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Original Article

Prognostic Significance of Nuclear Factor Kappa B and CD9/Motility-related Protein-1 in Stage II-III Rectal Cancer Patients Treated with Postoperative Chemoradiotherapy

Postoperatif Kemoradyoterapi ile Tedavi Edilen Evre II-III Rektum Kanserli Olgularda Nüklear Faktör Kappa B ve CD9/Motility Related Protein-1'in Prognostik Önemi

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ABSTRACT

Objective: The aim of this study is to investigate the prognostic significance of nuclear factor kappa B (NFKB) and CD9 (MRP-1) proteins in stage II-III patients with rectum cancer threated by surgery and adjuvant chemoradiotherapy.

Material and Methods: Between May 2003 and April 2008, 5 µm sections were taken from paraffin-blocked tissue samples of 45 patients diagnosed with rectal cancer and treated with radiotherapy and 5FU-based chemotherapy at our clinic. Immunohistochemical staining with CD9 and NFKB was performed. The effects of CD9 and NFKB positivity on local-regional recurrence, disease-free survival, and overall survival were investigated. Statistical analyses were performed using the SPSS 15.0 software package.

Results: A statistically significant difference was found in the CD9 positive group in terms of five-year local control (p=0.026). However, no statistically significant difference was found in 5-year disease-free survival and overall survival between CD9 positive and negative cases (p=0.223, p=0.205). No statistically significant difference was found in 5-year disease-free survival, overall survival and local control between NFKB positive and negative cases (p=0.794, p=0.362 and p=0.805, respectively).

Conclusion: It was thought that CD9 positivity may have prognostic significance in terms of local-regional recurrence in our rectal cancer cases. The prognostic significance of CD9 positivity or negativity in terms of 5-year disease-free and overall survival in rectal cancer cases could not be demonstrated. The prognostic significance of NFKB positivity or negativity in terms of 5-year disease-free survival, local control, and overall survival in rectal cancer cases could not be demonstrated.

Keywords: CD9, NFKB, stage II-III rectum cancer, adjuvant chemoradiotherapy

ÖZ

Giriş: Bu çalışmada; postoperatif kemoradyoterapi uygulanan evre II-III rektum kanserli hastalarda, nükleer faktör kappa B (NFKB) ve CD9 (MRP-1) proteinlerinin prognostik önemi araştırıldı.

Gereç ve Yöntemler: Mayıs 2003-Nisan 2008 tarihleri arasında kliniğimizde rektum kanseri tanısı ile radyoterapi ve 5FU temelli kemoterapi uygulanan 45 hastanın, parafin bloklanmış doku örneklerinden alınan 5 µm'lik kesitlere CD9 ve NFKB ile immünohistokimyasal boyama uygulandı. CD9 ve NFKB pozitifliğinin yerel-bölgesel yineleme, hastalıksız sağkalım ve genel sağkalıma etkileri incelendi.

Bulgular: Beş yıllık lokal kontrol bakımından CD9 pozitif gurupta istatistiksel olarak anlamlı fark bulundu (p=0,026). Ancak, CD9 pozitif ve negatif olgularda 5 yıllık hastalıksız sağkalım ve genel sağkalım açısından istatistiksel olarak anlamlı fark saptanmadı (p=0,223, p=0,205). NFKB pozitif ve negatif olgularda 5 yıllık hastalıksız sağkalım, genel sağkalım ve lokal kontrol açısından istatistiksel olarak anlamlı fark bulunmadı (sırasıyla; p=0,794, p=0,362 ve p=0,805).

