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The expression of PRMT5 is associated with postoperative chemotherapeutic outcome in colon cancer

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Abstract

Background Postoperative chemotherapy is an essential treatment in locally advanced colon cancer, however, effective biomarkers for predicting patients who will benefit from this therapy are lacking. This study aims to explore the clinical value of protein arginine methyltransferase 5 (PRMT5) in guiding adjuvant chemotherapy in patients with colon cancer.

Methods PRMT5 expression was determined via immunohistochemistry (IHC) in tumor and paratumor samples from 199 colon cancer patients who underwent radical surgery. The correlation between PRMT5 expression and clinicopathological parameters, as well as clinical outcomes, was subsequently investigated.

Results The protein expression levels of PRMT5 were significantly elevated in colon cancer tissues compared to paratumor tissues ($P < 0.01$). However, the expression of PRMT5 in colon cancer did not show a significant association with various clinicopathological parameters, including sex, age, tumor location, histological differentiation, TNM stage, vascular invasion, or microsatellite status. Notably, a strong correlation was observed between PRMT5 expression and adjuvant therapeutic outcomes: patients with high PRMT5 expression exhibited a lower 5-year disease-free survival (DFS) rate compared to those with low PRMT5 expression within the chemotherapy group (50% vs. 67.2%, $P = 0.039$). In contrast, PRMT5 expression did not correlate with clinical outcomes in the non-chemotherapy group. Furthermore, multivariate analysis indicated that PRMT5 expression, along with N stage and microsatellite status, served as independent risk factors for 5-year DFS in patients undergoing adjuvant chemotherapy.

Conclusion This study highlights PRMT5 as a prognostic marker for adjuvant chemotherapy in patients with colon cancer. The findings suggest that PRMT5 expression may serve as an important predictor of therapeutic outcomes, providing valuable insights for clinical decision-making and personalized treatment strategies.

Keywords PRMT5, Colon cancer, Adjuvant chemotherapy

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Introduction

Colon cancer stands among the most frequently diagnosed and deadly digestive malignancies worldwide, with a notable upward trend in incidence over recent years [1, 2]. Surgery remains the principal treatment modality, whereas adjuvant chemotherapy assumes an additional role in mitigating the risk of recurrence and prolonging survival [3]. Owing to the restricted response rate to chemotherapy, individual adjuvant therapy strategies remain unfeasible in clinical practice. This underscores the critical need for predictive biomarkers to evaluate the potential benefits of adjuvant chemotherapy for patients, thereby enhancing the individualized chemotherapy [4].

PRMT5 is a type II arginine methyltransferase that catalyzes the symmetric dimethylation of arginine in target proteins [5], and plays a multifaceted role in DNA damage repair (DDR) and the maintenance of genome stability through epigenetic regulation, RNA processing, and posttranslational modifications (PTMs) of key DDR proteins. It catalyzes the symmetric dimethylation of histone arginine residues (e.g., H2AR3, H3R2, H3R8, and H4R3). This recruitment of reader proteins either activates or suppresses the transcription of DDR genes, such as KU70/80, RAD51, and BRCA1/2, and consequently facilitates homologous recombination (HR) and nonhomologous end joining (NHEJ) pathways [6, 7]. In RNA processing, PRMT5 guarantees splicing fidelity by methylating Sm proteins and regulates RNA m6A modification to stabilize DDR-related mRNAs, such as BRCA1, through the action of the RNA demethylase ALKBH5 [8, 9]. Additionally, the regulatory pathway employed by PRMT5 for genome stability is PTM, which can directly methylate DDR proteins, including p53, 53BP1, FEN1, and TDP1, increasing their stability, DNA-binding capacity, and repair function [10–13]. For instance, methylated 53BP1 facilitates NHEJ-mediated repair. In contrast, methylated FEN1 and TDP1 respectively enhance the efficiency of base excision repair (BER) and nucleotide excision repair (NER). Moreover, PRMT5 modulates transcription factors such as p65/RelA, HOXA9, and GLI1, regulating the DDR transcriptional programs and cell cycle checkpoints. By activating the Chk1 pathway through the methylation of Rad9, PRMT5 triggers cell cycle arrest, thus providing sufficient time for DNA repair. These mechanisms collectively enable PRMT5 to enhance DDR pathways. As a result, it contributes to tumor survival and chemotherapy resistance, clearly indicating its potential as a therapeutic target for making cancer cells more sensitive to DNA-damaging agents. Our previous studies demonstrated that PRMT5 modulated Fanconi anemia (FA) pathway genes, which are critical for interstrand crosslink repair. The inhibition of PRMT5 disrupts the function of the FA pathway, sensitizing cancer cells to DNA-damaging chemotherapies [14]. Furthermore, PRMT5 enhances the DNA damage response and promotes tumor chemoradiation resistance by increasing the transcription of RNF168, an E3 ubiquitin ligase that activates H2AX through ubiquitination and prevents its proteasomal degradation [15]. These findings highlight PRMT5 as a master regulator of genomic stability and a driver of chemoresistance.

