TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2025;40(1):20–29
doi: 10.5505/tjo.2024.4461

ORIGINAL ARTICLE

Prognostic Significance of Maspin Expression in Locally Advanced Rectal Cancer: A Comprehensive Study

Gülşah ATBİNER EROĞLU,[1] Osman SÜTCÜOĞLU,[2] Betül ÖĞÜT,[3] Nuriye ÖZDEMİR[2]

[1]Department of Internal Medicine, Gazi University, Ankara-*Türkiye*
[2]Department of Medical Oncology, Gazi University, Ankara-*Türkiye*
[3]Department of Pathology, Gazi University, Ankara-*Türkiye*

OBJECTIVE

Maspin is a member of the serpin family that targets proteinases and exhibits characteristics of a tumor suppressor protein. The aim of our study is to evaluate the impact of maspin expression on survival rates in patients diagnosed with locally advanced rectal cancer.

METHODS

A retrospective analysis was conducted on a dataset of 60 patients who had received a histopathological diagnosis of rectal cancer. Maspin expression was assessed using the Ventana Benchmark XT device with automatic immunohistochemical staining via the streptavidin-biotin immunoperoxidase technique. A survival analysis was performed by examining maspin in the specimens of these patients.

RESULTS

In terms of maspin staining, 37 patients (61.7%) were negative, while 23 patients (38.3%) were positive (18 cytoplasmic, 2 nuclear, and 3 both). The 3-year overall survival (OS) was 91.3% in maspin-positive patients and 73% in maspin-negative patients. Clinical T stage was significantly related to OS (p=0.028). Multivariate analysis showed nuclear maspin staining was significantly associated with DFS (p=0.004), and T stage was a significant factor for OS, independent of nuclear maspin expression (p=0.011).

CONCLUSION

Our study underscores the strong link between nuclear maspin staining and disease-free survival in rectal cancer patients, highlighting its promising potential as a prognostic biomarker for future research.

Keywords: Maspin; neoadjuvant therapy; rectal cancers; survival analyses.

INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT) is recommended as the standard treatment for locally advanced rectal cancer.[1] Pathological complete response (pCR) rates with chemoradiotherapy (CRT) alone range between 13% and 17%.[2,3] When total neoadjuvant therapy (TNT) is utilized, the pCR rate increases to approximately 27%.[4–6] Recent research supports the efficacy of TNT, demonstrating a significant increase in pCR rates.[7,8] Significant numbers of patients are unable to achieve pCR, highlighting the importance of intensifying treatments. Therefore, it is essential to identify which groups are unlikely to respond. Even though a great deal of research has been conducted on molecular markers, clinical tumor characteristics, and biological factors to

Received: October 05, 2024
Revised: November 12, 2024
Accepted: November 18, 2024
Online: December 17, 2024

Accessible online at:
www.onkder.org

Dr. Gülşah ATBİNER EROĞLU
Gazi Üniversitesi,
İç Hastalıkları Anabilim Dalı,
Ankara-Türkiye
E-mail: gulsahatbiner@hotmail.com

predict how a tumor will respond to chemoradiotherapy before surgery in patients with rectal cancer, no definitive conclusions have been reached.[9] Therefore, it is essential to identify the group unlikely to respond.

Maspin, also known as a mammary serine protease inhibitor, is a member of the serpin family that targets proteinases and exhibits characteristics of a tumor suppressor protein. This protein has a variety of functional capabilities, including inhibition of invasion, enhancement of apoptosis, and modulation of urokinase plasminogen activator (uPA) and tissue plasminogen activator activities.[10–13] Maspin, also known as SERPINB5, is a type II tumor suppressor that is mostly found in normal breast myoepithelial cells as well as in the prostate, epidermis, lung, and corneal stromal cells.[14] Remarkably, it has been observed that maspin expression decreases or even disappears in primary breast cancer cell lines and invasive breast carcinoma.[9] Nonetheless, some studies have proposed an apparently contradictory function for maspin. In advanced stages of diseases such as inflammatory bowel disease and gastric and colorectal malignancies, elevated maspin expression has been detected, suggesting that the tissue of origin of the tumor significantly influences the role of maspin in cancer progression.[15] Notably, the role of the SERPINB5 gene in the prognosis of rectal cancer has only been examined once in the existing literature, with our study being the first to examine maspin expression in this context.[16]

The aim of our study is to evaluate the effects of maspin expression on survival in patients diagnosed with locally advanced rectal cancer. Our secondary objective is to assess the pathologic response rates to nCRT.

