Unresected colorectal liver metastases: prognostic value of laboratory variables

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SUMMARY

Objective — To search for laboratory variables having independent prognostic signification in patients with unresected colorectal liver metastases.

Methods — We have systematically reviewed the biomedical literature using the methodology recommended by the Committee on Evidence-Based Laboratory Medicine of the International Federation of Clinical Chemistry and Laboratory Medicine, and taking into account the Consolidated Standards of Reporting Trials Statement.

Results — Of 644 publications retrieved, the application of strict exclusion and inclusion criteria allowed us to include only eight studies in our systematic review. The main laboratory variables evaluated in these eight studies were serum carcino-embryonic antigen, alkaline phosphatase, albumin, bilirubin, and plasma prothrombin time. None of these variables were unanimously found to have an independent prognostic significance. A meta-analysis was not possible, mainly because of heterogeneity within the primary studies and these contradictory results.

Conclusions — Current evidence would not support the routine use of laboratory variables as independent prognostic variables in patients with unresected colorectal liver metastases. Taking into account the inadequate quality of the published studies, this negative conclusion might be provisional only. Until better designed studies are published, a number of arguments would support to recommend pre-treatment measurement of serum carcino-embryonic antigen and alkaline phosphatase in patients participating in clinical trials.


[5, 7, 8] were used for the literature review. The manual and electronic search strategies used were published in our recent review [6] on biological prognostic factors for resected metastases. The following key words were used: colorectal cancer, colorectal metastases, liver (or hepatic) metastases, survival (or prognosis, or prognostic), laboratory variables (or parameters), and carcinoembryonic antigen. After examination of the first selection, the following other key words were used: prothrombin time, albumin, bilirubin, alkaline phosphatase, transaminase, lactate dehydrogenase, blood cell count and CA 19-9 (carbohydrate antigen 19-9).

### Inclusion and exclusion criteria

Criteria used for study inclusion were the following: articles considering patients with colorectal liver metastasis, full-length original articles written in English, French, Italian, or German (the only languages understood by at least two of the three co-authors), studies which evaluated the prognostic significance (survival) of pre- and/or post-therapeutic biological variables which can be measured in biological fluids, studies using multivariate analysis taking into account potential non-biological prognostic variables. The following exclusion criteria were used: abstracts, studies uniquely including operated patients, studies reporting less than 100 patients. Finally, in light of our objective, the only studies included in the final analysis were those which evaluated at least one biological variable with a demonstrated independent prognostic value in at least one study meeting our other inclusion criteria. Because of the very heterogeneous nature of the studies published (to be explained below in Results and Discussion), a meta-analysis could not, in our opinion, provide valid information.

The corresponding author for this review (JW) read and classified all the included or excluded studies. The two other co-authors, read and categorized all the included articles.

### Laboratory methods used

We identified studies in which the pre-analytical and/or analytical methods used to measure biological variables were described, either in part or totally [9]. Pre-analytical methodology included patient preparation (duration of fasting state, with or without infusions, etc.), time of blood sampling, sampling material and methods, mode and duration of sample transportation, any storage in the laboratory before assay, any methods used for separation or preservation of the plasma and/or serum samples before assay. Analytical methods corresponded to assay methods used by the laboratory. These methods were termed as “completely described” when the pre-analytical and analytical methods were detailed sufficiently in the article to allow an independent team to reproduce the methodology with precision.

### Results

Among the 644 publications analyzed, only 8 were finally included in our review [10-17]. The full list of the 636 excluded publications is available upon request to the corresponding author (JW). None of the studies examined the independent prognostic value of a biological variable assayed in a biological fluid other than blood.

The pre-analytical methods used for the biological analyses were never detailed. Only one study [17] indicated the method used to assay CEA, but did not provide details. Sensitivity, specificity, accuracy of the biological tests, and the methodology of the pathology techniques was never described in detail.

The characteristic features of the patients included in the 8 studies are summarized in table I. The variables found to be significant in at least one of the 8 studies are indicated in table II. All the included studies evaluated overall survival. One study [13] also provided an analysis of disease-free survival.

The threshold levels used were very heterogeneous, varying from one article to another, not only for the biological variables, but also for the non-biological variables (table II). Pre- and/or post-therapeutic CEA level was the only biological variable that was evaluated in all the included studies. None of the studies examined a biological variable as a continuous variable. Only one study evaluated the kinetics of the studied variable [10]. This same study was the only one that evaluated a biological variable measured following treatment (table II).

No one factor was found to have a significant prognostic influence in all the studies (table II). Among the factors that were frequently evaluated in the 8 included studies, 3 were found to be significant: liver metastasis (8/8, i.e. 100%, this was either assessed in terms of number and/or size of the metastases and/or in terms of the proportion of the liver tissue replaced by the tumor), treatment and/or response to treatment (5/5, i.e. 100%), and pre- and/or post-therapeutic CEA levels (4/8, i.e. 50%). Biological variables other than CEA were evaluated less often and/or found less frequently significant less often. Considering all biological variables taken together, 6 of the studies (75%) concluded that this type of variable had independent prognostic significance (table II). Two studies found that the performance of ALP was better than CEA for prediction of patient survival; two other studies came to the opposite conclusion (table II). One of the two studies including the largest number of

