

Prognostic relevance of preoperative CA 19-9 values in stage III rectal adenocarcinoma: retrospective analysis and clinical implications

Edin Hodžić^{1,*}, Sadat Pušina¹, Adi Mulabdić¹, Mirhan Salibašić¹, Emsad Halilović¹, Mujo Kadrić²

¹Clinic for General and Abdominal Surgery, ²Clinic for Oncology; Clinical Centre of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To investigate prognostic significance of preoperative levels of the Carbohydrate antigen 19-9 (CA 19-9) in patients with stage III rectal adenocarcinoma who underwent a treatment at the Clinical Centre of the University of Sarajevo.

Methods A retrospective cohort study included 84 patients who underwent radical anterior rectal resection due to grade III rectal adenocarcinoma, followed by adjuvant chemotherapy according to the FOLFOX protocol (Oxaliplatin, Leucovorin, 5-Fluorouracil (5-FU)). The patients were divided into two groups according to CA 19-9 values (≥ 27 U/mL and < 27 U/mL, respectively).

Results High preoperative CA 19-9 values predicted an increased probability of postoperative metastases, especially liver, lung and abdominopelvic metastases, as well as three-year disease-free survival (3Y-DFS) and three-year overall survival (3Y-OS). The 3Y-DFS rate for patients with high CA 19-9 was 64.5%, while for those with low CA 19-9 it was 87.2%. The 3Y-OS rate for patients with high CA 19-9 was 89.8%, while for those with low CA 19-9 it was 65.7%. Univariate and multivariate regression analysis confirmed that a high level of CA 19-9 is an independent predictor for DFS and OS shorter than three years.

Conclusion Preoperatively elevated values of CA 19-9 in rectal adenocarcinoma have a significant role in predicting the outcome in patients with stage III rectal adenocarcinoma.

Keywords: biomarkers, colorectal surgery, neoplasms, patient outcome assessment

INTRODUCTION

Colorectal cancer (CRC), as the third most common malignancy, represents a challenge in treatment, especially when diagnosed at a late stage (1–3). The treatment of choice for patients with stage III is curative bowel resection, with adjuvant chemotherapy lasting for six months (4). Standard procedures for stage III rectal cancer include anterior resection and abdominoperineal resection of the rectum with total mesorectal excision

(TME) (5). Adjuvant therapy aims to reduce the risk of disease recurrence (6–8).

Carbohydrate antigen 19-9 (CA 19-9) serum level is one of the most commonly used tumour markers in the evaluation of gastrointestinal malignancies, especially in pancreatic and biliary tract cancers (9–11). European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines do not recommend routine measurement of preoperative CA19-9 levels before CRC surgery (12). Previous studies have shown that the preoperative CA19-9 level can be used as an additional marker to monitor the disease process after CRC resection, and that increased preoperative CA 19-9 levels predict poor overall survival (OS) and disease-free survival (DFS) (13,14). Many deficiencies were identified in previous studies, including issues related to sam-

* Corresponding author: Edin Hodžić

Clinic for General and Abdominal Surgery, Clinical Centre of the University of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina

Phone: +387 33297179;

E-mail: edin.hodzic@hotmail.com

ORCID: <https://orcid.org/0000-0003-2764-0414>

ple heterogeneity (15), varying adjuvant protocols (16,17), and the absence of standardization across different laboratories (18,19).

The aim of this study was to contribute to better understanding of prognostic factors and optimization of therapeutic approaches providing answers to the question of relevance of preoperative CA19-9 levels in the context of the prognosis of patients with stage III rectal adenocarcinoma.

PATIENTS AND METHODS

Patients and study design

This retrospective cohort study included 84 patients who underwent radical anterior rectal resection at the Clinic for General and Abdominal Surgery, Clinical Centre of the University of Sarajevo, for rectal adenocarcinoma between January 2015 and May 2020. After surgery, all included patients received adjuvant chemotherapy according to the FOLFOX (Oxaliplatin, Leucovorin, 5-Fluorouracil (5-FU) protocol (20). Based on preoperative CA 19-9 values, patients were divided into two groups: those with high CA 19-9 values (≥ 27 U/mL) and those with low CA 19-9 values (< 27 U/mL). The study included patients with grade I and II according to the American Society of Anesthesiologists (ASA) (21), followed for a minimum of six months after surgery. Exclusion criteria were the patients with rectal adenocarcinoma stage TNM (T-tumour, N-nodes, M-metastases) (22) higher or lower than III, those who received neoadjuvant therapy, had tumours on other parts of the colon, different histological types of rectal tumours and metastatic tumours, as well as the patients who received other adjuvant therapy and those who underwent emergency surgery.

