J Ankara Univ Fac Med 2026;79(1):40-46
DOI: 10.65092/autfm.1788633
Research Article / Araştırma Makalesi

Role of Vitamin D in Patients with Rectum Cancer Receiving Neoadjuvant Treatment

Neoadjuvan Tedavi Alan Rektum Kanseri Tanılı Hastalarda Vitamin D'nin Rolü

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ABSTRACT

Background: Relationship between vitamin D level and pathological response and survival in rectal cancer patients receiving neoadjuvant therapy, is an unstudied issue.

Aim: We planned to investigate the relationship between vitamin D level and pathological response in this population.

Materials and Methods: Patients diagnosed with rectal cancer and followed up at Ankara University Faculty of Medicine, Medical Oncology Clinic between January 2012 and May 2023 were included. Patients' demographic data, vitamin D level, stages, chemotherapy and radiotherapy protocols, type of surgery and postoperative pathological responses were recorded and compared statistically.

Results: Eighty-three patients were included in the study. Median vitamin D level at the time of diagnosis was 15.89 ng/mL. Each 1-year increase in age was associated with a 0.22 ng/mL decrease in vitamin D levels. No significant relationship between vitamin D level and pathological response was found. Vitamin D levels were 13 ng/mL lower in stage 4 compared to stage 1 disease, but the difference was not significant. Relapse and survival rates were not significantly related with Vitamin D levels. When patients over 60 years of age were evaluated, vitamin D levels were significantly lower in patients with ypT4 against ypT0 disease.

Conclusion: No significant relationship could be demonstrated between vitamin D levels and pathological response. More studies are needed to investigate the effect of vitamin D levels on prognosis and pathological response in older age and more advanced disease.

Keywords: rectum cancer, vitamin D, neoadjuvant treatment

ÖZET

Giriş: Neoadjuvan tedavi alan rektum kanseri hastalarında D vitamini seviyesi ile patolojik yanıt ve sağkalım arasındaki ilişki, henüz yeterince araştırılmamış bir konudur.

Amaç: Bu popülasyonda D vitamini seviyesi ile patolojik yanıt arasındaki ilişkiyi araştırmayı planladık.

Gereç ve Yöntem: Ocak 2012 ile Mayıs 2023 tarihleri arasında Ankara Üniversitesi Tıp Fakültesi Tıbbi Onkoloji Kliniği'nde rektum kanseri tanısı alan ve takip edilen hastalar çalışmaya dahil edildi. Hastaların demografik verileri, D vitamini seviyesi, evreleri, kemoterapi ve radyoterapi protokolleri, cerrahi tipi ve postoperatif patolojik yanıtları kaydedildi ve istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmaya 83 hasta dahil edildi. Tanı anında medyan D vitamini seviyesi 15,89 ng/mL idi. Yaşta her 1 yıllık artış, D vitamini seviyelerinde 0,22 ng/mL'lik bir düşüşle ilişkilendirildi. D vitamini seviyesi ile patolojik yanıt arasında anlamlı bir ilişki bulunamadı. Evre 1 hastalığa kıyasla evre 4'te D vitamini seviyeleri 13 ng/mL daha düşük bulundu, ancak fark anlamlı değildi. Nüks ve sağkalım oranları, D vitamini seviyeleri ile anlamlı bir ilişki göstermedi. 60 yaş üzeri hastalar değerlendirildiğinde, ypT0 hastalığa kıyasla ypT4 hastalığı olan hastalarda D vitamini seviyeleri anlamlı olarak daha düşüktü.

Sonuç: D vitamini seviyeleri ile patolojik yanıt arasında anlamlı bir ilişki gösterilemedi. İleri yaş ve daha ileri evre hastalıkta D vitamini seviyelerinin prognoz ve patolojik yanıt üzerindeki etkisini araştırmak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: rektum kanseri, D vitamini, Neoadjuvan tedavi

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Received: 22.09.2025 **Accepted:** 27.01.2026 **Publication Date:** 27.03.2026
Cite this article as: Yalçıner, M., et al. Role of vitamin D in patients with rectum cancer receiving neoadjuvant treatment. *J Ankara Univ Fac Med*. 2026;79(1):40-46.