In colorectal cancer (CRC), the overexpressiong of PRMT5 is correlated with poor prognosis and enhanced tumor progression [16–18]. Mechanistically, PRMT5 promotes CRC cell growth and EMT by activating the EGFR/Akt/GSK3β signaling cascade, which drives tumor proliferation and metastasis. Additionally, PRMT5 methylates SMAD4, a critical mediator of TGF-β signaling, thereby enhancing CRC metastasis. These findings underscore the role of PRMT5 in the pathogenesis of CRC and highlight its potential as a therapeutic target. Moreover, PRMT5 inhibitors have shown promise in preclinical models, demonstrating efficacy in sensitizing CRC cells to chemotherapy and reducing the tumor burden, with several drugs targeting PRMT5 currently in preclinical and clinical trials [10, 19, 20]. However, the relationship between PRMT5 and adjuvant therapeutic outcomes in patients with colon cancer remains unclear, and the value of PRMT5 in guiding postoperative treatment still needs to be illuminated.

Patients and methods

Patients

A total of 199 consecutive patients diagnosed with primary colorectal cancer who underwent radical surgical resection at Beijing Cancer Hospital from August 2006 to December 2012 were recruited retrospectively. Patients with familial adenomatous polyposis (FAP) or Lynch syndrome were excluded. Additionally, we excluded those with a history of prior chemotherapy or radiotherapy for colorectal cancer, individuals with synchronous malignancies, patients who had incomplete clinical or follow-up data, and those with severe comorbidities that could significantly impact treatment outcomes or survival. These exclusion criteria were implemented to ensure a homogeneous study population and minimize confounding factors. Adjuvant chemotherapy based on oxaliplatin and fluorouracil (FOLFOX) or capecitabine (CAPOX) was recommended for patients with stage III tumors and for patients with stage II tumors deemed at high risk for recurrence. High-risk criteria included the presence of cancer perforation, pT4N0 tumors with vascular embolization, and/or intestinal obstruction [21]. Adjuvant chemotherapy was administered in accordance with standard protocols. For FOLFOX, patients received oxaliplatin (85 mg/m^2) and leucovorin (400 mg/m^2) followed by fluorouracil (400 mg/m^2 bolus and 2400 mg/m^2 continuous infusion over 46–48 h) every two weeks

for six months. For CAPOX, patients received oxaliplatin (130 mg/m² on day 1) and capecitabine (1000 mg/m² twice daily for 14 days) every three weeks for six months. The selection of regimen was based on patient tolerance and physician discretion. Tumor staging was performed according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging system, which was the standard during the study period. Although the AJCC staging system has since been updated, the 6th edition criteria were consistently applied to all patients in this study. Adjuvant chemotherapy recommendations were founded on these staging criteria. In total, 100 patients with Stage III disease received chemotherapy, along with 27 high-risk patients with Stage II tumors. Postoperative follow-up was conducted meticulously, with patients assessed every three months for the first three years, every six months for the subsequent two years, and annually thereafter after five years. Tumor progression was monitored via serum carcinoembryonic antigen (CEA) levels, colonoscopy, chest radiography, and computed tomography. Patients who failed to complete follow-up assessments were excluded from the analysis. The demographic and clinical characteristics of the included patients have been summarized in the Table S1. All participants provided informed consent prior to treatment initiation, and the study protocol was approved by the ethics committee of Peking University Cancer Hospital (Resolution #: 20110225).