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ÖZ

Sonuç: CD9 pozitifliğinin rektum kanserli olgularımızda yerel-bölgesel yineleme açısından prognostik önemi olabileceği düşünüldü. CD9'un pozitif veya negatif olmasının 5 yıllık hastalıksız ve genel sağkalım açısından rektum kanserli olgularda prognostik önemi gösterilemedi. NFKB pozitif veya negatif olmasının rektum kanserli olgularda 5 yıllık hastalıksız sağkalım, lokal kontrol ve genel sağkalım açısından prognostik önemi gösterilemedi.
Anahtar Kelimeler: CD9, NFKB, evre II-III rektum kanseri, adjuvan kemoradyoterapi

INTRODUCTION

While the prognosis of early-stage rectal cancer (RC) is favorable, outcomes worsen as the tumor extends distally within the rectum and progresses to a higher stage. Unlike in colon cancer, local and regional recurrences are particularly important in RC. Compared with colon cancer at the same stage, RC has higher rates of locoregional recurrence following treatment. Reasons include the lack of a serosal barrier (facilitating local invasion) and anatomical limitations that make it difficult to achieve wide tumor-free lateral (radial, circumferential) surgical margins even when proximal and distal margins are adequate (1).

Surgery is the primary treatment for RC. However, due to the high potential for local and systemic relapse in stage II-III cases, adjuvant treatment is necessary. Combined chemotherapy (CT) and radiotherapy (RT), either preoperatively or postoperatively, is the standard treatment for stage II-III RC. In a multidisciplinary setting, RT is usually applied as an adjuvant therapy, with or without CT, either preoperatively or postoperatively (2).

The CD9 antigen is a surface marker on leukemic and lymphohematopoietic cells. It is expressed on mature B lymphocytes and serves as a surface marker of leukemia arising from differentiating cells. It has also been demonstrated in a wide range of hematopoietic and non-hematopoietic tissues. CD9 is associated with cellular stimulation, growth, motility, adhesion, tumor metastasis, and nervous system development and protection. CD9 (MRP-1) is one of 20 members of the transmembrane 4 superfamily and is localized on chromosome 12 (12p13). It plays roles in cell growth, adhesion, and motility (3).

Nuclear factor kappa B (NFKB) regulates the expression of many genes responsible for cell growth, differentiation, regulation of apoptosis, cytokine production, and neoplastic transformation. Studies indicate that NFKB plays a role in preventing apoptosis in several cancer types (e.g., lung, gastric, and prostate cancers). However, it is also involved in regulating apoptosis (4).

The aim of this study was to evaluate the prognostic significance of the NFKB and CD9 (MRP-1) proteins in patients with stage II-III RC treated with postoperative CT-RT.

MATERIALS and METHODS

This study was conducted in the Departments of Radiation Oncology and Pathology in our university's Faculty of Medicine. Forty-five patients with locally advanced RC (T3-T4 and/or lymph node-positive) who were admitted to our Oncology Hospital between May 2003 and April 2008 were retrospectively included in the study. Patients underwent abdominoperineal resection (APR), low anterior resection (LAR), anterior resection (AR), or total colectomy (TC). All patients received adjuvant concurrent CT-RT after curative surgery, followed by maintenance CT. Ethics committee approval was obtained from the Dean's Office of Erciyes University Faculty of Medicine in the presence of the professors (desicion number: 142, date: 26.02.2010).

Radiotherapy Protocol

Pelvic RT included the tumor bed and the perirectal, internal iliac, external iliac, and presacral lymph node regions. A total dose of 45 Gy was delivered in 25 fractions (1.8 Gy/day, 5 days/week). After pelvic RT, a boost of 5.4 Gy was applied to the primary tumor bed.

Chemotherapy Protocol

Patients received weekly RT concurrently with 5-fluorouracil (425 mg/m^2) and folinic acid (20 mg/m^2).

Immunohistochemical Staining

Immunohistochemical staining for CD9 (MRP-1) and NFKB was performed on paraffin-embedded rectal carcinoma tissue samples using the streptavidin-biotin immunoperoxidase method.

