Original article

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A small rise in CEA is sensitive for recurrence after surgery for colorectal cancer

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Abstract

Objective Rise in carcinoembryonic antigen (CEA) above normal limits can indicate recurrent colorectal cancer. The aim of this study was to evaluate whether a small rise in CEA, even within normal limits was a sensitive indicator of recurrence.

Method 150 patients aged 22–87 years were followed up for a mean of 27 months after colorectal surgery with CEA 3 and 6 monthly computerized tomography. We analysed whether a rise in CEA > 1 ng/ml correlated with recurrence of metastases.

Results Forty-six of 139 patients in final analysis had recurrent disease. A rise in CEA > 1 had a predictive value of 74% for recurrence or metastases (sensitivity 80%, specificity 86%). These findings were similar whether or not the CEA was normal preoperatively.

Conclusion If CEA is measured after surgery for colorectal cancer, a rise of >1 in the patient's postoperative value is predictive for recurrence or metastases with an overall sensitivity of 80% and specificity of 86%. Previous studies have recognized the role of large rises in CEA in predicting recurrence but this study shows that small changes in CEA may be significant even if these levels would be traditionally within 'normal' limits.

Keywords Carcinoembrionic antigen, colorectal cancer, recurrence

Introduction

Carcinoembryonic antigen (CEA) is a cell surface glycoprotein expressed in large amounts by some colorectal tumours. First discovered in 1965 by Gold and Freedman [1], it has been measured serially in follow up after colorectal cancer surgery since the 1970s.

Elevated serum levels of CEA predict recurrence or metastases after surgery with a reported sensitivity of 60–95% [2], being most sensitive for liver metastases [3,4]. Other markers of recurrence have been studied [5], but CEA is regarded as the marker of choice for monitoring patients after curative surgery for colorectal cancer [6]. Despite this, CEA monitoring has had little impact on mortality [7,8] and CEA directed second look surgery often finds extensive recurrence that is not amenable to resection [9].

The aim of the present study was to establish whether small rises in CEA are more sensitive for recurrence or metastases, even if the CEA remains within traditional normal limits. It also looked at whether CEA measurement could detect recurrence or metastases in tumours with a low level of CEA expression.

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Method

This study is a retrospective study of 150 patients who had curative surgery for colorectal cancer in The Whittington Hospital between 1 January 1996 and 31 October 2000. All patients were followed up in a joint monthly surgical/oncology clinic according to a strict protocol. CEA was measured preoperatively and postoperatively and 3 monthly for the first 2 years, then 6 monthly to 5 years. Patients had 6-monthly computerized tomography (CT) scans for the first 2 years following surgery. Information was obtained from case notes, hospital computer records and the colorectal cancer database. Details including age, sex, date of operation, Duke's stage, CEA results, CT results, date and site of recurrence or metastases and outcome were all recorded.

Carcinoembryonic antigen was measured using the Bayer immunoassay, which at the levels in this study has an error rate of 2.3%. A small rise in CEA was taken to be

>1 ng/ml above the patients first postoperative value. The traditional upper limit of normal CEA was taken to be 10 ng/ml as this is the level at which most centres would investigate patients for recurrence. The CEA measurements for each patient were analysed twice, once looking for a small rise in CEA and again looking for a CEA value that rose above the traditional normal limit.

Exclusions

All patients referred during this period who had palliative surgery or were treated nonoperatively were excluded. We further excluded 11 patients who either developed metastases or recurrence within 3 months of 'curative' surgery or who had persistently elevated CEA levels after resection. We felt that these patients had not truly undergone a curative procedure. This left us with 139 patients who had curative surgery.

Results

The study population consisted of 69 women and 81 men with a mean age of 67.4 years (range: 22–87). Of the 139 patients included in the final analysis 46 (33%) developed recurrence or metastases. One of 10 patients with Duke's A tumours, 21 of 82 Duke's B and 24 of 47 patients with Duke's C cancers developed recurrence (Fig. 1). The liver was the commonest site for metastases (44%; Fig. 2).

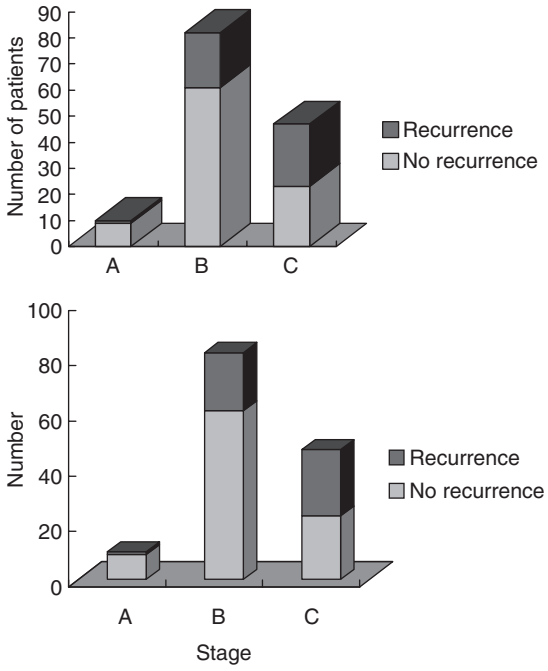

Figure 1 Duke's stage of tumours and relationship with recurrence.