MATERIALS AND METHODS

Following approval from the Gazi University Ethics Committee, a retrospective analysis was performed on a dataset consisting of 60 patients who had received a histopathological diagnosis of rectal cancer. These patients presented to the Medical Oncology Department of Ankara Gazi University Faculty of Medicine between January 2009 and January 2018. People with adenocarcinoma of locally advanced rectal cancer who were staged as T3 or T4 or had metastases in their pelvic lymph nodes were included in the study. This was confirmed by pelvic magnetic resonance imaging (MRI) staging.

The inclusion criteria for the study consisted of patients who were 18 years of age or older and had a planned neoadjuvant chemoradiotherapy treatment. The exclusion criteria for this study included several factors: individuals who had been diagnosed with anal squamous cell carcinoma; those who had undergone preoperative or postoperative pathology at a facility outside of the study center; individuals with known immunosuppression; those who did not have a pelvic MRI; individuals with distant metastases; those who had previously received chemotherapy in addition to neoadjuvant chemoradiotherapy (nCRT); those who received neoadjuvant short-course radiation therapy; patients who declined to undergo surgery; and individuals who opted for a "watch and wait" management approach.

Demographic information, clinical characteristics, Eastern Clinical Oncology Group performance scores (ECOG), and pathological data were gathered. In addition, we documented the specific chemotherapy and radiotherapy treatment protocols administered to the patients. Prior to the initiation of chemoradiotherapy (CRT), baseline assessments were conducted. The assessments conducted encompassed the quantification of serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA 19–9), a comprehensive analysis of blood composition, and an extensive array of biochemical tests on the serum. The administration of a cumulative dose of 45 Gy was carried out over a span of 5 weeks, consisting of 25 fractions, in accordance with the established protocol. This treatment was accompanied by the use of either capecitabine or 5-fluorouracil as the chemotherapeutic agent.

Tissue Sampling

Preoperative tissue specimens from the selected patients were retrieved from the archive. The pathologist had no information about the patients. These hematoxylin and eosin-stained preparations were re-examined by a single pathologist. Tumor blocks, where tumor cell concentration was highest and necrosis was minimal, were identified and selected for further analysis. Sections of 4 micrometers in thickness were prepared from the formalin-fixed, paraffin-embedded tissues and placed onto positively charged slides.

To assess maspin expression, staining was conducted on the Ventana Benchmark XT device using the automatic immunohistochemical staining method, employing the streptavidin-biotin triple indirect immunoperoxidase technique. The Ultraview Universal DAB Detection Kit was used in conjunction with the maspin antibody (polyclonal, Invitrogen, 1/200 dilution). Normal breast tissue served as the positive control. For expression prevalence, tissues with staining of 10% and above were classified as maspin-positive staining (Fig. 1). The Modified Ryan Tumor Regression Grade was

