

Circulating secretory component in relation to early diagnosis and treatment of liver metastasis from colorectal carcinomas

D Kvale, J Norstein, G I Meling, O P Børner, P Brandtzaeg, F Langmark, T O Rognum

Abstract

Aims: To evaluate serum secretory component in relation to early detection and clinical management of liver metastasis in patients with colorectal cancer.

Methods: Secretory component and carcinoembryonic antigen (CEA) were analysed in serial serum samples from 23 patients who had liver metastases as the only apparent recurrence, and in sera from 54 matched controls. Results of surgical treatment of recurrences were classified peroperatively as radical when no residual tumour was apparent and resection margins were free of disease.

Results: In total, 18 (78%) patients had increased secretory component during the whole follow up period (median 16 months); 12 (52%) had raised secretory component concentrations before clinical recurrence (median lead time 5.2 months). There was no difference before recurrence between circulating secretory component and CEA in sensitivity and lead times. Seventeen patients underwent surgery for hepatic metastasis; seven had radical hepatic resection of which only two (29%) showed increased secretory component concentrations before clinical recurrence; both had concurrent raised CEA values. By contrast, secretory component was raised in 83% of those cases considered inoperable.

Conclusions: Although serum secretory component clearly increases in most patients with liver metastases, its clinical value seems questionable because secretory component apparently indicates mainly inoperable hepatic metastases.

secretory component concentrations and the presence and progression of liver metastasis.^{1,2}

Secretory component is a transmembrane receptor for polymeric IgA (pIgA) and pIgM in secretory epithelial cells, including the colonic epithelium.³ It mediates translocation of pIgA and pIgM into exocrine fluids where its extracellular segments, in conjunction with the respective ligands, become part of the secretory immunoglobulins (SIgA and SIgM) or appear as free secretory component. The small amounts of secretory component appearing in normal peripheral blood exist only as part of circulating SIgA and SIgM due to the large molar excess of pIgA and particularly pIgM in serum.⁴

Secretory component is also expressed by malignant secretory epithelial cells, particularly in colonic carcinomas.^{5,6} Increased release of secretory component from adenocarcinomas to peripheral blood could conceivably raise the amounts of circulating secretory component. We therefore measured SIgA and SIgM in preoperative serum samples from 100 patients with colorectal carcinoma. A follow up study of the same patient group indicated that secretory component increased in four of the five patients who were later found to have liver metastasis; the median lead time before clinical recurrence was 5.5 months.² However, the small number of patients, and the fact that hepatic resection was not performed, did not permit assessment of the clinical value of these measurements. In view of the recent promising experience with resection of liver metastasis from colorectal carcinoma,^{7,8} this study aimed to relate concentrations of circulating secretory component in serial serum samples to the clinical outcome of patients subjected to such treatment. The clinical value of secretory component as a tumour marker in colorectal carcinoma could thereby be more firmly established, in relation to early diagnosis of liver metastasis, but particularly as to whether increased secretory component concentrations could indicate if hepatic lesions could be radically removed.

Methods for the early detection of primary tumours, local recurrences, and metastases from colorectal cancer are of considerable clinical interest. We studied the value of circulating secretory component to this end, and found a strong association between increased

Laboratory for Immunohistochemistry and Immunopathology (LIIPAT) and Medical Department A, University of Oslo, The National Hospital, Rikshospitalet, N-0027 Oslo 1, Norway
D Kvale
P Brandtzaeg

Surgical Department B, The National Hospital, Oslo
J N Norstein

Institute for Forensic Medicine, The National Hospital, Oslo
G I Meling,
T O Rognum

Central Laboratory, The Norwegian Radium Hospital, Oslo
O P Børner

Cancer Registry of Norway, Oslo
F Langmark

Correspondence to: D Kvale

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Characterisation of patients

n = (m + f)*	Age (years)†	Dukes' stage (A + B + C + D)‡	Primary location (colon + rectum)	Recurrence time (months)†**	Recurrences operated n (%)	Follow up (months)†	Samples per patient†
23 (11 + 12)	68 (30 - 83)	4 + 6 + 11 + 2	19 + 4	8 (4 - 26)	17 (74%)	16 (1 - 33)	5 (1 - 16)

*Males + females.

†Median (range).

‡Distant organ metastasis or irremovable tumour was assigned stage D according to Turnbull *et al.*¹⁴ Patients with stage D had their metastasis removed at the primary operation.

