Prognostic value of translationally controlled tumor protein in colon cancer

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Abstract. The translationally controlled tumor protein (TCTP) is a highly conserved protein involved in a variety of normal cell functions and disease processes. Preclinical studies revealed that TCTP has anti-apoptotic properties, promotes cell growth and division and is involved in cancer progression by promoting invasion and metastasis. The present study explored the potential value of TCTP as a prognostic marker in colon cancer. A retrospective analysis of 74 patients with colon cancer was performed. Using immunohistochemistry, TCTP levels in the primary tumor were assessed semi-quantitatively by the calculation of cytoplasmic and nuclear H-score. Cytoplasmic TCTP levels in the primary tumor had no statistically significant association with disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS) in the present patient population. Patients whose primary tumors had a negative nuclear TCTP expression had significantly improved clinical outcomes. The PFS for the negative nuclear TCTP expression group was 7.7 months [95% confidence interval (CI), 5.8-9.5] compared with 5.5 months (95% CI, 3.2-7.8) in the group with positive nuclear expression (P=0.023, Mantel-Cox log-rank). Patients with a negative nuclear expression of TCTP had a significantly higher median OS (22.2 months; 95% CI, 16.1-28.3) compared with those with positive TCTP nuclear expression (median 13.2 months; 95% CI, 10.1-16.3; P=0.008, Mantel-Cox log-rank). In a multivariate Cox regression model, a positive nuclear TCTP H-score was an independent risk factor for worse PFS and OS. The 1-year OS rate in the group with negative nuclear TCTP expression was 86.3% compared with 56.5% in patients with positive nuclear TCTP expression (P=0.008). The present study suggested that semiquantitative H-score measurement of TCTP levels in the nuclei of tumor cells from the primary tumor is a potential prognostic marker for clinical outcomes in patients with colon cancer.

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Introduction

Colorectal cancer is the third most common malignancy worldwide and the second most common cause of cancer-related mortality (1). Global projections predict an increasing number of colorectal cancer cases with an alarming trend of rising incidence among younger adults (2). Advances in understanding of the pathophysiology of the disease has increased the available treatment options for local and advanced disease (3). The 5-year survival rate has risen over the past several decades and exceeds 60% (4). As more prognostic and predictive factors related to the tumor biology, including tumor sidedness, RAS and BRAF mutations and microsatellite instability (MSI), are validated, it is becoming increasingly evident that colorectal cancer is a highly heterogeneous disease with different outcomes across patient subgroups (5). Further research into prognostic markers is warranted to guide appropriate treatment decisions.

The translationally controlled tumor protein (TCTP) is a highly conserved protein present in virtually all eukaryotic organisms (6). TCTP is involved in a variety of normal cell functions and disease processes. TCTP levels are upregulated in mitotically active tissues, which implies a crucial role in cell growth and proliferation (7). Various growth signals and cytokines induce TCTP synthesis (8,9). The structural similarity to specific chaperone proteins, the ability to affect microtubule dynamics and cell morphology and its anti-apoptotic properties suggest a cytoprotective function of TCTP (10-12).

Increasing evidence supports an association between TCTP and oncogenic transformation. TCTP expression levels tend to be higher in tumors compared with the corresponding normal tissue (12,13). TCTP was found to bind the tumor suppressor p53 and repress its transcription thus preventing apoptosis in tumor cells and promoting malignant transformation (14,15). Inhibition of TCTP expression suppresses the malignant phenotype in cancer cells (13) and renders them more sensitive to cell death due to oxidative and metabolic stress (16). In addition, increased TCTP levels are associated with the chemoresistance of cancer cells (17,18). TCTP is found to be involved in cancer progression via inhibition of apoptosis,

acceleration of mitotic exit and induction of invasion and metastasis (19).

