

Posttherapeutic follow-up of colorectal cancer patients treated with curative intent

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Rezumat

Monitorizarea post-terapeutică a pacienților cu cancer colorectal (CCR) tratați cu viză curativă

Scop: Pornind de la datele din literatură care arată că aproximativ 50% din pacienții cu cancer colorectal (CCR) tratați cu viză curativă vor prezenta recidive ale bolii și de la rezultatele meta-analizelor care arată ameliorarea supraviețuirii în cazul utilizării unor programe de urmărire post-terapeutică intensă, prin prezentul studiu am evaluat beneficiul suplimentar al introducerii ecografiei abdominale de rutină în monitorizarea pacienților cu CCR.

Material și metodă: Am efectuat un studiu prospectiv, pe un număr de 107 de pacienți diagnosticați cu CCR stadiul III. Urmărirea pacienților studiați a inclus: anamneza și examenul fizic, determinarea CEA și ecografia abdomino-pelvină la fiecare 3 luni.

Rezultate: Recidiva a fost diagnosticată în 36% din cazuri, după un interval mediu de urmărire de 24 luni. Ficatul a fost cel mai frecvent sediu unic de recurență al bolii (62%). Nivelul seric al CEA a crescut în majoritatea cazurilor de recidivă (69%). Un procent mare de recidive a fost diagnosticat de ecografia de rutină (62%).

Concluzii: Studiul nostru ilustrează beneficiul urmăririi post-terapeutice intense (CEA, ecografie), după tratamentul curativ al CRC.

Cuvinte cheie: cancer colorectal, recurență, metastaze, antigen carcinoembrionar, ecografie abdominală

Abstract

Background and aim: Based on published data showing that despite a curative intent treatment approximately 50% of colorectal cancer (CRC) patients will present with disease relapse, and on the results of meta-analysis which showed improved survival by using intense posttreatment follow-up programs, we aimed in the present study to evaluate the additional benefit of routine abdominal ultrasound in the follow-up program of CRC patients.

Material and method: We conducted a prospective study, on 107 patients diagnosed with stage III CRC. Patients follow-up included: history and physical examination, CEA determination, and abdomino-pelvic US every 3 months.

Results: Recurrent disease was observed in 36% of cases after a median follow-up interval of 24 months. The liver was the most frequent isolated site of disease recurrence (62%). Serum CEA level increased in most patients (69%) with recurrent disease. Also, a high percentage of relapses was diagnosed by routine abdominal US (62%).

Conclusions: Our study illustrates the benefit of intense follow-up (CEA, abdominal US) after curative treatment of CRC.

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Key words: colorectal cancer, recurrence, metastases, carcino-embryonic antigen, abdominal ultrasound

Introduction

Although over 2/3 of colorectal cancer (CRC) patients benefit from radical surgery, 30-50% of stage II/III patients will present local relapses, distant metastases or metachronous CRC during a postoperative follow-up period of 5 years, and 85% of CRC recurrences are diagnosed within the first 3 years after primary tumor resection (1,2).

Routine use of imaging in the follow-up programs of CRC patients treated with curative intent is still under debate. Also, ultrasound (US) screening for liver metastases in CRC patients has not been investigated in prospective randomized trials, and most studies which have assessed intense follow-up programs in CRC patients treated with curative intent, used CT-scans (3). It is clear that the sensitivity and specificity of US are not higher when comparing with CT, but unlike CT, US is a simple, accessible, affordable and non-irradiating imagistic method. In addition, the introduction of new contrast agents, has increased US accuracy in the diagnosis and characterization of liver lesions, to a level that is comparable to that of contrast spiral CT or MRI and with the advantage of cost and time savings (4).

Based on published data showing that despite a curative intent treatment approximately 50% of CRC patients will present with disease relapse, mainly liver metastases, mean overall survival not exceeding 2 years in the case of unresectable disease (1,3), and on the results of meta-analysis which showed improved survival by using intense posttreatment follow-up programs (1,5,6), we aimed in the present study to evaluate the additional benefit of routine abdominal US in CRC patients followed-up by regular clinical examination and serum CEA determination, whatever their CEA level at presentation.