Turk J Oncol 2025;40(1):20–29
doi: 10.5505/tjo.2024.4461

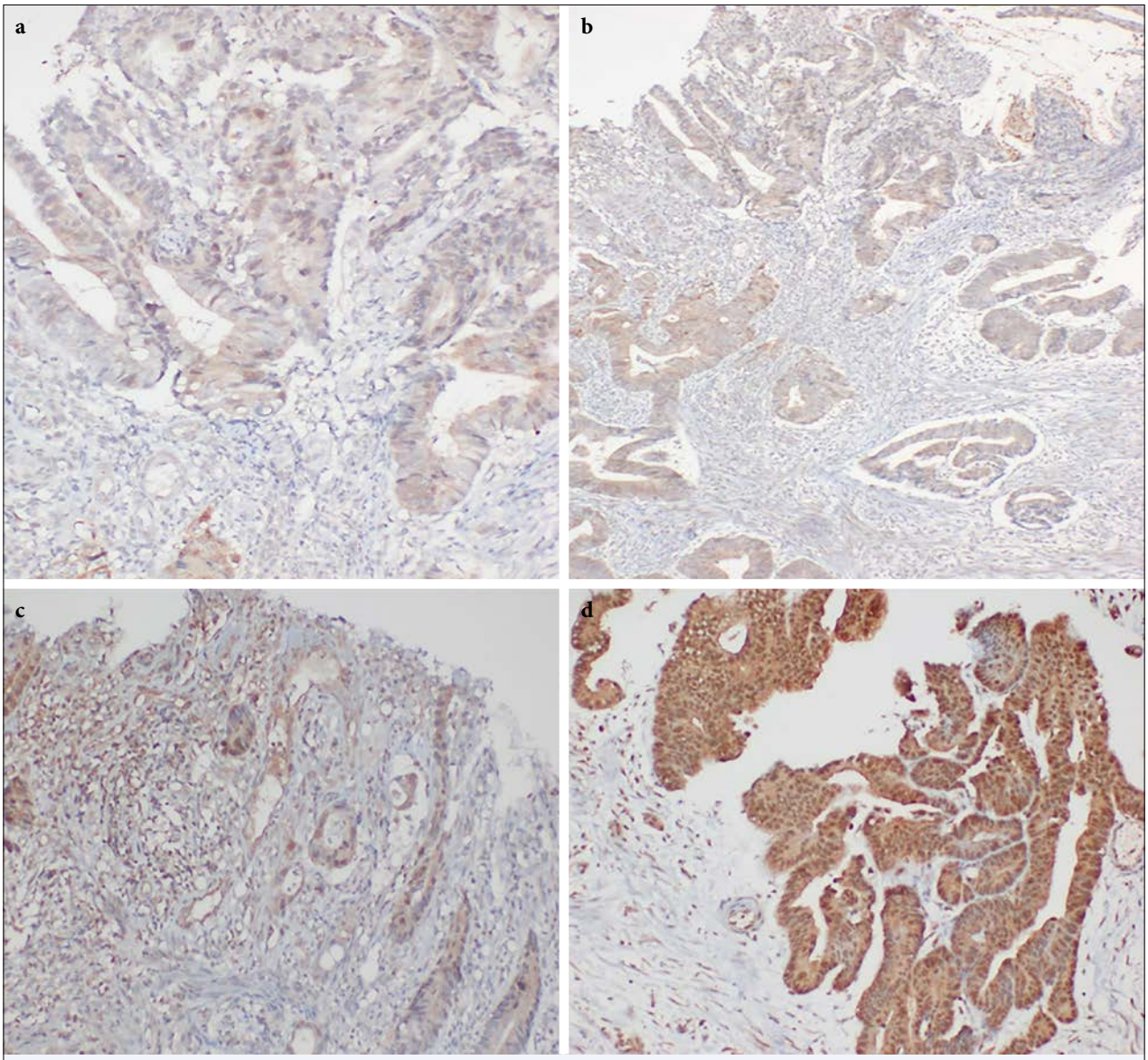

Fig. 1. (a, b) Cytoplasmic expression of maspin (×100 and ×200, respectively) (c) Solely nuclear expression of maspin (×200) (d) Both cytoplasmic and nuclear expression (×200) (Tissues with 10% or more staining in terms of expression prevalence were considered maspin positive staining).

employed in the pathological response assessment. Patients with a tumor regression grade of 0 or 1 were categorized as good responders, while patients with grades of 2 or 3 were categorized as poor responders.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) program. For categorical data, frequencies were reported, while for continuous data—based on the distribution—either means±standard deviations or medians (with minimum-maximum ranges) were presented. The Kolmogorov-Smirnov test was planned to evaluate the normality of data distribution. For variables conforming to a normal distribution, parametric tests (Independent Sample T-Test) were employed, while non-parametric tests (Chi-Square, Mann-Whitney U Test) were used for variables not conforming to normal distribution.

Univariate analyses concerning parameters affecting survival times were conducted using the Log-Rank test in Kaplan-Meier analysis. Multivariate analyses with parameters affecting survival times were performed via Cox Regression analysis. The threshold for statistical significance in this study was set at $p \leq 0.05$.

Table 1 Demographic and clinical characteristics of patients

	n	%
Age		
<65	28	46.7
≥65	32	53.3
Gender		
Male	41	68.3
Female	19	31.7
Localization (the distance from the anal canal)		
<5 cm	24	40
5–10 cm	26	43.3
>10 cm	10	16.7
Differentiation		
Well	16	26.7
Moderate	16	26.7
Poor	2	3.3
Unknown	26	43.3
T stage		
1	1	1.7
2	5	8.3
3	43	71.7
4	11	18.3
N stage		
Negative	12	20
Positive	48	80
Involvement of CRM		
Negative	35	58.3
Positive	25	41.7
Tumor regression grade		
Good response	25	41.7
Poor response	35	58.3
Pretreatment CEA levels		
Low (<5)	42	70
High (>5)	18	30
Pretreatment CA 19–9 levels		
Low (<34)	42	70
High (>34)	18	30
Maspin expression		
Negative	37	61.7
Positive	23	38.3
Cytoplasmic	18	30
Nuclear	2	3.3
Both	3	5

CRM: Circumferential resection margin; CEA: Carcinoembryonic antigen; CA: Cancer antigen