Tumor reversion is the process in which tumor cells lose their malignant phenotype (20). During the process of tumor reversion, a significant downregulation of TCTP has been demonstrated, which increases the interest in TCTP as a potential therapeutic target (21). Knockdown of TCTP in colon cancer cells inhibits invasion and migration *in vitro* and liver metastasis *in vivo* (22).

TCTP is overexpressed in various types of cancers (23,24). TCTP expression is identified in the cytoplasm, the nuclei and extracellularly (25,26). The prognostic value of TCTP expression has not been extensively investigated (27). In colorectal cancer, high TCTP expression is associated with a higher pathological grade and a metastatic stage at diagnosis but little evidence is present about survival outcomes (26,27).

The present retrospective study evaluated the performance of TCTP expression in the primary tumor as a prognostic marker for patients with colon cancer.

Materials and methods

Patient selection. A retrospective analysis of the UMHAT Sveta Marina Clinic of Medical Oncology (Varna, Bulgaria) database was conducted. All consecutive colon cancer patients who were diagnosed and treated between 1 January 2015 and 31 December 2015 and met the following predefined eligibility criteria were included in the analysis. Adult patients with a histologically verified diagnosis of colon cancer who underwent resection of the primary tumor and initiated systemic anticancer therapy within the prespecified period were included in the study. Only patients requiring systemic treatment were included: Stage IV patients and patients with a high risk of relapse in whom adjuvant chemotherapy was indicated (Stage III and high-risk Stage II). Patients were excluded if the archived primary tumor sample was unavailable for analysis or if the database did not include information about key study variables such as date of diagnosis, disease-free survival (DFS), progression-free survival (PFS) or overall survival (OS). Patient data which included demographic information, disease characteristics, treatment regimens, response to therapy and clinical outcomes were retrospectively obtained from the hospital's archive of patients' files. Patient characteristics are given in Table I. The present study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Medical University Varna Ethics Review Committee (approval no. 34/13.11.2014). The patients provided written informed consent to participate.

Immunohistochemical staining. Archival samples from the primary resected tumor of all colon cancer patients in the study were obtained. All tissue samples were fixed with a 10% neutral buffered formalin for 24 h. Tissue sections (5-μm thick) were cut from the paraffin blocks and placed on glass slides. Sections were deparaffinized with xylene and rehydrated in a graded series of ethanol to deionized water. Antigen retrieval was performed in pre-heated EnVision FLEX Target Retrieval Solution (Agilent Technologies, Inc.) in PT Link tanks and incubated for 30 min at 97˚C in a medium at pH 9. After cooling, the slides were placed in a diluted FLEX Wash Buffer (20x; Agilent Technologies, Inc.) for 1-5 min. Sections were stained using the FLEX protocol in Dako Autostainer/Autostainer Plus (Dako; Agilent Technologies, Inc.). Samples were incubated with polyclonal rabbit antibody against TCTP (cat. no. ABIN701089; antibodies-online GmbH). The antibody (anti-TCTP, diluted 1:400) was incubated for 20 min. Analysis of expression levels of TCTP was performed using the UltraVision detection system with the anti-polyvalent HRP/diaminobenzidine (DAB). The reaction was developed with the appropriate substrate-chromogen (DAB) reagent. Counterstaining was performed using Mayer's hematoxylin for 1 min at room temperature. Digital images were obtained using the Leica Aperio ScanScope AT2 device (Leica Microsystems, Inc.) and further analyses of the scanned images were performed with ImageScope v12.1.0.5029 (Leica Microsystems, Inc.).

H-score assessment. A semiquantitative assessment of TCTP levels in the cells of primary tumors was performed. Two independent pathologists blinded from the clinical data calculated separate TCTP H-scores in the cytoplasm and the nuclei of the tumor cells. Staining intensity was classified into four grades: 0 (no staining), 1 (weak staining, yellow), 2 (moderate staining, deep yellow) and 3 (strong staining, brown). The H-score was defined as the percentage of cells with weak stain intensity, plus two times the percentage of cells with-moderate stain intensity, plus three times the percentage of cells with strong stain intensity (28). The mean values of the H-score assessments of both pathologists for each sample were used in the analyses.

