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review

Early postoperative serum carcinoembryonic antigen levels in patients operated for colorectal carcinoma - a new method for following-up

Bojan Veingerl

Department of Thoracic Surgery, Maribor Teaching Hospital, Maribor, Slovenia

Background. *The only method of treatment offering a favourable prognosis for colorectal carcinoma is radical resection of the part of the colon or rectum including the pertaining lymph nodes and eventual radical removal of metastases. But even such presumably curative surgery does not warrant full recovery of all operated patients as recurrences are frequent and according to most analyses 5-year survival is lower than 50%. Therefore, additional treatment is attempted in some patients. Various prognostic factors of disease recurrence are helpful. One such prognostic sign is serum carcinoembryonic antigen (CEA) level measured soon after surgery.*

Conclusions. *All patients with radical R0 resection, according to their postoperative serum CEA levels and the CEA half-life fall into three groups: $_{CEA}$ R0, $_{CEA}$ R1 and $_{CEA}$ R2 resected patients. A statistically significant difference regarding survival and number of recurrences was noted among patients categorized by the stage of disease, particularly between the three groups of patients and the group having been undergone presumably curative surgery.*

Key words: colorectal neoplasms; carcinoembryonic antigen - blood; prognosis; follow-up studies

Introduction

In Slovenia there are about 850 new cases of colorectal carcinoma (CC) per year. The incidence is increasing steeply.[1,2] In about 550 cases per year in Slovenia, CC is also the cause of death. Of the newly detected cases, about 75% are treated surgically, 5% only with chemotherapy and/or radiotherapy, 20% are not receiving treatment. The major aim of the operation is R0 resection of the colon with the pertaining lymphadenectomy and radical removal of eventual metastases, i.e. complete removal of malignant cells which would lead to the full recovery of the patient.[3-16] This is logical as the classification of resections by radicality or by residual tumour is based on the surgeon's intraoperative evaluation and on the pathologist's analysis of the operative specimen.[17-25] This means that, in radical resection, the surgeon believes that no malignant cell is left in the patient's body (he is only aided by his vision, tactile sense and some-

Correspondence to: Bojan Veingerl, MD, MSc, Department of Thoracic Surgery, Maribor Teaching Hospital, Ljubljanska 5, SI-2000 Maribor, Slovenia; Phone: +386 2 321 1417; Fax: +386 2 312 393; E-mail: bojan.veingerl@sb-mb.si

times intraoperative US), while the pathologist's evaluation is based only on the analysis of the operative specimen and the investigation of its margins, rarely on additional biopsy done by the surgeon during the surgical procedure. Hence, the evaluation of the residual tumour, i.e. malignant cells remaining in the body, is only approximate.[26-32] With the aid of his senses and US during surgery, the surgeon cannot exclude residual malignant cells in the body, and the pathologist can only evaluate the tissue removed.[33-42]

Radical removal of all malignant cells from the body should result in a drop in CEA level regardless of its half-life in the form of an exponential curve to normal levels.[43-57] In the patients in whom surgical treatment was not so successful, such a serum CEA drop did not occur because the residual malignant cells kept on producing CEA which is reflected in a slower drop of the serum CEA level.[57]

CEA and curative resection

In the patients in whom the CEA level dropped as expected, it is more likely that curative resection was successful. In those in whom the CEA levels were dropping more slowly than expected, an earlier detection of recurrence is possible by strict following up or the delayed drop of CEA level could indicate to carry out additional chemotherapy immediately after surgery.

For easier work and comprehension, the following new terms are recommended:

$_{CEA}$R0 resection, $_{CEA}$R1 resection and $_{CEA}$R2 resection (Figure 1).

$_{CEA}$R0 resection represents R0 resection according to surgical and histological evaluation in which the expected drop in CEA level - with regard to half-life - was noted in the serum of patients after surgery for CC.

$_{CEA}$R1 resection represents R0 resection according to surgical and histological evaluation in which a slower drop in CEA level than expected was noted in the serum of patients after surgery for CC.

$_{CEA}$R2 resection represents R0 resection in which no drop in CEA level was noted in the serum of patients after surgery.

