using the log-rank test. Multivariate analysis using the Cox proportional hazard model was performed to evaluate the independent prognostic value of each covariate.

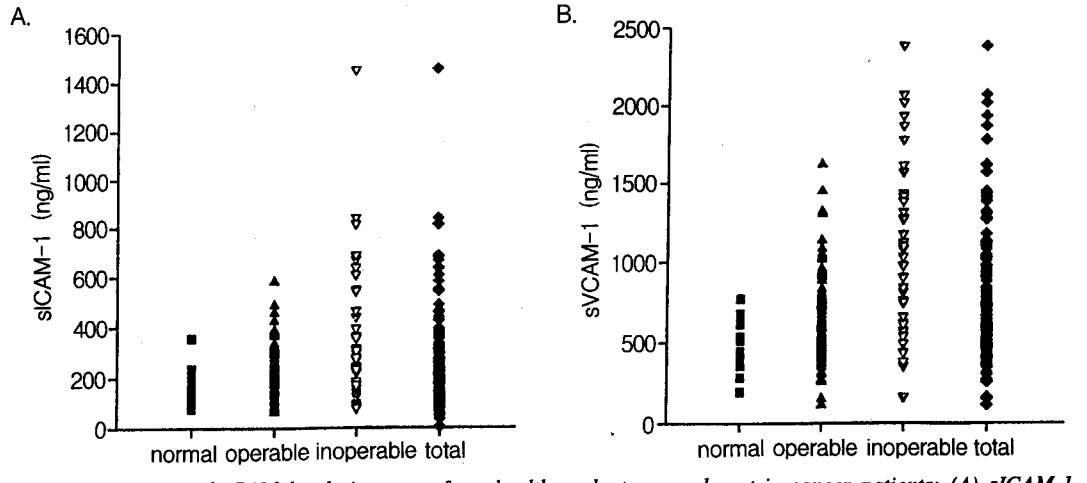

Fig. 1. Measurements of sCAM levels in serum from healthy volunteers and gastric cancer patients: (A) sICAM-1, (B) sVCAM-1.

Table 1. Comparison of sICAM-1, sVCAM-1 levels and sero-positivity based on cancer progression

		Serum level (ng/ml)		Sero-positivity (%)	
		sICAM-1	sVCAM-1	sICAM-1	sVCAM-1
Healthy volunteers	(n=20)	180±67	469±136	5.0	5.0
Total patients	(n=142)	274±179	777±411	21.8	43.0
operable	(n=95)	225±94	639±257	13.7	28.4
advanced/relapsed	(n=47)	371±257	1057±501	38.3	72.3
without liver metastasis	(n=35)	305±183	1050±521	25.7	71.4
with liver metastasis	(n=12)	570±342	1080±487	75.0	66.6

mean±standard deviation

RESULTS

sICAM-1 and sVCAM-1 positivity in gastric cancer patients

Both of the sCAM levels increased in order of the healthy controls, operable patients and inoperable patients (Fig. 1). Serum levels higher than 2× standard deviation above the mean values of healthy volunteeers were considered as sero-positive of sICAM-1 and sVCAM-1 (315 ng/ml, 742 ng/ml, respectively). With these values as cut-off points, two volunteers were beyond normal range; one in each sCAM. The sero-positive rate was 21.8% in sICAM-1 (I 1/14, II 5/21, III 5/43, IV 2/17, advanced 18/47) and 43.0% in sVCAM-1 (I 4/14, II 8/21, III 9/43, IV 6/17, advanced 34/47). The synchronous positivity of both sCAMs was higher in the inoperable group (31.9%) than in the operable group (6.3%) (p=0.001). The sICAM-1 positivity increased further with liver metastasis, whereas that of sVCAM-1 showed no difference (Table 1). The portal vein sICAM-1 and sVCAM-1 levels were 212 ±62 ng/ml, 630±311 ng/ml, respectively. Portal vein sero-positivity of sICAM-1 and sVCAM-1 were 7.1% and 32.1%, respectively. From the portal vein, only one patient (3.6%) showed concurrent positivity of both sCAMs, whereas 61 patients (64.2%)