The median cytoplasmic TCTP H-score in our patient population was 180. The median was used to categorize tumors with low (≤180) and high (>180) cytoplasmic H-score for subsequent categorical statistical analyses. The median nuclear TCTP H-score in the sample was 0. Patients were stratified into two groups; those with negative nuclear TCTP expression (H-score=0) and patients with positive nuclear TCTP expression (H-score>0; Fig. 1). Cytoplasmic and nuclear TCTP H-score assessments were performed on adjacent healthy tissue taken at the surgical resection margins for each analyzed sample following the same procedures.

Endpoints. Disease-free survival (DFS) was defined as the time to relapse or mortality, from any cause, in patients who received initial curative treatment in the adjuvant treatment setting. Progression-free survival (PFS) was defined as the time elapsed between initiation of first-line treatment for metastatic disease and tumor progression or mortality from any cause. Overall survival (OS) was defined as the time between the initial diagnosis of the disease and mortality. Radiologic tumor response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors v1.1 (29). Radiographic assessments were regularly performed with a tomographic imaging method such as computerized tomography (CT) and/or positron emission tomography-CT during follow-ups of patients. Disease control rate (DCR) was defined as the proportion of patients achieving complete response, partial response, or stable disease during the first line of treatment for metastatic disease.

Table I. Patient characteristics in cytoplasmic and nuclear TCTP expression subgroups.

Clinicopathological characteristics	TCTP cytoplasmic expression			TCTP nuclear expression		
	Low (%)	High (%)	P-value	Low (%)	High (%)	P-value
Age			0.056			0.621
≤64	24 (75.0)	8 (25.0)		21 (65.6)	11 (34.4)	
>64	22 (54.4)	20 (47.6)		30 (71.4)	12 (28.6)	
Sex			0.323			1
Male	31 (67.4)	15 (32.6)		32 (69.6)	14 (30.4)	
Female	15 (53.6)	13 (46.4)		19 (67.9)	9 (32.1)	
ECOG			0.622			0.606
0	30 (65.2)	16 (34.8)		33 (71.7)	13 (28.3)	
1	16 (57.1)	12 (42.9)		18 (64.3)	10 (35.7)	
G			0.757			0.173
2	39 (62.9)	23 (37.1)		45 (72.6)	17 (27.4)	
3	7 (58.3)	5 (41.7)		6 (50.0)	6 (50.0)	
RAS			0.630			0.802
Wild-type	24 (58.5)	17 (41.5)		29 (70.7)	12 (29.3)	
Mutant	22 (66.7)	11 (33.3)		22 (66.7)	11 (33.3)	
Primary tumor location			0.229			0.612
Left colon	24 (55.8)	19 (44.2)		31 (72.1)	12 (27.9)	
Right colon	22 (71.0)	9 (29.0)		20 (64.5)	11 (35.5)	
Stage groups at diagnosis			0.280			0.266
Non-metastatic	10 (50)	10 (50)		16 (80)	4 (20)	
Metastatic	36 (66.7)	18 (33.3)		35 (64.8)	19 (35.2)	
Stage at diagnosis			0.420[a]			0.447[a]
Stage II	1 (50)	1 (50)		2 (100)	0 (0)	
Stage III	9 (50)	9 (50)		14 (77.8)	4 (22.2)	
Stage IV	36 (66.7)	18 (33.3)		35 (64.5)	19 (35.5)	
Best response to first-line therapy			0.277[a]			0.784[a]
CR	1 (33.3)	2 (66.7)		3 (100)	0 (0)	
PR	6 (85.7)	1 (14.3)		5 (71.4)	2 (28.6)	
SD	15 (53.6)	13 (46.4)		19 (67.9)	9 (32.1)	
PD	22 (66.7)	11 (33.3)		21 (63.6)	12 (36.4)	
DCR			0.474			0.613
CR+PR+SD	22 (57.9)	16 (42.1)		27 (71.1)	11 (28.9)	
PD	22 (66.7)	11 (33.3)		21 (63.6)	12 (36.4)	

[a]Fisher's Exact Test. TCTP, translationally controlled tumor protein; ECOG, Eastern Cooperative Oncology Group; CR, complete response to treatment; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate.

