A critical comparison of the value of pregnancy-associated alpha_2-glycoprotein and carcinoembryonic antigen assays in patients with colorectal cancer


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SUMMARY Absolute serum concentrations of pregnancy-associated alpha_2-glycoprotein (a_2-PAG) and carcinoembryonic antigen (CEA) were compared in 54 patients before and after surgery for colorectal cancer. Preoperatively, elevated levels of a_2-PAG were found in 32 (59%) and of CEA in 35 (65%). Postoperatively, elevated a_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, a_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 a_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 alpha_2-glycoprotein (a_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 a_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 a_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 a_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 a_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 µg/l (Wood et al., 1976). Values were referred to a purified CEA preparation provided by Professor A. M. Neville. Pregnancy-associated alpha_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 α2-PAG was provided by Dr H. Bohn, Behringwerke AG, West Germany.

Results

Preoperatively (Table 1) elevated α2-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 α2-PAG occurred in 16 of 23 (70%), and elevated CEA in 18 of 23 (78%). In patients who underwent 'curative' resection, α2-PAG was elevated preoperatively in 16 of 31 (52%) and CEA in 17 of 31 (55%).

Table 1 Comparison of serum α2-PAG and CEA levels preoperatively

<table>
<thead>
<tr>
<th></th>
<th>α2-PAG</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Curative' resection</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Local invasion</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Disseminated tumour</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>32</td>
</tr>
</tbody>
</table>

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 α2-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 α2-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 α2-PAG levels. Of the 13 patients with distant metastases, eight (62%) had elevated α2-PAG levels and all had elevated CEA.

Table 3 Postoperative changes in serum α2-PAG and CEA levels in patients with tumour recurrence

<table>
<thead>
<tr>
<th></th>
<th>α2-PAG</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased levels from normal preoperative levels</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Persistently elevated</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>No change from normal levels</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

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 α2-PAG levels; in three patients levels became abnormal though normal preoperatively. In only one of these did α2-PAG levels rise before CEA. In five patients with elevated preoperative levels α2-PAG remained persistently elevated.

Discussion

The role of pregnancy-associated α2-PAG as a tumour marker has not been fully assessed. Increased serum concentrations of α2-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 α2-PAG and CEA in the same patients with colorectal cancer, taking into account the age and sex relatedness of α2-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. α2-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 µg/l). All patients with tumour recurrence after 'curative' surgery showed elevated CEA levels.
whereas α₂-PAG was falsely negative in 38%. In patients with residual local tumour or distant metastases, the proportion of patients with elevated α₂-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 α₂-PAG levels as related to the preoperative level may give an indication of tumour recurrence (Wood et al., 1978), the present study clearly shows that measurement of absolute concentrations of α₂-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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References


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