Table 2 Pathological outcomes of patients operated after neoadjuvant chemoradiotherapy

Group	n	%
Type of surgery		
APR	10	16.7
Low anterior resection	50	83.3
pCR		
No	50	83.3
Yes	10	16.7
TRG		
0–1	25	41.6
2–4	35	58.4
ypT		
0	11	18.3
1	1	1.7
2	18	30.0
3	29	48.3
4	1	1.7
ypN		
0	43	71.7
1	11	18.3
2	6	10
Perineural invasion		
No	48	80.0
Yes	12	20.0
Lymphovascular invasion		
No	51	85.0
Yes	9	15.0

APR: Abdomipelvic resection; pCR: Pathologic complete response; TRG: Tumor regression grade; ypT: Tumor stage after neoadjuvant therapy; ypN: Nodal stage after neoadjuvant therapy

RESULTS

A total of 60 patients were included in the study. The demographic and clinical characteristics of the patients are shown in Table 1. With a median age of 65.6 years (range: 29–91 years), the cohort consisted of 41 men (68.3%) and 19 women (31.7%). In 24 of these patients (40%), the tumor was located in the lower rectum (less than 5 cm from the anal verge). At the time of diagnosis, 54 (90%) of the patients had a clinical T3 or T4 tumor. Clinical nodal involvement was found in 48 patients (80%). Maspin staining was negative in 37 patients (61.7%) and positive in 23 patients (38.3%). Cytoplasmic maspin staining was seen in 18 of these patients (30%), nuclear staining in 2 (3.3%), and both cytoplasmic and nuclear staining in 3 (5%).

A pathologically complete response was observed in 10 patients (16.7%). No pathological complete response was detected in any of the 5 patients with nuclear maspin positivity (p=0.296). Among the 21 patients with cytoplasmic maspin staining, 2 (9.5%) had a pathological complete response (p=0.276). It was determined that 25 of the patients had a good response according to TRG. The tumor stage (ypT) and nodal stage (ypN) after neoadjuvant therapy are presented in Table 2.

Turk J Oncol 2025;40(1):20–29
doi: 10.5505/tjo.2024.4461

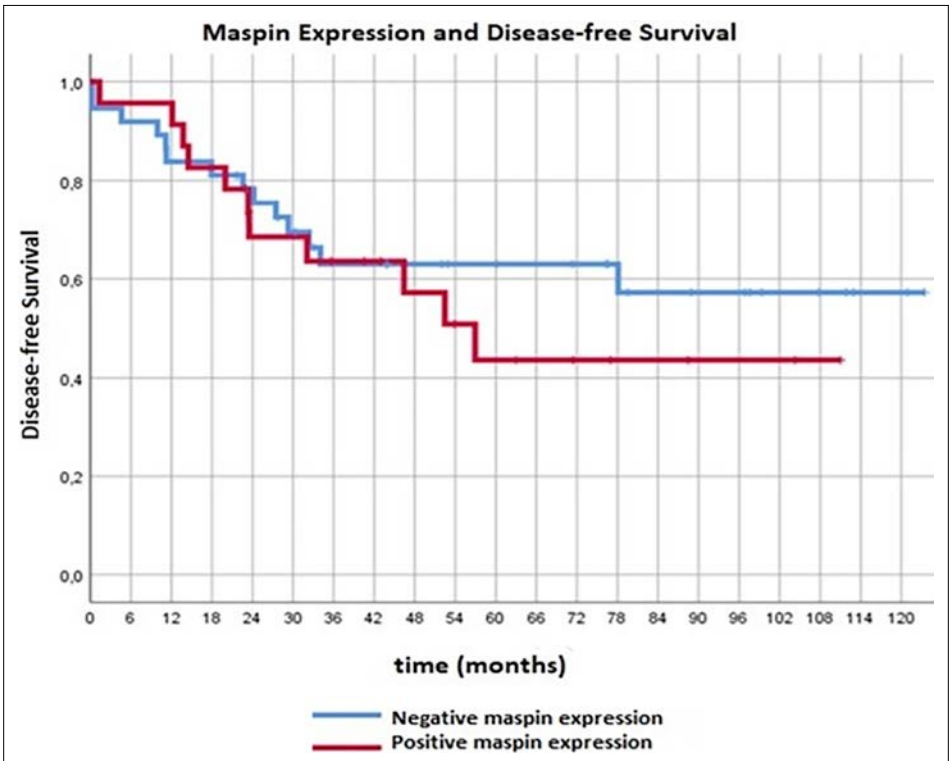

Fig. 2. Maspin expression and disease-free survival.