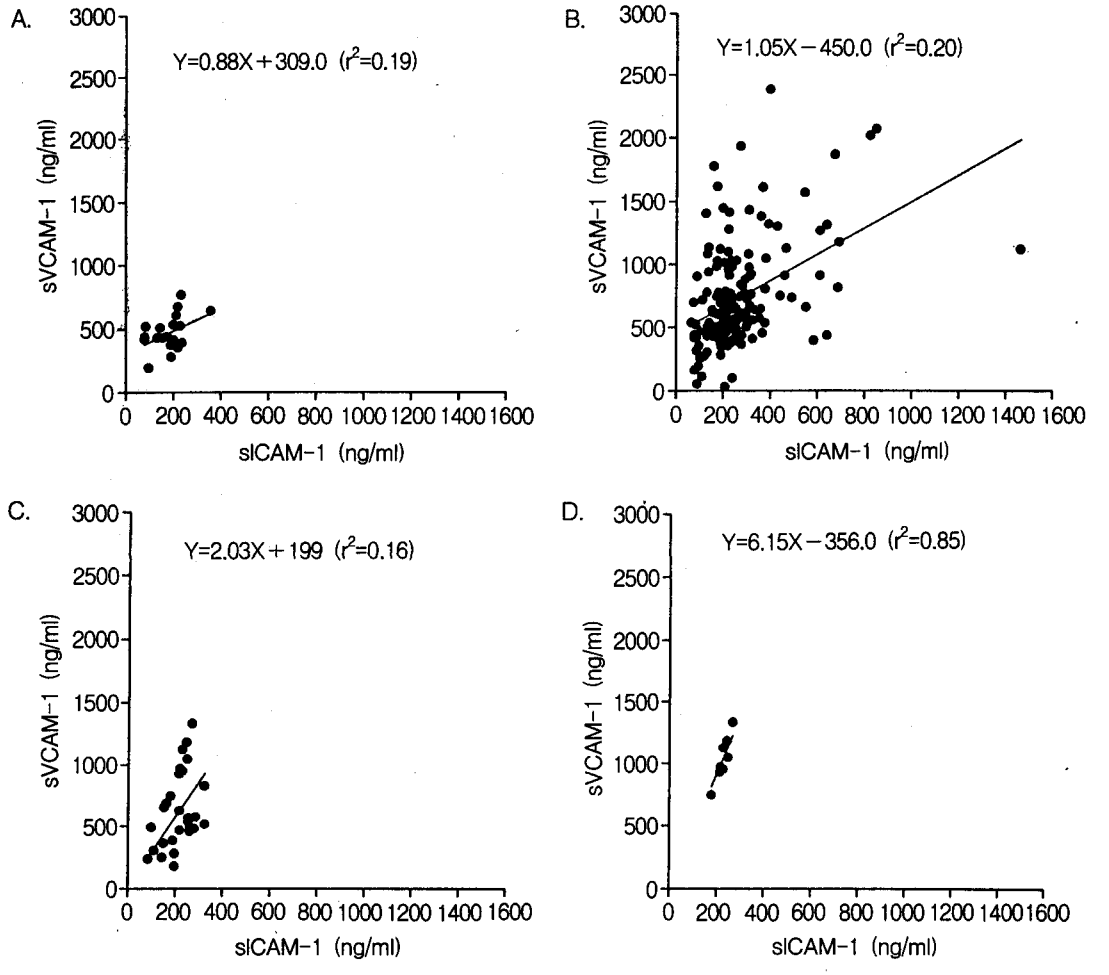

Fig. 2. Correlation between sICAM-1 and sVCAM-1 levels in: (A) healthy volunteers, (B) peripheral blood of cancer patients, (C) portal blood of cancer patients, (D) sVCAM-1 positive patients.

showed no elevation of either sCAM.

Correlation of sICAM-1 and sVCAM-1

There was no correlation between sICAM-1 and sVCAM-1 levels in healthy volunteers. In gastric cancer patients, they also did not correlate with each other either in peripheral or in portal blood. However, in a sVCAM-1-positive subgroup of portal blood (n=8), a strong relationship was found between sICAM-1 and sVCAM-1 (Fig. 2).