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Introduction

It is known that colorectal cancer (CRC) is the third most common malignancy and the second in mortality over the world in 2022 cancer statistics(1). Many genetic and environmental risk factors have been identified for CRC, such as inflammatory bowel diseases and family history, and there are many studies in the literature on the effect of Vitamin D levels on cancer incidence and survival. Although some results are contradictory, there have been many recent studies on vitamin D levels and CRC risk and prognosis.

A recent meta-analysis including eight studies showed that vitamin D increased transcriptomic changes associated with antitumor effects, but no association was found with 5-year recurrence-free survival. The same study demonstrated that vitamin D supplementation significantly modulated expression levels of CRC biomarkers, including TGFα, TGFβ1, and APC. Furthermore, the researchers reported that while vitamin D supplements exhibited protective and risk-reducing properties, calcium intake was associated with opposing effects on these outcomes(2). There are other studies in the literature showing that serum vitamin D level is inversely proportional to the incidence of CRC(3).

There are also studies investigating vitamin D-related polymorphisms and the relationship with the anatomical region. In a recent study, a decreased risk was shown in patients carrying all GC or VDR genotypes except two specific genotypes, and serum vitamin D levels were shown to be associated with a lower incidence of CRC, and the incidence decreased as the level increased. In the same study, the relationship with the anatomical region was also investigated, and it was seen that this relationship with colon cancer was not detected in the rectum cancer(4). Another study showed that vitamin D intake before diagnosis reduced the risk of proximal colon cancer, but no association was found in distal colon or rectum cancer(5). The relationship between vitamin D levels and anatomical region is not clearly known.

The effect of vitamin D levels on survival has also been investigated. A recent study including stage 3 colon cancer patients reported that patients with normal vitamin D levels had better disease-free and overall survival(6). A recently published study showed a relationship between postoperative vitamin D levels and overall survival, but the same finding was not observed with preoperative vitamin D levels(7).

Despite the inverse correlation often observed between vitamin D status and CRC incidence, the efficacy of therapeutic supplementation remains a subject of debate. Notably, the VITAL study reported no statistically significant reduction in CRC risk following vitamin D supplementation, highlighting the complexity of its role in cancer prevention(8). COLON study showed that vitamin D and magnesium intake were associated with reduced mortality in CRC patients(9,10).

It is clear that more studies are needed to determine the effect of vitamin D levels on mortality, its relationship with anatomical localization and chemotherapy response. Additionally, information specifically on rectal cancer and neoadjuvant treatment is quite limited. In this study, we planned to investigate the relationship between basal vitamin D levels and pathological response in rectal cancer patients receiving neoadjuvant therapy.

Materials and Methods

Patients diagnosed with rectal cancer and followed up at Ankara University Faculty of Medicine, Medical Oncology Clinic between January 2012 and May 2023 were scanned for eligibility. The criteria for inclusion in the study were:

- Histologically confirmed diagnosis of rectal cancer.
- Age ≥ 18 years at the time of diagnosis.
- Receipt of neoadjuvant chemotherapy and/or radiotherapy.
- Undergone surgery with subsequent pathological response evaluation.

Patients were excluded from the analysis based on the following criteria:

- Age <18 years.
- Presence of inoperable disease (defined clinically and radiologically as the presence of locally

advanced or metastatic disease, with or without fixation to unresectable structures where an R0 resection was not achievable, or the presence of severe medical comorbidities that precluded the patient from undergoing major surgical intervention).

- Failure to receive any neoadjuvant treatment.
- Incomplete primary data, defined as the absence of baseline serum vitamin D levels or lack of a definitive pathological response status.

The patients' demographic data such as age, gender, pathological diagnosis, vitamin D levels at diagnosis, diagnosis dates, stages, applied chemotherapy and radiotherapy protocols, type of surgery performed, postoperative pathological responses, recurrence status, and survival of the patients were recorded and compared. Subgroup analyses included pathological responses in ypT and ypN staging after neoadjuvant therapy and clinical staging in diagnosis.