While DFS in maspin-positive patients was 56.9 months (min-max: 38.8–75.0 months) (p=0.485). In maspin-positive patients, the 1-year, 2-year, and 3-year disease-free survival (DFS) rates were found to be 95.6%, 69.4%, and 65%, respectively. In maspin-negative patients, these rates were 83.8%, 78.4%, and 65%, respectively (Fig. 2). In patients with poor tumor regression grade, DFS was 46.4 months (min-max: 13.4–79.3 months) (p=0.013). On univariate analysis, poor TRG response, high CA-19 level, and nuclear maspin positivity were found to negatively impact DFS (Table 3).

The 3-year overall survival was significantly higher in the maspin-positive group at 91.3% compared to 73% in the maspin-negative group (Fig. 3). Median overall survival (mOS) was not reached in the entire patient group. There was a significant association between clinical T stage and overall survival (OS) (p=0.028). For overall survival, the median tumor regression grade was not reached in either good or poor responders (p=0.052) (Table 4).

In multivariate analysis, only nuclear maspin staining was found to be significantly associated with DFS (p=0.004, HR=2.982, 95% CI=1.052–8.450) (Table 3). Although only clinical T stage was found to be significant for overall survival in univariate analyses, nuclear maspin staining was statistically significant for DFS and was therefore included in the multivariate analysis. In addition, multivariate analysis identified clinical T stage as a significant factor associated with mOS independent of nuclear maspin expression (p=0.011, HR=3.452, 95% CI=1.330–8.962).

DISCUSSION

Rectal cancers, which comprise approximately 30% of colorectal malignancies, maintain their pivotal role in management primarily via surgical excision.[17] Responses to neoadjuvant therapy in rectal cancer are heterogeneous. There is an ongoing search for biomarkers to aid in the selection of the right treatment for the right patient. Extant literature suggests maspin's potential oncogenic role in colorectal neoplasms, linking it with unfavorable prognostic markers.[18] However, given maspin's characteristics, such as inhibition of invasion and enhancement of apoptosis, in this study, we evaluated the relationship between maspin expression and neoadjuvant therapy. While we identified a relationship between nuclear maspin staining and DFS, we did not find a correlation with pCR or OS.

Table 3 Univariate and multivariate analyzes to determine the parameters affecting disease-free survival

		Univariate		Multivariate	
Parameter	**n**	**Relapse (%)**	**p**	**HR (95% CI)**	**p**
Age					
<65	28	10 (35.7)	0.549	–	–
>65	32	15 (46.8)			
Gender					
Female	19	6 (31.5)	0.278	–	–
Male	41	19 (46.3)			
Localization					
<5 cm	24	7 (29.1)	0.351	–	–
5–10 cm	26	13 (50)			
>10 cm	10	5 (50)			
T stage					
1	1	0 (0)	0.079	–	–
2	5	2 (40)			
3	43	15 (34.8)			
4	11	8 (72.7)			
N stage					
Negative	12	5 (41.6)	0.636	–	–
Positive	48	20 (41.6)			
Involvement of CRM					
Negative	35	10 (28.5)	0.060	–	–
Positive	25	15 (60)			
Involvement of EMVI					
Negative	42	17 (40.4)	0.443	–	–
Positive	18	8 (44.4)			
Tumor regression grade					
Good response	25	6 (24)	0.013	2.538 (0.972–6.621)	0.057
Poor response	35	19 (54.2)			
Pretreatment CEA levels					
Low (<5)	42	16 (38.1)	0.303	–	–
High (>5)	18	9 (50)			
Pretreatment CA 19–9 levels					
Low (<34)	42	14 (33.3)	0.019	1.724 (0.743– 4.001)	0.205
High (>34)	18	11 (61.1)			
Maspin expression					
Negative	37	14 (37.8)	0.485	–	–
Positive	23	11 (47.8)			
Maspin cytoplasmic					
Negative	39	16 (41)	0.972	–	–
Positive	21	9 (42.8)			
Maspin nuclear					
Negative	55	20 (36.3)	0.002	2.982 (1.052–8.450)	0.04
Positive	5	5 (100)			

HR: Hazards ratio; CI: Confidence intervals; CRM: Circumferential resection margin; EMVI: Extramural vascular invasion; CEA: Carcinoembryonic antigen; CA: Cancer antigen

In our study, we employed the Modified Ryan Tumor Regression Grade (TRG) System to evaluate the pathological response subsequent to neoadjuvant therapy. A notable association was identified between TRG and disease-free survival. Among the cohort, 19 of the 35 patients (54%) exhibited tumor regression grades of 2 and

