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Research Article

The cluster of differentiation 47 expression in rectal cancer and efficacy of neoadjuvant therapies

Rektal kanserde farklılaşma kümesi 47 ekspresyonu ve neoadjuvan tedavilerin etkinliği

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Abstract

Aim: To investigate the relationship between CD47 expression levels, clinicopathological features, and survival in rectal cancer.

Material and Methods: It was designed as a retrospective case-control study. CD47 was analyzed in tumor tissue from patients with stage II and III rectal cancer who received neoadjuvant treatment. Patients were classified as negative, low, or high based on the CD47 H score. The pathological features of the disease, responses to neoadjuvant treatment, and overall survival were examined in relation to CD47.

Results: There were CD47 negative (n = 19, 31%), low (n = 18, 30%), and high (n = 24, 39%) patients. CD47 positivity was more common in female patients (p = 0.023). No significant differences were observed between the groups regarding relapse (p = 0.822), tumor location (p = 0.379), T stage (p = 0.360), preoperative lymph node status (p = 0.332), tumor grade (p = 0.801), perineural invasion (PNI) (p = 0.160), lymphovascular invasion (LVI) (p = 0.294), budding (p = 0.043), CEA level (p = 0.413), neoadjuvant treatment type (p = 0.650), T downstaging (p = 8.39), N downstaging (p = 0.530), surgery type (p = 0.717), pathological complete response (p = 0.747), tumor regression score (p= 0.836), positive surgical margin (p = 0.309), or (p = 0.028). The 5-year OS was 88% for patients with negative CD47, 74% for those with low CD47, and 57% for high CD47 (p=0.035).

Conclusion: Pretreatment CD47 score is important in terms of survival and prognosis in rectal cancer. The function of CD47 is more complex and needs to be further studied.

Keywords: rectal cancer, CD47, prognosis, survival

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Öz

Amaç: Rektum kanserinde CD47 ekspresyon düzeyinin klinikopatolojik özellikler ve sağkalım ile ilişkisini araştırmak.

Gereç ve Yöntemler: Retrospektif bir vaka-kontrol çalışması olarak tasarlandı. CD47 ekspresyonu, neoadjuvan tedavi alan evre II ve III rektum kanseri hastalarının tümör dokusundan çalışıldı. Hastalar CD47 H skoruna göre negatif, düşük veya yüksek olarak kategorize edildi. Hastalığın patolojik özellikleri, neoadjuvan tedaviye yanıtlar ve genel sağkalım CD47 ile ilişkili olarak incelendi.

Bulgular: CD47 negatif (n = 19, %31), düşük (n = 18, %30) ve yüksek (n = 24, %39) hastalar vardı. CD47 pozitifliği kadın hastalarda daha sıktı (p = 0.023). Gruplar arasında nüks (p = 0.822), tümör lokalizasyonu (p = 0.379), T evresi (p= 0.360), preoperatif lenf nodu durumu (p=0.332), tümör gradesi (p = 0.801), perinöral invazyon (PNİ) (p = 0.160), lenfovasküler invazyon (LVİ) (p = 0. 294), tomurcuklanma (p=0.043), CEA düzeyi (p = 0.413), neoadjuvan tedavi tipi (p=0.650), T evre azalması (p = 8.39), N evre azalması (p = 0.530), cerrahi tipi (p = 0.717), patolojik tam yanıt (p = 0.747), tümör regresyon skoru (p=0.836), pozitif cerrahi sınır (0.309) (p = 0.028) bakımından anlamlı fark yoktu. 5 yıllık OS, negatif CD47 için %88, düşük CD47 için %74 ve yüksek CD47 için %57 idi (p = 0.035).

Sonuç: Tedavi öncesi CD47 skoru rektum kanserinde sağkalım ve prognoz açısından önemlidir. CD47'nin işlevi daha karmaşıktır ve daha fazla çalışılması gerekmektedir.

