Preoperative Carcino-embryonic Antigen and Carbohydrate Antigen 19-9 Serum Levels: Which Usefulness in Localised Colorectal Cancer?

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ABSTRACT

Purpose. Although carcino-embryonic antigen (CEA) and carbohydrate antigen (CA19-9) have been widely used for almost 30 years, their clinical and prognostic value is still not clear. Our aim was to investigate the correlation between high initial markers and clinicopathological characteristics. We also assess their role as prognostic factor; and their utility for early diagnosis of recurrence.

Methods. Records of patients with localised colorectal cancer followed at the Institute Curie-Rene Huguenin were retrospectively reviewed. Eligible cases had CEA and CA19-9 levels determined at diagnosis before any treatment.

Results. A total of 84 patients were collected. CEA and CA 19-9 were elevated prior to curative surgery in 24% and 15% of patients, respectively. High serum level was not correlated to any of the investigated clinicopathological characteristics (Age, site, stage, tumour differentiation, lymph node involvement). After a median follow-up of 60 months, patients with initial high level markers experienced more recurrences (40% vs 15%). DFS ($p=0.002$) and OS ($p=0.031$) were significantly lower among this group. Markers were useful for early diagnosis of recurrence but with no statistically significant difference.

Conclusions. Our study confirms that high level of both CEA and CA19-9 at initial diagnosis is correlated with significantly poorer prognosis.

INTRODUCTION

The stage as defined by the Union International Cancer Classification (UICC) and American Joint Committee on Cancer classifications (AJCC) represents the main prognostic factor for patients with colorectal cancer (CRC) [1]. However, recent data suggest that prognostication of newly diagnosed CRC should not rely only on this traditional TNM stage, as CRC is heterogeneous in survival within staging categories [1,2]. Tumour extent, lymph node status, tumour grade and lymphatic or venous invasion are also established as important morphological prognostic factors [3]. Other markers, as biologic and molecular factors, are necessary to assess molecular prognostic tools to guide adequate treatment of aggressive CRC patients with adjuvant systemic chemotherapy or targeted therapy [4].

In this context, what can be the contribution of carci- o-embrionic Antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) in assessing prognostic models? These tumour markers have been widely used for both localised and metastatic CRC, their clinical value as indicator of prognosis in localised CRC, remains unclear. The Colorectal Working Group of the AJCC suggests adding both CEA and CA19-9 into the current TNM staging system [5].

Inspired by this proposal, we conducted this study. Our first aim was to provide updated data to determine the prognostic value of preoperative serum CEA and CA19-9 levels. We also investigate whether CEA and CA19-9 are useful markers in the management of patients with localised CRC.
METHODS

Patients:

Between January 1980 and December 2008, we retrospectively reviewed localised CRC patients from the database of the Institute Curie-Rene Huguenin.

Patients with stage II and III CRC, who underwent potentially curative resection for non-metastatic CRC were selected. We included those who had preoperative serum determinations of both antigens. They should not have evidence of residual disease after radical treatment.

Clinicopathological characteristics and associated follow-up data were collected by reviewing available medical files. Cut-off levels were defined by reference value: 2.5 ng/ml for CEA and 37 UI/ml for CA 19-9.

Statistical analyses:

Statistical evaluation was performed using the statistical package SPSS for Windows (Version 13.0; SPSS Inc., Chicago, IL).

Disease-free survival (DFS) and overall survival (OS) were calculated with the Kaplan-Meier method for categorised variables. The log rank test was used to find statistical differences between the curves. p < 0.05 was considered statistically significant.

RESULTS:

Patient characteristics:

This study included 84 patients. Median age was 63 years (range 36-80) with sensible female predominance. The clinicopathological characteristics are resumed in Table 1.

High preoperative levels of CEA and CA19-9 were observed in 23.8% and 15% of patients, respectively.

All patients had a curative surgery. 88% of them had adjuvant chemotherapy.

Markers and clinicopathological data:

The serum level of CEA and CA19-9 was evaluated with respect to patient clinicopathological features and the results detailed in Table 2.

In both univariate and multivariate analysis, there was no significant correlation between high levels of CEA or CA19-9 and all investigated characteristics: Age, patient gender, site of the primary tumour, differentiation grade and lymph node involvement.

Table 1: Clinicopathological data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>64.2%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>35.8%</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>18</td>
<td>21.4%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>66</td>
<td>78.6%</td>
<td></td>
</tr>
<tr>
<td>Differentiation grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>41</td>
<td>48.8%</td>
<td></td>
</tr>
<tr>
<td>Not well differentiated</td>
<td>25</td>
<td>29.8%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>18</td>
<td>21.4%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Initial Markers level and patient clinicopathological data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High CEA n (%)</th>
<th>Normal CEA n (%)</th>
<th>p Value</th>
<th>High CA19-9 n (%)</th>
<th>Normal CA19-9 n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (7.2%)</td>
<td>24 (28.5%)</td>
<td>0.63</td>
<td>5 (6)</td>
<td>25 (29.8%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Female</td>
<td>14 (16.7%)</td>
<td>40 (47.6%)</td>
<td></td>
<td>7 (8.4%)</td>
<td>47 (56%)</td>
<td></td>
</tr>
<tr>
<td>Site:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>14 (16.7%)</td>
<td>33 (39.2%)</td>
<td>0.22</td>
<td>6 (7.2%)</td>
<td>41 (48.7%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Rectum</td>
<td>6 (7.2%)</td>
<td>31 (36.9%)</td>
<td></td>
<td>6 (7.2%)</td>
<td>31 (36.9%)</td>
<td></td>
</tr>
<tr>
<td>Differentiation grade:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>7 (8.4%)</td>
<td>34 (40.5%)</td>
<td>0.18</td>
<td>3 (3.6%)</td>
<td>38 (45.2%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Not well</td>
<td>8 (9.5%)</td>
<td>17 (20.1%)</td>
<td></td>
<td>4 (4.7%)</td>
<td>21 (25%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (6%)</td>
<td>13 (15.5%)</td>
<td></td>
<td>5 (6%)</td>
<td>13 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>63</td>
<td>64</td>
<td>0.8</td>
<td>67</td>
<td>63</td>
<td>0.23</td>
</tr>
<tr>
<td>Lymph node involvement:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>18 (21.4%)</td>
<td>48 (57.2%)</td>
<td>0.29</td>
<td>10 (11.9%)</td>
<td>56 (66.7%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Absent</td>
<td>2 (2.4%)</td>
<td>16 (19%)</td>
<td></td>
<td>2 (2.4%)</td>
<td>16 (19%)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical usefulness of preoperative serum levels of tumour markers:

*For detection of relapse:

23 Patients relapsed. Among patients who had high initial level of tumour markers, 40% relapsed; comparatively to only 15% of patients with normal initial markers.

Early diagnosis of the relapse was assessed by various criteria:

- Increase of markers: CEA in 17.3% of cases; CA19-9 in 4.3% of cases; and both in 13% of cases.
- Radiological exams (chest X-ray; pelvic or abdominal ultrasound) in 26% of cases.
- Colonoscopy in 13% of cases.
- Clinical signs were responsible of detection of relapses in 8.7% of cases.

Recurrence was not more often diagnosed by tumour markers among patients who had initial high level markers as shown in table III.

*For evaluation of prognosis:

Disease-free survival:

After a median follow up of 60 months, local and metastatic recurrences were observed in 27.4 % of the patients. High initial level of CEA and CA 19-9 was significantly correlated to more recurrences (p = 0.002) (Figure 1).

It was also statistically significant when analysing separately CEA (p=0.018) but not and CA 19-9 (p=0.26).

Overall survival:

When comparing OS, patients with normal initial markers achieve better survival than those with high-level markers. The difference was statistically significant (p=0.031) (Figure 2).

Multivariate analysis revealed that high preoperative serum CEA was a significant independent prognostic factor for overall survival (P = 0.02) but not CA19-9 (p=0.4).

DISCUSSION:

CEA and CA19-9 are the most used tumour markers in management of CRC: At initial diagnosis, at the evaluation of response in metastatic setting and during the follow-up. However their clinical impact is still not validated, especially for localised CRC. In particular, dosing of these markers at initial diagnosis remains controversial, due to their relative low sensitivity and specificity [6-11]. Sensitivity of CEA and CA19-9 is 70% and 40%, respectively [12].

In our study, we have observed that only 24% and 15% of cases had increasing CEA and CA19-9, respectively.

Although the increase of tumour markers is not frequent in localised CRC, previous studies have shown that preoperative high serum markers (CEA or/and CA19-9) is associated with a poor prognosis: shorter disease-free period and OS [13-26].

The actual international guidelines do not recommend tumour markers for diagnostic screening, but they confer a worse prognosis to patients with high level markers before curative surgery; dosing ACE or/and CA19-9 would be useful for staging, prognosis and planning adjuvant treatment [27-31].
Such findings have been observed in our study, confirming that a high level of both serum tumour markers (CEA and CA19-9) is related to a high risk of recurrence and poor prognosis. However, a preoperative isolated elevation of serum CA19-9 does not have the independent prognostic significance as compared with preoperative isolated elevation of CEA.

Previous reports demonstrated that the combination of both antigens can provide more information than CEA or CA19-9 alone for prognosis of recurrence and survival [32].

In a study of 103 patients, Nozoe T found that preoperative elevation of both markers proved to be an independent prognostic indicator; however, an elevation of only one of the two markers did not obtain a prognostic significance [32].

Currently, pathological stage is recognised as the main prognostic factor in colorectal cancer; other clinicopathological factors such as cellular differentiation, lymphatic or venous or perineural invasion, bowel obstruction and perforation, involvement of resection margins, DNA ploidy, and oncogene expression may also have prognostic value [33].

The prognostic value of tumour marker (CEA and/or CA19-9) in addition to the common prognostic factors is still debated and studied in many series by multivariate analyses [34-38].

As we have found, two other large retrospective studies report the same result: preoperative serum CEA level was the only significant prognostic factor for patients with stage II and III CRC [35,36].

In node negative CRC, two studies reported an independent prognostic value of CA19-9 [37] and CEA [34], whereas Sato found a significant prognostic value in CRC with lymph nodes metastases [38]. Determining the prognostic in patients with Stage II disease is pri-mordial because the benefits of adjuvant chemotherapy in this population category is not certain; dosing tumour markers can be useful to define the prognostic independently of the others factors [35].

Patients with a high level of both CEA and CA19-9 in stage II of colorectal cancer have a significantly poorer prognosis than those with normal levels of these markers [38], but the actual data are still insufficient to support the use of tumour markers to determine whether to treat a patient with adjuvant chemotherapy; prospective randomised trials are still recommended.

Another interest of tumour markers is the early detection of recurrence [40-42], especially when they are initially elevated. CEA is the choice marker for monitoring patients with colorectal cancer, in 65% of the cases it was the first indicator of relapse [27]. In our study, elevation of markers allows the diagnosis of most recurrences. It was the first sign of relapse 34.6% of patients.

CONCLUSION:

In conclusion, the measurement of preoperative serum levels of CEA and CA19-9 help in predicting the prognosis of patients with localised colorectal cancer; elevated values indicate high risk of cancer recurrence and poor survival. We think it is reasonable to add preoperative CEA and CA19-9 together to the current staging system. The use of both CEA and CA 19-9 definitely needs to be established by larger prospective studies.

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