Correlation between portal and peripheral vein sCAMs

From 28 patients, we were able to compare sCAM levels between portal and peripheral blood. In 17 patients (61%), the peripheral blood sICAM-1 level decreased in comparison to those of portal vein, whereas the levels were reversed in 11 patients. Among 4 peritoneal seeding patients, 3 patients showed an increased peripheral level over the portal vein level. The mean change of the peripheral sICAM-1 level compared to the portal level was a 6.0% decrease (range −56% to +44%) after hepatic circulation. In sVCAM-1, 16 patients (57%) showed decreased peripheral vein sVCAM-1 levels in comparison to those of portal vein. Peripheral blood sVCAM-1 level relatively correlated with that of portal blood (r^2=0.54). All 4 stage IV patients showed increased peripheral levels over portal levels, whereas 8 out of 9 stage I-II patients showed lower peripheral levels than portal levels. The peripheral sVCAM-1 level increased 1.0% (range −70% to +

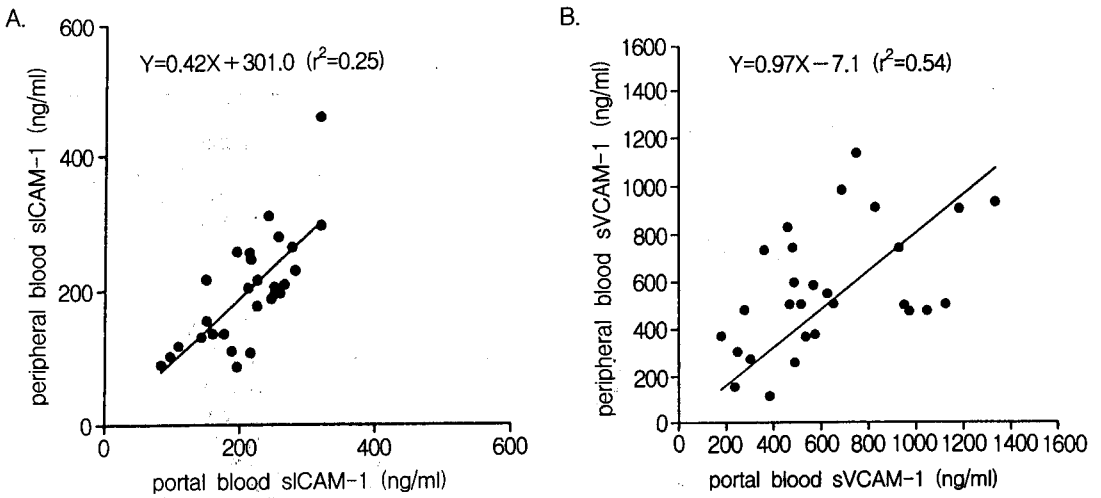

Fig. 3. Correlation of sCAMs between portal and peripheral blood: (A) sICAM-1, (B) sVCAM-1.

Table 2. Incidence of sICAM-1, sVCAM-1 and αFP expression based on liver metastasis in 47 patients with inoperable gastric cancer

	sICAM-1(+)	sVCAM-1(+)	αFP(+)	sICAM(+), sVCAM(+)	sICAM-1(+), sVCAM-1(+), αFP(+)
without metastasis(n=35)	9(25.7%)	26(74.3%)	1(2.9%)	8(22.9%)	0(0.0%)
with metastasis(n=12)	9(75.0%)	8(88.9%)	4(33.3%)	7(58.3%)	3(25.0%)
p-value	0.004	0.44	0.01	0.03	0.01

Table 3. Predictability of liver metastasis with sICAM-1, sVCAM-1 and αFP positivity in 47 patients with inoperable gastric cancer

		with liver metastasis	without liver metastasis	p-value
sICAM-1(+)	(n=18)	9 (50.0%)	9 (50.0%)	
(−)	(n=29)	3 (10.3%)	26 (89.7%)	0.004
sVCAM-1(+)	(n=34)	8 (23.5%)	26 (76.5%)	
(−)	(n=13)	4 (30.8%)	9 (69.2%)	0.44
αFP (+)	(n=5)	4 (80.0%)	1 (20.0%)	
(−)	(n=42)	8 (19.0%)	34 (81.0%)	0.01
sVEGF (+)	(n=22)	8 (36.4%)	14 (63.6%)	
(−)	(n=25)	12 (48.0%)	13 (52.0%)	0.31
both sCAMs (+)	(n=15)	7 (47.0%)	8 (53.0%)	−
both sCAMs, αFP (+)	(n=3)	3 (100.0%)	0 (0.0%)	−

108%) compared to those of portal vein after hepatic circulation (Fig. 3).