The influence of different factors on patient outcome including age, gender, tumour differentiation, number of resected lymph nodes, TNM tumour stage, preoperative serum value of carcinoembryonic antigen (CEA) and CA 19-9 levels, the time of occurrence of postoperative metastases, three-year disease-free survival (3Y-DFS) and three-year overall survival (3Y-OS) according to preoperative CA 19-9 values were analysed.

Methods

All patients underwent anterior rectal resection using an open approach. The sigmoid colon was resected at the junction with the left descending colon. High ligation of the upper hemorrhoidal artery was performed. Further dissection included total mesorectal excision with preservation of the lower hypogastric plexus. Resection of the colon was done 4-5 cm distal to the lower border of the tumour, and colorectal anastomosis was created mechanically using a circular stapler (23).

Pathohistological analysis was performed at the Clinic for Clinical Pathology, Cytology and Human Genetics at

the Clinical Centre of the University of Sarajevo. Based on pathohistological analysis, patients were postoperatively categorized as low-risk stage IIIa (with T1-3, N1) or high-risk stage IIIb (with T4, N1-2 or any T, N2 stage) (22).

The patients were monitored every three months during the first two years after surgery, and then semi-annually during the following year. 3Y-OS was defined as the period from tumour resection to the date of death from any cause within three years of follow-up. 3Y-DFS was defined as the period from tumour resection to the occurrence of death, disease recurrence (including metastases), or the last follow-up of the patient within three years.

Statistical analysis

The optimal cut-off values of CA 19-9 for the purposes of the study were identified by ROC curve analysis. The χ^2 test was used to examine the association between qualitative variables. Univariate and multivariate regression analysis were applied to assess the influence of different factors on patient outcomes. Kaplan-Meier analysis was used to evaluate the time of the occurrence of postoperative metastases, 3Y-DFS and 3Y-OS according to preoperative CA 19-9 values.

RESULTS

Patients with a high level of CA 19-9 showed a statistically significantly increased probability of postoperative metastases ($p < 0.001$; 95% CI: 0.011, 0.129). Patients with a high level of CA 19-9 had 3.74 times higher probability of developing liver metastases ($p = 0.02$; 95% CI: 0.089, 0.806), 9.43 times higher probability of developing lung metastases ($p = 0.006$; 95% CI: 0.022, 0.524), and 4.54 times higher probability of developing abdominopelvic metastases ($p = 0.04$; 95% CI: 0.054, 0.901) (Table 1).

The 3Y-DFS rate for patients with high CA 19-9 was 64.5%, while for those with low CA 19-9 it was 87.2% ($p = 0.017$) (Figure 1A). The 3Y-OS rate for patients with high CA 19-9 was 65.7%, while for those with low CA 19-9 it was 89.8% ($p = 0.007$) (Figure 1B).

Multivariate regression analysis for 3Y-DFS showed a statistically significant predictive ability of high preoperative values of tumour markers CEA and CA 19-9 for DFS shorter than three years. High CEA values were associated with 3.71 times higher probability for DFS of less than three years ($p = 0.03$; CI 95%: 0.082, 0.880), while patients with elevated CA 19-9 marker values had 4.62 times higher probability ($p = 0.01$; CI 95%: 0.064, 0.735) for the same outcome. Other analysed variables did not show statistical significance as predictors of 3Y-DFS in the multivariate regression model (Table 2).

Multivariate regression analysis for 3Y-OS revealed a statistically significant predictive value of TNM tumour

Table 1. Postoperative metastatic pattern and univariate regression analysis according to preoperative CA 19-9 levels

Type of metastases		No (%) metastases at preoperative CA 19-9 marker level		p*	95% CI
		<27 U/mL	≥27 U/mL		
Metastases overall	NO	38 (90.5)	4 (9.5)	<0.001	(0.011; 0.129)
	YES	11 (26.2)	31 (73.8)		
Liver	NO	43 (65.2)	23 (34.8)	0.019	(0.089; 0.806)
	YES	6 (33.3)	12 (66.7)		
Lung	NO	47 (65.3)	25 (34.7)	0.006	(0.022; 0.524)
	YES	2 (16.7)	10 (83.3)		
Abdominopelvic	NO	46 (63.0)	27 (37.0)	0.035	(0.054; 0.901)
	YES	3 (27.3)	8 (72.7)		