The pathological response to neoadjuvant therapy was evaluated based on the examination of surgical specimens by specialized gastrointestinal pathologists. Pathologic complete response (pCR) was defined as the total absence of viable tumor cells in the primary tumor site and regional lymph nodes (ypT0N0). Partial response was defined as the presence of residual cancer cells with varying degrees of fibrosis, while no response was defined as the absence of significant regression or the predominance of viable tumor tissue over fibrosis.

Serum 25-hydroxyvitamin D (25(OH)D) levels were measured at the time of initial diagnosis using a Chemiluminescence Immunoassay (CLIA). Due to the retrospective nature of the study, specific categorization into summer or winter cohorts was not performed, although the laboratory reference ranges for both seasons (Winter: 10-60 ng/mL; Summer: 20-120 ng/mL) were noted.

The study protocol was approved by the institutional ethics committee. All patient data were recorded into electronic database with all the identities blinded. Informed consent for participation in retrospective studies was obtained from all individual patients prior to their initial admission.

Statistical analysis was performed with the R version 4.1 (R foundation) program. The distribution of the variables was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro Wilk tests). Descriptive statistics were given as median, minimum and maximum for variables that were not normally distributed, and as mean and standard deviation for normally distributed variables. Survival-related variables were evaluated with univariable Cox regression analysis, and univariable logistic regression models were utilized to evaluate the individual factors associated with neoadjuvant therapy response. Baseline vitamin D levels were treated as the primary independent predictor in these models. In these regression models, the beta coefficients were reported to represent the estimated change in the log-odds (for logistic regression) or the log-hazard (for Cox regression) of the outcome for every one-unit increase in the predictor variable.

Results

A total of 83 patients were included in the study. The cohort consisted of 53 (63.9%) male and 30 (36.1%) female patients. The median age of the population was 61.7 years (SD ± 11.8). At the time of diagnosis, the median serum vitamin D level was 15.89 ng/mL (range: 5–49.7). Regarding tumor histology, 74 (89.2%) patients had adenocarcinoma and 9 (10.8%) had mucinous carcinoma. At initial diagnosis, the clinical stage distribution according to the AJCC TNM 8th edition was as follows: 1 (1.2%) stage I, 4 (4.8%) stage II, 52 (62.7%) stage III, and 2 (2.4%) stage IV disease. For neoadjuvant treatment, 32 (38.6%) patients received short-course radiotherapy with chemotherapy, and 26 (31.3%) received long-course radiotherapy with chemotherapy. Surgery consisted of low anterior resection in 60 (72.3%) patients and abdominoperineal resection in 12 (14.5%) patients. Following neoadjuvant therapy, a complete pathological response was achieved in 18 (21.7%) patients, while 64 (77.1%) showed a partial response. Details of patient demographics and disease related properties are given in Table 1.

There was a significant relationship between age and vitamin D levels in linear regression. Each 1-year

Table 1: Patient demographics and disease related properties

Parameter	n (%) or Mean ± SD
Age (years)	61.7 ± 11.8
Gender	
Male	53 (63.9%)
Female	30 (36.1%)
Vitamin D level at diagnosis (ng/mL, median, min-max)	15.89 (5–49.7)
Tumor Histology	
Adenocarcinoma	74 (89.2%)
Mucinous carcinoma	9 (10.8%)
Clinical Stage (AJCC TNM 8th Edition)	
Stage I	1 (1.2%)
Stage II	4 (4.8%)
Stage III	52 (62.7%)
Stage IV	2 (2.4%)
Missing/Not Staged	24 (28.9%)
Neoadjuvant Treatment	
Long-course RT + Chemotherapy	26 (31.3%)
Short-course RT + Chemotherapy	32 (38.6%)
Radiotherapy only	1 (1.2%)
Chemotherapy only	3 (3.6%)
Other/Missing	21 (25.3%)
Type of Surgery	
Low anterior resection	60 (72.3%)
Abdominoperineal resection	12 (14.5%)
Other	11 (13.2%)
Pathological Response	
Complete Response (ypT0)	18 (21.7%)
Partial Response	64 (77.1%)
No Response	1 (1.2%)

increase in age was associated with a 0.22 ng/mL decrease in vitamin D levels (p = 0.01).