Synchronous elevation of both sICAM-1 and sVCAM-1 in liver metastasis

In 47 inoperable patients, 58.3% of the patients with liver metastasis and 22.9% of the patients without liver metastasis showed synchronous expression of both sCAMs (p=0.03) (Table 2). In synchronously sCAM-positive patients, liver metastasis was found in 47.0%(7/15) (Table 3), which was only 20.0% in both sCAM-negative groups (2/10). αFP positivity was not found in 50 operable cancer patients, whereas it was 11% (5/47) in inoperable patients. Synchronous sero-positivity of both sCAMs and αFP increased with liver metastasis (p=0.01) (Table 2). We then compared the predictability of liver metastasis with both sCAM and αFP sero-positivity. With the increment of positivity of these molecules, the liver metastasis rate increased as follows: in all negative, 11% (1/9); in one positive, 18% (4/22); in two positives, 31% (4/13); in all three positives, 100% (3/3) (p=0.01).

Comparison of sCAMs and sVEGF levels in inoperable gastric cancer

We also measured serum sVEGF levels in 47 inoperable gastric cancer patients and compared them to sICAM-1 and sVCAM-1 levels. The mean sVEGF level was 336±222 ng/ml (range 81～859 ng/ml) in patients with liver metastasis, and 274±

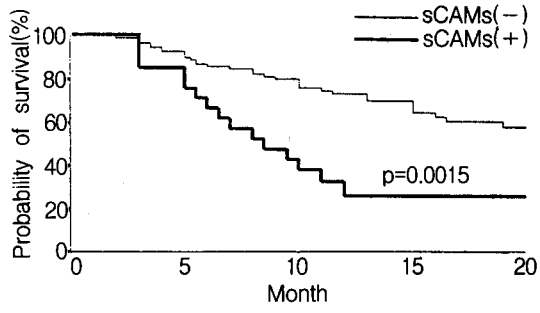

Fig. 4. Comparison of overall survival based on synchronous sCAMs expression. sCAMs(−); both sICAM-1 and sVCAM-1 negative, sCAMs(+); both sICAM-1 and sVCAM-1 positive.

269 ng/ml (range 0～1,020 ng/ml) in patients without liver metastasis (p=0.45). The sero-positivity of sVEGF was 43% (15/35) and 67% (8/12) in patients without liver metastasis and liver metastasis, respectively (p=0.14). The sVEGF level correlated with neither sICAM-1 nor sVCAM-1 levels regardless of liver metastasis.

Comparison of survivals based on synchronous sCAMs expression

Median survival duration in patients with synchronous sCAM elevation was only 9 months, while the median survival duration has not yet been reached in patients without sCAM elevation (Fig. 4). In univariate analysis, age (p=0.04), tumor size (p=0.003), node involvement (p=0.0001), stage (p=0.05), sICAM-1 expression (p=0.001), sVCAM-1 expression (p=

Table 4. Univariate and multivariate analysis of the prognostic factors

prognostic factors	univariate	multivariate
age	0.04	–
differentiation	0.57	–
tumor size	0.003	0.01
tumor depth	0.07	0.002
node involvement	0.0001	–
stage	0.05	–
sICAM-1 expression	0.001	–
sVCAM-1 expression	0.03	–
sCAMs synchronous expression	0.0001	0.02

0.03) and synchronous sCAM expression (p=0.0001) appeared as possible prognostic factors. But in multivariate analysis, only tumor size (p=0.01), node involvement (p=0.002) and synchronous sCAM expression (p=0.02) were the independent risk factors (Table 4).

