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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Factors contributing to survival in hepatic dysfunction due to colorectal cancer

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SUMMARY

Introduction/Objective Colorectal cancer (CRC) is currently the third most common cancer in incidence in the United States and accounts for about 8.5% of all cancer related deaths. Our study aim was to determine the parameters that contribute to the survival of CRC patients with hepatic dysfunction, attention to the positive effects on survival when the most appropriate clinical approaches.

Methods Patients with CRC, diagnosed with hepatic dysfunction, and who were followed up in our inpatient service in the last two years were included in our study. Survival rates were analyzed starting from after the development of hepatic failure.

Results A total of 57 patients were included in the study, 44 (77.2%) were colon carcinoma, and 13 (22.8%) were rectal carcinoma patients, and 14 (24.56%) were female. Bile duct dilatation (BD) was detected in 19 (33%) of 57 patients with imaging methods. The median OS was calculated as 4 *vs*. 1.4 months in patients with BD compared to patients without BD ($p < 0.001$). Survival times were significantly higher in patients with BD compared to those without dilatation, and in patients without renal failure compared to those with renal failure.

Conclusion In cancer patients with hepatic dysfunction, those with additional renal failure had shorter survival times and a worse prognosis. The longer survival of patients with BD was attributed to the optimal timing of the percutaneous transhepatic cholangiography insertion, close clinical and inflammation marker follow-ups, and early prevention of external biliary drainage, therefore preventing a possible septic complication early on.

Keywords: colorectal cancer; hepatic dysfunction; percutaneous transhepatic biliary drainage; survivability

INTRODUCTION

About 149,500 new colorectal cancer (CRC) cases are diagnosed each year in the United States, of which 104,270 are colon cancer, and the remainder are rectal cancer [1]. According to Globocan 2020 data, CRC is ranked third after breast and lung cancer according to the frequency of new cases and second after lung cancer in mortality rates [2].

In the evaluation of liver function, aspartate aminotransferase (AST), serum albumin, and prothrombin time are measured, cellular damage is evaluated with alanine aminotransferase (ALT) concentrations, and bile cholestasis is assessed with alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), and bilirubin levels. Serum bilirubin levels are a specific indicator of severe liver injury and an essential indicator of loss of liver function [3]. Therefore, in our study, when determining liver dysfunction, we considered the elevation of bilirubin (simultaneous total and direct bilirubin) as the main antecedent parameter and accepted it as the first parameter to be evaluated in patient selection. Then, the clinical reflections of the changes in all other liver function tests were evaluated.

The mechanism by which cancer causes liver dysfunction is multifactorial. This may occur through a direct reduction in liver volume, or it may occur with the development of intrahepatic or extrahepatic biliary obstruction [3]. It has also been reported that some cancer-related immunological factors may increase cholestasis and inflammatory liver damage. Development of liver dysfunction secondary to metastatic CRC is considered a poor prognosis and reduces median survival to only a few weeks [4].

Our study aimed to determine the parameters that contribute to the survival of CRC patients with hepatic dysfunction, regardless of the development of liver metastasis, and to draw the patients' attention to the positive effects on survival when the most appropriate clinical approaches and optimal treatment are performed with the earliest timing.

METHODS

The patients aged 18 years and older who were hospitalized and followed up with liver dysfunction and diagnosed with CRC at our health center in the last two years were included in the study. The study was conducted in accordance with the Declaration of Helsinki. Patient information was recorded by retrospectively scanning the hospital database. Patients who did not

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meet the inclusion criteria as well as those who withdrew their voluntary consent during the study were excluded.

The study's ethics committee approval was obtained from the ethics committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital with the number 2022-02/1669, dated 23.02.2022.

In the analyzes, the effects of hemogram, serum glucose, ALT and AST, total bilirubin, direct bilirubin, ALP, GGT, albumin, international normalized ratio, blood urea nitrogen, and creatinine parameters, as well as bile duct dilatation (BD), sex, and age parameters on survival after the development of hepatic dysfunction were calculated.