Anahtar Kelimeler: rektum kanseri, CD47, prognoz, sağkalım

Introduction

Approximately 5-10% of rectal cancer patients are diagnosed at a locally advanced stage. These individuals undergo multimodal treatments, including radiotherapy, chemotherapy, and surgical intervention [1,2]. Neoadjuvant treatment of rectum cancer involves chemoradiotherapy (CRT) or short-course radiotherapy. Total mesocolic excision is performed after neoadjuvant treatment [3,4]. In recent years, there has been a trend toward the preoperative administration of full-dose chemotherapy and CRT, characterized as total neoadjuvant treatment (TNT) [5]. There is still a need for additional evidence regarding tumor behavior. Personalized treatment planning that considers the patient's characteristics and the disease may improve treatment outcomes.

Increased expression of the Cluster of Differentiation 47 (CD47) has been observed in various tumors, including ovarian cancer, gastric cancer, lung squamous cell carcinoma, bladder cancer, and breast cancer[6-9]. Research indicates that CD47 levels are elevated in colorectal cancer (CRC) cells compared to non-neoplastic colonic mucosa [10-11]. However, the clinical significance of this situation has been a matter of curiosity.

CD47 is involved in multiple cellular functions, significantly influencing areas such as cell proliferation, apoptosis, adhesion, migration, and various immune responses [8]. CD47, which is present on tumor cells, plays a crucial role in helping these cells evade detection by the immune system, primarily by preventing macrophages from engulfing them. Understanding how this mechanism functions is crucial, as it reveals the strategies that cancer cells use to evade the immune system responses. CD47 expression in CRC has been associated with activation of various oncogenic pathways and an immune-intensive tumour microenvironment (TME).

The expression of genes associated with damage-related molecular patterns positively correlates with the CD47 levels expression. In tumors exhibiting high levels of CD47, there was a notable activation of key oncogenic pathways, including the transforming growth factor beta, angiogenesis, phosphoinositide 3-kinase, and mitogen-activated protein kinase [12]. Additionally, the expression levels of several adaptive immune checkpoint genes and the estimated presence of immune cells in the tumor microenvironment (TME) were significantly increased in tumors with high CD47 expression [12]. By focusing on this signal, we can potentially improve the efficacy of immunotherapies, enabling the immune system to better identify and eliminate tumor cells [13-15]. Multiple antibodies and CD47 inhibitors have been investigated, many of which are currently in clinical trials [16,17].

This study explored CD47 expression in patients with

locally advanced rectal cancer, assessing response rates to neoadjuvant therapy and its influence on survival. The investigation analyzed the correlation between CD47 expression, clinicopathological features, and clinical outcomes, aiming to determine its potential use in clinical practice.

Patients and Methods

Study Design and Sample

This investigation was structured as a retrospective, case control study based at a single center. The local ethics committee approved the study protocol (ethical approval#: 2025-02/19 on February 20, 2025). The research adhered to the ethical guidelines set forth in the Declaration of Helsinki. Given the study's retrospective nature and the anonymity of the data, written informed consent was not obtained from the participants.

The population for the study included all rectal cancer patients followed up at the tertiary oncology center from 2010 to 2022. Data for the research were sourced from the patients' medical records and the hospital's information system. The study's inclusion criteria were being 18 years of age or older, having stages II or III rectum cancer, and having neoadjuvant treatment. Conversely, the study excluded individuals under 18 years of age, those admitted with metastatic or stage I rectal cancer, and those with a second primary cancer. Additionally, patients whose clinical data were lost during follow-up, those who did not proceed with surgery after neoadjuvant treatment, and those with insufficient archived tumor tissue for immunohistochemical analysis were als. All patients were followed up at 3-6 month intervals in the Oncology Center outpatient clinics. Recurrences, metastases, and types of metastases were recorded during the follow-up visits. Overall survival (OS) was defined as the duration from a diagnosis of rectal cancer to either death or the most recent follow-up. Patients' TNM stages based on clinical and radiographic findings and after surgery based on the American Joint Committee on Cancer (AJCC) staging system, 8 th edition undergoing neoadjuvant treatmen [18]. Recurrences, metastases, and types of metastases were recorded during the follow-up visits. The time from rectal cancer diagnosis to death or the last follow-up was defined as overall survival (OS). Modified Ryan Grading system was used to evaluation of neoadjuvant treatment pathological response.