Immunohistochemistry and tissue microarray

PRMT5 expression was evaluated by immunohistochemistry (IHC) on formalin-fixed, paraffin-embedded (FFPE) tumor and matched paratumor tissues. Tissue microarrays (TMAs) were constructed as follows: Representative tumor and normal tissue regions were firstly identified on H&E-stained slides, and three 3-mm cores per sample were extracted using a manual tissue microarrayer (Quick-Ray, UT06, Japan). Cores were embedded in triplicate into recipient paraffin blocks, sectioned at 4 μm, and mounted on charged slides. Automated IHC was performed on the Leica Bond MAX system using a PRMT5-specific antibody (Cell Signaling, Cat# 79998, 1:500 dilution), with negative controls (primary antibody omitted) included for specificity validation [22]. The expression levels of PRMT5 were assessed via the immunoreactive score (IRS) system, which combines the staining intensity (0 = negative, 1 = weak, 2 = moderate, 3 = strong) with the percentage of positively stained cells (0 = < 5%, 1 = 5–25%, 2 = 25–50%, 3 = 50–75%, 4 = > 75%). The final IRS was calculated as the product of the intensity and proportion scores, with scores > 6 classified as high expression and scores ≤ 6 classified as low expression. Specificity was confirmed in negative controls, which were stained without primary antibody incubation. All samples were independently evaluated by two pathologists blinded to the clinical and research data.

The Cancer Genome Atlas (TCGA) data analysis

The expression and prognostic value of PRMT5 was analyzed using TCGA database based on RNA-seq data, via GEPIA2 portal (http://gepia2.cancer-pku.cn) [23]. The expression level of PRMT5 was evaluated by Expectation-Maximization (RSEM) values (log2-transformed), with which, the patients was stratified into high- and low-expression groups using the median as a cutoff value (median RSEM = 57.12); namely, tumors with expression level above the median were classified into high-expression group, while those below the median were classified into low-expression group.

Statistical analysis

Clinical data were analyzed via SPSS 25.0 (IBM Corp., Armonk, NY). Paired t tests were used to assess differences in PRMT5 expression between tumor and paratumor tissues. Associations between PRMT5 levels and clinicopathological features were examined via Pearson chi-square tests. Kaplan–Meier survival curves and log-rank tests were used to evaluate DFS and overall survival (OS). We performed multivariate Cox regression analysis (Wald backward method) to assess the independent prognostic value of PRMT5 expression and other clinical variables in terms of DFS. Statistical significance was set at a two-sided P value < 0.05, and the P value of variable removal was > 0.1 in the Cox regression model.

Results

Expression of PRMT5 in colon cancer patients in the TCGA dataset

To explore the expression level of PRMT5 and its importance in colon cancer, we analyzed TCGA colon cancer data via the RNA-seq database (Fig. 1). We found that the expression level of PRMT5 was significantly greater in tumor tissue than in paratumor tissue in colon cancer ($P < 0.01$) (Fig. 1A), which was independent of TNM stage (Fig. 1B) and long-term survival rate (Fig. 1C and D).