Turk J Oncol 2025;40(1):20–29
doi: 10.5505/tjo.2024.4461

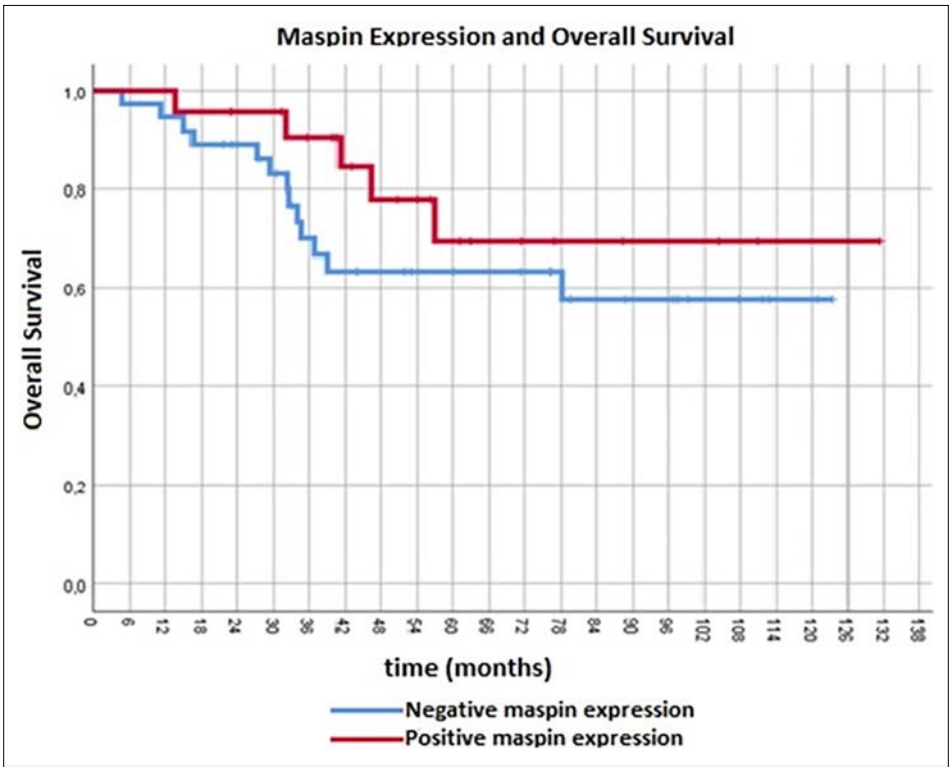

Fig. 3. Maspin expression and overall survival.

3 (indicative of a poor response). A research study led by Huh et al.[19] in 2019, which encompassed 639 patients over a 56.7-month follow-up span, unveiled a significant correlation between the 5-year overall survival and disease-free survival rates in relation to TRG. Specifically, the 5-year disease-free survival was discerned to be 93% for TRG 0 and 1, and 68% for TRG 2–3. Such revelations underscore the importance of TRG as an autonomous prognostic determinant for survival among rectal cancer patients undergoing neoadjuvant therapy.

Our multivariate survival analysis illuminated a significant association between nuclear maspin staining in patients and disease-free survival, wherein recurrence was observed in 100% of these patients. Conversely, no consequential association emerged regarding overall survival among those with nuclear maspin staining. A comprehensive review of existing literature manifests that while cytoplasmic maspin staining is often correlated with a favorable prognosis in tissues exhibiting high tumor density, nuclear maspin staining is linked with markers of poor prognosis such as lymphovascular and perineural invasion, lymph node metastasis, enhanced tumor aggressiveness, and diminished survival durations.[20]

In comparing our findings with those of Chang et al.,[16] several notable similarities and differences emerge. Both studies underscore the prognostic significance of maspin expression in rectal cancer. Chang et al.[16] focused on SERPINB5 expression and its association with chemoradiotherapy (CCRT) response and overall prognosis. Their results indicated that SERPINB5 overexpression was linked to a poor response to CCRT, as well as reduced disease-specific survival, local recurrence-free survival, and metastasis-free survival. Similarly, our study identified a significant relationship between nuclear maspin staining and disease-free survival (DFS), with poor tumor regression grade (TRG) and high CA-19 levels also negatively impacting DFS. However, unlike Chang et al.,[16] who reported SERPINB5's influence on various survival metrics, our data did not show a significant correlation between maspin staining and overall survival (OS) in univariate analysis. Instead, clinical T stage emerged as a significant factor for OS in multivariate analysis. Notably, our study found no pathological complete response in patients with nuclear maspin positivity, aligning with Chang et al.[16]'s findings on SERPINB5's association with adverse outcomes. This comparison highlights the potential of maspin as a prognostic biomarker in rectal cancer and underscores the need for further research to clarify its role in treatment response and long-term survival.