Statistical design and analysis. IBM SPSS software version 23 (IBM Corp.) was used to perform the statistical analyses. Patient characteristics between different nuclear and cytoplasmic TCTP expression subgroups were compared with the Chi-squared test or Fisher's exact test as appropriate based on the number of observations within each subgroup. Paired samples t-test was used for the comparison of TCTP expression between tumor cells and adjacent healthy tissue. The Mann-Whitney U test and Jonckheere-Terpstra test were used to compare and identify associations between TCTP levels in the primary tumor and clinicopathological characteristics. The probability of survival was estimated using the Kaplan-Meier method and differences in survival in each subgroup were evaluated with a log-rank test. Survival data were censored at the time of analysis. Cox proportional hazards regression was used to investigate associations between patient survival and clinicopathological characteristics including TCTP levels in the primary tumor with the calculation of hazard ratios (HRs). $P<0.05$ was considered to indicate a statistically significant difference.

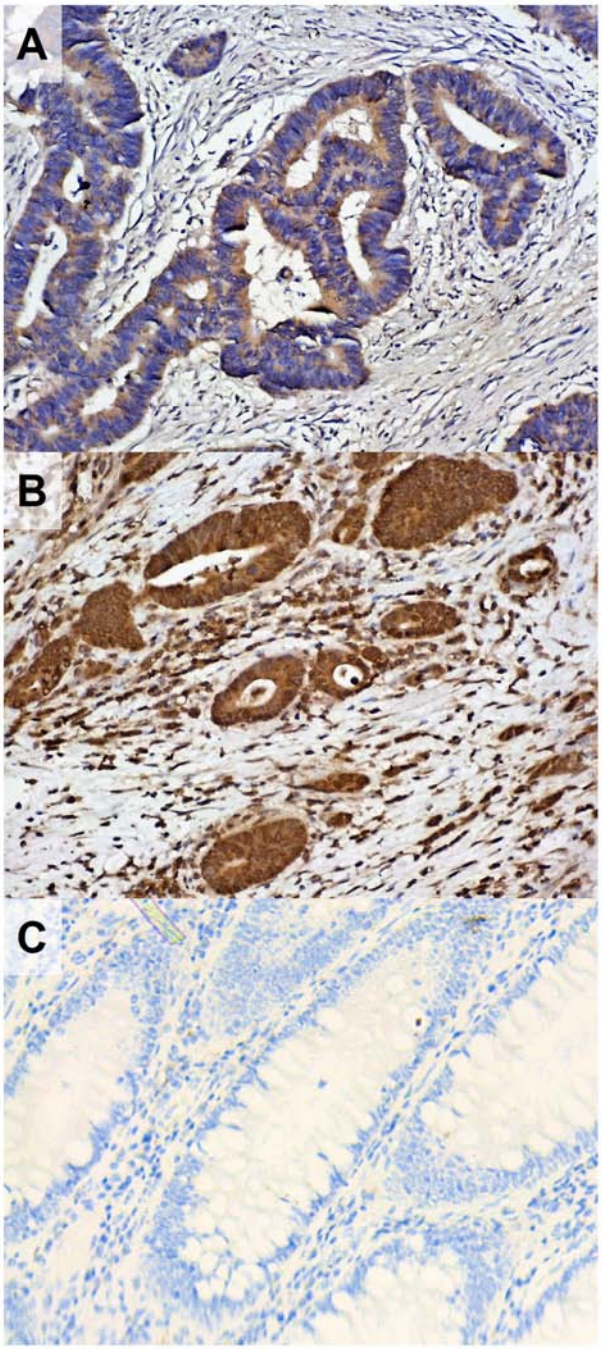

Figure 1. Immunohistochemical staining of TCTP in human colon cancer (magnification, x100). (A) Patient with a low nuclear TCTP expression. (B) Patient with a high nuclear TCTP expression. (C) Adjacent healthy colon tissue. TCTP, translationally controlled tumor protein.