Protein expression of PRMT5 in colon cancer and its associations with clinicopathological variables

We then analyzed PRMT5 protein expression in tumor and paratumor tissues from 199 colon cancer patients via immunohistochemistry (IHC). The results demonstrated that PRMT5 expression was markedly higher in tumor tissue than in paratumor tissue ($P < 0.01$) (Fig. 2A). We analyzed the associations between PRMT5 expression and clinicopathological variables in patients and detected no significant associations between PRMT5 expression and clinicopathological parameters, including sex, age, tumor location, histological differentiation, T stage, N

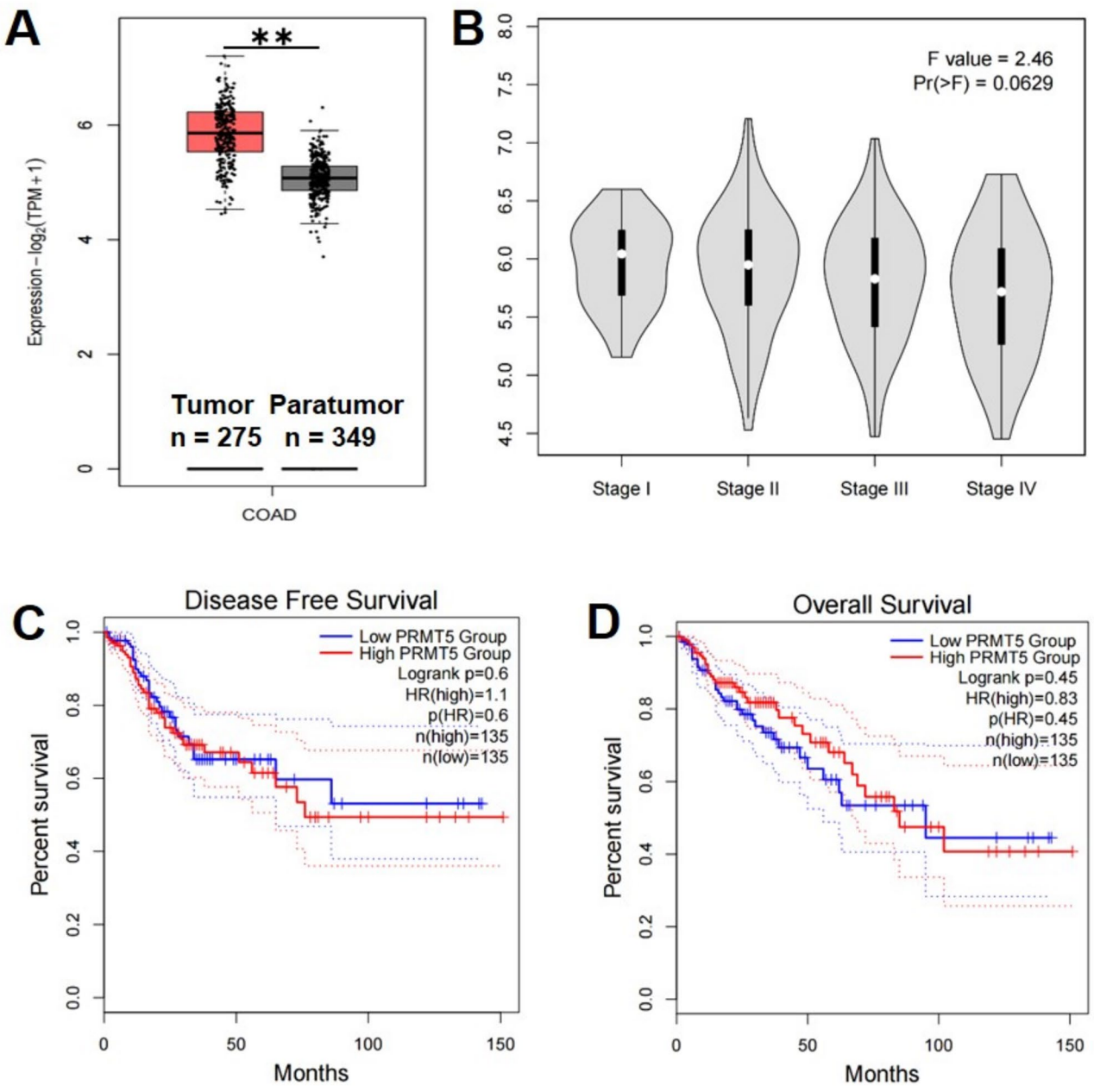

Fig. 1 Expression of PRMT5 in colon cancer in TCGA data via the GEPIA2 portal (Tang, Z. et al. *Nucleic Acids Res* 2019, https://doi.org/10.1093/nar/gkz430; http://gepia2.cancer-pku.cn). (**A**) The expression level of PRMT5 is significantly higher in tumor tissue than in paratumor tissue in colon cancer ($P < 0.01$). (**B**) The expression level of PRMT5 is independent of TNM stage. (**C**) and (**D**) The expression level of PRMT5 is independent of long-term DFS and OS (** $P < 0.01$)

stage, vascular invasion, or microsatellite instability (MSI) (Table 1). Survival analysis revealed no significant difference in DFS or OS between the high- and low-PRMT5 expression groups (Fig. 2B and C). However, when we focused on patients receiving adjuvant chemotherapy, high expression of PRMT5 was associated with a worse 5-year DFS (50% vs. 67.2%, $P = 0.039$), whereas this difference was not observed in patients not receiving adjuvant chemotherapy (87.9% vs. 80%, $P = 0.410$) (Fig. 2D and E). To identify the independent prognostic factors for cancer progression in patients undergoing chemotherapy, we performed multivariate analysis of 5-year DFS via a Cox proportional hazards regression model, which revealed that PRMT5, along with N stage and microsatellite status, was an independent prognostic indicator for adjuvant chemotherapeutic outcome (Table 2). Multivariate analysis revealed that high PRMT5 expression was associated