*Univariate regression analysis for metastases occurrence; CI, confidence interval;

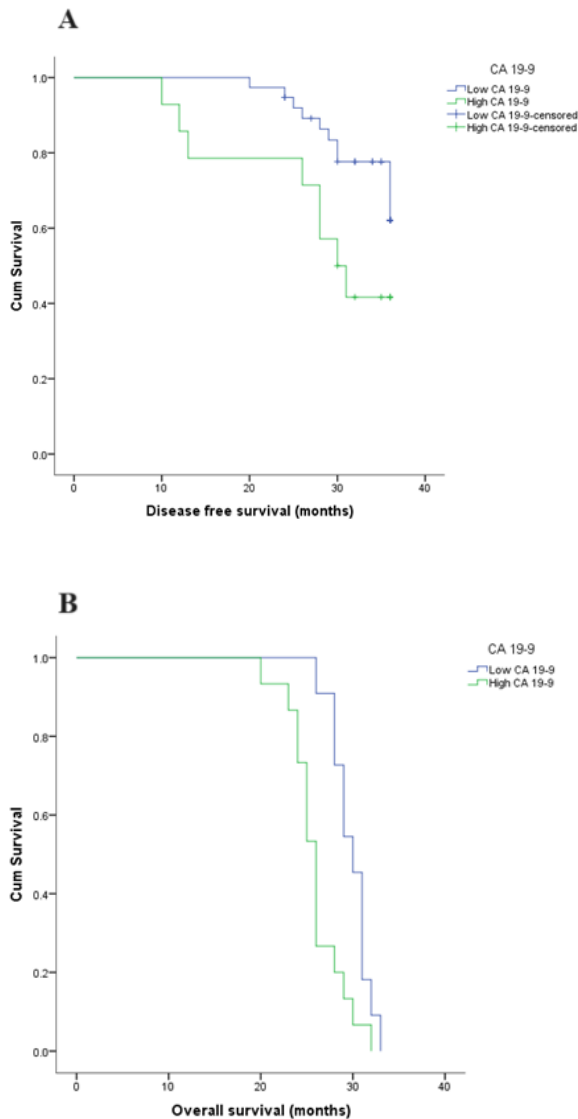


Figure 1. Three-year disease free survival (3Y-DFS) (A) and overall survival (3Y-OS) (B) in patients who underwent surgery for rectal cancer by CA 19-9 level

stage, preoperative CEA values, and preoperative CA 19-9 values for OS shorter than three years. Patients with stage IIIb had 2.71 times higher probability for OS shorter than three years ($p=0.045$; CI 95%: 0.069, 0.967). Also, patients with elevated preoperative CEA had 5.21 times higher probability for OS shorter than three years ($p=0.009$; CI 95%: 0.056, 0.659). Patients with elevated preoperative CA 19-9 values had 5.92 times higher probability for OS shorter than three years ($p=0.012$; CI 95%: 0.042, 0.678). Other variables did not show a statistically significant predictive ability for three-year OS in the multivariate regression model (Table 2).

DISCUSSION

High levels of CA19-9 preoperatively could reflect biological aggressiveness and the presence of tumour micrometastases, which remain undetected at the time of surgery (24,25).

In a similar study conducted by Similarly, Wenhao et al. study (26) demonstrated a statistically significantly increased risk of metastases in the five-year postoperative period in patients with preoperatively elevated CA 19-9 levels, both overall and metastases in the lungs and abdominopelvic area.

Although CA 19-9 is not directly associated with liver cells, elevated levels of this marker in patients with gastrointestinal cancers may indicate the presence of liver metastases (27,28). Rectal cancer commonly spreads to the liver because a considerable portion of venous drainage from the rectum flows through the portal vein (29). Liver metastases most often occurred in the first three years after the diagnosis of colorectal cancer, which coincides with the length of follow-up of our patients (30).

