A critical comparison of the value of pregnancy-associated α_2 -glycoprotein and carcinoembryonic antigen assays in patients with colorectal cancer

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SUMMARY Absolute serum concentrations of pregnancy-associated α_2 -glycoprotein (α_2 -PAG) and carcinoembryonic antigen (CEA) were compared in 54 patients before and after surgery for colorectal cancer. Preoperatively, elevated levels of α_2 -PAG were found in 32 (59%) and of CEA in 35 (65%). Postoperatively, elevated α_2 -PAG levels were found in 10 of 18 patients (56%) without clinical evidence of recurrence whereas elevated CEA levels were present in three (16%). In patients who developed clinical evidence of tumour recurrence, α_2 -PAG levels were elevated in 8 of 13 (62%) while CEA levels were uniformly abnormal. It is concluded that, in this cross-sectional study, measurement of α_2 -PAG concentrations is less reliable than CEA in the detection of tumour recurrence after apparently curative surgery for colorectal cancer.

Carcinoembryonic antigen (CEA) is well established as a tumour marker in colorectal cancer, particularly in the early detection of tumour recurrence after apparently curative surgery (Holyoke *et al.*, 1972; Mach *et al.*, 1974; Mackay *et al.*, 1974). Pregnancy-associated α_2 -glycoprotein (α_2 -PAG), a high molecular weight serum protein probably produced by circulating leucocytes (Stimson and Blackstock, 1975; Thomson *et al.*, 1978), occurs in high serum concentrations in pregnancy (Bohn, 1972; Horne *et al.*, 1973) but in only trace amounts in normal individuals (von Schoultz *et al.*, 1976). Raised serum α_2 -PAG concentrations have been reported in several malignant conditions (Horne *et al.*, 1973; Stimson, 1974; Than *et al.*, 1975; Burt *et al.*, 1978). Further, it has been claimed that elevated α_2 -PAG levels occur in patients with breast cancer before clinical recognition of recurrent disease (Stimson 1975a and b; Anderson *et al.*, 1976).

We have shown previously that where serum α_2 -PAG levels are expressed as a percentage change of the preoperative level, they reflect the clinical course of colorectal cancer (Wood *et al.*, 1978). In the present cross-sectional study, we have compared critically the value of α_2 -PAG and CEA

assays as monitors of disease progression in patients with colorectal cancer.

Patients

Fifty-four patients (22 men, 32 women; mean age 59 years; range 30-75 years) with histologically proven large bowel cancer were studied. Serum samples were obtained preoperatively in all cases and at regular intervals in the postoperative period. The follow-up interval was up to 13 months.

Methods

Carcinoembryonic antigen estimations were performed on unextracted serum using a double antibody technique (Laurence *et al.*, 1972). The upper limit of normal for our laboratory was 25 μ g/l (Wood *et al.*, 1976). Values were referred to a purified CEA preparation provided by Professor A. M. Neville. Pregnancy-associated α_2 -glycoprotein estimations were performed on unextracted serum by an electroimmunoassay technique modified (Bohn, 1972) from that described by Laurell (1966). The upper limit of normal for men was 5 mg/l but for women the upper limit was higher, being 30 mg/l at age 30 years and rising to 60 mg/l

by age 75 years (MacMillan *et al.*, 1977, unpublished data). Levels greater than 60 mg/l in women were taken to be elevated in this study. A standard reference preparation of α_2 -PAG was provided by Dr H. Bohn, Behringwerke AG, West Germany.

Results

Preoperatively (Table 1) elevated α_2 -PAG levels were found in 32 patients (59%) and elevated CEA levels in 35 (65%). In patients in whom curative surgery was not possible due to extensive local tumour spread or metastases, elevated levels of α_2 -PAG occurred in 16 of 23 (70%), and elevated CEA in 18 of 23 (78%). In patients who underwent 'curative' resection, α_2 -PAG was elevated preoperatively in 16 of 31 (52%) and CEA in 17 of 31 (55%).