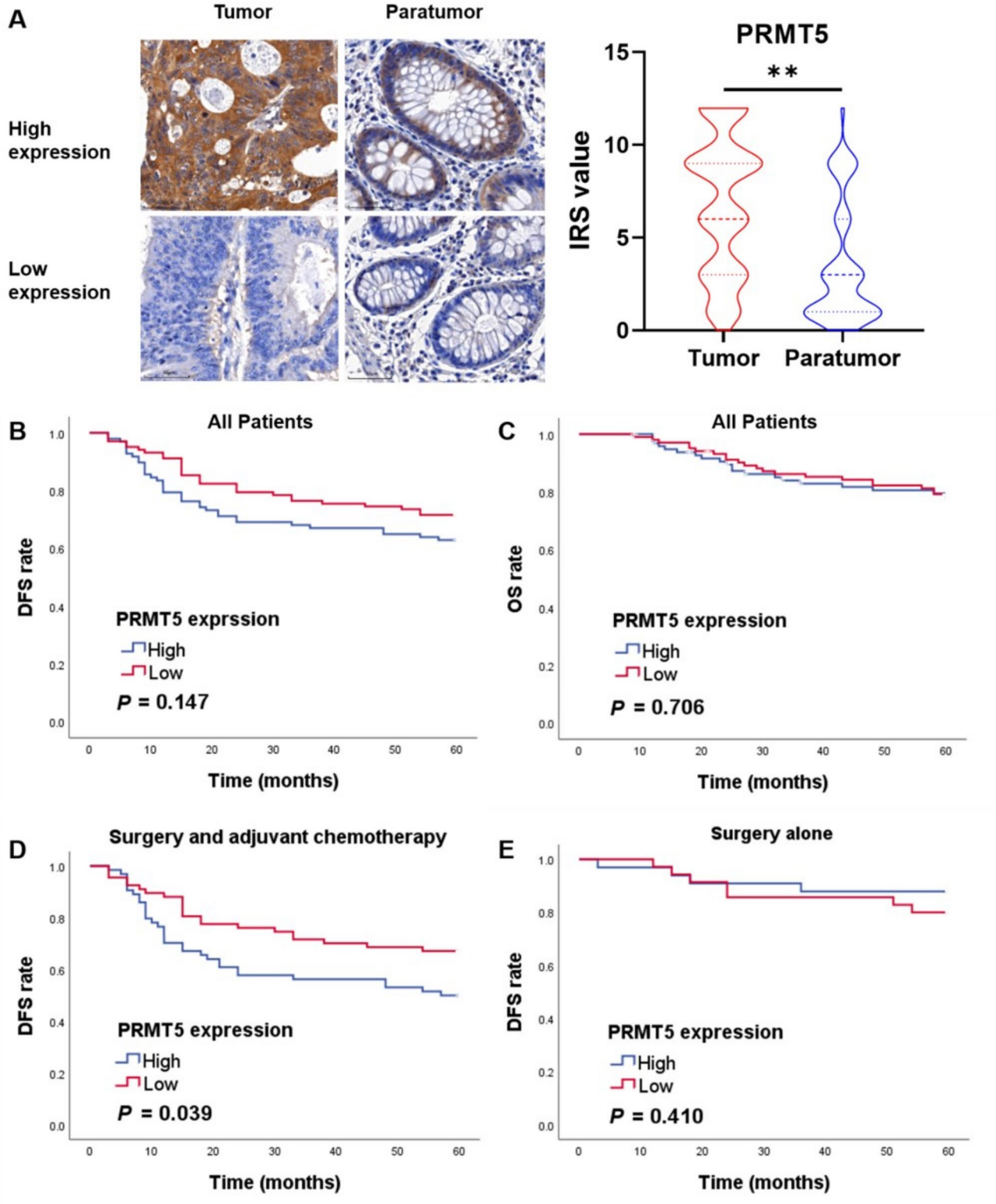

Fig. 2 (**A**) PRMT5 expression was markedly higher in tumor tissue than in paratumor tissue ($P < 0.01$). (**B**) and (**C**) There was no significant difference in disease-free survival (DFS) or overall survival (OS) between the high- and low-expression groups of PRMT5. (**D**) and (**E**) High-expression of PRMT5 expression was associated with a worse 5-year DFS (50% vs. 67.2%, $P = 0.039$) in the patients who received postoperative chemotherapy, while this difference was not observed in the patients without adjuvant chemotherapy (87.9% vs. 80%, $P = 0.410$) (** $P < 0.01$)

Table 1 The relationship between PRMT5 expression and various clinicopathological features

	PRMT5		*P* value
	High	Low	
Gender			
Male	49(50.5%)	58(56.9%)	0.369
Female	48(49.5%)	44(43.1%)	
Age			
≤ 60	30(30.9%)	29(28.4%)	0.7
> 60	67(69.1%)	73(71.6%)	
Tumor location			
Right	53(54.6%)	45(44.1%)	0.138
Left	44(45.4%)	57(55.9%)	
Histological differentiation			