Results

Patient characteristics. A total of 74 patients with colon cancer were included in the present retrospective study. The mean age of the patients was 64.9±9.0 years. Forty-six patients were male (62.2%) and 28 were female (37.8%). The number of patients with RAS wild-type tumors was 41 (55.4%), whereas 33 (44.6%) patients had a mutation in the RAS genes. According to histopathological tumor grading, 62 (83.8%) patients had moderately differentiated tumors (G2) and 12 (16.2%) had poorly differentiated tumors (G3).

According to the stage at diagnosis, 54 (73%) patients were diagnosed with primary metastatic disease and 20 (27%) patients were diagnosed with nonmetastatic disease. Among the latter group, 17 patients further progressed to stage IV while three patients remained disease-free at the time of analysis. All patients diagnosed with nonmetastatic colon cancer were treated with adjuvant chemotherapy. Primary metastatic patients and those who relapsed received at least one line of chemotherapy in the metastatic setting.

Associations between TCTP levels and demographic and clinicopathological characteristics. Chi-squared tests of independence showed that there were no significant associations between TCTP cytoplasmic and nuclear expression subgroups and patients' age, sex, Eastern Cooperative Oncology Group (ECOG) PS, tumor grade, RAS status, primary tumor location, stage at diagnosis and best response to first-line chemotherapy. The associations between TCTP expression and clinicopathological characteristics are summarized in Table I. Patients with higher nuclear TCTP H-score tended to have a higher number of metastatic sites at diagnosis (P=0.059; Jonckheere-Terpstra test). A higher nuclear TCTP H-score was associated with a higher tumor grade (P=0.049, Mann-Whitney; Fig. 2). Mean cytoplasmic and nuclear TCTP H-scores in tumor cells were significantly higher compared with adjacent normal colon tissue (P=0.004 and P<0.001; paired samples t-test).

Effects of TCTP expression on survival outcomes. Cytoplasmic expression levels of TCTP had no statistically significant association with DFS (P=0.723), PFS (P=0.377) and OS (P=0.990).

Patients whose primary tumors had a negative nuclear TCTP H-score had statistically significant improved clinical outcomes. The PFS for the negative nuclear TCTP expression group was 7.7 months [95% confidence interval (CI), 5.8-9.5] compared with 5.5 months (95% CI, 3.2-7.8) in the group with positive nuclear expression (P=0.023; Mantel-Cox log-rank; Fig. 3). Patients with a negative nuclear expression of TCTP also had a significantly higher median OS (22.2 months; 95% CI, 16.1-28.3) compared with those with positive TCTP nuclear expression (median 13.2 months; 95% CI, 10.1-16.3; P=0.008; Mantel-Cox log-rank; Table II; Fig. 4). In univariate Cox regression analysis, a positive nuclear TCTP H-score was a statistically significant risk factor for worse PFS [hazard ratio (HR) 1.797; 95% CI, 1.073-3.010; P=0.026] and OS (HR 1.995; 95% CI, 1.189-3.348; P=0.009; Table III). In a multivariate Cox regression model, a positive nuclear TCTP H-score was an independent risk factor for worse PFS and OS (Table IV). The 1-year OS rate in the group with negative nuclear TCTP expression was 86.3% compared with 56.5% in patients with positive nuclear TCTP expression (P=0.008). There was a statistically significant negative correlation between nuclear TCTP H-score and OS (ρ=-0.287; P=0.013). The DFS in patients diagnosed with nonmetastatic disease did not differ among nuclear TCTP expression subgroups (P=0.813).

