RESEARCH ARTICLE

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The Prognostic and Predictive Value of METTL3 in Metastatic Colorectal Cancer

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Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer-related deaths worldwide, and its incidence continues to rise. The prognosis remains poor, especially for patients with metastatic disease. Methyltransferase-like 3 (METTL3) is the primary catalytic enzyme in the N6-methyladenosine (m6A) methyltransferase system. METTL3 plays a dual role, acting as either an oncogene or a tumor suppressor depending on the cancer type. It also plays a significant role in the response to treatment. However, its specific function in CRC remains unclear. **Methods:** A prospective cohort of sixty patients with metastatic colorectal cancer (mCRC) was enrolled at the South Egypt Cancer Institute (SECI). METTL3 expression was evaluated using immunohistochemistry (IHC). This study aimed to investigate METTL3 expression in CRC and its association with clinicopathological features and clinical outcomes in patients treated with oxaliplatin (OX)- and 5-fluorouracil (5-FU)-containing regimens. **Results:** Our findings revealed that elevated METTL3 expression correlated with increased synchronous metastasis and a greater number of metastatic sites. In addition, elevated METTL3 was associated with increased lymphovascular invasion, perineural invasion, a non-brisk immune response, and greater tumor depth. Notably, right-sided tumors exhibited significantly higher METTL3 expression compared to those on the left side and in the rectum. Finally, METTL3 overexpression was associated with a lower response rate to OXA-based therapy, as well as shorter progression-free survival (PFS) and overall survival (OS), all with $p < 0.05$. **Conclusion:** METTL3 may serve as both a prognostic and predictive biomarker in colorectal cancer (CRC).

Keywords: Methyltransferase-like 3- Prognostic biomarker- IHC- Metastasis- Oxaliplatin

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Introduction

CRC is the third most frequently diagnosed cancer worldwide and the second leading cause of cancer-related mortality. In 2022, around 1.9 million people were diagnosed with CRC [1]. In Egypt, CRC ranks 7th and constitutes 3.9% of all cancer diagnoses. It ranks fifth among women and seventh among men, according to GLOBOCAN 2022 [2]. The overall mortality rate of CRC is 60%, which represents the second leading cause of cancer-related death. In recent decades, the mortality rates of CRC patients have declined, largely attributable to earlier diagnosis and the novel therapeutic strategies [3].The relative five-year survival rate is 90% for CRC diagnosed at an early stage compared with only 13% for advanced stages [4]. Variation in CRC patients' prognosis underscores the urgent need for new molecular biomarkers to complement the traditional TNM staging system for clinical practice [5, 6].

RNA modification pathways as epigenetic mechanisms cause cancer growth and can be effectively targeted for cancer therapy [7].

N6-methyladenosine (m6A) is the most prevalent and widespread ribonucleic acid (RNA) alteration. The m6A modification process in mammals is dynamically reversible and regulated by writers, erasers, and readers [8]. Recent research indicates that m6A modification is crucial for tissue development, stem cell formation, differentiation, circadian clock regulation, and tumorigenesis [9, 10]. In tumors, *METTL3*, as a pivotal m6A methyltransferase writer, remains a topic of contention. Specific research indicated that *METTL3* exhibited an oncogenic function in myeloid leukemia, liver cancer, breast cancer, glioblastoma, bladder cancer, and lung cancer. Other investigations suggested that *METTL3* is a tumor suppressor in renal cell carcinoma and glioblastoma [11]. These investigations indicated that *METTL3*'s influence on tumorigenesis may be specific to certain tumors. Some studies have shown that *METTL3* expression is consistently elevated in CRC, is associated with poor clinicopathological features, and poor survival [12]. However, other studies, such as those by Deng et al.,

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have reported that positive *METTL3* expression inhibits cell proliferation, migration, and invasion in CRC [13].

OXA with a 5-FU regimen is universally considered one of the most effective treatments for mCRC, particularly when combined with target therapy. Although the antitumor effect of OXA is limited because of the development of drug resistance [14].

Through m6A modification, *METTL3* plays a crucial role in regulating the tumor microenvironment dynamics in CRC, thereby facilitating tumor progression and affecting its response to treatment via distinct pathways [15]. To this aim, we investigate the prognostic and predictive value of *METTL3* in mCRC.

