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Review

The diagnostic accuracy of carcinoembryonic antigen to detect colorectal cancer recurrence – A systematic review

Caspar G. Sørensen [a, *], William K. Karlsson [a], Hans-Christian Pommergaard [b], Jakob Burcharth [c], Jacob Rosenberg [c]

[a] Faculty of Health Sciences – University of Copenhagen, Blegdamsvej 3 – 2200 København N, Denmark
[b] Hvidovre Hospital – University of Copenhagen, Department of Surgery, Kettegård Alle 30 – 2650 Hvidovre, Denmark
[c] Herlev Hospital – University of Copenhagen, Centre for Perioperative Optimization, Department of Surgery, Herlev Ringvej 75 – 2730 Herlev, Denmark

HIGHLIGHTS

- Reporting on the reference standards used was not optimal.
- Results point toward a sensitivity of CEA ranging between 50% and 80%.
- Results point toward a specificity and negative predictive value above 80%.
- A clinically relevant effect on patient mortality remains to be proven.

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ABSTRACT

Introduction: Carcinoembryonic Antigen (CEA) has been used as a tumor marker in the follow-up of colorectal cancer for more than 40 years. Controversy exists regarding its diagnostic applicability due to a relatively low sensitivity and a questionable effect on mortality. The aim of this review was to assess the diagnostic accuracy of CEA in detecting recurrence after intended curative surgery for primary colorectal cancer.

Methods: Systematic literature searches were performed in PubMed, EMBASE and Cochrane databases, and articles were chosen based on predefined inclusion criteria. Reference lists from included articles were manually searched for additional publications of relevance.

Results: Forty-two original studies with generally representative populations and long follow-up were included. Data were reported on outcomes from 9,834 CEA tests during follow-up. Reporting on the reference standards used was not optimal. Sensitivity of CEA ranged from 17.4 % to 100 %, specificity ranged from 66.1 % to 98.4 %, positive predictive value ranged from 45.8 % to 95.2% and negative predictive value ranged from 74.5 % to 100 %.

Conclusion: Results point toward a sensitivity of CEA ranging between 50 % and 80 %, and a specificity and negative predictive value above 80 %. Results on positive predictive value showed low reliability. Overall, CEA did not effectively detect treatable recurrences at an early stage, and a clinically relevant effect on patient mortality remains to be proven.

1. Introduction

Colorectal cancer is the third most common cancer worldwide, accounting for almost 10% of all cases [1]. Recent studies with large cohorts show recurrence rates of 20–30% [2,3]. Follow-up after curative treatment, remains a complex challenge for the healthcare system, both in terms of diagnostics, treatment and monetary costs. As a means of assistance, biomarkers have become increasingly popular to use in cancer follow-up.

Discovered in 1965, Carcinoembryonic Antigen (CEA) is an oncofetal antigen produced by endodermally derived epithelial tumor cells in the digestive tract [4]. As a blood-borne biomarker, CEA represents a potentially cheap [5], safe and noninvasive test for the follow-up of colorectal cancer patients. However, results

* Corresponding author. Godthåbsvej 89, 4. tv, 2000 Frederiksberg, Denmark.
E-mail address: caspar_sorensen@hotmail.com (C.G. Sørensen).

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concerning its effect on reducing mortality have been contradictive [6,7], and CEA can be elevated due to a number of reasons, that is both malignant [8] and benign diseases [9], as well as in smokers [10].

The purpose of this systematic review was to assess the diagnostic accuracy of CEA in detecting recurrence, after intended curative surgery for primary colorectal cancer.

2. Material and methods

2.1. Protocol and reporting

A protocol was developed and registered in the PROSPERO database of systematic reviews [11].

This systematic review was reported in accordance with the PRISMA guidelines [12].

2.2. Data sources and search methods

A literature search was conducted in PubMed, EMBASE and Cochrane databases on October 8, 2014.

