

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

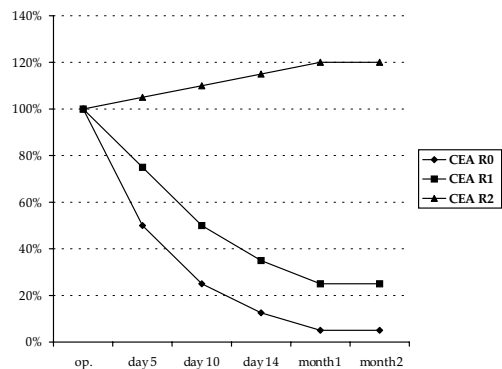


Figure 1. Graphic presentation of serum CEA value in ${}_{CEA}R0$, ${}_{CEA}R1$ and ${}_{CEA}R2$ resections.

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.

References

1. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J, editors. *Cancer incidence in five continents*. Vol. 6. Lyon: International Agency for Research on Cancer; 1992. (IARC Sci Publ No.120).
2. Pompe-Kirn V. Epidemiološke značilnosti raka širokega črevesa in danke v Sloveniji. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. p. 79-85.
3. Repše S, editor. *Priporočila za celostno obravnavo bolnikov z rakom prebavil*. Ljubljana: Ministrstvo za zdravstvo R Slovenije; 1997. p. 23-32.
4. Sing S, Morgan MBF, Broughton M, Caffarey S, Topham C, Marks CG. A 10-year prospective audit of outcome of surgical treatment for colorectal carcinoma. *Br J Surg* 1995; **82**: 1486-900.
5. Harris DR, Blake JRS. Computerised audit for colorectal cancer. *Ann R Coll Surg Engl* 1993; **75**: 268-71.
6. Beart RW, Steele GD, Menck HR, Chimel JS, Ocwieja KE, Winchester DP. Management and survival of patients with adenocarcinoma of the colon and rectum: a national survey of the commission on cancer. *J Am Coll Surg* 1995; **181**: 225-36.
7. Mäkelä JT, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. *Arch Surg* 1995; **130**: 1062-7.
8. McIntosh G, Young G. Diet and large bowel cancer prevention. *Cancer Forum* 1995; **19**: 160-3.
9. Potter JD. Nutrition and colorectal cancer. *Cancer Causes and Control* 1996; **7**: 127-46.
10. Schottenfeld D, Winawer SJ. Large intestine. In: Schottenfeld D, Fraumani J Jr, editors. *Cancer epidemiology and prevention*. Philadelphia: Saunders; 1982. p. 703-27.
11. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal tumor-development. *New Engl J Med* 1988; **319**: 525-32.
12. Fenoglio CM, Pascal RR. Colorectal adenomas and cancer: pathologic relationships. *Cancer* 1982; **50**: 2601-8.
13. Winawer SJ, Zauber A, Diaz B. Temporal sequence of evolving colorectal cancer from the normal colon. *Gastrointestinal Endosc* 1987; **33**: 167-72.
14. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ, eds. *AJCC manual for staging of cancer*. 4th edition. Philadelphia: J.B. Lippincot; 1992.
15. Hermanek P, Wittekind C. The pathologist and the residual tumor (R) classification. *Pathol Res Pract* 1994; **190**: 115-23.
16. Bračko M, Lamovec J. Patologija in klasifikacija karcinoma širokega črevesa in danke. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. p. 86-92.
17. Jass JR, Love SB, Northover JMA. A new prognostic classification of rectal cancer. *Lancet* 1987; **I**: 1303-6.
18. International Union Against Cancer. Colon and rectum. In: Sobin LH, Wittekind Ch, editors. *TNM Classification of malignant tumors*. 5th edition. New York: Wiley-Liss; 1997. p. 66-9.
19. Krasna MJ, Flancbaum L, Cody RP, Shneibaum S, Ben Ari G. Vascular and neural invasion in colorectal carcinoma. Incidence and prognostic significance. *Cancer* 1988; **61**: 1018-32.
20. Winawer SJ, Enker WE, Lightdale CJ. Malignant tumors of the colon and rectum. In: Berk JE, editor. *Bockus gastroenterology*. 4th edition. Vol.4. Philadelphia: W.B. Saunders Company; 1985. p. 2531-74.
21. Speight VO, Johnson MW, Staltemberg PH, et al. Colorectal cancer: current trends in initial clinical manifestations. *Sought Med J* 1991; **84**: 575-8.
22. Dixon AR, Thornton HJ, Cheetan HM. General practitioners awareness of colorectal cancer, a 10 years review. *Br Med J* 1990; **301**: 152-3.
23. Žitko A. Rak širokega črevesa in danke-klinične značilnosti in naravni potek bolezni. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. p. 93-8.
24. Filding LP, Padmanabhan A. Clinical features of colorectal cancer. In: Misiewicz JJ, Pounder RE, Venables CW, editors. *Disease of the gut and pancreas*. 2nd edition. Oxford: Blackwell Scientific Publications; 1994. 877-92.
25. Rankin GB. Indications, contraindications and complications of colonoscopy. In: Sivak MV, editor. *Gastrointestinal endoscopy*. Philadelphia: Saunders; 1987. p. 783-878.
26. Foutch PG, Mai H, Pardy K, DiSario JA, Manne RK, Kerr D. Flexible sigmoidoscopy may be ineffective for secondary prevention of colorectal cancer in asymptomatic average-risk men. *Dig Dis Sci* 1991; **36**: 924-8.