Table 1 Comparison of serum α_2 -PAG and CEA levels preoperatively

	α_2 -PAG		CEA	
	Normal	Elevated	Normal	Elevated
'Curative' resection	15	16	14	17
Local invasion	2	8	2	8
Disseminated tumour	5	8	3	10
Total	22	32	19	35

Marker levels during the 13-month postoperative period are compared in Table 2. The analysis includes the last recorded results in four patients with distant metastases who died within this period. Ten of 18 patients (56%) who had undergone 'curative' surgery and who remained apparently free of tumour showed elevated α_2 -PAG levels, whereas only three (16%) showed elevated CEA levels. Further investigation of the latter patients failed to reveal occult tumour. Of the 13 patients who had developed clinical signs of tumour recurrence, eight (62%) had elevated α_2 -PAG levels while CEA levels were uniformly elevated. All the 10 patients with extensive tumour spread at operation had elevated CEA levels and eight had elevated

Table 2 Comparison of serum α_2 -PAG and CEA at 13 months postoperatively

	α_2 -PAG		CEA	
	Normal	Elevated	Normal	Elevated
'Curative'				
(a) Tumour free	8	10	15	3
(b) Tumour recurrence	5	8	0	13
Local invasion	2	8	0	10
Disseminated tumour	5	8	0	13
Total	20	34	15	39

α_2 -PAG levels. Of the 13 patients with distant metastases, eight (62%) had elevated α_2 -PAG levels and all had elevated CEA.

Table 3 Postoperative changes in serum α_2 -PAG and CEA levels in patients with tumour recurrence

	α_2 -PAG	CEA
Increased levels from normal preoperative levels	3	5
Persistently elevated	5	8
No change from normal levels	5	—
Total	13	13

Table 3 analyses the temporal pattern of marker levels in the 13 patients with tumour recurrence after 'curative' surgery. All patients had elevated CEA levels; in five, levels became abnormal before clinical detection of tumour recurrence, while in the other patients, CEA levels never returned to normal after surgery. Eight patients (62%) showed elevated α_2 -PAG levels; in three patients levels became abnormal though normal preoperatively. In only one of these did α_2 -PAG levels rise before CEA. In five patients with elevated preoperative levels α_2 -PAG remained persistently elevated.

Discussion

The role of pregnancy-associated α_2 -PAG as a tumour marker has not been fully assessed. Increased serum concentrations of α_2 -PAG have been noted during the clinical course of malignant diseases (Horne *et al.*, 1973; Stimson, 1975a and b; Than *et al.*, 1975; Wood *et al.*, 1978) but this finding is disputed by other groups (Damber *et al.*, 1976; Burnett *et al.*, 1977).

The purpose of the present study was to compare the clinical value of measurement of absolute concentrations of α_2 -PAG and CEA in the same patients with colorectal cancer, taking into account the age and sex relatedness of α_2 -PAG values (von Schoultz *et al.*, 1976; MacMillan *et al.*, 1977, unpublished data). Preoperatively, a similar proportion of patients showed elevated marker levels. Postoperatively, CEA assays were clearly superior in indicating tumour burden and in predicting tumour recurrence after 'curative' surgery. α_2 -PAG assays were frequently falsely positive, 53% of patients showing elevated values in the absence of clinical evidence of tumour recurrence up to 13 months after operation. Only 16% of these patients had elevated CEA levels, and these included one patient with a single marginally elevated value (26 μ g/l). All patients with tumour recurrence after 'curative' surgery showed elevated CEA levels

whereas α_2 -PAG was falsely negative in 38%. In patients with residual local tumour or distant metastases, the proportion of patients with elevated α_2 -PAG levels increased only slightly from 70% preoperatively to 80% after operation whereas all the patients showed elevated CEA levels in the follow-up period.

Although, in longitudinal studies, postoperative changes in α_2 -PAG levels as related to the pre-operative level may give an indication of tumour recurrence (Wood *et al.*, 1978), the present study clearly shows that measurement of absolute concentrations of α_2 -PAG is less reliable than that of CEA both in reflecting tumour burden and in the early detection of tumour recurrence after apparently curative surgery for colorectal cancer.

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