Immunohistochemical Study and Evaluation of CD47 Expressions

From blocks of patients who were diagnosed with rectum cancer, sections measuring 3 microns in thickness were sliced and placed onto adhesive-coated slides. Following this, the CD47 primary antibody (rabbit monoclonal, EPR21794, diluted 1:2000, from Abcam, Cambridge, UK) was used for incubation. To ensure staining accuracy, tissue samples were processed in conjunction with positive control tonsil tissue for CD47, and negative control liver tissue for CD47 was also incorporated into the study. All immunohistochemical staining procedures were carried out using the Roche Ventana Benchmark Ultra automated device, located in Tucson, AZ, USA. Pathologist then evaluated the stained slides. The intensity of CD47 expression was categorized as follows: 0 for none, 1 for weak, 2 for moderate, and 3 for strong staining. The staining extent was classified as: 0 = 0%, 1 = 1–19%, 2 = 20–50%, and 3 = more than 50%. The H-score for CD47 was computed in an identical manner and was grouped into three categories based on the H-score: negative (0), low (1–3 points), and high (4–6 points) (Figures 1a,b). [12].

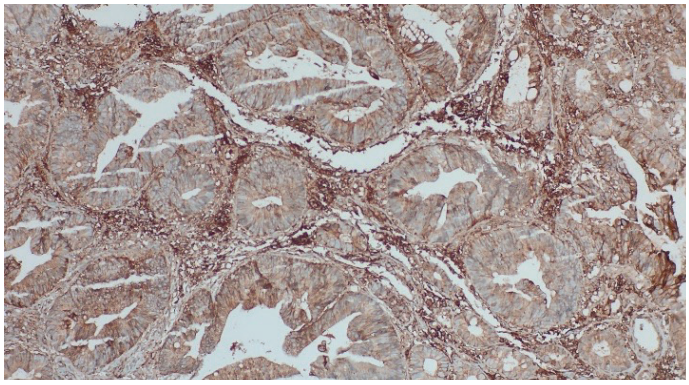

Figure 1A. CD47 positive rectal cancer.

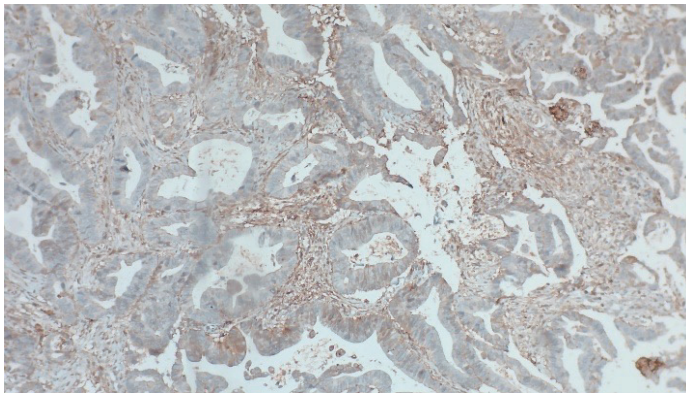

Figure 1B. CD47 negative rectal cancer.

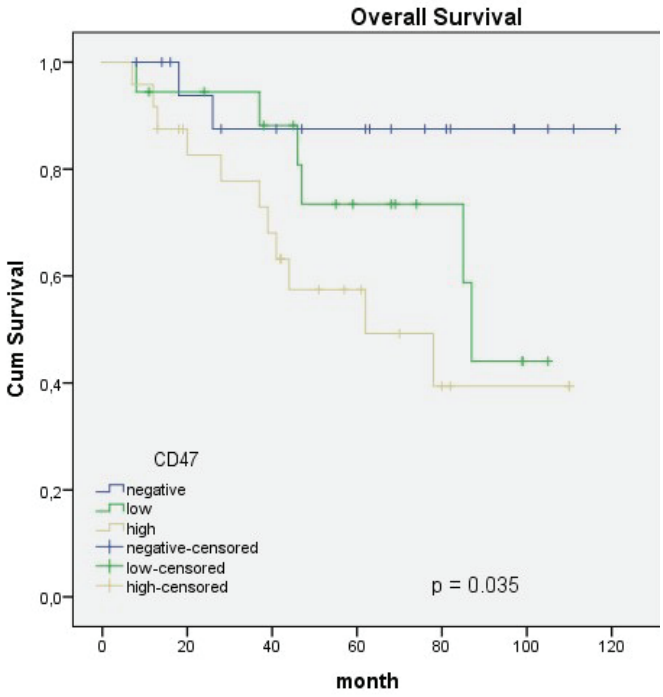

Figure 2. The Kaplan-Meier survival analysis with Log Rank test showing the survival outcomes