On logistic regression, no significant relationship between vitamin D levels and pathological response was observed (p = 0.30 for partial response and p =

0.26 for complete response) and no significant relationship was found in the analysis results for ypT (p = 0.26) and ypN (p = 0.30) (Table 2).

Table 2: Logistic regression analysis of relationship between vitamin D levels and pathological response

Pathological Response	Predictor	ß	SE	p
Partial-Total	Vitamin D Level	-0.02828	0.02743	0.30
None-Total	Vitamin D Level	0.10473	0.09259	0.26

ß: beta estimate, SE: standard error

Regarding the tumor location, no significant relationship was found between vitamin D level and the tumor location (R^2 = 0.004, p = 0.59). There was no significant relationship between tumor diameter and Vitamin D level (p = 0.61). No significant relationship was found with the N stage of the tumor (p = 0.45).

When comparing the stage at diagnosis, vitamin D levels were found to be 13 ng/mL lower in stage 4 compared to stage 1 disease, but the difference was not statistically significant (Table 3).

Table 3: Linear regression analysis of relationship between stage and Vitamin D level at diagnosis

Predictor	ß	SE	p
TNM Stage (reference: stage I)			
III	-3.6417	10.13	0.72
IV	-13.2800	12.29	0.28

ß: beta estimate, SE: standard error

No significant relationship was found between vitamin D level and recurrence (Mean (SD) = 18.5 (10.3), HR = 0.99 (0.89-1.09), p = 0.79). There was no significant relationship between mortality and vitamin D level (Mean=18.1 (10.0), HR= 1.03 (0.92-1.16), p=0.59).

In subgroup analyses, patients over 60 years of age were evaluated separately and the vitamin D level was significantly lower in patients with ypT4 compared to ypT0 disease. The ypT0 rate was significantly higher in patients with higher vitamin D levels (OR < 0.01; 95% CI: 0.001–0.05; p < 0.01) (Table 4). No relationship was found between ypN2 and ypN0 with Vitamin D levels in the same subgroup. (OR = 0.97, p = 0.76)

Table 4: Relationship between vitamin D and ypT in patients over 60 years of age

ypT	Predictor	ß	SE	OR	95% CI	p
ypT4 vs. ypT0	Vitamin D Level	-17.88350	2.18245	<0.01	0.001–0.05	< 0.01

ß: beta estimate; SE: standard error; OR: odds ratio; CI: confidence interval. **The comparison direction evaluates the likelihood of ypT4 status relative to the reference ypT0 (complete response) category.*

Discussion

There are many studies in the literature investigating the incidence and pathophysiology relationship between Vitamin D and CRC. Calcitriol, the active form of vitamin D, has been shown to regulate gene expression in many targets and is associated with many features of the tumor, such as proliferation, differentiation, and angiogenesis, especially in in vitro studies(3,11). There are many variables, such as the diversity of pathways and vitamin D receptor polymorphisms(12), demographic differences in the studied populations, variability in measurement methods, site of tumor (i.e. right, left or rectum) and differences between genders, making the subject difficult to study. As a result, there are many contradictory results on the subject in the literature.

83 patients were included in our study, and although the female patients' rate was slightly lower, the difference was not significant. Demographic characteristics, tumor histology, stage and other patient and disease characteristics were consistent with literature. It was observed that vitamin D levels decreased significantly with age. It is known that advanced age is associated with Vitamin D deficiency due to changes in both production and metabolism of Vitamin D, which makes this an expected finding(13).