DISCUSSION

In cancer, the ICAM-1 is expressed not only on most malignant cells but also on stromal cells (fibroblasts and endothelial cells) near cancer cell nests (Rice and Bevilacqua, 1989; Momosaki *et al.* 1995). The expression of ICAM-1 increases according to the tumor growth and distant metastasis (Banks *et al.* 1993). And the extravasation of the tumor cell is controlled by ICAM-1 and VCAM-1 expressed on both circulating tumor cells or vascular endothelium. Also, the amount of released ICAM-1 is correlated generally with that of surface ICAM-1 (Momosaki *et al.* 1995). The significance of this shedded molecule is not quite clear but it may have profound implications for tumor metastasis.

Soluble forms of CAMs contained most of the extracellular domain of CAMs and kept their biological activity (Johnson *et al.* 1989). In our study, serum levels of sICAM-1 and sVCAM-1 of healthy volunteers were in the reported range of the literature excluding two volunteers. These two volunteers probably had minor undetected inflammatory lesions. Even if we did perform neither the fibergastroscopic examination nor the follow-up measurement of sCAMs, the two volunteers have been doing well without any symptoms for the follow-up period of 2 years now. When we measured the peripheral blood sCAM levels, gastric cancer patients showed increments of both absolute levels and sero-positivity rates of both sCAM with cancer progression. However, no difference of the sCAMs levels was found in operable cancers based on stages both in portal and peripheral levels. Similar findings have been reported in hepatoma (Klein *et al.* 1995). Next, as we did not have any data about normal ranges of portal vein sCAMs, we compared them to the peripheral blood normal ranges. The portal blood positive rates were similar to those of the peripheral blood in both sCAMs. And between portal and peripheral blood, the sVCAM-1 levels correlated more than sICAM-1 did. These data suggest that, in a low tumor burden state, the shedded amount of sCAMs may not be enough to saturate the blood levels to be in a steady state. Whether the shedding mechanism and the cytokine responsible for inducing sCAMs is tumor- or host-derived are matters of speculation and we found that synchronous expression rate of the both sCAMs increased with cancer progression. These increments of sCAM levels suggest that peripheral sCAMs can be biochemical markers to monitor tumor burden at least in the advanced stage. And the peripheral blood sVCAM-1 level represented the portal sVCAM-1 level more closely than peripheral sICAM-1 represented the portal sICAM-1 level. As it is more reasonable to use benign gastric disease patients with gastric surgery as normal controls, we are now planning to measure the changes of sCAM levels after surgery in operable cancer and after chemotherapy in unresectable patients with those of healthy controls and benign gastric disease patients with surgery.

After rIL-2 infusion, there was a direct relationship between the increased serum level of sICAM-1 and sVCAM-1 (Fortis *et al.* 1995). However, in our data, sICAM-1 and sVCAM-1 levels did not correlate well with each other either in healthy volunteers or in gastric cancer patients. This discrepancy might come from our blood sampling points at different cancer stages in contradiction to constant sampling after rIL-2 treatment. But in a subset of sVCAM-1 positive patients, both sCAM levels cor-

related well with each other suggesting there might be a concurrent stimulation on both sCAM expression and shedding in this subgroup. Aside from this phenomenon, sVCAM-1 positive rates were higher than those of sICAM-1 in both peripheral and portal blood. Also, the sVCAM-1 level arrived in the plateau state earlier than sVCAM-1 during cancer progression. These findings supported the belief that sVCAM-1 elevation is an earlier and more widespread event than sICAM-1 elevation during gastric cancer metastasis, even though its expression is more restricted than that of sICAM-1. This difference between the sICAM-1 and sVCAM-1 levels reflected possible differences in the origin of sCAM expression, kinetics of excretion, and induction signals. To evaluate these points, we are now planning to check the CAM levels in tissue cytosol and compare the grade of inflammatory cell infiltration in tissue sections.