**Time interval between primary operation and clinical recurrence.

Methods

Serial serum samples were taken from 23 patients with liver metastases as the only clinical manifestation of recurrence from colorectal carcinoma (table). Cases were selected from a larger group of patients currently subjected to clinical follow up studies.

Liver metastases were confirmed by ultrasound scan, computed tomography, or liver biopsy specimen. The results of surgical treatment of recurrences were classified peroperatively as curative (radical) when no residual tumour was present and the resection margins were microscopically free of tumour.

IMMUNOASSAYS FOR CIRCULATING SECRETORY COMPONENT AND CARCINOEMBRYONIC ANTIGEN (CEA)

Total serum secretory component was estimated by combining the results from enzyme linked immunosorbent assays (ELISAs) for SIgA and SIgM as described in detail elsewhere.⁹ All patient sera were analysed simultaneously with samples from 54 age and sex matched controls. The upper reference limits for SIgA, SIgM, and secretory component were defined as the 97.5 percentile values in the control group.¹⁰

CEA was measured in a running laboratory routine by an immunoradiometric assay and with controls as described.¹¹

CRITERIA FOR ESTABLISHING INCREASE IN CIRCULATING SECRETORY COMPONENT AND CEA

Secretory component and CEA in serial samples were considered to be increased if the

serum concentrations were above the upper normal reference limits or permanently increased to at least two-fold the values obtained immediately after the primary operation, even when the raised values were within the normal reference limits.

Lead time was defined as the interval between the first serum sample showing increased secretory component or CEA and the clinical recognition of recurrence.

Comparisons between patient groups were based on the Wilcoxon's two-sample test. Fisher's test of exact probability was used for comparisons of frequency distributions.

Results

CIRCULATING SECRETORY COMPONENT AND CEA IN RELATION TO RECURRENCE

The upper normal reference limits for SIgA, SIgM, and total secretory component in serum were 42 mg/l, 33 mg/l, and 11.9 mg/l, respectively, as calculated from the results in the control group.

Altogether, 18 (78%) patients developed increased secretory component concentrations throughout the whole follow up period. The first positive samples had a median value of 16.3 mg/l (range 5.4–90.7 mg/l). However, only 12 (52%) showed raised secretory component before clinical recurrence with a median initial increased value of 14.6 mg/l (range 5.4–23.3 mg/l); median lead time was 5.2 months (range 0.1–11.3 months). Four of these 12 patients had samples showing increased secretory component concentrations (according to the criteria defined above) within the normal range (fig 1), but secretory component later continued to increase above the upper normal reference limit in all of them.

CEA was raised before clinical recurrence in 14 (61%) of the patients (fig 1) with a median lead time of 2.7 months (range 0.3–14.5 months). There was no difference in sensitivity or lead times between the secretory component and CEA measurements. However, no correlation was found between an increase in secretory component and CEA. Thus 19 (83%) of the patients developed either increased secretory component CEA values, or both, before recurrence, giving a higher combined sensitivity than that of each maker ($p = 0.03$ and $p = 0.09$, respectively) (fig 1).

CIRCULATING SECRETORY COMPONENT AND CEA IN RELATION TO SURGICAL TREATMENT

The patients were divided into three groups: (a) those who were peroperatively classified as radically resected ($n = 7$); (b) patients not radically operated on at laparotomy ($n = 10$); and (c) patients who were considered inoperable after clinical examination ($n = 6$).

Only two (29%) of the radically resected patients had developed raised circulating secretory component concentrations before recurrence and both had increased CEA at the same time. In contrast, the sensitivity of raised secretory component concentrations tended to be higher in the patients who were not operated on (83%, $p = 0.08$). Altogether, 10 (63%)