CD9 (MRP-1) Staining

5 µm-thick sections were cut from paraffin-embedded tissue blocks and mounted on poly-L-lysine-coated slides. After deparaffinization at 60 ˚C for one hour and rehydration through graded alcohols (99%, 96%, 70%), endogenous peroxidase activity was blocked by incubation with 0.3% hydrogen peroxide for 10 minutes. The slides were washed in phosphate-buffered saline (PBS) and incubated overnight at 4 ˚C with primary CD9 antibody. The following day, sections were treated with biotinylated anti-mouse and anti-rabbit immunoglobulins, each for 10 minutes, followed by streptavidin-peroxidase conjugate for 10 minutes. After washing with PBS, diaminobenzidine (DAB) chromogen was applied for 10 minutes. Counterstaining was performed with Mayer's hematoxylin, after which the slides were washed, mounted with balsam, and covered with a glass coverslip.

NFKB Staining

Sections 5 µm thick were cut from paraffin-embedded tissue blocks and mounted on poly-L-lysine-coated slides. The slides were deparaffinized at 60 ˚C for one hour, then cleared

in xylene, rehydrated through decreasing concentrations of ethanol, and rinsed in distilled water. Antigen retrieval was performed using 10 nM citrate buffer (pH 6.0) in a microwave oven at 200 ˚C for 20 minutes. After cooling to room temperature, endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide for 10 minutes. The sections were washed with PBS and incubated with the NFKB primary antibody for 30 minutes at room temperature. They were then treated with biotinylated anti-mouse and anti-rabbit immunoglobulin for 10 minutes, followed by streptavidin-peroxidase conjugate for 10 minutes. After washing in PBS, DAB chromogen was applied for 10 minutes, followed by rinsing in distilled water. Counterstaining was performed with iron hematoxylin, and the slides were washed, mounted with balsam, and covered with a glass coverslip.

Evaluation of Immunohistochemical Staining

Tissue-internal staining was used as the positive control. Tonsil tissue served as the positive control for CD9, and prostate tissue served as the positive control for NFKB.

CD9 (MRP-1) Evaluation

Cases showing cytoplasmic staining in more than 5% of tumor cells at 10× magnification were considered positive; others were considered negative.

NFKB Evaluation

Cytoplasmic staining in more than 10% of tumor cells at ×10 magnification was considered positive; cytoplasmic staining in less than 10% of tumor cells at ×10 magnification was considered negative.

Statistical Analysis

Data were analyzed using SPSS 15.0 for Windows (Statistical Package for the Social Sciences). The Shapiro-Wilk test was used to assess normality. Categorical variables were compared using the chi-square test, and survival analyses were performed using the Kaplan-Meier method. A p-value <0.05 was considered statistically significant.

RESULTS

The average age of the patients was approximately 56 (26-78) years. 23 (51%) male and 22 (49%) female patients were included in the study fifteen patients underwent APR, eight underwent AR, twenty-one underwent LAR, and one underwent TC surgery. Lymph node metastasis was present in 21 patients (47%). Forty-two of the patients were diagnosed with adenocarcinomas and three with signet-ring cell carcinomas. Vascular invasion and perineural invasion were each seen in 15 patients. The mean follow-up period for the patients was 37 months (range: 3-77 months), and distant metastases occurred during follow-up in the liver (9), lung (7), brain (2), mesentery (1), and inguinal lymph nodes (1). There were 15 (33%) patients who were NFKB-negative and 30 (67%) who were NFKB-positive. Sixteen (36%) patients were CD9-negative and 29 (64%) patients were CD9-positive. The mean overall survival, mean local control time, and mean disease-free survival time were 37±17.56, 36±16.87, and 36±18.11 months, respectively.

Among CD9-positive patients, the five-year disease-free survival, local control, and overall survival rates were 65%, 90%, and 82%, respectively. In contrast, these rates were 48%, 66%, and 46% in CD9-negative patients.

Although there was no statistically significant difference between CD9-positive and CD9- negative groups in terms of five-year disease-free survival or overall survival (p=0.223 and p=0.205, respectively), both parameters were numerically higher in the CD9-positive group. However, the five-year local control rate was significantly higher in the CD9-positive group (p=0.026).

