# Serum levels of soluble E-selectin in colorectal cancer*

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Adhesion molecules play an important role in tumor metastasis. E-selectin can support adhesion of colon cancer cells through the recognition of specific carbohydrate ligands. High levels of soluble E-selectin (sE-selectin) had been reported in melanoma and some epithelial tumors, especially in colorectal carcinoma. The concentrations of the sE-selectin were investigated in serum samples of 64 patients (32 men and 32 women) with colorectal cancer and 16 healthy subjects. Median age was 57 (range 20–75). Nineteen patients were staged as Dukes D, 9 of whom had liver metastasis. Serum levels of sE-selectin were determined by ELISA. In the study group, sE-selectin concentrations (mean $\pm$ SE, ng/ml) were not significantly elevated, compared with the control group ($41.09 \pm 4.57$ in the control group and $43.80 \pm 1.88$ in patients, $p>0.05$). Mean sE-selectin levels were $42.27 \pm 1.85$ in non-metastatic and $47.42 \pm 4.57$ in metastatic patients ($p>0.05$). Serum concentrations of sE-selectin were significantly elevated in patients with colorectal cancer metastatic to liver ($59.07 \pm 7.52$) in comparison to other patients without liver metastasis ($p=0.013$). There were no significant correlations between sE-selectin levels and other parameters such as age of patients, stage of disease, histopathological differentiation or localization of primary tumor. Elevated sE-selectin levels were confirmed as correlating with poor overall survival. In conclusion, sE-selectin concentrations may not be used as a predictive marker of metastasis in colorectal carcinoma, but high levels of sE-selectin may support diagnosis of liver metastasis.

*Key words: sE-selectin, adhesion molecule, colorectal cancer, liver metastasis*

Colorectal cancer is still a major health problem, and currently accounts for approximately 15% of all cancers. More than one-third of patients who undergo curative resection for colorectal cancer eventually develop recurrence, and most of those patients ultimately die of their disease. Surgery remains the main treatment for colorectal cancer, but adjuvant chemotherapy and radiotherapy have been investigated as methods for improving outcome. Recent reports have identified patients who are at high risk for recurrence after attempted curative resection of colorectal carcinoma; however, the optimum adjuvant treatment schedule is a matter of controversy [7]. Oncologists need tools that allow earlier diagnosis of colon cancer recurrence. Carcinoembryonic antigen (CEA) is one tumor marker that is valuable for identifying high-risk patients, and for detecting recurrence before radiologic signs appear during follow-up. Knowledge of the biology of tumor metastasis has expanded, and researchers have identified new markers that they claim facilitate the diagnosis of colon cancer metastasis in clinical practice.

Adhesion of tumor cells to vascular endothelium and migration through this barrier are critical steps in metastatic invasion. Research has shown that sialosyl Lewis X and sialosyl Lewis A antigens may be detected on the surface of metastatic cells, and that these antigens are involved in the binding of tumor cells to E-selectin on the surface of target endothelial cells. E-selectin is one of the adhesion molecules from the selectin family that mediates the interaction of circulating leukocytes with vascular endothelium. It has also been shown that E-selectin plays a role in colon

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cancer cell adhesion to activated endothelial cells [13]. Soluble forms of E-selectin (sE-selectin) have been detected in the serum of cancer patients [11]. Further, some reports indicate that these soluble forms are of prognostic and diagnostic importance in colorectal cancer and other malignancies [2, 9, 12, 17]. As well, there is controversy in the literature regarding how sE-selectin may be linked to life expectancy and specific sites of metastasis [4, 20].

The purpose of this prospective study was to investigate whether serum sE-selectin levels in peripheral venous blood are good predictors of hematogenous dissemination of tumor cells and life expectancy in patients with different stages of colorectal carcinoma.

## Patients and methods

Soluble E-selectin levels were measured in 64 colorectal cancer patients and 16 controls. The patient group included 32 women and 32 men (median age, 57 years; age range, 20–75 years) who were diagnosed with histologically confirmed primary epithelial colon carcinoma from February 1998 through June 1999. Patient characteristics are listed in Table 1. At the time of blood collection for sE-selectin analysis, 25 patients were Dukes' stage B, 20 were stage C, and 19 were stage D (defined as locally advanced disease and/or distant metastases). Of the 19 patients with metastasis, 8 had liver metastasis alone, 7 had locally advanced disease alone, 1 had both liver metastasis and locally advanced disease, 1 had both lung metastasis and locally advanced disease, and 2 had peritonitis carcinomatosa. All patients were followed from the time of diagnosis to June 2003. Relapses and deaths were noted.