Statistical analyzes were performed using the Statistical Package for the Social Sciences program SPSS for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Normality analyzes were performed for the distribution of numerical variables. Continuous quantitative variables were reported using the median (interquartile range) (min–max) for non-parametrically distributed and mean (SD) for parametrically distributed variables. Qualitative categorical variables were reported using Pearson's χ^2 or Fisher exact test. Survival analyses were performed with Cox regression analysis, while survival curves were created using the Kaplan–Meier method. A p-value of < 0.05 was considered significant.

RESULTS

A total of 57 patients were included in the study by scanning the retrospective database. Of these, 44 (77.2%) were colon carcinoma, and 13 (22.8%) were rectal carcinoma patients, and 14 (24.56%) were female.

The performance statuses were evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status. There were 33 (57.9%) patients with ECOG ≤ 2 and 24 (42.1%) patients with ECOG ≥ 3.

When the age distributions were categorized as over 50 years old and 50 years old and below, the median overall survival (OS) in the > 50 years *vs.* ≤ 50 age group was higher, with a value close to significance of 4.1 *vs.* 1.5 months, respectively (p = 0.08) (Table 1).

The R-value (R factor), an additional factor in determining the possible type of liver injury in patients, was calculated based on serum ALT and ALP levels. Values of five and above were considered hepatocellular damage, while values of two and below were considered as cholestatic damage. The median R factor was 1 (1–3). While 55 (96.5%) of our patients had cholestatic damage, hepatocellular damage was present in two (3.5%).

When albumin values were similarly categorized as < 3 g/dL and ≥ 3 g/dL, the median OS was 2.1 *vs.* 1.4 months in the group with albumin above 3 mg/dL (p = 0.015) (Table 1).

In our patients, no pathology supporting chronic renal failure was present in the pre-hepatic dysfunction, both in the past laboratory findings and in the current urinary system ultrasound imaging. When the kidney functions were evaluated, the median OS was 2.72 *vs.* 1.41 months in the group with serum blood urea nitrogen values of 15 mg/dl and below and in the group with over 15 mg/dl (p = 0.016). In the group with creatinine values below 1.5 mg/dl, OS was calculated as 2.2 *vs.* 0.98 months compared to 1.5 mg/dl and above (p < 0.001) (Table 1).

Table 1. Survival analyzes of demographic characteristics and laboratory parameters

Parameters	Median OS (95% CI)	p value
Age, median		
≤ 50	4.1 (0.1–11.25)	0.08
> 50	1.5 (1.19–1.95)	
Sex		
Male	1.7 (0.91–2.5)	0.470
Female	1.3 (1.1–1.4)	
Glucose		
< 126	1.7 (0.85–2.5)	0.799
≥ 126	1.5 (1.2–1.8)	
Alanine transaminase		
< 40	1.5 (0.74–2.4)	0.443
≥ 40	1.6 (1.1–2.1)	
Aspartate transaminase		
< 40	1.3 (0.45–2.2)	0.108
≥ 40	1.7 (1.2–2.1)	
Alkaline phosphatase		
< 140	1.5 (1.2–1.9)	0.948
≥ 140	1.7 (1–2.4)	
Gamma-glutamyl transferase		
< 340	2.7 (1.11–4.34)	0.036
≥ 340	1.6 (1.12–2.04)	
Albumin		
< 3	1.4 (1.1–1.6)	0.015
≥ 3	2.1 (1–3.2)	
International normalized ratio		
< 1.5	1.5 (1–2)	0.61
≥ 1.5	1.3 (0.66–2)	
Blood urea nitrogen		
< 15	2.72 (0.43–5.02)	0.016
≥ 15	1.41 (1.09–1.73)	
Creatinine		
< 1.5	2.2 (1.31–3.09)	< 0.001
≥ 1.5	0.98 (0.84–1.12)	
Hemoglobin		
< 11	1.4 (1.1–1.7)	0.211
≥ 11	1.9 (1.1–2.6)	
Bile duct dilatation		
Present	4 (0.01–8.59)	< 0.001
Absent	1.4 (1.19–1.63)	
Kaplan–Meier survival analysis		

BD was detected in 19 (33%) of 57 patients with imaging methods. In the evaluations made according to the patients who developed BD and therefore had percutaneous transhepatic cholangiography (PTC) and those who did not have PTC, it was determined that 16 (84.2%) of 19 patients underwent PTC procedure. The median OS was calculated as 4 *vs.* 1.4 months in patients with BD compared to patients without dilatation (p < 0.001) (Tables 1 and 2, Figure 1).