27. Bond JH. Evolving Strategies for Colonoscopic Management of patients with Colorectal Polyps. *Endoscopy* 1995; **27**: 38-42.
28. Laufer I, Levine MS. *Double contrast gastrointestinal radiology*. 2nd edition. 1992. p. 423-95.
29. Hernandez-Socorro CR, Guerra C, Hernandez-Romero J, Rey A, Lopez-Facal P, Alvarez-Santullano V. Colorectal carcinomas: diagnosis and preoperative staging by hydocolonic sonography. *Surgery* 1995; **117**: 609-15.
30. Thoeni RF. Colorectal cancer: cross-section imaging for staging of primary tumor and detection of local recurrence. *AJR* 1991; **156**: 909-15.
31. Allgoewer M. Das Coloncancer. In: *Chirurgische gastroenterologie 2*. Allgoewer M, Harder F, Hollender LF, Siewert JR, editors. Berlin: Springer; 1981. p. 776-96.
32. Welch CE, Ottinger LW, Welch JP. Manual of lower gastrointestinal surgery. New York: Springer; 1980.
33. Gall FP, Hermanek P. Wandel und derzeitiger stand der chirurgischen behandlung des colorectalen carcinoms. *Chirurg* 1992; **63**: 227-34.
34. Beger A. Chirurgische therapie des primaeren kolonkarzinoms. In: Smola MG, Jatzko GR, editors. *ACO consensus-bericht kolonkarzinom*. Graz: ACO; 1995.
35. Herfarth Ch, Hohenberger P. Radikalitaet mit eingeschaenktet resection in der carcinomchirurgie des gastrointestinaltrakts. *Chirurg* 1992; **63**: 235-41.
36. Siewert JR, Fink U. Multimodale therapieprinzipsen bei tumoren des gastrointestinaltrakts. *Chirurg* 1992; **63**: 242-50.
37. Repše S. Standardne, razširjene in multivisceralne resekcije pri raku širokega črevesa. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. p. 131-36.
38. Žakelj B. Nizka sprednja resekcija. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. 137-40.
39. Yeatman TJ, Bland KI. Sphincter-saving procedures for distal carcinoma of the rectum. *Ann Surg* 1989; **209**: 1-17.
40. Čalić M. Abdominoperinealna ekscizija rektuma. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. p. 141-44.
41. Rothenberger D, Douglas Wong W. Abdominoperineal resection for adeno-carcinoma of the low rectum. *World J Surg* 1992; **16**: 478-85.
42. Mac Farlane JK, Ryall RDH, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **20**: 457-60.
43. Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *J Exp Med* 1964; **121**: 439-42.
44. Krupey J, Wilson T, Freedman SO, Gold P. The preparation of purified carcinoembryonic antigen of the human digestive system from large quantities of tumor tissue. *Immunochemistry* 1972; **9**: 617-22.
45. Mai M, Takahashi Y. Prediction of recurrence of gastrointestinal cancer from standpoint of biological malignancies-tumor marker doubling time and its half life period line. *Hum Cell* 1993; **6**: 82-7.
46. Steward AM, Nixon D, Zamcheck N, Aisenberg A. Carcinoembryonic antigen in breast cancer patients: serum levels and disease progress. *Cancer* 1974; **33**: 1246-52.
47. Oehr P, Schlosser T, Adolphs HD. Applicability of an enzymatic test for the determination of CEA in serum and CEA-like products in urine of patients with bladder cancer. *Tumor Diagnostik* 1980; **1**: 40-4.
48. Reynoso G, Chu TM, Holyoke D, Cohen E, Nemoto T, Wang JJ, et al. Carcino-embryonic antigen in patients with different cancers. *JAMA* 1972; **220**: 361-5.
49. Ewing HP, Newson BD, Hardy JD. Tumor Markers. *Curr Probl Surg* 1982; **19**: 53-94.
50. Zamcheck N. CEA in diagnosis, prognosis, detection of recurrence, and evaluation of therapy of colorectal cancer. Symposium on Clinical Application of CEA and Other Antigenic Markers Assays. Nice, France. October 1977. Amsterdam: Medica Excerpta; 1978. p. 64.
51. Martin EW Jr, Cooperman M, King G, Rinker L, Carey LC, Minton JP. A retrospective and prospective study of serial CEA Determinations in the early detection of recurrent colon cancer. *Am J Surg* 1979; **137**: 167-9.
52. Skarin AT, Delwiche R, Zamcheck N, Lokich JJ, Frei E 3rd. Carcinoembryonic antigen: clinical correlation with chemotherapy for metastatic gastrointestinal cancer. *Cancer* 1974; **33**: 1239-45.
53. Lokich JJ, Zamcheck N, Lowenstein M. Sequential carcinoembryonic antigen levels in the therapy of