In NFKB-positive patients, the five-year disease-free survival rate, local control rate, and overall survival rate were 60%, 84%, and 70%, respectively. In NFKB-negative patients, these rates were 56%, 75%, and 76%. There was no statistically significant difference between NFKB-positive and NFKB-negative groups in terms of disease-free survival, local control, or overall survival (p=0.794, 0.362, and 0.805, respectively).

DISCUSSION

In our study, patient characteristics and distribution by NFKB expression are shown in Table 1.

In a retrospective study by Zvieriev et al. (5), tumor specimens from 153 patients with head and neck tumors who received external beam RT were evaluated immunohistochemically for CD9 expression. CD9 positivity was found in 108 patients (71%), whereas 45 (29%) were CD9 negative. Five-year disease-free survival was significantly higher in CD9-positive patients.

Similarly, Wang et al. (6) investigated 40 patients with pancreatic cancer and reported CD9 positivity in 15 (38%) cases. One-year overall survival rates were lower among CD9-negative patients (0-25.5%) than among CD9-positive patients. Median survival time was also longer in CD9-positive patients (397 vs. 226 days) (7).

In another study by Guo et al. (8) increased NF-κB pathway activity leads to increased growth of breast cancer cells and an increased risk of breast cancer metastasis to bones, lymph nodes, lungs, and liver (9).

Lind et al. (10) evaluated 146 patients with stage III colon cancer and found CD9 positivity in 69 (47%) cases and negativity in 77 (53%) cases. Three-year overall and disease-free survival rates were significantly higher among CD9-positive patients (p<0.001).

Multiple studies in the literature including those on breast, lung, osteosarcoma, bladder, esophageal, and prostate cancers have demonstrated that CD9 positivity is associated with

Table 1. Distribution of patients according to NFKB expression

Parameters		NFKB (-)	NFKB (+)
n		15 (33%)	30 (67%)
Age (years)		54 (26-76)	58 (26-76)
Gender	Female	7 (16%)	15 (33%)
	Male	8 (18%)	15 (33%)
Operation type	APR	4 (9%)	11 (25%)
	LAR	6 (13%)	15 (33%)
	AR	4 (9%)	4 (9%)
	TC	1 (2%)	0 (0%)
Histopathology	Adenocarcinoma	13 (29%)	29 (65%)
	Signet-ring cell carcinoma	2 (4%)	1 (2%)
Grade	Grade I	0 (0%)	5 (11%)
	Grade II	10 (22%)	20 (45%)
	Grade III	5 (11%)	5 (11%)
LVI	Present	5 (11%)	10 (22%)
	Absent	10 (22%)	20 (45%)
PNI	Present	3 (6%)	12 (27%)
	Absent	12 (27%)	18 (40%)
T stage	T3	12 (27%)	27 (61%)
	T4	3 (6%)	3 (6%)
N stage	N(-)	6 (13%)	18 (40%)
	N1	3 (7%)	9 (20%)
	N2	4 (9%)	2 (4%)
	N3	2 (4%)	1 (3%)

NFKB: Nuclear factor kappa B, LVI: Lymphovascular invasion, PNI: Perineural invasion, APR: Abdominoperineal resection, LAR: Low anterior resection, AR: Anterior resection, TC: Total colectomy

improved overall and disease-free survival (11).

Of 45 patients with RC in the present study, 29 (64%) were CD9 positive (Figure 1; Tables 2 and 3) and 16 (36%) were CD9 negative. As this is the first study on RC evaluating CD, 9 and NFKB expression together, our results were compared with findings from non-RC studies.