Well	7(7.2%)	9(8.8%)	0.103
Moderate	85(87.6%)	79(77.5%)	
Poor	4(4.1%)	6(5.9%)	
Mucinous and signet-ring	1(1%)	8(7.8%)	
T stage			
T1-2	10(10.3%)	9(8.8%)	0.85
T3	72(74.2%)	81(79.4%)	
T4	15(15.5%)	12(11.8%)	
N stage			
N0	45(46.4%)	52(51%)	0.219
N1	25(25.8%)	32(31.4%)	
N2	27(27.8%)	18(17.6%)	
Vascular invasion			
Yes	24(24.7%)	18(17.6%)	0.22
No	73(75.3%)	84(82.4%)	
MSI			
Yes	15(15.5%)	9(8.8%)	0.151
No	82(84.5%)	93(91.2%)	

Table 2 The Cox proportional hazards regression model for 5-year DFS multivariate analysis (Wald backward method, $P < 0.1$ is identified as significant)

	HR	95% CI		*P* value
		Lower	Upper	
PRMT5 expression	0.621	0.356	1.085	0.094
N stage	2.061	1.352	3.140	0.001
MSI	0.487	0.228	1.0410	0.063
Tumor location	0.719	0.414	1.247	0.241
Histological differentiation	1.016	0.611	1.688	0.952
T stage	1.087	0.548	2.155	0.811
Vascular invasion	0.642	0.362	1.171	0.148

with poor 5-year DFS in patients receiving chemotherapy (HR = 0.62, 95% CI: 0.36–1.085, $P = 0.094$).