Materials and Methods

Study design and patients: A prospective cohort study included 60 patients with mCRC who presented to the Medical Oncology Department, SECI, Assiut University, between June 2022 and December 2024. All patients underwent comprehensive clinical, laboratory, and pathological evaluations, including Rat Sarcoma (RAS) and V-Raf Murine Sarcoma Viral Oncogene Homolog B (*BRAF*) testing. *METTL3* expression was assessed using IHC. Chest, abdominal, and pelvic computed tomography (CT) scans were performed at baseline and after every three treatment cycles to evaluate response.

Inclusion criteria comprised individuals aged > 18 years, of both genders, who were diagnosed with mCRC and received oxaliplatin-based first-line therapy (CAPOX or FOLFOX), with disease-free survival > 1 year for metachronous cases who received oxaliplatin in an adjuvant setting. Exclusion criteria: patients with concomitant double malignancies, severe comorbidities, pregnancy or lactation, poor performance status, or age <18

METTL3 IHC

The hematoxylin and eosin-stained slides were initially reviewed, and the tumors were classified using the American Joint Committee on Cancer (AJCC) staging system [16]. The expression of *METTL3* antibody by IHC on available Formalin-Fixed, Paraffin-Embedded (FFPE) specimens.

Steps were done according to the protocol of USA Bioss Inc. for IHC. The FFPE tissue sections were cut in 3-micron thick, and mounted on positively charged glass slides. Sections were deparaffinized and rehydrated through graded alcohols to distilled water. Slides were immersed in unsealed plastic containers filled with enough antigen retrieval solution (Tris EDTA) in a heated water bath at 90 °C for 45 minutes [17].

Primary rabbit polyclonal anti-*METTL3* receptor antibody (Catalog bs-2987R, Bioss Inc., USA) at 1:200 overnight at 4˚C. Universal staining kit "Polyo stain 2 step detection system goat Anti-mouse/rabbit HRP, peroxidase quench, DAP-kit (Ready-To-Use)" (Protaqs® Quartett, catalog # DK-211-015, BIOCYC Gesellschaft für Bio-technologies, Kosmetik und Recycling verfahren mbH & Co. Entwicklung KG, Am Mühlenberg 11, 14476 Potsdam, Germany) was applied at room temperature for one hour following the manufacturer's instructions. After three washes with PBS, the staining was visualized using 3, 3'-diaminobenzidine tetrahydrochloride, followed by counterstaining with Mayer's haematoxylin.

Evaluation of METTL3 expression

The immune-stained slides were examined at a lower magnification (X10) to identify the positive cells and calculate the percentage of positive cells by two independent, blinded pathologists. The immunoreactivity in the nucleocytoplasmic of tumor cells was assessed, where staining intensity was classified as (0) Absent, (1) Weak, (2) Moderate, and (3) Strong. The H-score was derived by multiplying the staining intensity by the percentage of positive cells for all cases. The H-score values ranged from 0 to 270, as shown in Table 1, the median of *METTL3* expression used as the ideal cut-off value in our investigation, which similar to many studies, with low expression defined as *METTL3* levels below the median and high expression as levels equal to or beyond the median [18]. So, our cases were classified as low *METTL3* expression (<100) and high *METTL3* expression (≥100).

Statistical analysis

The data were collected, tabulated, and statistically analyzed using SPSS (Statistical Package for the Social Sciences; SPSS Inc., ARMONK, NY, USA) version 26. For comparing categorical variables, the Chi-square (χ^2) test was applied, and when expected cell counts were below 5, Fisher's Exact test was utilized. The exact version of the McNemar test was used in cases of small sample sizes to evaluate paired nominal data. PFS (defined as the time from treatment initiation (1st line) until the first documented tumor progression or death) and OS (defined as the duration from the date of diagnosis to the time of death from any cause or last follow up) were assessed by using the Kaplan-Meier method, with differences assessed via the log-rank test. Cox proportional hazards regression was used to identify factors influencing PFS and OS among metastatic CRC cases. The p-value is significant at <0.05.

Results

Pattern of METTL3 expression

Immunostaining results showed that *METTL3* expression was high in 53.3% of specimens, while 46.7% of specimens showed low *METTL3* expression, as shown in Figure 1. The tissue of CRC had higher expression than the adjacent tissue (which were negative or lower), with a p-value of 0.03, as shown in Table 1.