Our CD9 positivity rate (64%) was comparable to the 71% positivity reported by Guo et al. (8) CD9 release appears to increase the spread of some cancers, while in others it seems to restrict spread and the degree of invasion. Therefore, this pathway is interconnected with the cell structure, the

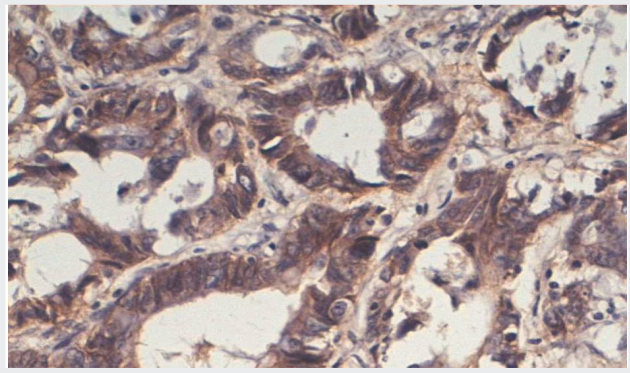

Figure 1. Positive CD9 staining in tumor tissue

Table 2. Distribution of patients according to CD9 expression

Parameters		CD9 (-)	CD9 (+)
n		16 (36%)	29 (64%)
Age (years)		60 (26-76)	53 (26-78)
Gender	Female	9 (20%)	13 (29%)
	Male	7 (16%)	16 (36%)
Operation type	APR	4 (9%)	11 (24%)
	LAR	9 (20%)	12 (27%)
	AR	3 (7%)	5 (11%)
	TC	0 (0%)	1 (2%)
Histopathology	Adenocarcinoma	14 (31%)	28 (62%)
	Signet-ring cell carcinoma	2 (5%)	1 (2%)
Grade	Grade I	3 (6%)	2 (5%)
	Grade II	11 (24%)	19 (42%)
	Grade III	2 (5%)	8 (18%)
LVI	Present	4 (9%)	11 (24%)
	Absent	12 (27%)	18 (40%)
PNI	Present	3 (6%)	12 (27%)
	Absent	12 (27%)	18 (40%)
T stage	T_3	13 (29%)	26 (59%)
	T_4	3 (6%)	3 (6%)
N stage	N (-)	7 (16%)	17 (38%)
	N_1	4 (9%)	8 (18%)
	N_2	3 (6%)	3 (6%)
	N_3	2 (5%)	1 (2%)

LVI: Lymphovascular invasion, PNI: Perineural invasion, APR: Abdominoperineal resection, LAR: Low anterior resection, AR: Anterior resection, TC: Total colectomy

Tablo 3. Comparison of survival according to CD9 and NFKB expression

Survival		CD9			NFKB		
		-	+	p	-	+	p
Disease-free survival	5-year	48%	65%	0.223	56%	60%	0.794
Local control	5-year	66%	90%	0.026	75%	84%	0.362
Overall survival	5-year	46%	82%	0.205	76%	70%	0.805

NFKB: Nuclear factor kappa B

microenvironment surrounding the cell, cell signaling, and the interaction of molecules involved. Consequently, CD9 serves as a reliable marker for leukemic cells, and its monitoring is particularly important in the diagnosis and control of acute lymphoblastic and myeloid leukemi (9,11,12). In our series, although five-year disease-free and overall survival rates were numerically higher in CD9-positive patients (65% vs. 48% and 82% vs. 46%, respectively), the differences were not statistically significant (p=0.223 and p=0.205). However, CD9-positive patients had significantly better local control (90% vs. 66%, p=0.026).

These findings are consistent with those of Wang et al. (6) activation of RelA, a member of the Rel/NF-kappaB transcription factor family, leads to the sustained activation of pancreatic adenocarcinoma cells. Inhibition of RelA in pancreatic tumor cells can reduce their potential for invasion and metastasis. In our study, the lack of statistically significant differences in disease-free and overall survival may be attributable to the small sample size.

No previous studies have directly evaluated the effect of CD9 expression on local control in RC. The observed improvement in local control without a corresponding increase in overall or disease-free survival might also be related to the limited number of patients.

In our study, Figure 2 and Table 3 show positive NFKB staining in tumor tissue.