### Table I. – Characteristics of the patients with metastatic colorectal carcinoma in the eight included studies.

<table>
<thead>
<tr>
<th>References</th>
<th>[10]</th>
<th>[11]</th>
<th>[12]</th>
<th>[13]</th>
<th>[14]</th>
<th>[15]</th>
<th>[16]</th>
<th>[17]</th>
</tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>100</td>
<td>152</td>
<td>117</td>
<td>151</td>
<td>112</td>
<td>175</td>
<td>544</td>
<td>484</td>
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<tr>
<td>Median age (years)</td>
<td>ND</td>
<td>57</td>
<td>56</td>
<td>58</td>
<td>60</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Treatments</td>
<td>IAC versus palliation</td>
<td>IAC</td>
<td>IAC</td>
<td>SC then surgery</td>
<td>IAC then SC</td>
<td>Palliation, SC</td>
<td>Palliation, surgery</td>
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<td>G</td>
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<tr>
<td>Median survival (months)</td>
<td>7.5 versus 13.5</td>
<td>Colon: 18</td>
<td>Rectum: 16</td>
<td>11.5</td>
<td>Resected: 48</td>
<td>Non-resected: 15.5</td>
<td>14</td>
<td>6.1</td>
</tr>
</tbody>
</table>

IAC: intra-arterial hepatic chemotherapy; SC: systemic chemotherapy; Years: inclusion year (year of publication); GB: Great Britain; F: France; G: Germany; ND: no data.
patients [16] was in the first category while the other [17] was in the second category.

**Discussion**

Considering the objective of this work, we only included studies which evaluated prognostic criteria with respect to survival and excluded studies evaluating response to treatment.

The 8 included studies did not form a homogeneous group. The heterogeneous nature of these studies resulted form their different inclusion and exclusion criteria, the diverse group of prognostic factors or variables evaluated, the cut-off levels for variables analyzed, the number of patients, the proportion of patients in whom the biological variables were measured compared with the inclusion population, the treatments used, the year and country of publication, the inclusion period, and the specialties of the co-authors for the different studies. In addition, at least 5 of the 8 studies were retrospective [11-15] and the methodology used to measure the biological variables studied was not indicated in any of the studies.

The 3 factors which appeared most frequently to be demonstrated to have prognostic value were factors related to the degree of liver invasion, to treatments used, and to biological variables (all taken together) (table II). The results concerning each of these biological variables when considered individually, were nevertheless quite contradictory (table II).

A meta-analysis could not be attempted due to the heterogeneous nature of the 8 studies included in this review and their contradictory results.

How can such contradictory results be explained?

The results of these studies could have been affected by different analytical, pre-analytical or biological events generating major bias. Several examples of such events have been explained and discussed elsewhere [6]. Random variability of more than 50% cannot be ruled out for certain biological variables used in the 8 studies examined in this review, particularly the multicentric studies. Use of threshold levels determined on the basis of unknown criteria could also explain some of the divergence. For an analysis of prognosis, biological variables (and probably certain non-biological variables) should probably be best used as continuous variables [9], but none of the studies examined this approach. Likewise, and despite the
most recent guidelines proposed by the American Society of Clinical Oncology [18], which state that, “if no other simple test can be used to indicate response, serum CEA should be assayed at treatment onset for metastatic disease and every two or three months during treatment”, only one study [10] appeared to provide kinetic data on CEA. This approach should be used more often [9].

Taking into account the criticisms concerning the methodologies used, and looking at the overall results whatever the treatment used, it was noted that 75% of the studies included in this review concluded that biological variables had significant independent prognostic value, suggesting that such variables should be systematically assayed in patients participating in clinical trials. Other arguments further support this opinion. In our opinion, the two principal arguments in favor of systematic CEA and ALP assays in these patients would be: a) the prognostic significance of CEA level was independent of surgery in the series of patients treated by the medicosurgical and scientific team that achieved the best results in terms of patient survival [1, 13]; b) performance of the CEA level was better than the ALP level in one of the two studies including the largest number of patients [17] and the performance of the ALP level was better than the CEA level in the other of these two studies [16]. In addition, these two studies were among the three which were apparently not retrospective. The prognostic value of the other biological variables listed in table II requires validation before proposing systematic assay in clinical trials.

As concluding remarks in this systematic review, and to help improve the performance of future clinical trials in this population of patients, we propose that the following points should be taken into consideration:

— Pre- and post-therapeutic prognostic factors should be evaluated separately using several multivariate statistical models;
— Precise indications concerning the analytic and pre-analytic methodologies used should be provided;
— Biological variables should be considered as continuous variables for statistical analysis and arbitrary threshold levels should be avoided. This latter proposition could also be applied to non-biological variables that can be expressed as continuous variables (patient age, percentage of liver invasion, for example). Whenever possible, the kinetics of the biological variables should also be considered;
— Considering that some tumors do not produce CEA, it would be interesting to compare the prognostic significance of CEA with that of other tumor markers such as CA 19-9 or tissue polypeptide antigen [19, 20];
— Other biological variables which are less expensive to assay [21] and which are frequently measured in these patients, for instance ALP or other serum liver enzymes, serum bilirubin, serum albumin, serum prothrombin, blood cell counts [3] could also be evaluated in clinical trials;
— Due to the wide variability of potential prognostic markers, each source of technical bias, it would be desirable to conduct clinical trials within the framework of a concerted multidisciplinary approach involving surgeons, clinicians, biostatisticians, biologists, pathologists, and fundamental scientists [22].

REFERENCES