Relation between METTL3 expression and clinicopathological parameters

*A substantial link existed between *METTL3* expression and increased synchronous metastasis, yielding a significant p-value of 0.001. The right side exhibited a significantly higher *METTL3* expression than the left side and rectum, with a P value of 0.048. Furthermore, elevated *METTL3* expression correlated with a greater

Table 1. *METTL3* Expression Pattern, Comparison between Tumor and Normal Tissue

METTL3 expression		%	
Low (H-score <100)	28	46.7	
High (≥100)	32	53.3	
Min. – Max.	0.0 – 270.0		
Mean ± SD.	114.5 ± 94.07		
Median (IQR)	100.0 (20.0 – 210.0)		
	Low	High	P value
Tumor tissue (n=60)	28	32	0.3
Adjacent normal tissue (n= 6)	9	0	

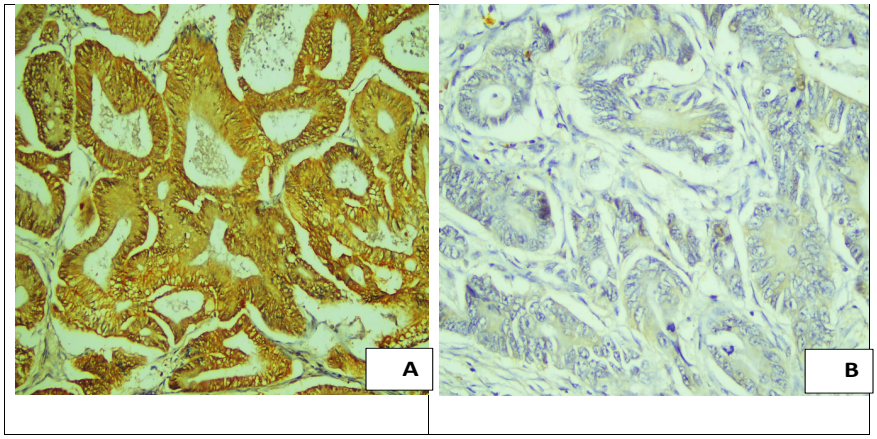


Figure 1. Immunohistochemical Expression of *METTL3*: (A) high (B) low, X400

number of metastatic sites and distant LN metastasis, yielding a statistically significant p-value of 0.001 and 0.017, respectively. Also, increased *METTL3* expression was associated with heightened lympho-vascular invasion and peri-neural invasion (p = 0.035 for both) as well as tumor depth (p = 0.00013) and non-brisk immune response (p = 0.0017). No association was found between *METTL3* and KRAS, BRAF, type of tumor or its grade, nodal involvement, or serum levels of CEA and CA19.9. Also, no correlation was found between *METTL3* and patients' age, sex, and family history, as shown in Table 2.

*There was a significant correlation between high *METTL3* and the occurrence of obstruction, with a p-value of 0.02, as shown in Table 2.

Treatment response according to *METTL3* expression: High expression of *METTL3* was associated with less response (CR and PR) with P value <0.001, and a Disease control rate (CR, PR, SD) with P value <0.001 for oxaliplatin based therapy (Figure 2).

The relation between METTL3 expression and survival

The median overall survival (OS) for all patients was 19.1 months. In patients with high *METTL3* expression, the median OS was 11.9 months, while it was not reached in those with low expression (P < 0.001). The median PFS for all patients was 7.3 months; it was 4.4 months in the high-expression group, whereas it was not reached in the low-expression group (P = 0.001), as shown in Figure 3, respectively. Multivariate analysis showed that *METTL3* was an independent prognostic marker for OS and PFS (Table 3).

Discussion

CRC is the third most common cancer worldwide and the second leading cause of death. It also ranks among cancers with high fatality rates. This poses a major risk to patient health [19]. mCRC accounts for 20% of new CRC cases, with about 80% of these cases being inoperable. The disease has complex signaling pathways. Its cause involves specific genetic and epigenetic changes. These changes lead to distinct tumor behaviors, treatment outcomes, and survival rates [20].