Discussion

As an essential form of posttranslational modification (PTM), protein arginine methylation has been identified as a significant regulatory mechanism of protein function [24]. Among the family of protein arginine methyltransferases, PRMT5 is classified as a type II protein methyltransferase, which catalyzes mono- and symmetric di-methylation of arginine residues in target proteins [25]. The evidence from various cancer types indicates that PRMT5 functions as an oncoprotein that is highly expressed in tumors, promoting cancer cell proliferation, metastasis and resistance to therapy [26–29]. Consequently, it has emerged as a valuable therapeutic target, with several ongoing clinical trials assessing the efficacy of its inhibitors [30, 31]. Postoperative chemotherapy plays a critical role in preventing tumor recurrence in patients with colon cancer [32]; however, the therapeutic benefits are often suboptimal due to low response rates and the associated toxicity of chemotherapy [33–35]. Although some prognostic factors are suggestive for clinical decisions on the regimen selection [36], there remains a dearth of effective biomarkers for identifying patients who would benefit from adjuvant therapy [37]. Our researches have demonstrated that PRMT5 expression is correlated with chemosensitivity across multiple cancer types [14, 15]. In this study, we demonstrated that PRMT5 serves as an independent predictor of adjuvant chemotherapy outcomes in patients with colon cancer, independent of TNM stage and other clinicopathological parameters, potentially contributing to personalized postoperative treatment strategies. The underlying mechanism is potentially attributed to the role of PRMT5 in enhancing DNA damage repair via multiple pathways, involving its ability to enhance DNA damage repair through the methylation of key proteins such as 53BP1 and H2AX [11, 38]. This mechanism allows cancer cells to survive chemotherapy-induced DNA damage, leading to treatment resistance. Our findings align with those of previous studies showing that PRMT5 overexpression is associated with poor chemotherapeutic outcomes in various cancers, including breast and pancreatic cancer [24, 25]. In colon cancer, PRMT5 has been shown to promote metastasis and tumor progression through the TGF-β signaling and EGFR/Akt pathways. Consequently, high expression levels of PRMT5 may facilitate the repair of chemotherapy-induced DNA damage, leading to chemoresistance and subsequent treatment failure in the clinic. Further studies are needed to fully elucidate the molecular mechanisms by which PRMT5 influences chemotherapy sensitivity. Therapeutically, targeting PRMT5 may offer a novel strategy to overcome chemoresistance in colon cancer. Several PRMT5 inhibitors are currently in clinical trials, showing promise in reducing tumor growth and enhancing chemosensitivity [30, 31]. Our study supports the potential of PRMT5 as a therapeutic target, particularly in patients with high PRMT5 expression who may benefit from combination therapies involving PRMT5 inhibitors and conventional chemotherapy. Variables such as tumor location, histological differentiation grade, T stage, and vascular invasion did

not significantly impact the 5-year disease-free survival (DFS) of chemotherapy-treated patients. Although these variables were significant in the univariate analysis, their prognostic value may be context-dependent and influenced by stronger predictive factors such as PRMT5 expression, N stage, and MSI (microsatellite instability) status. These findings suggest that PRMT5 expression, along with N stage and microsatellite status, is a more robust predictor of chemotherapeutic outcome. The integration of PRMT5 testing into existing clinical decision-making processes could enhance prognostic accuracy and guide personalized treatment strategies. For example, PRMT5 expression can be combined with other biomarkers such as microsatellite instability (MSI) and KRAS mutation status to stratify patients into distinct risk groups. Patients with high PRMT5 expression and MSI-high status may benefit from immune checkpoint inhibitors, while those with high PRMT5 expression and KRAS mutations may require more aggressive chemotherapy regimens. Future studies should explore the synergistic effects of combining PRMT5 with other biomarkers to refine prognostic models and optimize treatment outcomes.