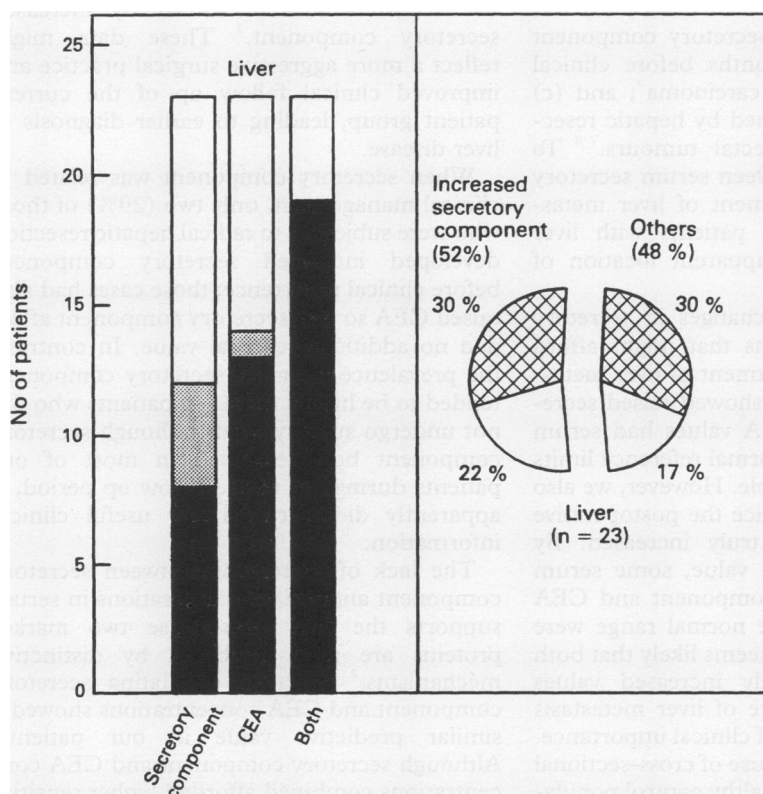
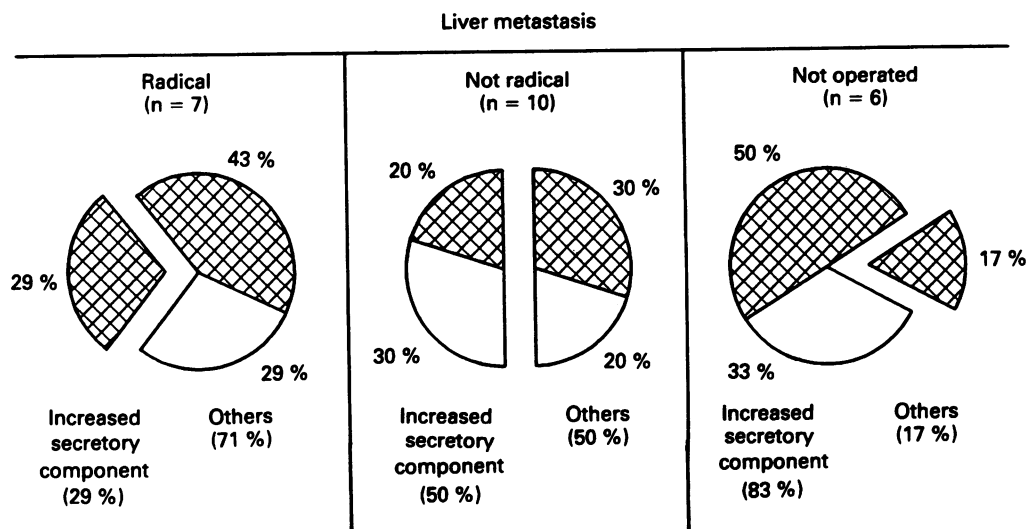


Figure 1 Left panel: Patients with increased serum values of secretory component, or CEA, or both before clinical recurrence; first increased serum sample either above upper normal reference values (filled bars), or within reference limits (shaded bars), as indicated. Right panel: Incidence of raised secretory component (unhatched areas) and CEA (hatched areas) in the same patients.

Figure 2 Prevalence of increased secretory component and CEA (hatched areas) before clinical recurrence in relation to surgical classification of patients with liver metastasis.



of the patients who were not radically treated had developed increased secretory component (fig 2).

The sensitivity of CEA for patients who underwent radical surgery tended to be higher (72%) than for secretory component (29%), but not significantly so. Moreover, there was no difference in CEA sensitivity between radically treated cases (72%) and the other patients (56%) (fig 2).

Discussion

This study was prompted by: (a) a significant association between high secretory component concentrations and liver metastasis¹; (b) our recent observation that secretory component may increase several months before clinical recurrence of colorectal carcinoma²; and (c) the positive results obtained by hepatic resection of secondary colorectal tumours.^{7,8} To evaluate the relation between serum secretory component and development of liver metastasis per se we studied patients with liver metastasis as the only apparent location of recurrence.