METTL3 is an enzyme encoded by the *METTL3* gene. It plays a crucial role in methylating internal adenosine residues in eukaryotic mRNAs. This forms m6A, a key RNA methylation modification. m6A is critical for epigenetic regulation in human diseases [21]. *METTL3* is involved in several biological processes related to cancer. These include tumor initiation, cancer cell proliferation, invasion, migration, metabolism, and drug resistance [22]. Limited reports exist about the potential of *METTL3* as a biomarker for CRC.

Consequently, this study aimed to investigate the association between *METTL3* expression, the clinicopathological features, survival outcomes, and treatment response. our results showed that most patients in this study exhibited high-risk pathological features, consistent with those of Yaeger et al. [23].

In our study, we found that *METTL3* expression was

Table 2. Correlation between *METTL3* Expression and Clinicopathological Parameters (n=60).

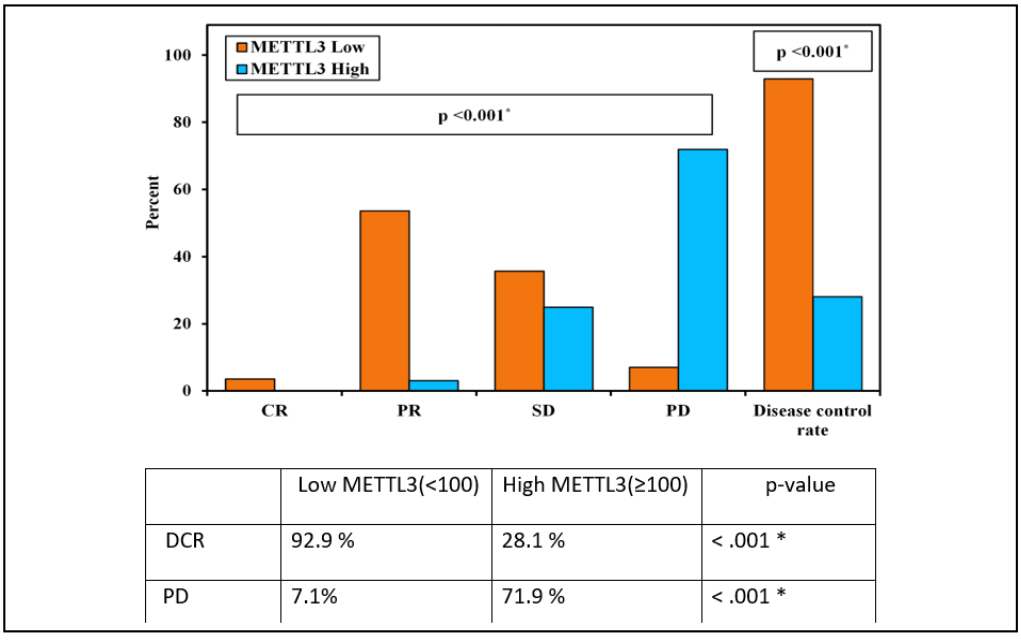
	METTL3				P
	Low (H score <100) (n = 28)		High (H score≥ 100) (n = 32)		
	No.	%	No.	%	
Sidedness					
Right	7	25.0	18	56.3	0.048*
Left	11	39.3	8	25.0	
Rectum	10	35.7	6	18.8	
Grade of tumor					
G1	6	21.4	13	40.6	0.125
G2	10	35.7	5	15.6	
G3	12	42.9	14	43.8	
Type					
Adenocarcinoma	22	78.6	24	75.0	0.744
Other	6	21.4	8	25.0	
Status of metastases					
Metachronous	22	78.6	12	37.5	0.001*
Synchronous	6	21.4	20	62.5	
Number of metastases					
Low (≤2)	23	82.1	12	37.5	<0.001*
High (>2)	5	17.9	20	62.5	
Metastatic sites					
Distant LN	3	10.7	12	37.5	0.017*
Deposit	11	39.3	14	43.8	0.726
Ascites	5	17.9	11	34.4	0.149
Lung	3	10.7	9	28.1	0.093
Bone	7	25.0	8	25.0	1.000
Liver	13	46.4	22	68.8	0.080
CEA					
Normal	9	32.1	15	46.9	0.245
High	19	67.9	17	53.1	
CA19.9					
Normal	12	42.9	18	56.3	0.301
High	16	57.1	14	43.8	
KRAS					
Mutated	14	50.0	12	37.5	0.330
Wild	14	50.0	20	62.5	
BRAF					.60
Mutated	15	53.5	15	46.9	
Wild	13	46.5	17	53.1	
T					
T1	4	14.2	0	0	.00013*
T2	10	35.7	4	12.5	
T3	2	7.1	19	59.3	
T4	12	43	9	28.2	
N (regional)					
N0	12	42.9	9	28.1	.233
N positive	16	57.1	23	71.9	
LVI					
Yes	9	32.1	19	59.4	.035*
No	19	67.9	13	40.6	