Table 4 Univariate and multivariateanalyzes to determine the parameters affecting overall survival

		Univariate		Multivariate	
Parameter	**n**	**Mortality (%)**	**p**	**HR (95% CI)**	**p**
Age					
<65	28	6 (21.4)	0.293	–	–
>65	32	12 (37.5)			
Gender					
Female	19	5 (26.3)	0.669	–	–
Male	41	13 (31.7)			
Localization					
<5 cm	24	6 (25)	0.786	–	–
5–10 cm	26	9 (34.6)			
>10 cm	10	3 (30)			
T stage					
1	1	0 (0)	0.028	3.452 (1.330–8.962)	0.011
2	5	0 (0)			
3	43	11 (25.5)			
4	11	7 (63.6)			
N stage					
Negative	12	2 (16.6)	0.570	–	–
Positive	48	16 (33.3)			
Involvement of CRM					
Negative	35	7 (20)	0.207	–	–
Positive	25	11 (44)			
Involvement of EMVI					
Negative	42	11 (26.1)	0.247	–	–
Positive	18	7 (38.8)			
Tumor regression grade					
Good response	25	4 (16)	0.052	–	–
Poor response	35	14 (40)			
Pretreatment CEA levels					
Low (<5)	42	10 (23.8)	0.085	–	–
High (>5)	18	8 (44.4)			
Pretreatment CA 19–9 levels					
Low (<34)	42	10 (23.8)	0.064	–	–
High (>34)	18	8 (44.4)			
Maspin expression					
Negative	37	13 (35.1)	0.262	–	–
Positive	23	5 (21.7)			
Maspin cytoplasmic					
Negative	39	13 (33.3)	0.443	–	–
Positive	21	5 (23.8)			
Maspin nuclear					
Negative	55	16 (29)	0.723	1.918 (0.411–8.955)	0.407
Positive	5	2 (40)			

HR: Hazards ratio; CI: Confidence intervals; CRM: Circumferential resection margin; EMVI: Extramural vascular invasion; CEA: Carcinoembryonic antigen; CA: Cancer antigen

According to the literature, the impact of maspin on prognosis has been investigated in various cancer types. Our study is one of the most important studies in the literature evaluating the prognostic significance of maspin in rectal cancer.[21,22] Currently, total neoadjuvant therapy (TNT) has become the standard in

Turk J Oncol 2025;40(1):20–29
doi: 10.5505/tjo.2024.4461

the preoperative treatment of rectal cancer. Our data does not include patients who received TNT. The prognostic value of maspin in patients who have received TNT is a subject that needs further investigation.

The limitations of our study include the small number of patients included in our center, its reliance on retrospective data, and the inclusion of only patients followed in our clinic. Additionally, the lack of literature data on this topic makes the interpretation of results difficult. Considering the aggregate data, discerning the precise role of maspin, an exclusive member of the serpin family, in oncology remains complex. Furthermore, understanding its response to neoadjuvant treatment and its implications for both disease-free and overall survival is challenging.

CONCLUSION

Our study underscores the crucial link between nuclear maspin staining and disease-free survival in rectal cancer patients, highlighting its potential as a prognostic indicator. To pave the way for potential maspin-centric therapeutic interventions, especially for patients predisposed to heightened risk of rectal cancer, a comprehensive understanding of maspin's molecular mechanisms within the oncogenic processes of rectal cancer is paramount.

Ethics Committee Approval: The study was approved by the Gazi University Clinical Research Ethics Committee (no: 53, date: 25/01/2021).

Authorship contributions: Concept – G.A.E., N.Ö.; Design – G.A.E., O.S., B.Ö.; Supervision – O.S., N.Ö., B.Ö.; Materials – G.A.E., B.Ö.; Data collection and/or processing – G.A.E., B.Ö.; Data analysis and/or interpretation – G.A.E., O.S.; Literature search – G.A.E., O.S., N.Ö.; Writing – G.A.E., O.S.; Critical review – O.S., B.Ö., N.Ö.

Conflict of Interest: All authors declared no conflict of interest.

Use of AI for Writing Assistance: No AI technologies utilized.