Of the 64 patients, 45 underwent tumor resection soon after they were diagnosed with colorectal cancer. The other 19 already had metastatic disease at the time of initial diagnosis. In the 45 surgery cases, the operation was followed by adjuvant chemotherapy with 5-fluorouracil (5-FU) and leucovorin repeated every 4 weeks for a total of six cycles (the Mayo Clinic regimen). Twenty-seven of these patients also underwent postoperative adjuvant pelvic radiotherapy. The 19 patients with metastasis were treated with various chemotherapy protocols and/or palliative radiotherapy.

The control group consisted of 16 healthy volunteers (8 women and 8 men; median age, 48 years; age range, 18–74 years). These subjects were confirmed free of disease on the basis of clinical history, physical examination and routine laboratory tests, including liver and renal function assessments.

*Soluble E-selectin assay*. Serum samples were obtained after surgery (before adjuvant therapy) in the 45 no-metastasis cases, and before chemotherapy/ radiotherapy in the 19 metastasis cases. Ten milliliters of venous blood from each subject were collected into an EDTA tube and then centrifuged at 5000 rpm for 5 min. Serum samples were stored at –40 ˚C until they were analyzed. The serum sE-selectin concentration (ng/ml) in each sample was determined using an enzyme-linked immunoassay (ELISA) kit (CHEMICON International Inc., Temecula, CA, USA) and following manufacturer's instructions. For this study, we defined elevated serum sE-selectin as any level above the 95th percentile in the healthy control group. This translated to a high-normal limit of 50 ng/ml.

*Statistical analysis*. Data analysis was carried out using the software program SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± standard error (SE). The Mann-Whitney U-test was used to evaluate differences between groups. Survival curves were derived by the Kaplan-Meier method, and differences in survival rates were statistically compared using the log-rank test. P values less than 0.05 were deemed statistically significant. Multivariate analysis with the Cox proportional hazards regression model was used to identify significant predictors of survival. The hazard ratio of sE-selectin was adjusted for age, sex, tumor location, level of tumor differ-

**Table 1. Patient characteristics**

| Patients (N=64) | No. (%) |
|---|---|
| Sex | |
| Male | 32 (50) |
| Female | 32 (50) |
| Age (yrs) median (range) | 57 (20–75) |
| Median follow-up time months (range) | 10 (2–22) |
| Stage at time of diagnosis | |
| Dukes' B1 | 4 (6) |
| Dukes' B2 | 21 (33) |
| Dukes' C1 | 4 (6) |
| Dukes' C2 | 16 (25) |
| Dukes' D | 19 (30) |
| Tumor location | |
| Rectosigmoid | 37 (58) |
| Transverse colon | 12 (19) |
| Descending colon | 7 (11) |
| Ascending colon | 8 (12) |
| Differentiation | |
| Well | 34 (53) |
| Moderate | 17 (27) |
| Poorly | 5 (8) |
| mucinous | 2 |
| signet-ring cell | 1 |
| Unknown | 8 (12) |
| Metastases | |
| Liver | 8 |
| Liver and local | 1 |
| Local | 7 |
| Lung and local | 1 |
| Peritoneum | 2 |

entiation, stage of disease, nodal status, distant metastasis and liver metastasis (univariate and multivariate analysis).

## Results

All the patients and controls had detectable levels of circulating sE-selectin. The mean (±SE) sE-selectin concentrations in these two groups were 43.80±1.88 ng/ml and 41.09±4.57 ng/ml, respectively (p=0.434).

Table 2 shows the serum sE-selectin levels with patients grouped according to sex, disease stage, level of tumor cell differentiation, metastasis versus no metastasis, and metastasis location. Comparison according to disease stage revealed that patients with Dukes' C1 and B1 cancer had the lowest sE-selectin levels (39.82±10.76 and 40.91±6.29 ng/ml, respectively). However, sE-selectin level was not different according to degree of differentiation and regional lymph node metastasis (Dukes' C stage) (Tab. 2). There was no statistically significant difference between the sE-selectin levels in patients with and without hematogenous metastasis. The mean sE-selectin level in the 9 patients with liver metastases (59.07±7.52 ng/ml) was significantly higher than that the levels in the 55 other patients (41.30±1.62 ng/ml; p=0.013) and in the 10 patients with metastasis to sites other than liver (36.94±2.32 ng/ml; p=0.01). The mean sE-selectin level in the group with metastases to sites other than the liver was lower than the control mean, but this difference was not statistically significant (p>0.05).