Tsujisaki *et al.* reported that patients with liver metastasis showed a higher sICAM-1 level than patients without liver metastasis (Tsujisaki *et al.* 1991). Thus, we sampled the portal and peripheral blood simultaneously during gastric surgery and compared the sCAM levels. Some 60% of the patients showed a more decreased peripheral sICAM-1 level than portal level. Interestingly, among 4 patients who had peritoneal seedings, 3 patients showed increased peripheral sICAM-1 levels over the portal level, suggesting that some amount of sICAM-1 had been added after hepatic circulation. These data partly supported our hypothesis of possible hepatic clearance of sICAM-1 during hepatic circulation. Therefore, in the remaining patients who had a higher peirpheral sICAM-1 level over the portal level, close prospective observation is being continued with the hypothesis that the elevated sICAM-1 might come from undetected extra-hepatic micrometastasis. In sVCAM-1, the difference between the portal and peripheral level was even greater. Even if 57% of the patients showed a decreased peirpheral sVCAM-1 level than that of portal vein, the mean change was 1.0% elevation after hepatic circulation. This change might come from cytokine responsive endothelial cells damaged during surgery, because we sampled the blood just before the gastric tumor resection which usually required two hours after abdominal wall incision. Fortis *et al.* found an in vitro dose responsive augumentation of sCAMs expression within 6 hours of cytokine exposure (Fortis *et al.* 1995). The second possible explanation is the release of sVCAM-1 from activated hepatic endothelial cells, especially in the subgroup of relatively high tumor burden stage (III), because most of the low tumor burden stages (I-II) showed lower peripheral blood sVCAM-1 levels than portal blood (data not shown).

In a mouse model, the melanoma itself was the source of the sICAM-1. Therefore, we hypothesized that if tumor cells activate hepatic endothelial cells to shed VCAM-1, and tumor cells themselves finally overproduce and shed ICAM-1, there might be a high possibility that both sCAMs can be detected in patients with liver metastasis. Our data showed both higher sICAM-1, sVCAM-1 levels and synchronous sICAM-1, sVCAM-1 positive rates in patients with liver metastasis than without metastasis. It has also been suggested that a subtype of gastric cancer which expresses αFP has a high tendency toward liver metastasis and poor prognosis (DeLorimier *et al.* 1993). Among 47 patients, only 3 co-expressed both sCAMs and αFP. This finding supported the fact that the expression mechanisms of sCAMs and αFP might be different. But the finding that all 3 patients who expressed the 3 biological markers showing liver metastasis suggested a high predictablity of liver metastasis, even if the number of patients was small. Therefore, sCAMs may provide valuable information in predicting cancer progression and hepatic metastasis where no adequate tumor marker is clinically applicable in gastric cancer.

VEGF has been thought to be one of the most important angiogenic factors and is observed in a variety of tumor cells and cancer tissues (Brown *et al.* 1993). In particular, VEGF is responsible for the neovascularization by paracrine and endocrine pathways (Yamamoto *et al.* 1996). We could find high sVEGF levels in gastric cancer, which increased with the cancer progression (manuscript in preparation). But no difference in sVEGF levels was found regarding liver metastasis in advanced patients in this study, nor did it correlate with either sICAM-1 or sVCAM-1. These findings suggest that sCAM and sVEGF expression may be controlled by different mechanisms or, at least, activated at different time points during cancer metastasis. Griffioen *et al.*

also found that VEGF did not alter ICAM-1 expression on endothelial cells, in contrast to the bFGF effects (Griffioen *et al.* 1996).

With cancer progression, there was a tendency toward increased expression of synchronous sCAMs (data not shown). In patients with synchronous sCAM elevation, the prognosis was poor suggesting high initial tumor burden, even if in patients without liver metastasis, the synchronous sCAM elevation also showed a poor prognosis (data not shown). These findings finally revealed synchronous sCAM expression to be an independent risk factor in gastric cancer. We are therefore doing a close follow-up in patients with synchronous sCAM expression who had no liver metastasis. Considering the fact that most clinicians depend on image studies during gastric cancer patient follow-up, our findings suggest a selorogical tool in the clinical field.

In conclusion, the serum levels and the sero-positive incidences of sICAM-1 and sVCAM-1 were higher in inoperable gastric cancer than in operable cancer or in healthy controls. The advanced cancer with liver metastasis showed higher levels of sCAMs. We therefore raise the possibility that sCAM levels may be useful monitors to determine tumor burden in gastric cancer.