Table 2. Continued

	METTL3				P
	Low (H score <100) (n = 28)		High (H score≥ 100) (n = 32)		
	No.	%	No.	%	
TR deposit					
No	12	42.9	17	53.1	0.4427
Yes	16	57.1	15	46.9	
PNI					
Absent	19	67.9	13	40.6	0.035 *
Present	9	32.1	19	59	
Immune response					
Non brisk	8	28.6	22	68.8	0.0017*
Brisk	20	71.4	10	31.2	
Age					
<=49	19	31.7	21	35	1
>49	10	16.6	10	16.6	
Sex					0.292
Male	18	30	11	18.4	
Female	14	23.3	17	28.3	
Family history of CRC					0.56
Yes	17	28.3	16	26.7	
No	11	18.3	16	26.7	
Complications related to CRC					
Obstruction	4	14.3	14	43.7	0.02
Perforation	7	25	8	25	0.93
Bleeding	6	21.4	4	12.5	0.35

higher in CRC tissues than in adjacent tissues. This result supports evidence from Li et al. [18] and Zhao et al. [24] because, *METTL3* promotes oncogene expression, suppresses tumor suppressor genes via m6A modification, and supports stem cell properties, CRC proliferation, and a pro-tumorigenic microenvironment key characteristics of cancer initiation.

Also, there was a statistically significant correlation between high expression of *METTL3* and a variety of adverse clinicopathological characteristics of CRC,



	Low METTL3(<100)	High METTL3(≥100)	p-value
DCR	92.9 %	28.1 %	< .001 *
PD	7.1%	71.9 %	< .001 *

CR= complete disease, PR =partial disease, SD= stationary disease, PD= progression, DCR = disease control rate (CR+PR+SD)

Figure 2. Correlation between *METTL3* Expression and Response to Treatment

Table 3. Univariate and Multivariate COX Regression Analysis

(a): COX regression analysis for OS

	Univariate			
	P	HR (LL – UL 95% CI)	P	HR (LL – UL 95% CI)
Regimen				
Folfox	0.731	1.135 (0.550 – 2.344)		
Capox		1.000		
KRAS				
Mutated	0.396	1.409 (0.638 – 3.110)		
Wild		1.000		
METTL3				
Low (<100)		1.000		1.000
High (≥100)	<0.001*	3.4 (1.003 – 4.133)	<0.001*	2.068 (1.388 – 3.476)
Status of disease				
Metachronous		1.000		1.000
Synchronous	0.013*	2.494 (1.214 – 5.121)	0.567	1.258 (0.573 – 2.758)
Number of metastases				
Low (≤2)		1.000		1.000
High (>2)	0.026*	2.276 (1.106 – 4.683)	0.919	1.042 (0.469 – 2.313)
Sidedness				
Left/ Rectum		1		1
Right	0.038*	1.5 (1.248 – 2.962)	0.209	1.03 (1.020 – 1.352)
LVI				
Yes	0.03*	2.27(1.106 – 3.683)	0.919	1.199 (1.286 – 2.019)
No		1.000		1.00
Immune response				
Non brisky		1.000		1.00
Brisky	0.020*	0.275 (0.093 – 0.816)	0.20	0.21 (0.020 – 2.30)
Sex				
Male		1.00		
Female	.8	1.789 (1.706 – 3.970)		
Age				
<= 49		0.762 (0.389 – 1.493)		
>49	0.428	1.00		

(b): COX regression for PFS.