The patients were followed closely regarding coagulopathy, another consequence of liver failure, and

Table 2. Survival analyzes of laboratory parameters (univariate and multivariate analyzes)

Parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Direct bilirubin	0.89 (0.803–0.999)	0.47	1.105 (0.956–1.278)	0.177
Gamma-glutamyl transferase	1.00 (1.000–1.001)	0.37	1.001 (1.000–1.002)	0.002
Blood urea nitrogen	1.02 (1.012–1.047)	0.001	1.032 (1.012–1.053)	0.002
Hemoglobin ≥ 11	0.56 (0.321–1.003)	0.51	0.761 (0.412–1.406)	0.384
Bile duct dilatation, present	3.26 (1.650–6.477)	0.001	0.197 (0.077–0.506)	0.001
HALP score	0.933 (0.827–1.054)	0.250	0.932 (0.819–1.050)	0.281
Cox Regression Analysis				

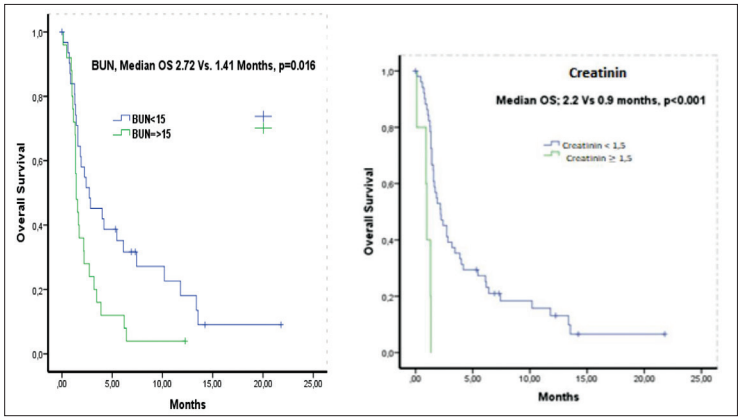

Figure 1. Overall survival related to blood urea nitrogen and creatinine in hepatic dysfunction

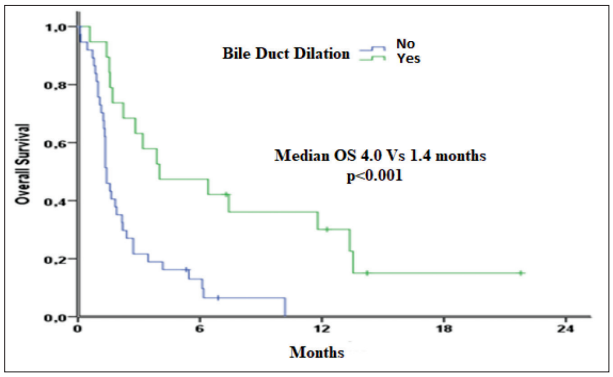

Figure 2. Overall survival in bile duct dilation

Table 3. Correlation of numerical variables

Parameters		Direct bilirubin	Total bilirubin	Gamma-glutamyl transferase	Lymphocyte	Neutrophil	Platelets
Direct bilirubin	r	1					
	p						
Total bilirubin	r	0.948**	1				
	p	**< 0.001**					
Gamma-glutamyl transferase	r	0.018	-0.021	1			
	p	0.892	0.877				
Lymphocyte	r	0.004	-0.005	0.317*	1		
	p	0.975	0.970	**0.016**			
Neutrophil	r	-0.172	-0.204	0.268*	0.180	1	
	p	0.202	0.127	**0.044**	0.181		
Platelets	r	0.338*	0.322*	0.439**	0.289*	0.379**	1
	p	**0.010**	**0.014**	**< 0.001**	**0.029**	**0.004**	
Spearman correlation analysis							

anti-vascular endothelial growth factor therapy [5]. However, no thrombosis or bleeding was reported.