Patients with preoperatively high CA 19-9 values have a high recurrence rate associated with lymphovascular

Table 2. Multivariate regression analysis of prognostic factors for three-year disease free survival (3Y-DFS) and three-year overall survival (3Y-OS)

Variable		3Y-DFS*		3Y-OS*	
		p	95 % CI	p	95% CI
Age	≤ 60 years	0.453	(0.178; 2.162)	0.980	(0.282; 3.483)
	>60 years				
Gender	Males	0.840	(0.672; 6.539)	0.254	(0.556; 9.260)
	Females				
Tumour differentiation	Good/moderate	0.244	(0.549; 10.593)	0.104	(0.043; 1.342)
	Bad/nondifferentiated				
Number of resected lymph nodes	<12 lymph nodes	0.202	(0.672; 6.539)	0.277	(0.578; 6.774)
	≥12 lymph nodes				
TNM tumour stage	IIIa	0.118	(0.106; 1.286)	0.045	(0.069; 0.967)
	IIIb				
Preoperative serum CEA (ng/ml)	≤5	0.030	(0.082; 0.880)	0.009	(0.056; 0.659)
	>5				
Preoperative CA 19-9 marker level	<27 U/mL	0.014	(0.064; 0.735)	0.012	(0.042; 0.678)
	≥27 U/mL				

*Multivariate regression analysis for 3Y-DFS and 3Y-OS;

3Y-DFS, three-year disease free survival; 3Y-OS, three-year overall survival; CI, confidence interval; TNM, T-tumour, N-nodes, M-metastases; CEA, carcinoembryonic antigen; CA, carbohydrate antigen 19-9;

and perineural invasion (31). Also, tumours with elevated CA 19-9 level may be less responsive to certain types of chemotherapy, influencing treatment effectiveness and resulting in shorter survival times (32). In a study conducted in Taipei in patients undergoing bowel resection for stage I-III CRC, it was demonstrated that normal preoperative CA19-9 levels lead to a significantly higher DFS rate (82.0%) compared to preoperatively high levels of CA19-9 (68%) in the five-year follow-up period (33). During the three-year follow-up of patients in our study, we noted consistency in the results.

In a study by Shin et al. (34), which included patients with any malignancy at any location in the colon and were followed for six years postoperatively, it was observed that patients with preoperatively normal CA19-9 levels had a significantly lower OS rate compared to those with high CA 19-9 levels (91.9% vs 79.7%), as also demonstrated in our study. In the same study, in accordance with our results, elevated preoperative levels of CA 19-9 and CEA were identified as predictors of a shorter DFS (34). A study conducted by Lekemeyer et al. (35) also reported the combination of these two markers as a predictor of shorter OS. Several studies have demonstrated a shorter OS rate in CRC patients with preoperatively elevated level of both CA 19-9 and CEA, consistent with the results of our study (34–36). The study conducted by the National Cancer Institute has demonstrated that the disease stage is an independent prognostic factor for survival, with longer OS observed in patients with stage IIIa compared to stage IIIb, which was also observed in our study (37). Patients with preoperatively elevated CA 19-9 levels in stages III and IV may benefit from so-called tailored monitoring, facil-

itating clinical decision-making regarding adjuvant therapy (34).

The retrospective nature of our analysis and the relatively small sample could lead to a limited general representativeness of the obtained results. This approach may limit the generalization of the conclusions to the wider population. Measurement of CA 19-9 level before surgery was performed only once, without a clearly defined time frame. This methodology may ignore dynamic changes in marker levels over time, which may affect the precision of the results. Despite the application of uniform surgical and adjuvant treatments, there is a need for careful observation of various molecular factors that may influence CA 19-9 levels in order to better understand their actual clinical significance (38).

The scientific novelty of our study is its focus on rectal adenocarcinoma, standing out from the majority of similar studies (19,26,34,35) that include the entire colon and different types of tumours. Within this specific population, we focused on patients with tumour grade III, further narrowing the research field compared to the studies that include all grades or only grade IV (13,15,19,29,34). Our research was conducted on patients undergoing the FOLFOX chemotherapy protocol, which further differentiates our approach from broader research initiatives contributing to more precise understanding of prognostic factors in rectal adenocarcinoma (16,17,20).

In conclusion, CA 19-9 alone as well as in combination with CEA is a predictor of shorter DFS and OS, especially identifying a high probability of postoperative metastases, including liver, lung and abdominopelvic

locations. Our results confirm the clinical significance of determining preoperative CA 19-9 level in patients with rectal adenocarcinoma. Further studies with a larger sample and more detailed follow-up are needed to improve guidelines for better treatment outcomes and care for this specific patient population.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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