When examined in the entire study population, no significant relationship was found between vitamin D levels and ypT and ypN stages. While our subgroup analysis in patients over 60 years of age showed a

significant relationship between Vitamin D and ypT4 stage, this must be considered a hypothesis-generating finding. Due to the small number of cases in this subgroup, this result may have occurred by chance and should be interpreted with caution. Further prospective studies with larger cohorts are necessary to validate this potential association. In addition, although not statistically significant, vitamin D levels were found to be 13 ng/mL lower in stage 4 compared to stage 1 disease. However, no effect on survival was seen, which may be due to the small sample size in these specific subgroups.

The lack of a significant relationship between Vitamin D levels and pathological response or survival in the general cohort may be attributed to several factors. Most notably, the median Vitamin D level at the time of diagnosis was 15.89 ng/mL, indicating a high prevalence of deficiency within our study population. When Vitamin D levels are universally low across a cohort, the lack of a 'normal' or 'sufficient' reference group makes it statistically challenging to identify meaningful clinical differences or protective effects. Consequently, the potential impact of Vitamin D might only be detectable in populations with a broader range of serum levels or through targeted supplementation trials.

In a meta-analysis including 2330 CRC patients, higher vitamin D levels (>75 nmol/L) were shown to be associated with reduced mortality and increase in vitamin D levels was shown to cause a decrease in overall and disease-specific mortality(14). Another meta-analysis evaluating 166 studies showed that higher vitamin D levels were significantly associated with overall survival and CRC-specific survival(15). Although the right and left colon tumors were examined separately, these large meta-analyses did not specifically examine rectal cancer patients that received neoadjuvant treatment. To our knowledge, our study is the first to investigate the relationship between vitamin D level and pathological response in patients diagnosed with rectal cancer who received neoadjuvant therapy. It is known that vitamin D levels decrease as age increases, as was shown in our study. Although significant, vitamin D levels in older patients with T4 disease seemed to predict the chemotherapy unresponsiveness, this result may be an incidental finding. Our findings indicate that the effect of Vitamin D levels on rectal cancer may be related to older age and more advanced disease. More prospective studies and randomized-controlled trials are needed on this subject.

The border between the rectum and sigmoid colon is not clearly defined and there are still debates on this issue. In our study, no significant relationship was found when Vitamin D levels were compared with tumor location. When evaluated together with our findings regarding the relationship on survival and pathological response, this finding suggests that the effect of vitamin D levels on rectal tumors may be different from right and left colon tumors. The effect of vitamin D levels on survival may be less pronounced than it is in other sites of colon. The number of studies specifically evaluating rectal tumors is quite low, and more studies on this subject are needed.

The strengths of our study are that a specific population, such as rectal cancer patients who received neoadjuvant therapy, was evaluated and a sufficient number of patients was included. Limitations include possible data loss due to the retrospective design of the study. Additionally, specific data regarding seasonal variations at the time of sampling and the use of Vitamin D supplements prior to diagnosis were not consistently recorded, which may have influenced baseline levels. It is important to emphasize that the associations observed in this study, particularly within our subgroup analyses, are exploratory in nature. Given the retrospective design, these findings should not be interpreted as establishing a causal relationship between baseline vitamin D status and pathological response. Several unmeasured confounding factors may have influenced serum vitamin D levels in our cohort, including individual variations in baseline nutritional status, presence of comorbid conditions, and differences in the timing of measurement relative to seasonal sunlight exposure.

In conclusion, no significant relationship could be shown between vitamin D level and pathological response in patients diagnosed with rectal cancer who received neoadjuvant treatment. Prospective studies and randomized-controlled trials are needed to investigate the effect of vitamin D level on prognosis and pathological response in older age and more advanced disease.

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Author contributions: Concept: M.Y., E.C.E, M.A.K., C.A., G.U., Data Collection or Processing: M.Y., Ç.T., E.C.E., M.A.K., C.A., G.U., Analysis or Interpretation: M.Y., E.C.E., M.A.K., C.A., G.U., Writing: M.Y., Ç.T., E.C.E., M.A.K., C.A., G.U.

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara University Faculty of Medicine (31.08.2023/No: 2023000501, 2023/501)

Consent to Participate: Informed consent was obtained from all individual participants included in the study.

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