When the patients with BD were evaluated according to their subgroups, the median serum ALT levels were calculated as 110 in the dilated group and 36 in the non-dilated group ($p = 0.06$). Other significant variables in bile dilatation were total and direct bilirubin values ($p < 0.001$, Table 1).

In the Spearman correlation analysis performed between numerical variables, the correlation of serum cholestasis enzymes with platelet, neutrophil, and lymphocyte values was evaluated. It was determined that platelet values had a significant positive correlation with bilirubin (total and direct bilirubin) and GGT, and neutrophil and lymphocyte values were also positively correlated with GGT (Table 3).

The HALP score (calculated by serum hemoglobin (g/dL) × albumin (g/L) × lymphocyte (10^9/L) / platelet (10^9/L) method) was calculated for all patients. The median value was calculated as 1.78 (0.23–16.6). The Cox regression analysis for the calculated HALP score is given in Table 2.

DISCUSSION

Survival in hepatic dysfunction due to cancer is expressed in weeks. Therefore, early identification of factors affecting this survival, initiation of treatment with optimal timing, or early interventions for treatment will increase survival times. Liver biopsy is the gold standard test for detecting liver damage and fibrosis. On the other hand, reasons such as the high cost, the risk of complications such as bleeding, the pathology results being time consuming, the lack of a practical evaluation method, and the fact that 24 (42.1%) of our patients with liver dysfunction consisted of patients with ECOG performance status of three and above, etc. have led to the need to search for methods that can provide rapid results and have an impact on the clinic. For this purpose, some laboratory parameters and clinical findings were evaluated in our patients.

PTC was not implanted in any of our 38 patients who developed hepatic dysfunction but did not have dilated BD. However, PTC was inserted in 16 (84.2%) of our 19 patients with BD. The longer survival of patients with BD was attributed to the fact that PTC fitted with optimal timing, close clinical and inflammation marker follow-ups, and early external biliary drainage could

be provided, and therefore, a possible septic picture that could develop was prevented early.

In some studies, the development of sinusoidal obstruction syndrome (SOS) has been shown in patients treated with oxaliplatin-containing regimens [6, 7, 8]. In another study, surgery-confirmed SOS was found in 24 of 60 patients who received neo-adjuvant oxaliplatin-based chemotherapy for over 12 weeks [9, 10]. In our study, SOS was diagnosed with the revised European Society for Blood and Marrow Transplantation criteria by the presence of two of the following findings in addition to a total bilirubin value ≥ 2: painful hepatomegaly, ≥ 5% weight gain, and ascites [11]. SOS was detected in a total of eight patients. All patients with SOS had received oxaliplatin-based treatment. Some reports state adding bevacizumab to the neoadjuvant oxaliplatin-based regimen may reduce the incidence and severity of oxaliplatin-related hepatic sinusoidal injury [10–13]. Of the 57 patients in our study, 16 received combined treatment with bevacizumab. Four (50%) of our patients with SOS had received bevacizumab.

Side effects of regimens containing irinotecan are more frequently associated with steatosis and steatohepatitis [14]. Publications are stating that patients with steatohepatitis have an overall survival difference of approximately three months compared to those without [15]. A total of 36 (63.1%) patients received irinotecan treatment at any step. In our study, a total of 32 (56.14%) patients had grade 1 and higher steatosis. Of these patients, 21 had received irinotecan treatment.

We determined that young age is an important parameter of survival. Therefore, patients with poor nutritional support should be considered when evaluating the significant survival difference in albumin values of three and above.

Hypoalbuminemia usually indicates severe liver injury with decreased albumin synthesis [16]. Therefore, serum albumin level is included in the Child–Turcotte–Pugh classification, a scoring system with prognostic significance in patients with liver cirrhosis [17]. Serum albumin is also decreased in nephrotic syndrome, as a negative acute phase reactant, in widespread systemic inflammation, and in severe nutritional disorders.

