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The Use of Prognostic Markers in Surgery for Colorectal Cancer

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The basis for prognostic prediction after surgery for colorectal cancer remains the various pathological staging systems based on that of Dukes. Serum prognostic markers have not shown significant independent prognostic power compared with these predictive tools. Much energy has been expended in examining the ability of serum markers to predict recurrent tumour prior to the onset of symptoms. Carcinoembryonic antigen (CEA) has been a particular subject of attention, and has been widely, though variably, advocated as a useful predictor in these circumstances. It has been estimated that around half a million Americans are presently undergoing regular postoperative CEA monitoring to this end. Controversy continues regarding the therapeutic utility of such monitoring. This may be resolved when the results of the only randomised trial in the field are published in the near future. No other serum marker, nor any combination of markers, has been shown clearly to be superior to CEA as a predictor of recurrent tumour.

Key words: prognostic markers, carcinoembryonic antigen
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PATHOLOGICALLY BASED prognostic classification of colorectal cancer had its beginnings in the 1930s, through the work of Cuthbert Dukes. The Dukes staging system, either in its original form or as one of its mutating progeny, has remained the basis for prediction of outcome in the common disease. Pathological staging has become the basis for advocating adjuvant therapy after radical surgery, radiotherapy and/or chemotherapy being offered to those with prognostically less favourable disease by surgeons and their oncology colleagues in many centres around the world. In the 1950s, Wangensteen offered repeated second-look surgery to those patients with Dukes stage C tumours in an attempt to improve outcome in those most likely to develop recurrent disease. Patients entering the programme underwent 6 monthly re-operation until they were deemed tumour-free [1]. This policy was abandoned when the operative mortality of these procedures outstripped any possible therapeutic benefit [2].

When carcinoembryonic antigen (CEA) was discovered in 1965 [3], it was hailed as *the* serum marker for colorectal cancer, with an obvious role in asymptomatic primary screening. But it soon became apparent that the serum level was raised in other cancers, in non-malignant bowel diseases, and also in some otherwise normal individuals when they changed their smoking or drinking habits suddenly. Moreover, serum CEA was normal in approximately 25% of patients with known bowel cancer. This lack of specificity and sensitivity ruled it out as a mass screening tool. CEA was seen to have a possible role as a prognostic marker; it was found that the risk of recurrent disease within 2 years of primary surgery was more than doubled in those in whom the serum CEA was raised pre-operatively, although in multivariate analyses performed more recently, it has not been found to be a powerful, independent prognostic variable. However, no system of pre-operative staging and prognostic prediction has displaced Dukes-based pathological systems. Serum prognostic markers have not been found to add to the predictive accuracy of such systems.

However, serum prognostic markers measured serially after primary surgery in order to predict recurrence, and hence to indicate those who might be candidates for second-look surgery, have been studied intensively. Although they have singularly failed to replace histopathological prognostic systems at the time of primary surgery, there has been a large body of surgical research directed at their post-operative use and, indeed, considerable resources are expended in their use; Moertel and associates have estimated that at any one time, 50 000 Americans are being sampled serially in order to predict recurrence prior to the onset of symptoms [4]. Whereas Wangensteen's use of Dukes staging failed as the basis for a second-look programme, there has been continuing advocacy of second-look surgery based on prognostic serum markers, CEA in particular. So what is the evidence that a policy of second-look surgery based on serial serum marker estimations might alter prognosis favourably? Should such a policy be adopted universally — or should it go the way of Wangensteen's programme and be consigned to the footnotes of the surgical history of colorectal cancer?