Follow-up of patients

The follow-up of patients after surgery for CC is particularly advisable in view of the possibility to detect curable recurrences of the disease in asymptomatic patients before they become unresectable.[58-61] The major aim of such follow-up after presumably curative surgery is the detection of metachronous colorectal tumours and recurrences which are radically resectable, such as local recurrences or resectable liver and lung metastases.[58,62-64] Various protocols elaborated by expert groups are an aid to the follow-up.[3,58,62-65] We used the recommendations by the expert group of the Ministry of Health for following up the patients after surgery for CC.[3]

In most analyses in the literature, a significant prognostic sign of CC recurrence and of survival is the preoperative serum CEA level or the so-called initial CEA.[66,67] But with respect to the cut-off point, the data regarding the serum CEA differ strongly. The difference is most obvious when the cut-off point is set

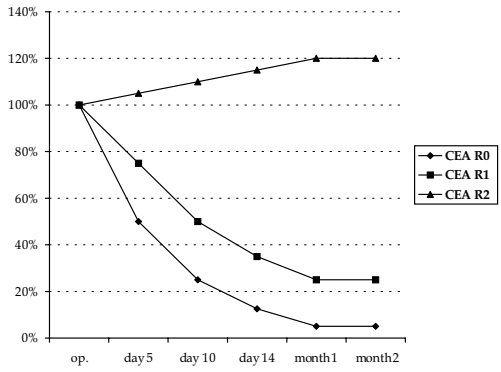

Figure 1. Graphic presentation of serum C EA value in $_{CEA}$ R0, $_{CEA}$ R1 and $_{CEA}$ R2 resections.

at 20 ng/mL CEA in the serum and when it decreases with the lowering of the cut-off point.[66,67]

In the study, the measurement early postoperative serum CEA levels proved to be a significant prognostic sign for the disease recurrence and for the survival of patient after surgery for CC, confirming completely the expectations. In the literature, several studies find the measurement of postoperative serum CEA levels imperative,[58,66-70] but with regard to CEA half-life, only a few find it significant to measure these levels soon after surgery.[71] Most studies classified the patients after surgery for CC into different groups, and practically all found that, in such patients, the postoperative drop in preoperatively increased serum CEA levels to normal levels - and remaining there (under 5 ng/mL) - was a significant prognostic sign of 5-year survival.[58,66,68,69,72-74] In the Maribor Teaching hospital, statistically significant differences were found between these groups as regards the prognostic value of two-year survival as well as disease recurrence. The results confirm that the $_{CEA}$R0 resected patients have an excellent prognosis regarding the survival and a lesser probability of recurrence. For other patients, eventual adjuvant treatment and a strict follow-up can be planned already in the perioperative period.[71]

The majority of our patients were operated in the advanced stage of disease, more than 50% in Dukes C and 8.6% in Dukes D. Although this is in accordance with the findings of some other authors,[2,16,23,75,76] it is a poor prognosis for total survival and curability of patients after surgery. Various authors describe 5-year survival after CC surgery for Dukes A as approximately 80-90%, for Dukes B 70-80%, for Dukes C 40-50% and for Dukes D 10-30%, and total survival between 40 and 60%.[1,2,4,6,7,19,66,67,70,75,76]

Conclusions

The study performed in Maribor Teaching Hospital proves that the results of early serum CEA level measurement after surgery for CC are good prognostic signs of the disease recurrence in the patients who are, according to pathohistologic criteria, assumed to be curatively operated on after having undergone R0 resection.[71]

The method, apart from being economical, is advantageous also because the patient is not exposed to any additional investigative methods, as the venous blood sample of several ml can be obtained during a regular postoperative hemogram check. Theoretically, only one measured postoperative serum CEA level, between day 3 and day 10 following the surgery, would suffice. Another advantage of the method is the possibility of repetition of measurements, if required.

The main disadvantage is that it is only suitable for about half of the patients operated for CC. Many patients exhibit no preoperative increase in the serum CEA level. In the patients requiring larger amounts of transfused blood the method is not applicable, either. However, in these patients other widely used methods would be inadequate as well.

A significant advantage of the method is that it yields the results quickly after the operative procedure is performed; giving the possibility of planning eventual adjuvant treatment and determining other methods of follow-up, such as more frequent controls of $_{CEA}$R1 and $_{CEA}$R2 resected patients.

The results of different studies, including ours, confirm the possibility of applying the method in the search for those patients who after presumably curative treatment require adjuvant therapy and/or precise follow-up - i.e. in the patients in whom we can most probably expect detecting recurrences, or metastasizing, or metachondrous intestinal tumours before they become unresectable, which is the basic aim of postoperative follow-up.

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