Discussion

Despite advances in screening, diagnosis and treatment, the prognosis for colorectal cancer remains poor, particularly in the advanced stages of the disease. Therefore, there is a need

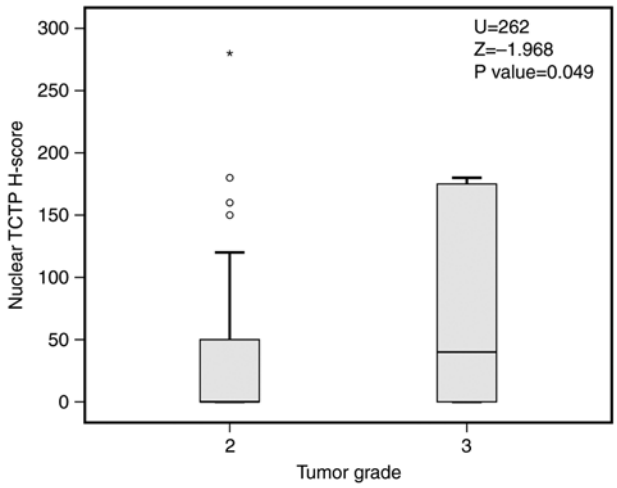

Figure 2. Nuclear TCTP H-score in patients with intermediate and high grade colon cancer. TCTP, translationally controlled tumor protein.

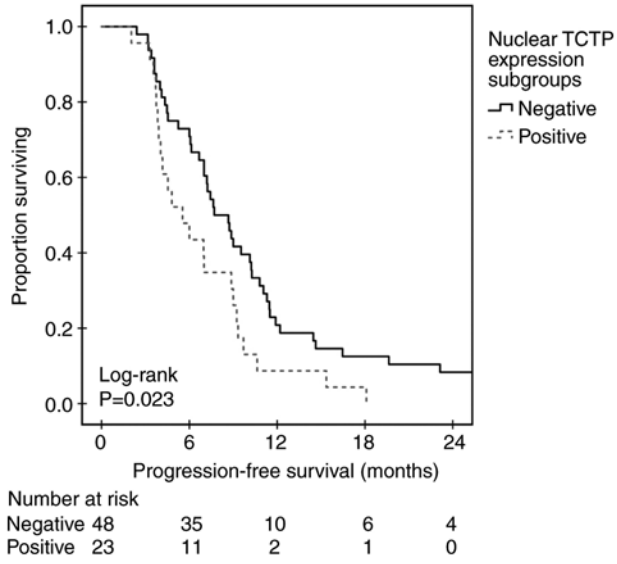

Figure 3. Comparison of progression-free survival based on nuclear TCTP levels. TCTP, translationally controlled tumor protein.

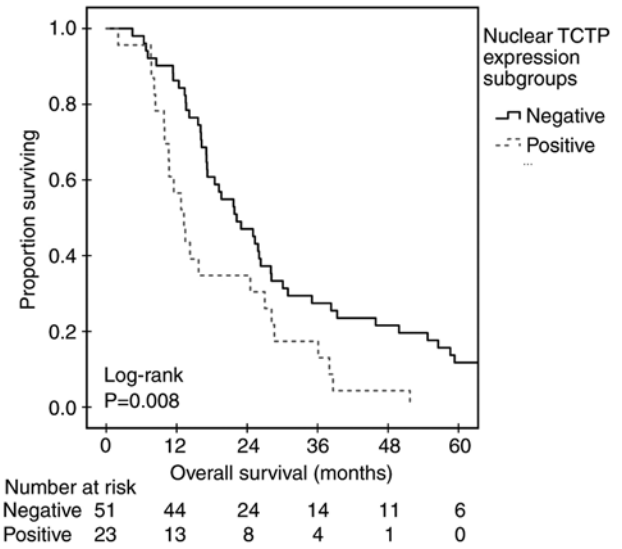

Figure 4. Comparison of overall survival based on nuclear TCTP levels. TCTP, translationally controlled tumor protein.

to identify new prognostic markers that can predict patient outcomes and guide treatment decisions.