According to the established cut-off level of 50 ng/ml, we found that 15 (23%) of the patients had elevated sE-selectin.

The above-mentioned 19 metastasis cases were identified at the time of diagnosis. During follow-up, lung metastasis was detected in three patients and liver metastasis was diagnosed in three other cases. In these six cases, no significant correlation was found between the mean sE-selectin level

**Table 2. Serum sE-selectin levels in relation to different parameters**

| Parameter | No. of pts | sE-selectin (ng/ml) | p value |
|---|---|---|---|
| Study subjects | | | |
| Patients | 64 | 43.80±1.88 | 0.434 |
| Control | 16 | 41.09±4.57 | |
| Patients only | | | |
| Sex | | | |
| Male | 32 | 42.12±2.83 | |
| Female | 32 | 45.51±2.48 | 0.175 |
| Dukes' stage | | | |
| A | – | – | |
| B | 25 | 43.77±2.74 | B vs C = 0.505 |
| C | 20 | 41.70±2.78 | B vs D = 0.751 |
| D | 19 | 45.63±4.11 | C vs D = 0.830 |
| Differentiation | | | |
| Well | 34 | 44.83±3.04 | w vs m = 0.769 |
| Moderate | 17 | 43.84±2.29 | w vs p = 0.892 |
| Poor | 5 | 43.24±9.33 | m vs p = 0.610 |
| Metastasis | | | |
| + | 19 | 47.42±4.57 | |
| – | 45 | 42.27±1.85 | 0.944 |
| Metastasis location | | | |
| Liver met[a] | 9 | 59.07±7.52 | a vs b = 0.013 |
| No liver met[b] | 55 | 41.30±1.62 | a vs c = 0.01 |
| Met type other than liver[c] | 11 | 36.94±2.32 | |

pts – patients, w – well, m – moderate, p – poor, met – metastasis

**Table 3. Hazard ratios for effect of clinicopathologic parameters on overall survival in the 64 patients with colorectal cancer**

| Univariate analysis | | Overall survival | |
|---|---|---|---|
| Variables | Categories | HR (95% CI) | p |
| Age | <50 vs ≥50 yrs | 1.08(0.46–2.51) | 0.85 |
| Sex | male vs female | 0.90(0.41–1.98) | 0.80 |
| Tumor location | colon vs rectum | 0.57(0.24–1.32) | 0.19 |
| Differentiation | w vs m+p | 0.80(0.35–1.82) | 0.60 |
| Dukes' stage | A+B vs C+D | 0.42(0.18–0.99) | 0.04* |
| Distant met | M0 vs M1 | 0.09(0.03–0.22) | <0.0001* |
| Liver met | + vs – | 0.05(0.02–0.16) | <0.0001* |
| **Multivariate analysis** | | **Overall survival** | |
| Variables | Categories | HR (95% CI) | p |
| Age | <50 vs ≥50 yrs | 0.51(0.18–1.40) | 0.19 |
| Sex | male vs female | 0.88(0.34–2.29) | 0.80 |
| Tumor location | colon vs rectum | 0.57(0.24–1.32) | 0.19 |
| Differentiation | w vs m+p | 0.30(0.11–0.83) | 0.20 |
| Dukes' stage | A+B vs C+D | 0.24(0.09–0.64) | 0.04* |
| Distant met | M0 vs M1 | 0.09(0.02–0.30) | 0.0001* |
| Liver met | + vs – | 0.08(0.02–0.33) | 0.0004* |

HR – hazard ratio, CI – confidence interval, w – well, vs – versus m – moderate, p – poor, *statistically significant