Statistical Analysis

Statistical analyses were performed utilizing the Statistical Package for Social Sciences (SPSS) version 23, developed by IBM SPSS Inc. in Chicago, IL, USA. To compare categorical variables, Pearson's chi-square test was used, while Fisher's exact test was applied when expected values were too low. Overall survival (OS) rates were estimated via the Kaplan–Meier approach, and differences in survival between groups were assessed using the log-rank test. For multivariate survival analyses, hazard ratios (HRs) alongside 95% confidence intervals (CIs) were determined through the Cox proportional hazard regression model. A statistical significance threshold was set at $p < 0.05$ for all tests.

Results

The study sample consisted of 61 consecutive non-metastatic rectal cancer patients, who were divided into three groups: CD47 negative (n = 19, 31%), low (n = 18, 30%), and high (n = 24, 39%). There were statistically significant differences between the groups in terms of gender (p = 0.023). CD47 positivity was more frequent in female patients. No significant differences were found between the groups in terms of relapse (p = 0.822), tumor localization (p = 0.379), T stage (p = 0.360), preoperative lymph node status (p = 0.332), tumor grade (p = 0.801), perineural invasion (PNİ) (p = 0.160), lymphovascular invasion (LVİ) (p = 0.294), budding (p = 0.043), CEA level (p = 0.413), neoadjuvant treatment type (p = 0.650), T downstaging (p = 0.839), N downstaging (p = 0.530), surgery type (p = 0.717), pathological complete response (p = 0.747), tumor regression score (p = 0.836), positive surgery margin (p = 0.309). Table 1 displays a comparison of the groups' characteristics.

When the effect of CD47 on OS was evaluated by the Kaplan-Meier test, 5-year OS was 88% for negative CD47, 74% for low CD47, and 57% for high CD47 (p = 0.035). Figure 2 shows the OS curves of the groups. In evaluating prognostic factors affecting OS, high CD47 levels were statistically significantly different in multivariate analysis (HR: 5.57, 95% CI: 1.25-26.58, p = 0.024). Table 2 shows the prognostic factors affecting OS.

Discussion

This study mainly focused on the prognostic effects of CD47 and demonstrated that high CD47 expression might be a marker of poor prognosis in locally advanced rectal cancer, independent of poor pathological features of the tumor.

Research indicates that CD47 expression is higher in CRC and metastatic lymph nodes than in normal tissue [19]. It was revealed that CD47 expression levels in CRC positively correlate with the activity of several oncogenic signaling pathways, including MAPK, PI3K, angiogenesis, and TGF-β. This suggests that various upstream oncogenic signaling pathways influence the transcriptional regulation of CD47, which in turn enhances downstream signaling pathways [20]. CD47 is reported to influence the tumor microenvironment by promoting M2 polarization and Tregs, contributing to the development of an immunosuppressive tumor microenvironment [21]. It is shown that high CD47 expression is associated with an increased amount of various types of immune cell infiltration into the tumor microenvironment. Regarding the CMS classification, CD47-high tumors exhibited a significantly greater proportion of CMS1 and CMS4 compared to CD47-low tumors. CMS1 is characterized by enhanced infiltration of cytotoxic T cells and NK cells, whereas CMS4 is characterized by increased infiltration not only of T cells but also of fibroblastic cells, endothelial cells, and myeloid cells [22].

Table 1. Clinicopathologic features of groups.