The current retrospective study discovered significant differences in survival outcomes in patients with colon cancer depending on nuclear TCTP expression levels. Despite having similar clinical and pathological characteristics (age, sex, ECOG PS, tumor grade, stage at diagnosis and RAS status), the median PFS and OS were significantly lower in patients with higher nuclear TCTP expression. In addition, multivariate analysis demonstrated that nuclear TCTP expression was an independent risk factor for worse PFS and OS in the present patient population. No prognostic value of cytoplasmic TCTP levels was found.

The prognostic value of TCTP expression in different types of cancer was previously evaluated. Previous research on breast cancer found that higher TCTP expression with predominantly nuclear staining was associated with a higher pathological grade and high Ki-67 expression as markers of disease aggressiveness (21). In another study on hepatocellular carcinoma high TCTP expression was determined to be an independent poor prognostic factor associated with higher disease stage and shorter OS (30). In patients with glioma, high TCTP expression was associated with advanced pathological grade and shorter OS (23). TCTP overexpression was associated with higher FIGO stage and tumor grade and lower OS in patients with epithelial ovarian carcinoma (31).

Information about the prognostic significance of TCTP expression in patients with colon cancer is limited, at least to the best of the authors' knowledge (26,27). Fischer *et al* (27) investigated the role of TCTP mRNA and protein expression levels as prognostic factors in different types of cancer. In their colon cancer dataset, no association between TCTP mRNA expression and OS was observed but, similarly to the present study, nuclear TCTP expression was associated with a higher tumor grade. In another study, Xiao *et al* (26) documented higher TCTP expression in patients with higher pathological grades and metastatic stage of the disease. The same study also reported that high TCTP expression correlated with poor metastasis-free survival.

The role of TCTP in carcinogenesis was inferred since its discovery and it received particular attention during the investigation of tumor reversion as a process (32). TCTP gene expression levels are significantly higher in malignant cells than in revertant cells (13). TCTP is shown to control tumorigenesis mainly through p53 degradation and subsequent inhibition of apoptosis (14). Targeting TCTP by inhibition or gene silencing promotes apoptosis in cancer cell lines and reduces tumor cell viability (33). TCTP knockdown improves treatment response to 5-fluorouracil and oxaliplatin in colon cancer cell lines (34).

While the potential of TCTP as a prognostic marker in colorectal cancer is promising, there are several challenges for the clinical translation of this marker. One challenge is the lack of standardization in the methods used to measure TCTP expression. Most studies have used immunohistochemistry to measure TCTP expression, but there is significant variability in the antibodies and scoring systems used. Standardization of these methods will be necessary to ensure that TCTP expression can be reliably measured and compared across

Table II. Median progression-free and overall survival in nuclear TCTP H-score subgroups.

	Progression-free survival			Overall survival		
		95% Confidence interval			95% Confidence interval	
Nuclear TCTP H-Score	Median	Lower bound	Upper bound	Median	Lower bound	Upper bound
Negative	7.700	5.852	9.548	22.200	16.069	28.331
Positive	5.533	3.238	7.829	13.233	10.155	16.311

TCTP, translationally controlled tumor protein.

Table III. Univariate Cox regression analysis for predicting progression-free and overall survival.