Several investigators have suggested that NFKB activation plays a key role in tumor development and progression by regulating genes involved in cell-cycle control, invasion, metastasis, angiogenesis, and inhibition of apoptosis in cancers such as pancreatic, breast (13), colorectal, hepatocellular, prostate, and gastric carcinomas (14). Furthermore, NFKB activation has been associated with resistance to anticancer therapy. Inhibition of NFKB has been shown to sensitize tumor cells including those from fibrosarcoma, lymphoma, melanoma, bladder cancer, breast cancer, and squamous cell carcinoma to the cytotoxic effects of TNF, chemotherapy, and RT (13).

Yıldız et al. (13) studied 49 patients with gastric carcinoma who were treated with adjuvant chemoradiotherapy and reported NFKB negativity in 29 patients (59%) and positivity in 20 patients (41%). No significant difference was found in progression-free survival; however, overall survival was shorter in NFKB-positive patients (p=0.033).

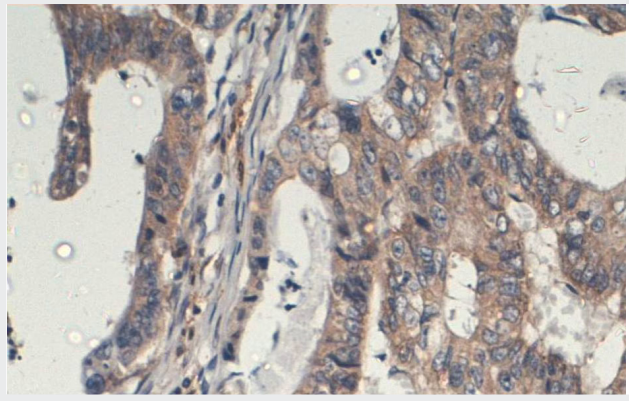

Figure 2. Positive NFKB staining in tumor tissue
NFKB: Nuclear factor kappa B

Eroğlu et al. (14) evaluated 28 patients with stage III non-small-cell lung cancer treated with concurrent chemoradiotherapy and reported NFKB negativity in 21 cases (75%) and NFKB positivity in 7 cases (25%). Eight-month progression-free survival was significantly higher in the NFKB-negative group (83% vs. 24%, p=0.046), while no significant difference was observed in 15-month overall survival (41% vs. 33%, p=0.94) (15).

Yamanaka et al. (15) studied 63 patients with gastric carcinoma, finding NFKB negativity in 42 patients (67%) and positivity in 21 patients (33%). Among 47 surgically treated patients, the NFKB-negative group had a significantly longer overall survival (p=0.015).

In our study, 15 patients (33%) were NFKB-negative and 30 patients (67%) were NFKB-positive. NFKB expression showed no significant impact on disease-free survival, overall survival, or local control rates in RC patients treated with postoperative concurrent chemoradiotherapy.

Kim et al. (16) demonstrated that high CD9 expression in rectal tumor cells was inversely correlated with tumor recurrence, particularly in left-sided colorectal cancer. However, they noted that it occupies a different position in immune cells regardless of the location of the primary tumor.

In their review, Sadati et al (17) stated that the NF-κB pathway plays a crucial role in the progression of colorectal cancer and that targeting this pathway may have therapeutic benefits.

Because our research was conducted in a single center with a relatively small sample size, the results should be interpreted with caution. We believe that larger, multicenter studies could provide more definitive conclusions. Future investigations incorporating molecular-level analyses may further elucidate the role of CD9 and NFKB in determining local recurrence and progression-free survival in RC and potentially guide the development of new therapeutic strategies.

CONCLUSION

Among stage II-III RC patients treated with surgery and adjuvant concurrent CT-RT, CD9 positivity was associated with significantly improved local control but did not affect disease-free or overall survival; NFKB positivity had no prognostic impact on survival or local control.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Dean's Office of Erciyes University Faculty of Medicine in the presence of the professors (desicion number: 142, date: 26.02.2010).

Informed Consent: This study is a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., OG.Y., I.S., S.S., Concept: OG.Y., I.S., S.S., Design: OG.Y., I.S., S.S., Data Collection or Processing: S.K., I.S., Literature Search: S.K., I.S., Writing: S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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