Role of carcinoembryonic antigen as a marker for colorectal liver metastases

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ABSTRACT

Carcinoembryonic antigen (CEA), a marker for colorectal adenocarcinoma, can monitor disease progression and treatment response. This study aims to determine the accuracy of CEA in the detection and resectability of colorectal liver metastases. Patients with primary colorectal cancer were divided into three groups: resectable hepatic metastases (group 1), unresectable metastases (group 2), and disease-free cases (group 3). The CEA concentration was recorded pre- and post-hepatectomy in group 1 and on radiological confirmation of disease state in the other groups. It was expressed as median (95% confidence interval [CI]), with predictors of concentration determined. Group 1 (n=141) had pre-operative CEA of 8.9 (4.6–13.1), with 38.1% of patients being normal. Maximum tumour diameter correlated with CEA level (r=0.41, P<0.0001). Post-hepatectomy CEA was 2.3 (1.9–2.7; P<0.0001), with 81.1% of patients being normal. Group 2 (n=158) had CEA of 20.6 (9.4–31.9). Group 3 (n=361) had CEA of 2.0 (1.8–2.2). Sensitivity of CEA pre- and post-hepatectomy was 61.2% and 69.3%, respectively, while specificity was 79.8% for both groups. Concentration was elevated in hepatic colorectal metastases but is not a marker of resectability. A CEA reduction post-resection indicates that it may be used as an indicator of treatment response, while CEA is increased by tumour burden and lesion size.

KEY WORDS: Carcinoembryonic antigen.
Colorectal neoplasms.
Neoplasm metastasis.
Neoplasm staging.

Introduction

Carcinoembryonic antigen (CEA), a glycoprotein first identified by Gold and Freedman in 1965, is regarded principally as a tumour marker of colonic adenocarcinoma.[1,2] Although very small amounts are found in the healthy adult colon, an elevated CEA may also occur in other benign conditions, such as ulcerative colitis or liver cirrhosis, and in malignant tumours arising from endodermal tissue, including breast and lung.[3–6]

Serum CEA can be used as a follow-up measure in colorectal cancer in an effort to detect local recurrence or distant metastatic disease, or as a measure of response to treatment. Elevated serum levels correlate with hepatic metastases, possibly due to adhesion between circulating CEA in the liver and the CEA bound to metastatic cells.[7,8]

The aim of this study is first to determine the accuracy of CEA in the detection of colorectal metastatic disease, and second to ascertain if CEA reflects the extent of disease recurrence and the surgical resectability of hepatic metastases.

Patients and methods

Three patient groups were identified and their details retrospectively collated from a prospectively maintained database. The common inclusion criteria were patients with a history of surgically resected primary colorectal adenocarcinoma. Exclusion criteria included palliative bypass or stenting without resection, a lack of radiological follow-up and no available CEA measurement at the time of radiological confirmation of disease status. Patients with equivocal disease status on computed tomography (CT) scanning, or who awaited further tests to determine disease status, were also excluded. Additional group-specific criteria are given below. Permission was obtained from the relevant clinicians to access the data, in accordance with data protection legislation. Formal ethics approval was not required due to the retrospective nature of the data collection.

Group 1 consisted of those deemed to have surgically resectable liver metastases following discussion at a multidisciplinary HPB meeting and subsequently underwent open surgery. These patients were identified from the theatre logbooks and the hepatobiliary database. The local unit protocol was to assess patients initially with a CT scan of the chest, abdomen and pelvis. This was followed by a positron emission tomographic scan (PET-CT) to ensure there was no extrahepatic disease prior to resection. A CEA concentration one month before hepatic resection or neoadjuvant therapy was recorded as well as three months post-operatively.

Histopathology details of the resected primary colorectal and secondary hepatic specimens were recorded. These included the tumour (T) and nodal (N) stage and tumour differentiation of the primary pathology, the number of secondary lesions with their maximum diameter, and liver tumour differentiation. Although thermal ablation has recently been introduced to the hepatobiliary unit, these patients were not included, as histopathology would not been available for correlation analysis.

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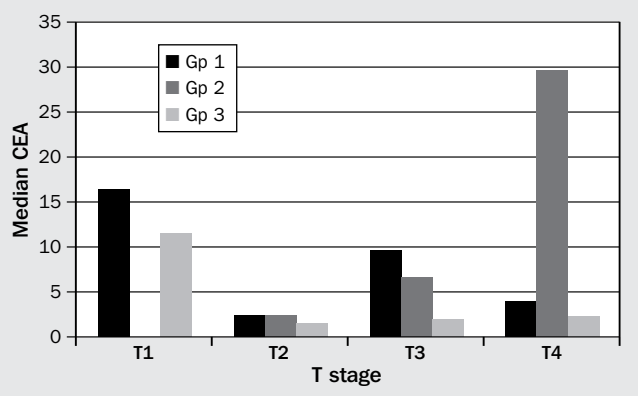

Fig. 1. Median CEA concentration according to T stage of the primary tumour.