CD47	Negative n (%)	Low n (%)	High n (%)	p
Gender: Male Female	 17 (90) 2 (10)	 12 (67) 6 (33)	 12 (50) 12 (50)	0.023
Carcinoembryonic antigen Normal (<2.5 ng/ml) High	 11 (69) 5 (31)	 11 (85) 2 (15)	 12 (63) 7 (37)	0.413
Localization Middle Distal	 10 (53) 9 (47)	 9 (50) 9 (50)	 8 (33) 16 (67)	0.379
Grade 1 2 3	 4 (21) 12 (63) 3 (16)	 3 (33) 10 (56) 2 (11)	 9 (38) 13 (54) 2 (8)	0.801
Preop T stage T3 T4	 10(53) 9 (47)	 6 (33) 12 (67)	 8 (33) 16 (67)	0.360
Preop N stage N(-) N(+)	 6 (32) 13 (68)	 3 (17) 15 (83)	 9 (38) 15 (62)	0.332
Lymphovascular İnvasion No Yes	 18 (95) 1 (5)	 15 (83) 3 (17)	 23 (96) 1 (4)	0.294
Perinueral invasion No Yes	 15 (79) 4 (21)	 17 (94) 1 (6)	 17 (71) 7 (29)	0.160
Extracapsular extension No Yes	 17 (90) 2 (10)	 16 (89) 2 (11)	 23 (96) 1 (4)	0.661
Treatment Chemoradiotherapy Total Neoadjuvant Treatment	 11 (58) 8 (42)	 13 (72) 5 (28)	 16 (67) 8 (33)	0.650
Surgery Type Low anterior recestion Ab- dominoperineal resection	 14 (74) 5 (26)	 14 (78) 4 (22)	 16 (67) 8 (33)	0.717
T downstage No Yes	 7 (37) 12 (63)	 5 (28) 13 (72)	 8 (33) 16 (67)	0.839
N downstage No Yes	 7 (37) 12 (63)	 9 (50) 9 (50)	 8 (33) 16 (67)	0.530
Complete Response No Yes	 16 (84) 3 (16)	 16 (89) 2 (11)	 22 (92) 2 (8)	0.747
Regression Scor Grade 0 Grade1 Grade2 Grade3	 3 (16) 3 (16) 10 (52) 3 (16)	 2 (11) 3 (17) 9 (50) 4 (22)	 2 (8) 3 (12) 10 (42) 9 (38)	0.806
Surgical Margine Negative Positive	 18 (95) 1 (5)	 16 (89) 2 (11)	 19 (79) 5 (21)	0.309
Relaps No Yes	 15 (79) 4 (21)	 13 (72) 5 (28)	 17 (21) 7 (29)	0.822

Table 2. The The prognostic factors affecting overall survival.

Variable	N (%)	5 year OS (%)	p value	HR (65% CI)	p value
CD47					
Negative	19 (31)	88	0.035	1	
Low	18 (30)	74		3.47 (0.69-17.34)	0.129
High	24 (39)	57		5.57 (1.25-26.58)	0.024
Gender					
Male	41 (67)	72	0.059		
Female	20 (33)	49			
Carcinoembryonic antigen Normal (<2.5 ng/ml)	40 (85)	68	0.337		
High	7 (15)	86			
Localization					
Middle	27 (44)	69	0.844		
Distal	34 (56)	68			
Grade					
1	16 (28)	81	0.133		
2	35 (60)	62			
3	7 (12)	67			
Preop N status					
Negative	18 (30	82	0.208		
Positive	43 (70)	67			
Treatment					
Chemoradiotherapy	40 (66)	72	0.945		
Total Neoadjuvant Treatment	21 (34)	72			
T downsstage					
No	20 (33)	58	0.048		
Yes	41 (67)	78			
N downstage					
No	24 (39)	72	0.901		
Yes	37 (61)	71			
Complete Response		70			
No	54 (89)	100	0.272		
Yes	7 (11)				
TM regression					
Grade 0	7 (11)	100			
Grade 1	9 (15)	67	0.569		
Grade 2	29 (48)	72			
Grade 3	16 (26)	57			
Surgical Margine					
Negative	53 (87)	71	0.244		
Positive	8 (13)	58			