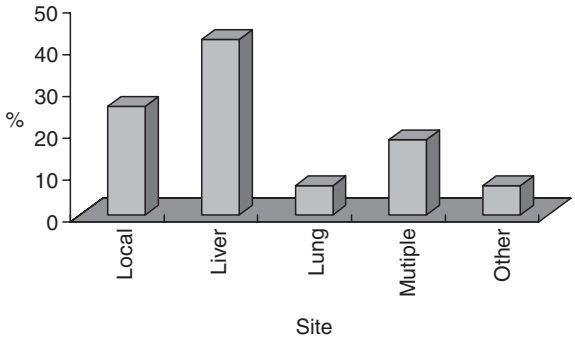

Figure 2 Sites of tumour recurrence/metastases.

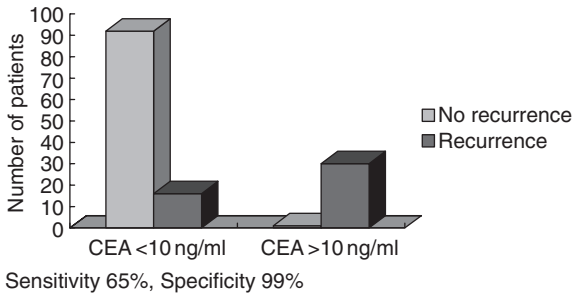

Figure 3 Use of a rise in carcinoembryonic antigen above normal limits (>10 ng/ml absolute value).

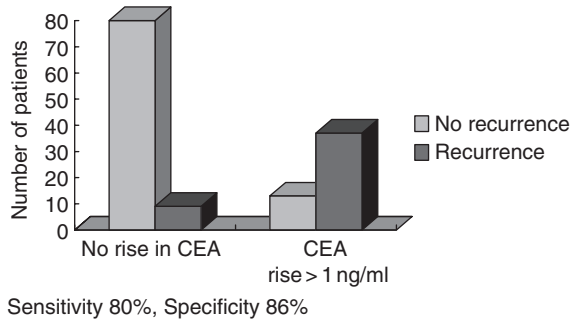

Figure 4 Use of a small rise in carcinoembryonic antigen (>1 ng/ml) above first postoperative level.

Most recurrences (70%) were in the first 2 years but two (4.4%) patients developed recurrence after 4 years.

Of the 46 patients who developed recurrence or metastases, 30 (65%) had a large rise in CEA levels (absolute CEA value: >10 ng/ml) predating radiological or clinical evidence of recurrence or metastases. Thus, looking for a CEA rise above the traditional 'normal' cut-off level gave this method of CEA monitoring a sensitivity of 65% and specificity of 99% (Fig. 3).

When we reanalysed all the results looking for a small rise in CEA, 37 of 46 (80%) of patients had a rise of

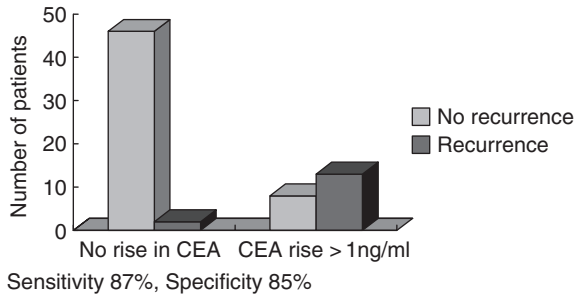

Figure 5 Patients with tumours with a low level of carcinoembryonic antigen (CEA) expression – normal CEA preoperatively.

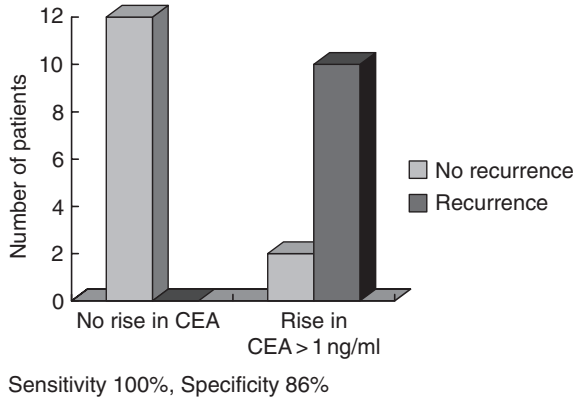

Figure 6 Patients with tumours expressing high levels of carcinoembryonic antigen (CEA) – preoperative CEA >10 ng/ml.