Hypoalbuminemia is aggravated as albumin synthesis is also affected by the addition of hepatic dysfunction to these clinical conditions, which are very common in many cancer patients. It was thought that the lower survival rate in patients with hypoalbuminemia was primarily related to liver dysfunction and poor nutritional support in these patients.

Hepatorenal syndrome is a state usually accompanied by acute renal failure in patients with acute or chronic liver disease. Although it is usually seen in patients with advanced cirrhosis, it can also be seen in portal hypertension due to metastatic tumors [18–21]. Since our study was retrospective, although hepatorenal syndrome was not diagnosed by considering the diagnostic criteria, it was shown that adding hepatic dysfunction to renal failure reduces patient survival.

Some publications show that the HALP score can be used as a prognostic marker. In a study by Topal et al. [22], an indirect relationship between the HALP score and tumor budding in patients with CRC was shown. Another analysis by Yalav et al. [23] found an independent prognostic factor for survival in patients with CRC who underwent curative resection. Our study determined that the HALP score did not make a statistically significant contribution in terms of survival. Therefore, it was thought that there is a need for studies on this subject with more patients and including patients at all stages.

CONCLUSION

Although liver function tests have an important place in cancer patients, early detection of liver dysfunction prolongs the survival of patients. A significant proportion of hepatic dysfunction in CRC patients develops with cholestatic occlusive damage. Therefore, in cases with dilated biliary tract, PTC should not be delayed and should be seen as a priority. Drug toxicities and even non-metastatic liver damage should also be considered since many of these patients receive multiple drug therapies.

Conflict of interest: None declared.

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Фактори који доприносе преживљавању болесника са дисфункцијом јетре услед колоректалног карцинома

Фатих Тај, Мустафа Бујукор, Ајше Оџак Дуран

Болница „Абдурахман Журтаслан“ за обуку и истраживање онкологије у Анкари, Одељење за медицинску онкологију, Анкара, Турска

САЖЕТАК

Увод/Циљ Колоректални карцином (КРК) тренутно је трећи најчешћи рак у Сједињеним Државама и чини око 8,5% свих смртних случајева повезаних са раком.

Циљ наше студије био је да се идентификују параметри који доприносе преживљавању болесника са КРК са дисфункцијом јетре, обраћајући пажњу на позитивне ефекте на преживљавање у најприкладнијим клиничким приступима.

Методе Наша студија је обухватила болеснике са КРК којима је дијагностикована дисфункција јетре традиционалним тестовима функције јетре и који су праћени у нашој болници у последње две године. Стопе преживљавања анализиране су од почетка отказивања јетре.

Резултати У студију је укључено укупно 57 болесника, 44 болесника (77,2%) имала су карцином дебелог црева, 13 њих (22,8%) били су болесници са КРК, а 14 (24,56%) жене. Откривена је дилатација жучних канала код 19 (33%) од 57 болесника са сликовним методама. Медијан ОС је израчунат као 4 наспрам 1,4 месеца код болесника са дилатацијом жучних канала у поређењу са болесницима без дилатације ($p < 0,001$). Време преживљавања је било значајно веће код болесника са дилатацијом билијарног тракта у поређењу са онима без дилатације, и код болесника без бубрежне инсуфицијенције у поређењу са онима са отказивањем бубрега.

Закључак Код болесника оболелих од рака са дисфункцијом јетре, они са додатном бубрежном инсуфицијенцијом имали су краће време преживљавања и лошију прогнозу. Дуже преживљавање болесника са дилатацијом жучних канала било је због оптималног времена перкутане трансхепатичке холангиографије, пажљивог клиничког праћења и контроле маркера упале и ране превенције спољне дренаже жучних путева, што омогућава спречавање могућих септичких компликација у ранојој фази.

Кључне речи: колоректални карцином; дисфункција јетре; перкутана трансхепатична билијарна дренажа; преживљавање