There is no doubt that serum CEA rises in the majority of cases prior to the appearance of symptoms and signs [5]; amongst more than 500 cases described in series published in the early 1980s, 75% demonstrated a CEA rise as first indicator of recurrent disease [6]. In the mid-1970s, there were several reports that regular monitoring led to early diagnosis of recurrence, up to 30 months before symptoms occurred [7–10]. Using historical controls, workers in Columbus, Ohio demonstrated

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that early re-operation, relying on CEA results as the sole indicator for surgery, led to macroscopic clearance of recurrence in more patients (79% compared with 27% in the symptom-led second-look series) [11, 12]. Others have reached the same conclusion from non-randomised studies [13–21], although others have remained unconvinced [22–26]. For many, it was taken as a "matter of faith that better efforts would produce better results" [27]; the Columbus group and others advocated very frequent CEA testing, monthly rather than 3 monthly [16, 28].

CEA assay has deficiencies in sensitivity and specificity. More frequently, it indicates the presence of unresectable hepatic recurrence rather than potentially curable disease [29], while in 10–25% of patients the raised CEA is misleading [4, 30–33], leading to a negative laparotomy. Conversely, a high proportion of patients are incurable at surgery [33, 34].

Efforts to improve the efficacy of CEA monitoring led to its combination with other tumour markers, but without significantly improved clinical utility [35]. In the absence of prospective control data, it remained impossible to demonstrate any survival advantage from a policy of CEA-led second-look surgery. Fletcher has indicated that "Americans have valued cure at almost any cost", while pointing out that society could not be expected to pay for this [27]. In the U.K. a national screening policy has been implemented only after development of convincing evidence of its clinical and economic utility.

It has been suggested that the efficacy of a CEA-based second-look policy could only be demonstrated by a randomised trial, but that statistical difficulties preclude any such study [4, 27]. Nevertheless, a trial (under the auspices of the Cancer Research Campaign, and initially funded by the U.S. National Institutes of Health) was set up in the U.K. in the 1980s, designed to optimise power and minimise sample size through the use of late randomisation — any therapeutic effect that might be present would more likely be detected by excluding from randomisation those individuals in whom no events would occur in the follow-up period.

After primary surgery, patients were registered with the Trial Centre after obtaining fully informed consent for participation in the full protocol. Patients were offered monthly CEA assay (as suggested by the Columbus group as vital to take full advantage of early diagnosis) as well as conventional clinical follow-up, and told that their clinician would not be informed of routine, normal results. Clinical follow-up conformed broadly with the standard pattern followed in the U.K.

Randomisation was performed at the Trial Centre only after a significant CEA rise as defined by the Trial CEA algorithm. Clinicians were only informed of the CEA rise if the patient was randomised to the "aggressive" arm, leading to examination of second-look surgery. Patients in the "conventional" arm continued to receive standard clinical follow-up, their clinicians remaining unaware of the CEA rise or the randomisation. In any patient at any stage (including patients already randomised to the conventional arm) in whom clinical evidence of recurrent disease became apparent, the clinican was at liberty to advise further surgery if it seemed appropriate.

Using this efficient and powerful trial design, it was possible to seek evidence of an effect on survival as a result of the introduction of a single item of data, a raised CEA level, into clinical management. The trial recruited almost 1500 patients, and closed in 1993. Data analysis is almost complete, so results should be published shortly.

Other prognostic serum markers have been developed, and have been used to try to detect presymptomatic recurrence of colorectal cancer; these include tissue polypeptide antigen (TPA), CA 19-9 and CA 50. There have been variable reports of their relative sensitivity and specificity compared with each other, with CEA and with combinations of these markers [35, 36]. Comparisons are difficult, mainly owing to differences in quoted normal ranges, but by conversion of inverse distribution function values into specificity–sensitivity diagrams, comparison for equivalent specificities is possible. On this basis, Putzki and others have shown no apparent advantage for other antigens or combinations, compared with CEA alone [35].

In summary, prognostic serum markers have so far proven disappointing in their application to the management of colorectal cancer. None has yet found a role as a primary marker for the disease, or as a useful independent prognostic variable at the time of primary surgery. CEA, in particular, is a fairly sensitive marker of recurrent disease in the asymptomatic individual, although its therapeutic utility as an indicator for second-look surgery remains unproven.

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