Material and Method

We conducted a prospective, longitudinal study, on 107 patients diagnosed with stage III CRC between January 2006 and December 2008. We reviewed all medical records of studied patients, and the tumors were staged according to TNM classification (7). Postsurgical follow-up period ranged between January 2006 and December 2010; the minimum follow-up interval was 24 months and the maximum 60 months. Follow-up interval was estimated from the time of surgery until death or last appointment.

The study was conducted in Gastroenterology, Internal Medicine, Oncology and Surgery Departments of Emergency County Hospital of Constanta. Follow-up of CRC patients was carried out by a multidisciplinary team, and included: history and physical examination, CEA determination, and abdomino-pelvic US every 3 months; colonoscopy at 6

months after surgery, if not done before, and at 1 year, if was done before surgery; chest X-ray every 12 months or if respiratory symptoms present. A serum level of CEA > 5 µg/l was considered as a positive criteria for relapse, because the positive predictive value of CEA in CRC is approximately 70-80% (8). Suspicion of relapse was confirmed by subsequent investigations: abdomino-pelvic contrast CT/MRI or contrast US, and contrast CT of the thorax.

Statistical analysis of data from our study was performed by using GraphPad Prism 4 (4.03).

Results

Patients enrollment in the study was as follows: 4 patients diagnosed in 2008, 47 patients diagnosed in 2007 and 56 patients diagnosed in 2006. The demographics of the patient population are presented in Table 1.

Recurrent disease was observed in 39 patients (36.44%) after a median interval of 24.31 ± 14.46 months (range 6-58 months, 95% CI, 19.59-29.03).

The risk of relapse was associated with stage IIIC and G2/G3 disease status (r=0.99; 95%CI, 0.79-0.99; P= 0.0044; R2= 0.99) (Table 2).

Twenty-four patients presented with solitary liver metastases, 5 patients had extra-hepatic recurrence only and 10 had multiple sites of relapse (Table 3).

Table 1. Demographic patient data (n=107)

Demographics	Data
Median age (years)	62.40 ± 12.25
Gender	
Men/Women	50/57 (P=0.4121)
Mean age at diagnosis men/women	62.35 ± 11.64/62.46 ± 13.03 (P=0.9636)
TNM stage at diagnosis	
IIIA	29 (27,10%)
IIIB	44 (41,12%)
IIIC	34 (31,77%)
Tumor grading	
G1 (well differentiated)	5 (4,67%)
G2 (moderate differentiation)	76 (71,02%)
G3 (undifferentiated/anaplastic)	26 (24,29%)
Site of primary	
Ascending colon (including cecum)	29 (27,10%)
Transvers colon	6 (5,60%)
Descending colon	14 (13,08%)
Sigmoid and rectosigmoid junction	30 (28,03%)
Rectum	28 (26,16%)

Table 2. Distribution of relapsed cases according to TNM stage and grading (n=39)

Grading	IIIA	IIIB	IIIC
G1 (n=1)	0	0	1
G2 (n=21)	6	7	8
G3 (n=17)	3	5	9
Total (n=39)	9	12	18

Table 3. Patients distribution according to site of relapse

Site of relapse	No. of patients	Colon	Rectum
Liver	24	16	8
Lung	3	–	3
Peritoneum	2	1	1
Lung + liver	5	1	4
Liver + peritoneum	4	3	1
Lung + peritoneum	1	–	1
Total	39	21	18

Table 4. Means of detection in patients with disease relapse

Site of relapse	No. of patients	Elevated CEA	US	Chest X-ray
Liver	24	19	18	–
Lung	3	2	–	3
Peritoneum	2	1	1	–
Lung + liver	5	2	4	5
Liver + peritoneum	4	2	1	–
Lung + peritoneum	1	1	–	1
Total	39	27	24	9