	PFS			OS		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age			0.682			0.606
≤64	1	-		1	-	
>64	1.105	0.685-1.782		1.134	0.703-1.828	
Sex			0.326			0.286
Male	1	-		1	-	
Female	1.284	0.779-2.117		1.301	0.802-2.111	
ECOG			0.109			0.012
0	1	-		1	-	
1	1.489	0.915-2.423		1.871	1.148-3.047	
G			0.311			0.006
2	1	-		1	-	
3	1.387	0.736-2.613		2.491	1.293-4.799	
RAS			0.485			0.002
Wild-type	1	-		1	-	
Mutant	1.184	0.737-1.900		2.113	1.306-3.420	
Primary tumor location			0.301			0.154
Left colon	1	-		1	-	
Right colon	1.287	0.798-2.075		1.422	0.877-2.305	
Stage groups at diagnosis			0.318			<0.001
Non-metastatic	1	-		1	-	
Metastatic	1.331	0.759-2.334		3.174	1.775-5.673	
TCTP-cytoplasmic expression			0.379			0.990
Low	1	-		1	-	
High	1.249	0.761-2.049		1.003	0.619-1.626	
TCTP-nuclear expression			0.026			0.009
Low	1	-		1	-	
High	1.797	1.073-3.010		1.995	1.189-3.348	

TCTP, translationally controlled tumor protein; ECOG, Eastern Cooperative Oncology Group.

studies. To the best of the authors' knowledge, most studies to date have been small and retrospective and there is a need for larger studies that include diverse patient populations that control for other prognostic factors.

The present research had several limitations. The main limitation was its retrospective nature. Selection bias was minimized by analyzing all consecutive patients with colon cancer within the prespecified period who met the eligibility

Table IV. Multivariate Cox regression analysis for predicting PFS and OS.

	PFS			OS		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Sex			0.456			0.024
Male	1	-		1	-	
Female	1.225	0.719-2.088		1.845	1.085-3.137	
G			0.290			0.003
2	1	-		1	-	
3	1.432	0.736-2.785		3.092	1.481-6.456	
RAS			0.809			0.009
Wild-type	1	-		1	-	
Mutant	1.063	0.646-1.750		2.050	1.196-3.512	
ECOG			0.097			0.043
0	1	-		1	-	
1	1.570	0.921-2.676		1.703	1.017-2.851	
Stage groups at diagnosis			0.853			0.005
Non-metastatic	1	-		1	-	
Metastatic	1.060	0.571-1.967		2.352	1.290-4.286	
TCTP nuclear expression			0.042			0.040
Low	1	-		1	-	
High	1.743	1.021-2.975		1.799	1.027-3.151	

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; TCTP, translationally controlled tumor protein.

criteria. However, information about more recently established prognostic and predictive markers such as the presence of BRAF mutations or MSI was unavailable. Thus, it was not possible to analyze possible associations between TCTP expression levels and routinely used prognostic markers in present clinical practice. Another possible limitation of the present study was the lack of concurrent p53 mutational status analysis.

While previous reports focus on the suppression of p53 by TCTP, it has been shown that TCTP mediates the process of tumor reversion in a pleiotropic manner (i.e., suppression of p53, acting as a transcription factor, regulation of translation and secretion of proteins and regulation of the cytoskeleton) (20). Other limitations of the present study include the small sample size and the single-center design of the study which did not allow for inclusion of a diverse patient population in terms of race and ethnicity. On the other hand, the long follow-up allowed for statistical analyses of survival outcomes.

In conclusion, the present study revealed that nuclear TCTP expression level is a potential prognostic marker for clinical outcomes in patients with colon cancer. A positive nuclear TCTP expression is associated with a higher tumor grade and worse PFS and OS. To the best of the authors' knowledge, this is the first study to demonstrate the value of nuclear TCTP expression as a prognostic marker for PFS and OS in patients with colon cancer. These findings may help to identify patients with more aggressive tumor biology and worse survival outcomes who are candidates for tailored intensified therapy.

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Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DS and ID performed the experiments and analyzed the data. DS, NC and MP wrote the manuscript. DS and NC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Medical University Varna Ethics Review Committee

(approval no. 34/13.11.2014). The patients provided written informed consent to participate.

Patient consent for publication

Not applicable.

Authors' information

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Competing interests

The authors declare that they have no competing interests.

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