Oh H et al. examined how CD47 expression affects the oncogenic traits of CRC and its importance for CRC patient prognosis. [23]. The expression of CD47 showed a significant correlation with PNI, LVI, cellular differentiation, cancer staging, the depth of invasion, lymph node metastasis, and distant metastasis. Tian OS et al. conducted a study examining the connection between CD47 expression levels and various clinical and pathological factors in colon cancer tissues. These factors comprise gender, age at diagnosis, T stage, N stage, and the overall TNM stage [24]. CD47 expression was significantly linked to both N stage and overall clinical stage of the disease, but not to sex, age, or T stage. While the immune system serves as the primary defense against tumors, an inflammatory cell-rich microenvironment may eventually aid tumor development. This scenario is often linked to unfavorable clinical outcomes. In our study, there were no differences in clinicopathological characteristics between the groups, as we examined a selected, limited cohort with locally advanced disease. Furthermore, methodological differences in assessing CD47 may also be associated with varying results.

In colon cancer, a significant correlation was found between CD47 and immune cell infiltration around the tumour. The potential role of this in supporting the speculation that CD47 contributes to tumour escape from the immune system by promoting a dysfunctional T-cell environment [25]. Spatial profiling indicated increased infiltration of myeloid cells and a shift in macrophage populations from pro-inflammatory to immune-suppressive subsets, accompanied by the upregulation of the CD47/SIRPα axis. This shift highlights the role of CD47 in creating an immunosuppressive tumor microenvironment [26]. Literature includes studies that question the effect of CD47 on survival in colorectal cancer patients. In one study, CD47 positivity was linked to short relapse-free survival. However, in a multivariate analysis that included factors such as T stage, N stage, and TNM stage, it did not appear as an independent factor affecting survival [19]. This difference in survival may be attributed to the adverse clinicopathological features associated with CD47 in tumors. Nonetheless, it has been proposed that CD47 facilitates CRC progression by promoting tumor cell apoptosis and angiogenesis, resulting in low survival rates among these patients [23]. It showed that CD47-positive CRCs had poor survival [27,28]. However, there are also studies in the literature that support the opposite view [20,24]. Our study indicates that elevated CD47 expression correlates with a poorer prognosis. In a multivariate analysis incorporating tumor clinicopathological characteristics, it was identified as an independent factor influencing overall survival. While there was no statistical link between neoadjuvant treatment response and CD47 expression, none of the patients exhibiting high CD47 levels achieved a pathological complete response. This clinical finding implies that CD47 positivity may contribute to treatment resistance, leading to a reduced survival. There is a pressing need for innovative treatment strategies that can modify the tumor microenvironment and enhance treatment responses in the neoadjuvant therapy for CD47-positive locally advanced rectal cancer, potentially leading to improved survival outcomes.

It showed that the microenvironment of the primary tumor and the microenvironment of metastasis may differ in CRCs, which may contribute to the heterogeneity of the disease. [24]. This inconsistency might stem from variations in study methodologies and samples, along with the specific characteristics of the subjects studied. Therefore, further research is essential to explore the specific mechanisms by which CD47 impacts various cancer types and how patient prognosis might be enhanced through the regulation of CD47 expression.

It is important to recognize the limitations of this study. The retrospective design and potential selection biases should be taken into account. The number of patients who received TNT is small, and the observation period for this group is short. Additionally, the study does not specify the percentages of molecular subtypes of rectal tumors.

In conclusion, this study showed that pretreatment CD47 score is significant for survival and prognosis in rectal cancer patients. However, the literature's findings on the relationship between CD47 expression and prognosis are inconsistent and contradictory. This indicates that the role of CD47 is more complex and requires further investigation.

Competing interests

The authors have no conflict of interest to disclose.

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The authors confirm that this is a self-funded study.

Ethics Approval and Consent to Participate

The present study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Sivas Cumhuriyet University on November 16, 2023 (permit # 2023-11/12)

Availability of data and materials

The datasets are available from the corresponding author upon reasonable request.

Authors' contributions

MU: Conceptualization, Methodology, Writing- Original draft preparation; MY: Data curation, Writing- Original draft preparation, Validation; EE: Conceptualization, Methodology, Validation; BY: Writing- Reviewing and Editing, Supervision.

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