**Table 4. Hazard ratios for effect of clinicopathologic parameters and sE-selectin level on overall survival in the 64 patients with colorectal cancer**

| Multivariate analysis | | Overall survival | |
|---|---|---|---|
| Variables | Categories | HR(95% CI) | p |
| sE-selectin level | N vs elevated | 0.26(0.08–0.79) | 0.01* |
| Age | <50 vs ≥50 yrs | 0.44(0.16–1.21) | 0.11 |
| Sex | male vs female | 1.11(0.41–3.04) | 0.82 |
| Tumor location | colon vs rectum | 0.41(0.15–1.13) | 0.08 |
| Differentiation | w vs m+p | 0.35(0.12–0.97) | 0.40 |
| Dukes' stage | A+B vs C+D | 0.17(0.06–0.49) | 0.0011* |
| Distant met | M0 vs M1 | 0.07(0.02–0.27) | 0.0001* |
| Liver met | + vs – | 0.12(0.02–0.56) | <0.006* |

HR – hazard ratio, N – normal, CI – confidence interval, w – well, vs – versus, m – moderate, p – poor, *statistically significant

post-surgery and the presence of new metastatic foci during follow-up. In one patient, non-Hodgkin's lymphoma was detected as a second primary malignancy after colorectal surgery. Twenty-three (36%) of the 64 patients died of colorectal cancer during follow-up and 41 survived. One of the survivors had lung metastasis at the end of the study period (21 months after initial diagnosis).

Table 3 shows the results of uni- and multivariate regression analysis of the various clinicopathologic parameters in relation to patient survival. Disease stage, distant metastasis, and liver metastasis were identified as independent predictors of survival. Multivariate Cox proportional hazard analysis for the clinicopathologic parameters and sE-selectin level are shown in Table 4. Comparison of the patients with normal sE-selectin level to patients with elevated sE-selectin revealed a 0.26 hazard ratio for prognosis of colorectal cancer (p=0.01).

Figure 1 shows the cumulative survival of the patients grouped according to the level of serum sE-selectin (normal versus elevated levels). For the 64 patients total, the median survival time after diagnosis was 43 months (range with SE, 40–46 months), and the survival rate at 60 months of follow-up was 57%. For the patients who had normal sE-selectin levels (≤50 ng/ml) after surgery/before chemotherapy, the median survival time was 47 months and survival at 60 months was 65%. The corresponding findings for the group with elevated sE-selectin (>50 ng/ml) were 27 months and 27%. The difference in the survival parameters between the normal sE-and the elevated sE-selectin group was found statistically significant. Log-rank analysis confirmed that elevated postoperative sE-selectin level was correlated with poor overall survival (p=0.0076, Fig. 1).

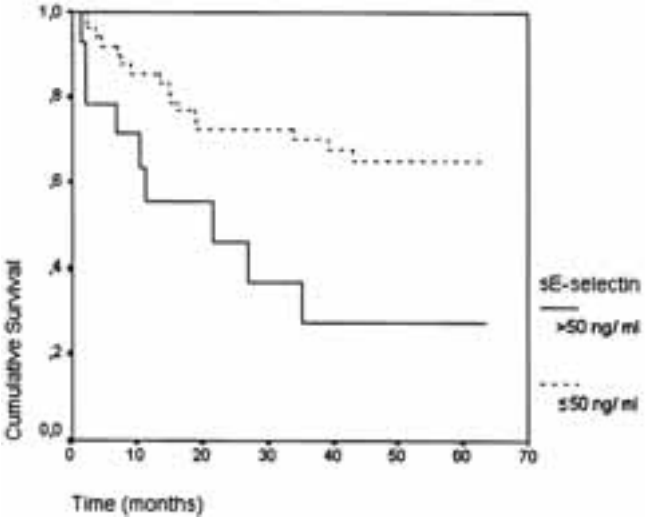


**Figure 1. The Kaplan-Meier curves for the groups with normal (...) and elevated (–) sE-selectin levels after surgery/before chemotherapy. The patients with normal serum sE-selectin had a significantly higher survival rate than patients with elevated serum sE-selectin (p=0.0076, log-rank test).**

## Discussion

In this study, we compared serum sE-selectin concentrations in patients with colorectal carcinoma to levels in healthy controls. The sE-selectin levels in the cancer patients with liver metastasis were significantly higher than the levels in patients without liver metastasis, and were also higher than control levels.