>1 ng/ml above their first postoperative CEA level. This increased the sensitivity of CEA monitoring to 80% with a specificity of 86% (Fig. 4). Seven of the 46 patients with recurrence (15%) showed a small rise in CEA which did not increase to >10 ng/ml in subsequent follow up. These patients would not have had their recurrence or metastases detected by the traditional method of CEA monitoring. Nine patients (20%) who developed recurrence did not show any change in their CEA levels even after clinical or radiological detection of recurrence. CEA monitoring was therefore of no value in these patients.

Patients with normal CEA levels before surgery were assumed to have tumours with a low level of CEA expression. Ninety-three patients in the study had preoperative CEA measurements. In this group with normal preoperative CEA levels, serial CEA measurement predicted the development of recurrence or metastases with a sensitivity of 87% and specificity of 85% (Fig. 5).

In patients who had tumours expressing high levels of CEA preoperatively, recurrence or metastases could be predicted by looking for a small rise in CEA with a sensitivity of 100% and specificity of 86% (Fig. 6).

There was also a time advantage to looking for a small rise in CEA. The mean time to clinical or radiological detection of recurrence or metastases was 29.2 months. The mean time for CEA to rise above traditional normal limits was 23.6 months. The mean time to develop a small rise in CEA was 16.9 months. Looking for a small rise in CEA therefore gives an average 6.7-month time advantage.

Discussion

There is still controversy regarding the role of intensive follow up after curative resection for colorectal cancer [10–12]. CEA monitoring is known to be a good predictor of the development of recurrence or metastases [13] after surgery and is relatively cheap and easy to perform [14]. Some authors have abandoned the use of liver imaging in follow-up programmes as CEA is so sensitive for the development of liver metastases [4]. Intensive follow up detects recurrence at an earlier stage [13], which intuitively should be more amenable to treatment [15,16]. Neither intensive follow-up programmes nor CEA monitoring has made a significant impact on mortality rates to date, [7,17–21]. Previous studies, which have looked at a small rise in CEA, have shown a survival benefit [22] but there is a suggestion that any improvement in mortality is due to lead time bias [23].

Engaras has recently reported a method of calculating an individual cut-off level for CEA monitoring [24] and the slope of the rise in CEA with time has also been studied and can be used to predict recurrence [25]. Our laboratory quotes a CEA level of >5 ng/ml as abnormal but in the literature CEA elevation alone does not usually lead to intervention until the value exceeds 10 ng/ml [26]. The value of 10 ng/ml was therefore chosen for the present study as we wanted to re-explore the usefulness of CEA monitoring.

Many studies looking at the role of CEA in detecting recurrence after surgery were carried out at a time when therapeutic options for patients with recurrence were limited. The treatment for colorectal cancer is constantly evolving and the outlook for a patient developing recurrence or metastases is better now than it was 15 years ago.

Out of all the investigations used in follow up, CEA is the test that patients are most compliant with [22]. Patients with CEA levels of <11 ng/ml undergoing second look surgery have a higher resectability rate [27] whereas patients with high levels of CEA usually have unresectable disease [28].

This study shows that a small rise in CEA after surgery is more sensitive for predicting recurrence or

metastases. This holds true even if the CEA is within traditional normal limits. About 15% of the patients in this study who developed recurrence did not develop a larger rise in CEA than 10 ng/ml and their recurrent disease would not have been detected by traditional CEA monitoring. CEA monitoring was also useful for patients with tumours with a low level of CEA expression as when these tumours recur or metastasize they often do not exhibit rises in CEA above traditional normal limits.

Although our numbers are small, CEA monitoring predicted recurrence/metastases in tumours with a high level of CEA expression with a sensitivity of 100%. If this held true for a larger study this could be a very exciting finding as CEA monitoring alone may be sufficient in these patients. Follow up could then be tailored to individual patients according to the level of CEA expression their tumour exhibits.

This study has also shown that there is a time advantage of looking for a small rise in CEA when following up patients after surgery. Our results suggest that patients develop a small rise in CEA 6 months before they reach the traditional threshold for investigation. We have changed our practice so that patients who exhibit a small rise in CEA postoperatively get up to date imaging and it remains to be seen whether this will lead to increased survival.

The development of spiral CT scanning and positron emission tomography (PET) scanning makes recurrent disease easier to detect at an early stage. Chemotherapy regimes have become more varied and effective and patients with liver metastases can now be offered resection or radiofrequency ablation.

Much of the work looking at CEA was carried out in the 1980s and early 1990s [29–31] and it is possible that if this research was repeated today the impact of CEA directed second look surgery or therapy would have a positive impact on survival. This study shows that small rises in CEA, even those, which would have been traditionally within normal limits, can provide a sensitive indicator of recurrence. This needs to be followed up to see if it can reduce the high mortality rates still associated with recurrent disease.

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