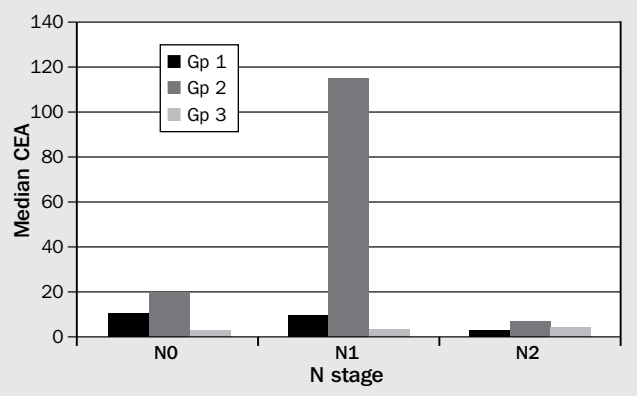

Fig. 2. Median CEA concentration according to N stage of the primary tumour.

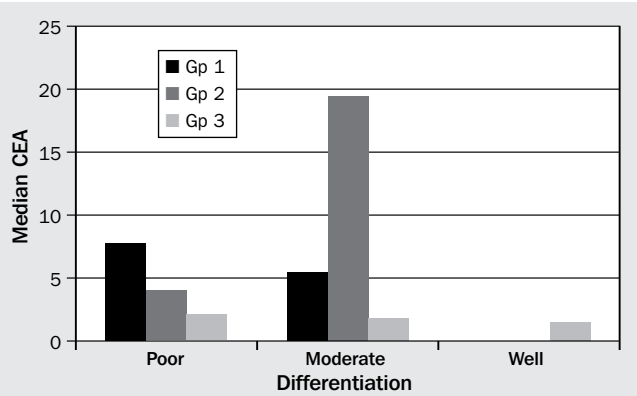

Fig. 3. Median CEA concentration according to differentiation of the primary tumour.

Groups 2 and 3 were recruited from a multidisciplinary database. Patients whose disease status was equivocal, or could not be confirmed on radiological records, were excluded. Group 2 included patients with unresectable hepatic metastatic disease, unresectable local recurrence or any other form of distant metastatic disease not amenable to surgical intervention. A CEA level was recorded at the time of first radiological confirmation by CT, but prior to commencement of any palliative chemotherapy.

Group 3 (control group) comprised patients with no detectable metastatic disease following primary resection. This was confirmed by a CT scan of the chest, abdomen and pelvis. A CEA level was recorded at the time of the CT scan, and this group acted as the control group for the other two groups. The tumour (T) and nodal (N) stage and tumour differentiation of the primary pathology in patients in groups 2 and 3 were also recorded.

Statistical analysis

Statistical analysis was performed using SPSS version 18 (SPSS, Chicago, IL, USA). The CEA measurement was expressed as the median (and 95% confidence intervals [CI]). Due to the distribution of the data, non-parametric tests were used for analysis. Inter-group comparisons of absolute CEA values were assessed by the Kruskal-Wallis test. The regional laboratory parameters of a normal CEA value (0–4) were used to categorise all pre- and post-operative results into abnormal and normal. Comparison of the proportion of normal and abnormal values in the groups and subgroups was by χ^2 test. Analysis of CEA measurements, and the correlation with pathological parameters, was assessed by Spearman rank correlation. $P<0.05$ was considered statistically significant for all tests.

The disease-free patients, as a control group, permitted the calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of CEA for the pre-hepatectomy and unresectable groups. Receiver Operator Curve (ROC) analysis was performed for groups 2 and 3 separately.

Table 1. Number of patients according to the pre- and post-hepatectomy CEA results.

Pre-operative	Post-operative	
	High	Normal
High	12	45
Normal	6	32

Results

Group 1: hepatectomy patients

In the period between January 2002 and December 2008, 141 (85 male) patients underwent hepatic resection for colorectal metastases. Six were excluded due to missing data. Median pre-operative CEA was 8.9 (4.6–13.1), with 38.1% patients having a normal result. The T stage of the original primary did not influence the CEA level ($P=0.21$; Fig. 1). The presence of nodal disease, however, did influence the CEA level ($P=0.04$; Fig. 2). Tumour differentiation of the original primary did not alter the CEA value ($P=0.23$; Fig. 3).