**Figure 1.** 61 years old patient, diagnosed with CRC in 2008. Standard Doppler US performed at 20 months during follow-up revealed 2 liver metastasis located in segments II and III of the left hepatic lobe, measuring 23 mm, respectively 26.5 mm**Figure 2.** 54 years old patient, diagnosed with CRC in 2007. Standard Doppler US performed at 18 months during follow-up revealed a liver metastasis located in the segment IV of the right hepatic lobe, measuring 38.5mm

The difference in recurrence rate in colon cancer (21/39) and rectal cancer (18/39) was not statistically significant ($P=0.6509$).

The liver was the most frequent isolated site of disease recurrence (61.53%), followed by isolated lung metastases (7.69%), but the pattern of recurrence was different between colon and rectal tumors, because all cases of isolated pulmonary metastases were associated with rectal cancer.

From the total number of 39 patients diagnosed with relapses during follow-up, 27 patients presented an elevated CEA level (69.23% of relapses), while 12 patients had a normal CEA level (30.76%) ($P=0.0014$). Relapses were diagnosed by routine US in 24 patients (61.53% of relapses; Fig. 1-3) and by chest X-ray in 9 cases (Table 4).

Increased CEA level correlated with the presence of liver metastases ($r=0.99$; 95%CI, 0.71-0.99; $P=0.0065$; $R^2=0.98$).

Resection of hepatic metastasis was possible in 12.50% of the cases (3/24 patients with liver metastases).

**Figure 3.** 64 years old patient, diagnosed with CRC in 2006. Standard Doppler US performed at 24 months during follow-up revealed a liver metastasis located in segment II of the left hepatic lobe, measuring 43.8 mm

Discussions

Recurrent disease after curative treatment of CRC cancer remains a challenge. Its frequency is related to the stage of the primary tumour, with relapse being more common in patients at high risk (stage II-III CRC) (9). We observed a recurrence rate of 36.44% which is similar to the generally reported rate of about 1/3 (10).

The present study aimed to evaluate the additional benefit of routine abdominal US in CRC patients followed-up by regular clinical examination and serum CEA determination, whatever their CEA level at presentation. Our study showed a high percentage of relapses diagnosed by routine abdominal US (61.53% of relapses). Our data confirm that the serum CEA level increases in most (69%) patients with recurrent disease. Also, in our study the CEA level was not increased ($< 5 \mu\text{g/L}$) in 31% (12/39) of our patients with relapse, and in these cases metastatic disease was detected by imaging studies without CEA increase.

The liver was the most frequent isolated site of disease recurrence (61.53%), followed by isolated lung metastases (7.69%). In our study all isolated lung metastases were found in rectal cancer patients. Rectal cancer is more likely than colon cancer to be associated with lung metastases without liver metastases because of the venous drainage of the lower rectum and/or anal canal into the iliac veins. However, chest X-ray or CT should also be performed in the follow-up of CRC patients, because the lungs are the second most frequent site of metastatic disease (11).

Metastases restricted to the liver were resectable in 12.50% of our cases (3/24), comparing with the 10%-30% reported resectability rates (10,12,13).

The ASCO guidelines (14) recommend CEA together with yearly thoraco-abdomino-pelvic contrast CT. CT has a higher sensitivity than US in the detection of liver metastases and may detect extrahepatic disease, in particular local recurrence or retroperitoneal nodal disease, but CT is more expensive and until stronger evidence is presented, the use of CEA combined with routine imaging every 3-6 months as performed in our study, remains a valid option in health care systems with limited resources.

Conclusions

Our study illustrates the benefit of intense follow-up (CEA, liver US and chest X-ray) after curative treatment of CRC.

Early detection of any type of recurrent disease is important because a smaller tumour burden, whether resectable or not, has a better prognostic outcome after curative or palliative modern treatment.

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