Leading articles

Carcinoembryonic antigen and recurrent colorectal cancer

It is 20 years since Gold and Freedman first described carcinoembryonic antigen. The fond hope that this would facilitate the primary diagnosis of colorectal cancer has long since evaporated, after the demonstration that carcinoembryonic antigen is produced by other tumours, in non-malignant disorders and, indeed, by normal individuals.

Since the early 1970s there has been much interest in the possible applications of carcinoembryonic antigen assay in the patient already known to have colorectal cancer. In particular, it has been examined in two roles – as a preoperative prognostic index and rather more interestingly, as a postoperative serial monitor to detect recurrence, particularly with a view to early second look surgery in the hope of cure.

Preoperative serum carcinoembryonic antigen levels in diagnosed colorectal cancer are raised in 40–70% of patients. Preoperative serum carcinoembryonic antigen correlates with tumour histology and pathological stage – carcinoembryonic antigen is raised in 95% of patients with well differentiated tumours, while the level is raised in only 30% of those with poorly differentiated adenocarcinomas. Around 40% of patients with normal carcinoembryonic antigen levels have Dukes' stage A lesions, while a similar proportion with a carcinoembryonic antigen above 10 ng/ml have disseminated disease. This correlation undoubtedly reflects the bulk of tumour present in individual cases.

There is disagreement between the various groups who have explored the relationship between preoperative carcinoembryonic antigen and prognosis, but most have found a correlation, sometimes as discriminating as pathological staging. In 1976 Herrera found that only 35% of those with a normal preoperative carcinoembryonic antigen had developed clinical evidence of recurrence by 18 months compared to 83% of those with a raised preoperative carcinoembryonic antigen.

In 1980 Goslin published similar findings, furthermore, when he excluded poorly differentiated tumours from his series, with their poor prognosis and low expression of carcinoembryonic antigen, the prognostic value was even more apparent. Others have not found preoperative carcinoembryonic antigen prognostically useful or have found its usefulness limited to certain pathological subgroups. There was sufficient evidence for the usefulness of carcinoembryonic antigen in this context for the National Institutes of Health to suggest in their 1981 Consensus Statement that it should be used as an adjunct to clinicopathological staging.

In the early 1970s several groups in Britain, Europe, and the United States published reports suggesting that monitoring of postoperative carcinoembryonic antigen could reliably detect recurrent colorectal cancer,
and it was hoped that this early warning would enable surgeons to reoperate in suitable cases to remove the recurrence curatively.\textsuperscript{2, 12, 14, 15} Since then many groups have published their results and conclusions, the protagonists appearing to be more eager to publish their results than the antagonists. In the early days only Moertel seriously questioned the usefulness of serial carcinoembryonic antigen monitoring, suggesting in scathing terms that the only demonstrable product for most patients was 'the needless anxiety produced by premature knowledge of the presence of a fatal disease'.\textsuperscript{16, 17} Since that time, in the absence of any controlled data, the subject has remained contentious.

Several important questions remain debatable or unanswered:

(1) IS SERIAL CARCINOEMBRYONIC ANTIGEN A RELIABLE MARKER OF RECURRENT DISEASE?
In the six large series reported since 1982 there were 2147 patients whose serum carcinoembryonic antigen had been followed postoperatively.\textsuperscript{5, 10, 18–20} and personal communication (J P Minton). Of those, 537 (25\%) have developed recurrent disease, of whom 404 (75\%) developed a rise in carcinoembryonic antigen before, or less commonly at the same time as, clinical evidence of recurrence. It must be remembered that in up to 12\% of patients a transient carcinoembryonic antigen rise may occur which is not due to recurrence,\textsuperscript{21} and can usually be attributed to some intercurrent disease affecting another system, or to a change in smoking or drinking habits. Such rises can usually be distinguished from the consistent rise produced by recurrent cancer. Of those patients undergoing laparotomy on the basis of a raised serum carcinoembryonic antigen, 85–90\% prove to have abdominal recurrent disease and most of the remainder are found to have extra-abdominal metastases within a year or so of true carcinoembryonic antigen rise.\textsuperscript{12, 22–25} Thus it would appear that serum carcinoembryonic antigen, although not uniformly sensitive or specific, is a reliable marker of recurrent disease.