The number of lesions in the liver ranged from one to eight, with no difference in CEA level ($P=0.16$). Hepatic tumour differentiation did not influence CEA (well differentiated: 6.8 [2.2–88.2]; moderately differentiated 10.25 [4.0–21.8]; poorly differentiated 1.6 [$P=0.07$]). There was significant and positive correlation between the maximum diameter of the lesion and CEA level ($r=0.41$, $P<0.0001$). Median CEA at three months post-operatively was significantly lower (2.3; 1.9–2.7 95%CI; $P<0.0001$), with 81.1% having a normal CEA. The proportion of abnormal and normal results is shown in Table 1.

Group 2: patients with unresectable metastases

During the study period, 158 (95 male) patients were identified with unresectable recurrent disease. A CEA level was available at the time of the CT scan and prior to any further treatment in 129 patients. The median CEA result was 20.6 (9.4–31.9). This was significantly different to the pre-hepatectomy result in group 1 ($P=0.02$). The CEA value did not differ with the various T stages of the colorectal primary ($P=0.31$; Fig. 1), nor did nodal status influence the CEA result. ($P=0.25$; Fig. 2). Differentiation of each primary tumour was also similar ($P=0.18$; Fig. 3).

Group 3: disease-free patients

Over the same time period, 361 (214 male) disease-free patients were identified from the multidisciplinary database. It was possible to obtain a CEA level at the time of the CT scan in 241 patients. Median CEA result was 2.0 (1.8–2.2). This was significantly lower when compared to group 1 pre-operatively ($P<0.0001$) and group 2 ($P<0.0001$); however, no difference was found when compared to group 1 post-operatively ($P=0.17$). The T stage of the primary tumour did not influence CEA in this group ($P=0.16$; Fig. 1), nor did N stage influence the result ($P=0.69$; Fig. 2). Differentiation of the primary tumour had no impact on the result ($P=0.44$; Fig. 3).

Inter-group analysis

The proportion of patients in each group was calculated for each aspect of the primary pathology. Overall T-stage distribution was different ($P<0.0001$) and a trend towards patients with more advanced primary pathology resulted in an increased metastatic tumour burden. There was a significant difference in N-stage distribution ($P<0.0001$), with the trend again reflecting current tumour burden. The differentiation of the primary tumour had no impact on the result ($P=0.56$).

Based on the disease-free state of patients in group 3, the results obtained with groups 1 and 2 were analysed further. For pre-hepatectomy patients, CEA had a sensitivity of 61.2%, specificity of 79.8%, PPV of 55.7%, NPV of 83.1%, and overall accuracy of 76.4%, with an area under the curve (AUC) on ROC analysis of 0.79 (Fig. 4). For patients noted to have unresectable metastatic disease, CEA had a sensitivity of 69.3%, specificity of 79.8%, PPV of 56.8%, NPV of 84.9% and overall accuracy of 74.3%, with an AUC on ROC analysis of 0.75 (Fig. 5).

Discussion

The early detection of hepatic metastases is pivotal to their successful management, with an increased likelihood of hepatic resectability. Carcinoembryonic antigen is frequently used as a potential marker of disease recurrence, but reliability for any such proposed marker is essential.[9] The results of this study provide an interesting insight into the factors influencing the CEA level related to metastatic spread.

The influence of primary tumour pathological staging on CEA at this time point has not been investigated previously. The tumour (T) stage of the primary colorectal tumour did not have any bearing on the subsequent CEA level in any of the three groups. This is seen against a background of increased risk of disease recurrence with more advanced primary pathology, as indicated by the inter-group T-stage distribution comparison. Therefore, despite the higher risk of recurrence and more extensive spread with higher T stage, there was no associated elevation of CEA in the presence of subsequent metastases.

The influence of nodal (N) stage of the primary tumour showed significance in the hepatectomy group, with inversion of the expected relationship. This would suggest a statistical type 1 error, which is confirmed by the lack of significance in the other two groups for nodal status. As with more locally advanced disease, there was a higher risk of recurrence and more extensive spread, with nodal spread at the time of primary resection. However, this did not result in elevation of CEA when the metastatic disease was first detected. The distribution of primary tumour differentiation was similar in each group, and, as with T and N stage, it did not influence subsequent CEA production.