Financial Support: None declared.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:22–40.
2. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351(17):1731–40.
3. Ulusoy C, Kamalı GH, Nikolovski A. Analysis of survival in complete pathological response after long-course chemoradiotherapy in patients with advanced rectal cancer. Curr Oncol 2023;30(1):1054–64.
4. Al-Sukhni E, Attwood K, Mattson DM, Gabriel E, Nurkin SJ. Predictors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. Ann Surg Oncol 2016;23(4):1177–86.
5. Hasan S, Renz P, Wegner RE, Finley G, Raj M, Monga D, et al. Microsatellite instability (MSI) as an independent predictor of pathologic complete response (pCR) in locally advanced rectal cancer: A national cancer database (NCDB) analysis. Ann Surg 2020;271(4):716–23.
6. Díaz-González JA, Calvo FA, Cortés J, García-Sabrido JL, Gómez-Espí M, Del Valle E, et al. Prognostic factors for disease-free survival in patients with T3–4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. Int J Radiat Oncol Biol Phys 2006;64(4):1122–8.
7. Nilsson PJ, van Etten B, Hospers GA, Påhlman L, van de Velde CJ, Beets-Tan RG, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer—the RAPIDO trial. BMC Cancer 2013;13:279.
8. Conroy T, Lamfichekh N, Etienne PL, Rio E, Francois E, Mesgouez-Nebout N, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: Final results of PRODIGE 23 phase III trial, a UNICANCER GI trial. J Clin Oncol 2020;38:4007.
9. Park YA, Sohn SK, Seong J, Baik SH, Lee KY, Kim NK, et al. Serum CEA as a predictor for the response to preoperative chemoradiation in rectal cancer. J Surg Oncol 2006;93(2):145–50.
10. Zhang M, Sheng S, Maass N, Sager R. mMaspin: The mouse homolog of a human tumor suppressor gene inhibits mammary tumor invasion and motility. Mol Med 1997;3(1):49–59.
11. Zou Z, Anisowicz A, Hendrix MJ, Thor A, Neveu M, Sheng S, et al. Maspin, a serpin with tumor-suppressing activity in human mammary epithelial cells. Science 1994;263(5146):526–9.
12. Sheng SJ, Pemberton PA, Sager R. Production, purification, and characterization of recombinant maspin proteins. J Biol Chem 1995;269:30988–93.
13. Sheng S, Carey J, Seftor EA, Dias L, Hendrix MJ, Sager R. Maspin acts at the cell membrane to inhibit invasion and motility of mammary and prostatic cancer cells. Proc Natl Acad Sci U S A 1996;93(21):11669–74.
14. Bailey CM, Khalkhali-Ellis Z, Seftor EA, Hendrix MJ. Biological functions of maspin. J Cell Physiol 2006;209(3):617–24.

15. Schaefer JS, Zhang M. Targeting maspin in endothelial cells to induce cell apoptosis. Expert Opin Ther Targets 2006;10(3):401–8.
16. Chang IW, Liu KW, Ragunanan M, He HL, Shiue YL, Yu SC. SERPINB5 expression: Association with CCRT response and prognostic value in rectal cancer. Int J Med Sci 2018;15(4):376–84.
17. Oronsky B, Reid T, Larson C, Knox SJ. Locally advanced rectal cancer: The past, present, and future. Semin Oncol 2020;47(1):85–92.
18. Payne CM, Holubec H, Crowley-Skillicorn C, Nguyen H, Bernstein H, Wilcox G, et al. Maspin is a deoxycholate-inducible, anti-apoptotic stress-response protein differentially expressed during colon carcinogenesis. Clin Exp Gastroenterol 2011;4:239–53.
19. Huh JW, Kim HC, Kim SH, Park YA, Cho YB, Yun SH, et al. Tumor regression grade as a clinically useful outcome predictor in patients with rectal cancer after preoperative chemoradiotherapy. Surgery 2019;165(3):579–85.
20. Banias L, Gurzu S, Kovacs Z, Bara T, Bara T Jr, Jung I. Nuclear maspin expression: A biomarker for budding assessment in colorectal cancer specimens. Pathol Res Pract 2017;213(9):1227–30.
21. Fokas E, Schlenska-Lange A, Polat B, Klautke G, Grabenbauer GG, Fietkau R, et al. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal cancer: Long-term results of the CAO/ARO/AIO-12 randomized clinical trial. JAMA Oncol 2022;8:e215445.
22. Fokas E, Allagauer M, Polat B, Klautke G, Grabenbauer GG, Fietkau R, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. J Clin Oncol 2019;37(34):3212–22.