Limitations

Although our study provides valuable insights into the role of PRMT5 in chemotherapy sensitivity, several limitations should be acknowledged. First, the single-center design may have introduced selection bias because of our institution-specific patient demographics and treatment regimens. This may limit the generalizability of our findings to the broader population. Second, despite the use of strict inclusion and exclusion criteria, potential patient selection bias may still exist. Third, the borderline significance of PRMT5 according to multivariate analysis ($P = 0.094$) suggests that although PRMT5 has potential as a prognostic marker, its predictive value still needs to be verified in a larger cohort. One limitation is that this study did not use an independent cohort for external validation, which is critical would be critical tofo confirming the robustness and generalizability of our results. Fourth, our data were collected from 2006 to 2012 and were retrospective, which may limit the applicability of our findings to current clinical practice, since chemotherapy regimens and diagnostic criteria have changed during the past decade. However, the molecular mechanisms of PRMT5 in chemotherapy resistance, especially its involvement in DNA repair pathways, remain relevant. Finally, the lack of functional experiments, such as gene knockdown or overexpression, limits our ability to establish a causal relationship between PRMT5 and chemotherapy resistance. Therefore, we are actively seeking collaboration with other institutions to obtain larger and more diverse multicenter studies to validate our results and reduce these biases. Alternatively, future studies should include in vitro and in vivo experiments to verify how PRMT5 regulates chemotherapy resistance, particularly through its involvement in DNA repair pathways. For example, the knockdown or inhibition of PRMT5 in colon cancer cell lines could be used to assess changes in chemotherapy sensitivity, while overexpression studies could further elucidate its role in promoting treatment resistance.

Conclusion

This study identified PRMT5 as a potential predictor of postoperative chemotherapy outcomes in patients with colon cancer, indicating its clinical relevance. However, further mechanistic insights, cohort validation, and clearer statistical interpretations are needed to confirm these findings and explore the therapeutic potential of targeting PRMT5 in colon cancer.

Abbreviations

PRMT5	Protein arginine methyltransferase 5
IHC	Immunohistochemistry
DFS	Disease-free survival
DDR	DNA damage repair
PTM	Posttranslational modification
HR	Homologous recombination
NHEJ	Nonhomologous end joining
BER	Base excision repair
NER	Nucleotide excision repair
FA	Fanconi anemia
CRC	Colorectal cancer
FAP	Familial adenomatous polyposis
AJCC	American Joint Committee on Cancer
CEA	Carcinoembryonic antigen
FFPE	Formalin-fixed, paraffin-embedded
TMAs	Tissue microarrays
IRS	Immunoreactive score
TCGA	The Cancer Genome Atlas
RSEM	Expectation-Maximization
OS	Overall survival
MSI	Microsatellite instability

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14161-5.

Supplementary Material 1

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Author contributions

Changzheng Du and Yifan Peng designed the study and supervise the program. Huan Li and Hongfang Yin reviewed pathological slides. Lu Lu, Feng Wang, Xiaowen Sun and Yanyun Chang collected patients' information and clinical data. Yuling Sheng and Qi Liu provided technical support. Changzheng Du reviewed and corrected manuscript. All authors participated in writing the manuscript. Lu Lu and Huan Li contributed equally to this work and share first authorship.

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Data availability
The datasets analysed during the current study are available in the TCGA repository at https://portal.gdc.cancer.gov/ and GEPIA2 portal at http://gepia2.cancer-pku.cn with accession numbers ENSG00000100462.15. The data generated and analyzed in this study could be requested from the corresponding author.

Declarations

Ethics approval and consent to participate
All participants provided informed consent prior to treatment initiation, and the study protocol was approved by the ethics committee of Peking University Cancer Hospital (Resolution #: 20110225) and conformed to the ethical standards for medical research involving human subjects, as laid out in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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