The results in the hepatectomy group indicate a positive and significant correlation with the maximum diameter of the liver lesion. This suggests that CEA production is increased by a higher tumour burden, which is substantiated by the inter-group CEA significant differences. While this is important, further research is necessary to ascertain the exact relationship between tumour burden and CEA concentration. It would be necessary to perform volumetric analysis of the hepatic disease to quantify this association precisely. Although perhaps more difficult to compute, the volume of extrahepatic disease may also reveal correlation with CEA level. The importance of this would be in the

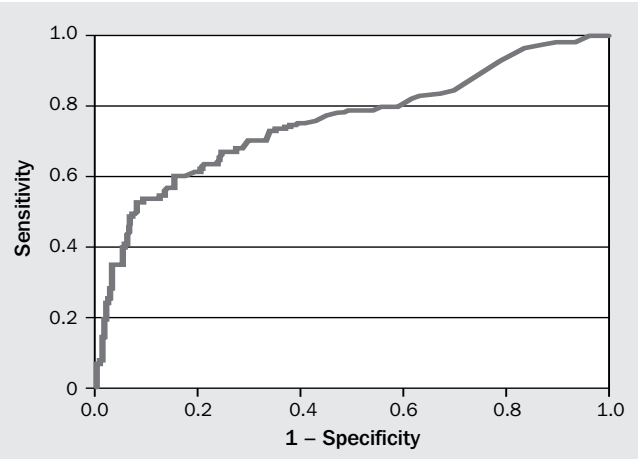

Fig. 4. The ROC analysis for pre-hepatectomy patients (Group 1).

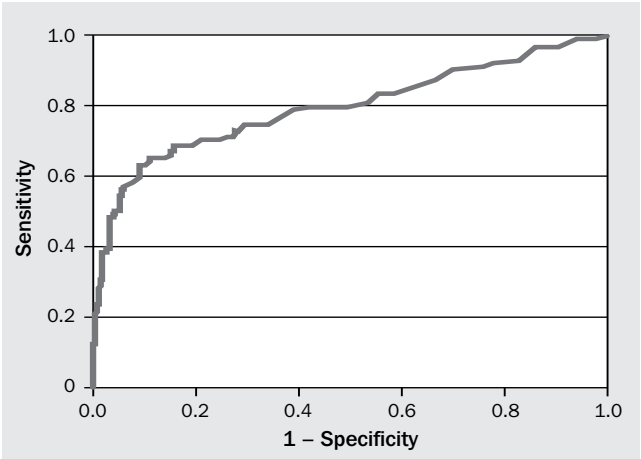

Fig. 5. The ROC analysis for unresectable patients (Group 2).

clinical application, where CEA could be used to estimate, more accurately than presently, the volume of residual disease and the response to treatment. This conclusion is strengthened by the substantial drop in CEA concentration following hepatectomy.

The importance of perioperative CEA has been demonstrated.[10–12] Oussoultzoglu *et al*. showed that survival is predicted by perioperative change in CEA as well as the CEA concentration six weeks after hepatectomy.[13] However, preoperative CEA did not affect outcome; thus, patients with persisting elevated CEA after resection may benefit from adjuvant therapy.[13]

The removal of tumour cells, either surgically or by chemotherapy, often resulted in a fall of serum CEA. Nevertheless, it is important to note that this was not always the case. A small number of patients, following hepatic resection, failed to return to a normal CEA level three months post-operatively, while a few had a normal level pre-operatively with elevation to abnormal post-operatively. There are several possible reasons for these results. First, although useful, CEA should not be regarded as a reliable marker, with other causes for its production and occasional lack of secretion despite the presence of disease. Second, the parameters of a normal result may be too stringent, with very slight elevation into the abnormal range having no clinical significance. Third, the persistence of CEA production may suggest the presence of previously undetected disease.

In the present study, 38/95 (40%) had a normal pre-hepatectomy CEA, compared to reported rates of 16–35%.[14–16] This was explained in previous studies as being due to neoadjuvant chemotherapy. Although the current study was designed to avoid this confounder, it is possible that some inadvertent contamination of data may have come from this source. However, it emphasises the fact that a normal CEA does not exclude recurrent disease.

The pre-hepatectomy CEA sensitivity of 61.2% compares favourably with other potential diagnostic modalities. Although CT and PET are reserved for disease staging, ultrasound is regarded as a rapid and cost-efficient means of liver assessment; however, its accuracy is user-dependent and reported sensitivity is 41–55%.[17–19] Thus, as a screening tool, although cost was not formally assessed in this study, serum CEA is likely to yield a more reliable and less expensive answer.

In conclusion, metastasis-associated CEA concentration is not influenced by the original pathological tumour stage. However, concentration correlates with the maximum diameter of the largest liver lesion. Carcinoembryonic antigen has a better sensitivity than ultrasound for disease detection but cannot be fully relied upon. □

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