- metastatic breast cancer. *Ann Intern Med* 1978; **39**: 902-6.
54. Zamcheck N. Carcinoembryonic antigen. Quantitative variations in circulating levels in benign and malignant digestive tract disease. *Adv Intern Med* 1974; **19**: 413-33.
 55. Go VL, Ammon HV, Holtermuller KH, Krag E, Phillips SF. Quantification of carcinoembryonic antigen-like activities in normal human gastrointestinal secretions. *Cancer* 1975; **36**: 2346-50.
 56. National Committee for Clinical Laboratory Standards. *Evaluation of precision performance of clinical chemistry devices*. 2nd edition. Tentative Guideline. NCCLS Document EP5-T2, March 1992.
 57. Mai M, Takahashi Y. Prediction of recurrence of gastrointestinal cancer from standpoint of biological malignancies - tumor marker doubling time and its a half life period line. *Hum Cell* 1993; **6**: 82-7.
 58. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg KG. Follow-up after curative surgery for colorectal carcinoma. *Dis Colon Rectum* 1995; **38**: 619-26.
 59. Northover J. Which Type of Follow-up? *Hepatogastroenterology* 2000; **47**: 335-6.
 60. Laghi L. Genetics of colorectal cancer. *Hepatogastroenterology* 2000; **47**: 315-22.
 61. Rudy DR, Zdon MJ. Update on colorectal cancer. *Am Fam Physician* 2000; **61**: 1759-70, 1773-4.
 62. Graham RA, Wang S, Catalano PJ, Haller DG. Postsurgical surveillance of colon cancer: preliminary cost analysis of physician examination, carcinoembryonic testing, chest x-ray, and colonoscopy. *Ann Surg* 1998; **228**: 59-63.
 63. Peethambaram P, Weiss M, Lomprinzi CL, Novotny P, O'Fallon JR, Erlichman C, et al. An evaluation of postoperative follow-up tests in colon cancer patients treated for cure. *Oncology* 1997; **54**: 287-92.
 64. Lucha PA Jr, Rosen L, Olenwine JA, Reed JF, Riether RD, Stasik JJ Jr, et al. Value of carcinoembryonic antigen monitoring in curative surgery for recurrent colorectal carcinoma. *Dis Colon Rectum* 1997; **40**: 145-9.
 65. Omejc M. Sledenje operiranih bolnikov z rakom širokega črevesa in danke. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. p. 196-9.
 66. Behbehani AE, Dashti H, Hussain T, Szymendera JJ. Five-year survival versus initial concentrations and longitudinal serum CEA patterns in patients with colorectal carcinoma. *Supp Nutr* 1995; **11**: 614-8.
 67. Dawson LA, Franssen E, Davey P. Postoperative borderline elevated CEA predicts for earlier relapse in patients with rectal cancer receiving adjuvant postoperative therapy. *Cancer J Sci Am* 1999; **5**: 374-9.
 68. Szymendera JJ, Nowacki MP, Szawlowski AW, Kaminska JA. Predictive value of plasma CEA levels: preoperative prognosis and postoperative monitoring of patients with colorectal carcinoma. *Dis Colon Rectum* 1982; **25**: 46-52.
 69. Filella X, Molina R, Pique JM, Grau JJ, Garcia-Valdecasas JC, Biete A, et al. CEA as a prognostic factor in colorectal cancer. *Anticancer Res* 1994; **14**: 705-8.
 70. Slenz K, Senagore A, Hibbert J, Mazier WP, Talbott TM. Can preoperative and pooperative CEA predict survival after colon cancer resection? *Am Surg* 1994; **60**: 528-32.
 71. Veingerl B. Serum CEA levels in patients operated for colorectal carcinoma. *Wien Klin Wochenschr* 2001; **113(Suppl 3)**: 32-8.
 72. Rapellino M, Piantino P, Pecchio F, Ruffini E, Cavallo A, Scappaticci E, et al. Disappearance curves of tumor markers after radical surgery. *Int J Biol Markers* 1994; **9**: 33-7.
 73. Sato T, Nishimura G, Nonomura A, Miwa K, Miyazaki I. Serological studies on CEA, CA19-9, STn and SLX in colorectal cancer. *Hepatogastroenterology* 1999; **46**: 914-9.
 74. Forones NM, Tanaka M. CEA and CA 19-9 as prognostic indexes in colorectal cancer. *Hepatogastroenterology* 1999; **46**: 905-8.
 75. Štor Z, Repše S, Juvan R, Omejc M. Rezultati operativnega zdravljenja raka širokega črevesa in danke-naša kazuistika iz obdobja 1989-1993. In: Repše S, editor. *Kirurgija širokega črevesa in danke*. Zbornik simpozija. Ljubljana; 1996. p. 200-9.
 76. Bergamaschi R, Arnaud JP. Routine compared with nonscheduled follow-up of patients with »curative« surgery for colorectal cancer. *Ann Surg Oncol* 1996; **3**: 464-9.