Authors have suggested that a number of adhesion molecules play crucial roles in hematogenous spread of metastases, and in adhesive interactions between tumor cells and the vascular endothelial cells of target organs [2, 8, 9, 17]. Also, experimental work has suggested that the efficiency of E-selectin-mediated binding of colonic carcinoma cells to human endothelium is correlated with tumor progression and hematogenous spread of metastases [13]. On account of this situation, E-selectin dependent cancer cell adhesion to vascular endothelium may be vital in the metastatic process of cancer.

In addition to CEA and CA 19.9, sE-selectin is one of many substances that have been investigated as potential markers of colorectal cancer. As mentioned, sE-selectin is known to be involved in the binding of metastatic tumor cells to the endothelial cells of various organs. Immunohistochemical investigations have demonstrated increased expression of E-selectin in organs with metastases [13, 14]. In one prospective study, TAKAHASHI et al [14] detected elevated sE-selectin levels before radiologic evidence of tumor in five of eight patients who developed colon cancer recurrence during follow-up. As well, most previous studies have documented increased sE-selectin levels in colorectal cancer patients with metastatic disease, and particularly high levels in cases of liver metastasis [1, 6, 8, 13, 14].

Initial research indicated that elevated levels of circulating E-selectin were most frequent in patients with metastatic gastrointestinal cancer, and that the levels in this group were significantly higher than levels in healthy control subjects [2]. High levels of E-selectin expression have been detected in the hepatic endothelium just near colon cancer metastases, and immunohistochemical investigations have also demonstrated increased E-selectin expressions in organs with metastases [19]. As a result of this, authors have suggested that E-selectin measurements can be used to diagnose hepatic metastases in patients with different types of colorectal cancer [19]. In our study, we found higher levels of sE-selectin in colorectal cancer patients with liver metastases than in patients who did not have hepatic metastases. Unfortunately, we observed no correlation between sE-selectin levels and different degrees of primary tumor differentiation.

In a study, the relationship of elevated sE-selectin with inflammation was investigated and no correlation was found between the levels of sE-selectin or the presence of

metastasis and the levels of inflammation markers. The authors concluded that elevated sE-selectin levels are specific for liver metastases of colorectal cancer and this elevation is related to the events of adhesion and neovascularization of metastatic cells [18].

Previous studies have revealed that Dukes' stage D patients have significantly higher levels of sE-selectin than Dukes' A, B or C patients, and healthy controls [6, 14]. Previous research has also shown that the mean serum sE-selectin level in patients with metastatic colon cancer is significantly higher than that in patients with non-metastatic tumors [14]. Comparing with the previous studies, the results of our study may seem to be partially contradictory. However, all of the colorectal cancer patients in the series reported by ITO et al [6] and TAKAHASHI et al [14] had metastases to the liver, so our results are actually in line with these authors' findings.

Interestingly, other investigations have demonstrated elevated serum sE-selectin in patients with liver diseases such as chronic hepatitis, liver cirrhosis, primary sclerosing cholangitis and hepatocellular carcinoma [3, 5]. Studies of colorectal cancer patients with hepatic metastases have shown that elevated sE-selectin level is associated with elevated alkaline phosphatase and decreased serum albumin [15, 16]. One possible explanation for elevated sE-selectin in this patient group is that soluble adhesion molecules are excreted via the biliary tract, and that clearance is impaired in the setting of intrahepatic cholestasis secondary to liver metastasis [15]. The association of elevated serum level of sE-selectin with survival was concluded as therefore more likely to be related to the location of metastatic disease rather than underlying tumor biology. In addition to this, different studies have also documented elevated levels of sE-selectin both in patients with pulmonary metastases from colorectal cancer [8] and in patients with various distant metastases from breast cancer [10].

In conclusion, our study indicates that elevated levels of serum sE-selectin were mostly found in colorectal cancers with hepatic metastases and the poor overall survival was found to be related to the presence of hepatic metastases in these patients. Our finding of elevated levels of serum sE-selectin in colorectal cancer patients with liver metastases is in line with other reports in the literature. Patients with all stages of colorectal cancer may exhibit low levels of sE-selectin during follow-up, and the prognostic significance of this is not clear. Elevated levels of sE-selectin may be an indicator of liver metastasis in this patient group. More research is needed to determine the importance of this molecule in relation to occult colon cancer metastases. Longitudinal studies involving large numbers of colon cancer patients and measurement of sE-selectin level during the course of the disease will hopefully provide more information.

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