We wanted to detect changes in secretory component concentrations that might afford earlier diagnosis and treatment of liver metastasis. Most patients who showed raised secretory component and CEA values had serum values above the upper normal reference limits in the first increased sample. However, we also defined values at least twice the postoperative concentration as being truly increased. By using this as a reference value, some serum samples with secretory component and CEA concentrations within the normal range were classified as increased. It seems likely that both these definitions of truly increased values might reflect the presence of liver metastasis which, in turn, could be of clinical importance. It may be argued that the use of cross-sectional reference values from a healthy control population is inappropriate for an individual patient over time.¹² Because our case study material was too small to meet the statistical criteria for estimation of a significant patient specific

increase,¹³ we defined an arbitrary two-fold increase of secretory component (and CEA) as a true increase. This limit nevertheless exceeds that of other serum variables.¹³

During the whole follow up period, 78% of the patients developed increased concentrations of circulating secretory component. This overall result corresponded well with the incidence (75%) observed in our previous study.² However, the sensitivity of secretory component for indicating hepatic spread was reduced from 78% to 52% before clinical recurrence, with a median lead time of 5.2 months. This result tended to be lower than in our preliminary follow up study, in which four (80%) of five recurrences were shown by increased secretory component.² These data might reflect a more aggressive surgical practice and improved clinical follow up of the current patient group, leading to earlier diagnosis of liver disease.

When secretory component was related to clinical management, only two (29%) of those who were subjected to radical hepatic resection developed increased secretory component before clinical recurrence; those cases had also raised CEA so that secretory component afforded no additional clinical value. In contrast, the prevalence of raised secretory component tended to be higher (83%) in patients who did not undergo surgery. Thus although secretory component became raised in most of our patients during the whole follow up period, it apparently did not add any useful clinical information.

The lack of correlation between secretory component and CEA concentrations in serum supports the view that these two marker proteins are shed to blood by distinctive mechanisms.² Notably, circulating secretory component and CEA concentrations showed a similar predictive value in our patients. Although secretory component and CEA concentrations combined afforded higher sensitivity for liver metastasis before clinical detection than either marker alone, this trend did not hold true for the patients who underwent radical resection.

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- 1 Kvale D, Rognum TO, Brandtzaeg P. Elevated levels of secretory immunoglobulins A and M in serum of patients with large bowel carcinoma indicate liver metastasis. *Cancer* 1987;59:203-7.
- 2 Kvale D, Rognum TO, Brandtzaeg P. Early detection of liver metastasis in patients with colorectal carcinoma by increased levels of circulating IgA- and IgM-associated secretory component. *Br J Cancer* 1987;56:629-32.
- 3 Brandtzaeg P, Halstensen TS, Kett K, et al. Immunobiology and immunopathology of human gut mucosa: humoral immunity and intraepithelial lymphocytes. *Gastroenterology* 1989;97:1562-84.
- 4 Kvale D, Brandtzaeg P. Does secretory component (SC) exist as free SC in human serum? *J Immunol Methods* 1988;113:279-81.
- 5 Rognum TO, Elgjo K, Brandtzaeg P, Ørjasæther H, Bergan A. Plasma carcinoembryonic antigen concentrations and immunohistochemical patterns of epithelial marker antigens in patients with large bowel carcinoma. *J Clin Pathol* 1982;35:922-33.
- 6 Brooks JJ, Ernst CS. Immunoreactive secretory component of IgA in human tissues and tumors. *Am J Clin Pathol* 1984;82:660-5.
- 7 Hughes KS, Rosenstein RB, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastasis. A multi-institutional study of long-term survivors. *Dis Colon Rectum* 1988;31:1-4.
- 8 Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastasis from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990;77:1241-6.
- 9 Kvale D, Brandtzaeg P. An enzyme-linked immunosorbent assay for differential quantitation of secretory immunoglobulins of the A and M isotypes in human serum. *J Immunol Methods* 1986;86:107-14.
- 10 Solberg HE. The theory of reference values, part 5. *J Clin Chem Clin Biochem* 1983;21:749-60.
- 11 Børner OP, Nustad K. Selection of monoclonal antibodies for use in an immunometric assay for carcinoembryonic antigen. *J Immunol Methods* 1990;127:171-8.
- 12 Harris EK, Yasaka T, Horton MR, Shakarji G. Comparing multivariate and univariate subject-specific reference regions for blood constituents in healthy persons. *Clin Chem* 1982;28:422-6.
- 13 Harris EK, Yasaka T. On the calculation of a "Reference Change" for comparing two consecutive measurements. *Clin Chem* 1983;29:25-30.
- 14 Turnbull RB, Kyle K, Watson FR, Spratt J. Cancer of the colon: The influence of no-touch isolation technique on survival rates. *Ann Surg* 1967;166:420-5.