(2) ARE THERE CASES IN WHICH RECURRENT COLORECTAL CANCER MAY BE CUREABLE?
There are many reports scattered through the literature of small series of curative resections of recurrent colorectal cancer.\textsuperscript{25–28} More recently Paul Sugarbaker, Head of the Colorectal Cancer Section at the US National Cancer Institute, and coworkers have surveyed world experience in the treatment of recurrent colorectal cancer. In their study 15\% of curative resections failed only locally. Of these, 20\% of patients were curable by further local surgery and on the basis of these data they suggested that an aggressive approach to local recurrence could achieve a 3\% improvement in the overall survival figures following primary resection.\textsuperscript{30} Their survey showed a wide disparity in the incidence of isolated liver recurrence: from 20 to 70\%. They found that in 25\% of patients liver metastases were locally resectable and of these 30\% were cured by such treatment. Most of the published experience derives from the United States and there remains a reluctance in Britain to treat hepatic recurrence aggressively. Although many surgeons, British and American, might argue with Sugarbaker's conclusions, there can be no doubt that there are patients with recurrent colorectal cancer who can be cured.
(3) **IS SERIAL CARCINOEMBRYONIC ANTIGEN ASSAY A BETTER INDICATOR OF RESECTABLE RECURRENCE THAN CONVENTIONAL CLINICAL SURVEILLANCE?**

There is great disparity in the results published by different groups, perhaps partly due to the variations in assay technique used in different centres. Hine and Dykes found that 67% of their patients had a carcinoembryonic antigen rise while the patient was still asymptomatic, while Wedell recorded a carcinoembryonic antigen rise in similar circumstances in only 18% of patients. In a series of patients followed with serial computed tomography scans, five of 13 with liver metastases – the condition most likely to induce a carcinoembryonic antigen rise – died with a normal serum carcinoembryonic antigen. Most workers, however, have found that serum carcinoembryonic antigen rises on average four months before there is clinical evidence of recurrence, but because serum carcinoembryonic antigen is related to tumour bulk it is often the case that carcinoembryonic antigen-indicated recurrence is beyond cure, despite the early warning. Moreover, in several series local recurrence has been detected clinically as often as by raised carcinoembryonic antigen, though it has yet to be determined whether recurrence detected while clinically silent responds to treatment differently from clinically overt disease. Several groups have had more promising results. Martin and Minton in Columbus, Ohio, have published consistently encouraging reports. They found that in a retrospective series of patients undergoing second look surgery for clinically apparent recurrence alone, only 27% had totally resectable intra-abdominal recurrent disease compared with 61% of patients in whom serum carcinoembryonic antigen had been used as the indicator to reoperate. Martin and Minton ascribed this difference to their very aggressive carcinoembryonic antigen follow up, in which blood samples were taken every month so that the lead time conferred by the assay was not wasted. Monthly assay has since been recommended by the National Cancer Institute. As a further refinement to make maximum use of carcinoembryonic antigen data, Wood et al, Staub et al and Bowie et al have all suggested carcinoembryonic antigen slope analysis techniques to help distinguish between local and distant recurrence, and to aid selection of patients for second look surgery. They suggest that patients with a slow rise are more likely to have localised resectable disease. To make use of these techniques, however, a period of follow up is required after the carcinoembryonic antigen has risen initially, requiring a delay in laparotomy.

(4) **HAS EITHER IMPROVED SURVIVAL OR DECREASED TUMOUR INDUCED MORBIDITY BEEN DEMONSTRATED AFTER CARCINOEMBRYONIC ANTIGEN PROMPTED SECOND LOOK SURGERY?**

This is the crucial question about carcinoembryonic antigen in relation to recurrent disease, but the one which has been most obliquely addressed. Despite the enormous literature on the subject and the frequently optimistic advocacy of aggressive carcinoembryonic antigen-based follow up and second look surgery, there is no evidence that this approach has a significant effect on mortality. Moreover, it is impossible to be sure that it prevents or delays morbidity. Sugarbaker's group, having examined the available data, felt that this policy could contribute to a cure of 20% of
patients with local or distant recurrence, decreasing the overall mortality of colorectal cancer by 5%.\(^\text{30}\) In the present situation in which the mortality of bowel cancer has remained static for decades such a survival benefit would be worthwhile, but it can be shown only by the execution of a large scale, controlled trial in which a carcinoembryonic antigen based policy is compared with the conventional, clinically based regimen.\(^\text{23 41 42}\) It is to be hoped that the multicentre, controlled trial set up in Great Britain in 1983 under the auspices of the National Institutes of Health and the Cancer Research Campaign, will answer this question.\(^\text{43}\) 

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