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Table 3. Predictability of liver metastasis with sICAM-1, sVCAM-1 and αFP positivity in 47 patients with inoperable gastric cancer

		with liver metastasis	without liver metastasis	p-value
sICAM-1(+)	(n=18)	9 (50.0%)	9 (50.0%)	
(−)	(n=29)	3 (10.3%)	26 (89.7%)	0.004
sVCAM-1(+)	(n=34)	8 (23.5%)	26 (76.5%)	
(−)	(n=13)	4 (30.8%)	9 (69.2%)	0.44
αFP (+)	(n=5)	4 (80.0%)	1 (20.0%)	
(−)	(n=42)	8 (19.0%)	34 (81.0%)	0.01
sVEGF (+)	(n=22)	8 (36.4%)	14 (63.6%)	
(−)	(n=25)	12 (48.0%)	13 (52.0%)	0.31
both sCAMs (+)	(n=15)	7 (47.0%)	8 (53.0%)	−
both sCAMs, αFP (+)	(n=3)	3 (100.0%)	0 (0.0%)	−

108%) compared to those of portal vein after hepatic circulation (Fig. 3).

Synchronous elevation of both sICAM-1 and sVCAM-1 in liver metastasis

In 47 inoperable patients, 58.3% of the patients with liver metastasis and 22.9% of the patients without liver metastasis showed synchronous expression of both sCAMs (p=0.03) (Table 2). In synchronously sCAM-positive patients, liver metastasis was found in 47.0%(7/15) (Table 3), which was only 20.0% in both sCAM-negative groups (2/10). αFP positivity was not found in 50 operable cancer patients, whereas it was 11% (5/47) in inoperable patients. Synchronous sero-positivity of both sCAMs and αFP increased with liver metastasis (p=0.01) (Table 2). We then compared the predictability of liver metastasis with both sCAM and αFP sero-positivity. With the increment of positivity of these molecules, the liver metastasis rate increased as follows: in all negative, 11% (1/9); in one positive, 18% (4/22); in two positives, 31% (4/13); in all three positives, 100% (3/3) (p=0.01).

Comparison of sCAMs and sVEGF levels in inoperable gastric cancer

We also measured serum sVEGF levels in 47 inoperable gastric cancer patients and compared them to sICAM-1 and sVCAM-1 levels. The mean sVEGF level was 336±222 ng/ml (range 81～859 ng/ml) in patients with liver metastasis, and 274± 269 ng/ml (range 0～1,020 ng/ml) in patients without liver metastasis (p=0.45). The sero-positivity of sVEGF was 43% (15/35) and 67% (8/12) in patients without liver metastasis and liver metastasis, respectively (p=0.14). The sVEGF level correlated with neither sICAM-1 nor sVCAM-1 levels regardless of liver metastasis.

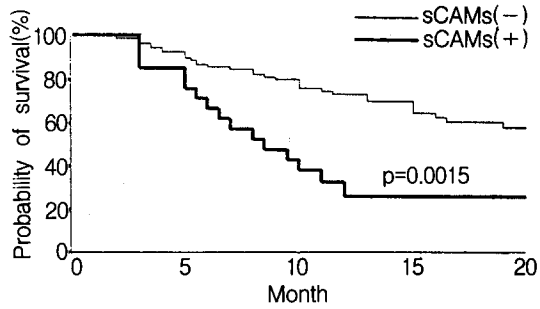

Fig. 4. Comparison of overall survival based on synchronous sCAMs expression. sCAMs(−); both sICAM-1 and sVCAM-1 negative, sCAMs(+); both sICAM-1 and sVCAM-1 positive.

Comparison of survivals based on synchronous sCAMs expression

Median survival duration in patients with synchronous sCAM elevation was only 9 months, while the median survival duration has not yet been reached in patients without sCAM elevation (Fig. 4). In univariate analysis, age (p=0.04), tumor size (p=0.003), node involvement (p=0.0001), stage (p=0.05), sICAM-1 expression (p=0.001), sVCAM-1 expression (p=