The full search was as follows:

((cancer of the colon) OR cancers of the colon) OR colon cancer) OR colon cancers) OR colon carcinoma) OR colon carcinomas) OR colon neoplasm) OR colon neoplasms) OR colon tumor) OR colon tumors) OR colon tumour) OR colon tumours) OR colonic cancer) OR colonic cancers) OR colonic carcinoma) OR colonic carcinomas) OR colonic neoplasm) OR colonic neoplasms) OR colonic tumor) OR colonic tumors) OR colonic tumour) OR colonic tumours) OR cancer of the rectum) OR cancers of the rectum) OR rectal cancer) OR rectal cancers) OR rectal carcinoma) OR rectal carcinomas) OR rectal neoplasm) OR rectal neoplasms) OR rectal tumor) OR rectal tumors) OR rectal tumour) OR rectal tumours) OR rectum cancer) OR rectum cancers) OR rectum carcinoma) OR rectum carcinomas) OR rectum neoplasm) OR rectum neoplasms) OR rectum tumor) OR rectum tumors) OR rectum tumour) OR rectum tumours) OR colorectal cancer) OR colorectal cancers) OR colorectal carcinoma) OR colorectal carcinomas) OR colorectal neoplasm) OR colorectal neoplasms) OR colorectal tumor) OR colorectal tumors) OR colorectal tumour) OR colorectal tumours))
AND
(((((((((CEA) OR carcinoembryonic antigen) OR carcinoembryonic antigens) OR CD66e Antigen) OR CD66e Antigens) OR CD66e-Antigen) OR CD66e-Antigens) OR CD66eAntigen) OR CD66eAntigens))
AND
((((((((recurrence) OR relapse) OR recrudescence) OR follow-up) OR follow up) OR surveillance) OR monitoring) OR sustained remission).

2.3. Eligibility criteria

Cohort studies and randomized controlled trials written in English were included.

No restrictions were made on the year of publication.

The populations had to comprise adult humans with primary colorectal cancer, operated on with curative intent.

At least one postoperative CEA measurement was required. Data for calculation of either sensitivity, specificity, positive predictive value or negative predictive value for CEA had to be available.

The diagnostic abilities of CEA in detecting recurrence, had to be compared with the standard of clinical diagnostics (biopsy, surgery, endoscopy, radiology, and clinical examination).

If patient data overlapped between publications, we selected the most appropriate publication to avoid duplicate data based upon the following factors in descending order: Data on both true positive, false positive, false negative and true negative values, size and relevance of the cohort (relevant exclusions, both colon and rectal cancers represented), and duration of follow-up.

2.4. Inclusions and exclusions

The following types of publications were excluded: Reviews, case–control studies, experimental studies, meeting abstracts, comments, correspondences etc.

Studies were also excluded for the following reasons:

- The methods or language used were unclear.
- The cohort consisted entirely of either recurred, CEA positive or CEA negative patients.
- A cut-off value for CEA was not stated, or if the same cut-off value did not apply to everyone.
- CEA was only measured within 3 months postoperatively, since this was considered as prognosticating to account for residual disease.

Furthermore, studies were excluded if data were mixed in an inappropriate way, e.g. curatively and non-curatively operated patients, primary cancers with recurrences, first time recurrences with second time recurrences or if results were calculated per test or per recurrence, instead of per patient.

2.5. Study selection

Results from the database search were transferred into a document making up one long list of publications. Publications written in English were assessed for duplicates. After this, authors CGS and WKK independently screened the titles and abstracts for potentially relevant publications. Disagreements were discussed and in cases of doubt, the discussion was settled by authors JB, JR and HCP.

2.6. Data extraction

Data were extracted independently by the first author into a predefined Excel sheet. This included article demographics, recurrence information, the diagnostic methods used and the diagnostic properties of CEA measurements. The Excel sheet was piloted using 10 studies, and revised.

If studies examined more than one cut-off value, data were reported on the cut-off the authors seemed to prefer or mentioned the most. If this was not clear, data were reported on the cut-off used in standard practice.

2.7. Definitions of outcome measures

- A true positive test was defined as a positive CEA test (CEA above cut-off) before or at the time of recurrence detection. However, five studies required a positive CEA test before the detection of recurrence [28,39,51–53], and these were handled like the other studies. Recurrences had to be detected within the follow-up period.
- A true negative was defined as a patient with negative CEA testing and no evidence of recurrence at the end of follow-up.
- A false negative was defined as a diagnosis of recurrence in a patient with normal CEA at the time. In five studies