	Univariate		Multivariate	
	P	HR (LL – UL 95% CI)	P	HR (LL – UL 95% CI)
Regimen				
Capox		1.000		
Folfox	0.675	0.835 (0.360 – 1.937)		
KRAS				
Mutated	0.906	1.049 (0.476 – 2.312)		
Wild		1.000		
METTL3				
Low (<100)		1.000		1.000
High (≥100)	<0.001*	6. 9(4.528 – 9.044)	<0.001 *	3.487 (2.803 – 6.804)
Status of cases				
Metachronous		1.000		1.000
Synchronous	0.013*	2.400 (1.202 – 4.791)	0.775	1.140 (0.466 – 2.788)

Table 3. Continued

(b): COX regression for PFS.

	Univariate		Multivariate	
	P	HR (LL – UL 95% CI)	P	HR (LL – UL 95% CI)
Number of metastases				
Low (≤2)		1.000		1.000
High (>2)	0.021*	2.991 (1.740 – 4.151)	0.154	1.959 (0.777 – 4.937)
Sidedness				
Right	0.299	1.518 (0.691 – 3.335)		
Left/ Rectum		1.000		
LVI				
Yes	0.314	1.815 (0.568 – 2.795)		
No		1.000		
Sex				
Male		1.00		
Female	.540	0.771 (0.336 – 1.769)		
Age				
>49		1.00		
<= 49	.246	0.545 (0.039 – 7.699)		
Immune response				
Non-brisky		1.00		
Brisky	.654	0.545 (0.039 – 7.699)		

including lympho-vascular, perineural invasion, tumor depth, and distant LNs involvement, with P values of .035, .035, .00013, .017, respectively. This was matched with Li et al. [18] and pan et al. [25], which support the role of *METTL3* in tumor invasion and systemic dissemination. Additionally, high *METTL3* expression was significantly associated with obstruction (p = 0.02), likely linked to larger tumor size.

However, no significant correlation was found between METTLE3 expression and regional node involvement or TR deposits. Furthermore, higher expression of *METTL3* in this study was significantly associated with non-brisk immune response, with a p-value of .0017. Similar to our findings, Guo et al. found that *METTL3* may play essential roles in modulating tumor immune response, especially T-lymphocytes in tumor-infiltrating lymphocytes, by its effect on basic helix-loop-helix 41(BHLHE41) protein, which is involved in immune cell signaling. So, high *METTL3* expression antagonizes the antitumor immune response and permits the tumor cells to escape from the immune system, resulting in tumor progression [26].

In this study, no significant connection was found between *METTL3* and KRAS, BRAF, Although KRAS/ BRAF mutations drive MAPK signaling in CRC, *METTL3* has been shown to activate parallel oncogenic pathways that may converge on similar downstream signaling networks which found with Sun et al [7]. No significant correlation between *METTL3* and CEA, CA19.9, absence of correlation in our study may reflect the independent biological roles of *METTL3* and CEA, rather than a lack of clinical relevance. Additionally, no statistical association was found between *METTL3* expression and demographic characteristics. These include age, sex, and family history, consistent with a study by Li et al. [18].

Our investigation revealed higher *METTL3* expression on the right side than on the left side or rectum. This finding is consistent with those of Missiaglia et al. [27] and Xiu et al. [28], who linked the right side to a poorer prognosis and distinct molecular characteristics, possibly due to biological and environmental factors and to delayed clinical manifestation. No direct studies have compared *METTL3* expression with CRC sidedness.

Furthermore, *METTL3* upregulation in our study was associated with a greater number of metastatic sites (p = 0.001). High *METTL3* expression was also significantly associated with more synchronous metastasis (p = 0.001), suggesting a relationship with more aggressive tumor biology [29].

Overexpressed *METTL3* was also associated with shorter survival (OS, PFS) and was an independent prognostic marker, consistent with Tang et al. [30], Wang et al. [31], and Pan et al. [32].

All of this is explained by *METTL3*'s role in tumor progression and metastasis through various mechanisms. These include regulation of epithelial-mesenchymal transition, oncogene activation, downregulation of tumor suppressor genes, and activation of specific signaling pathways linked to CRC [33]. *METTL3* also promotes miRNA maturation by interacting with the microprocessor protein DGCR8. This reduces PTEN levels and ultimately promotes cancer proliferation [34, 35]. *METTL3* inhibition can also induce cancer cell apoptosis by regulating the expression of apoptosis-related genes in an m6A-dependent manner [36, 37]. It also plays a role in angiogenesis. Yao et al. [38], who found that microvessel density was significantly higher in tumor tissues with high

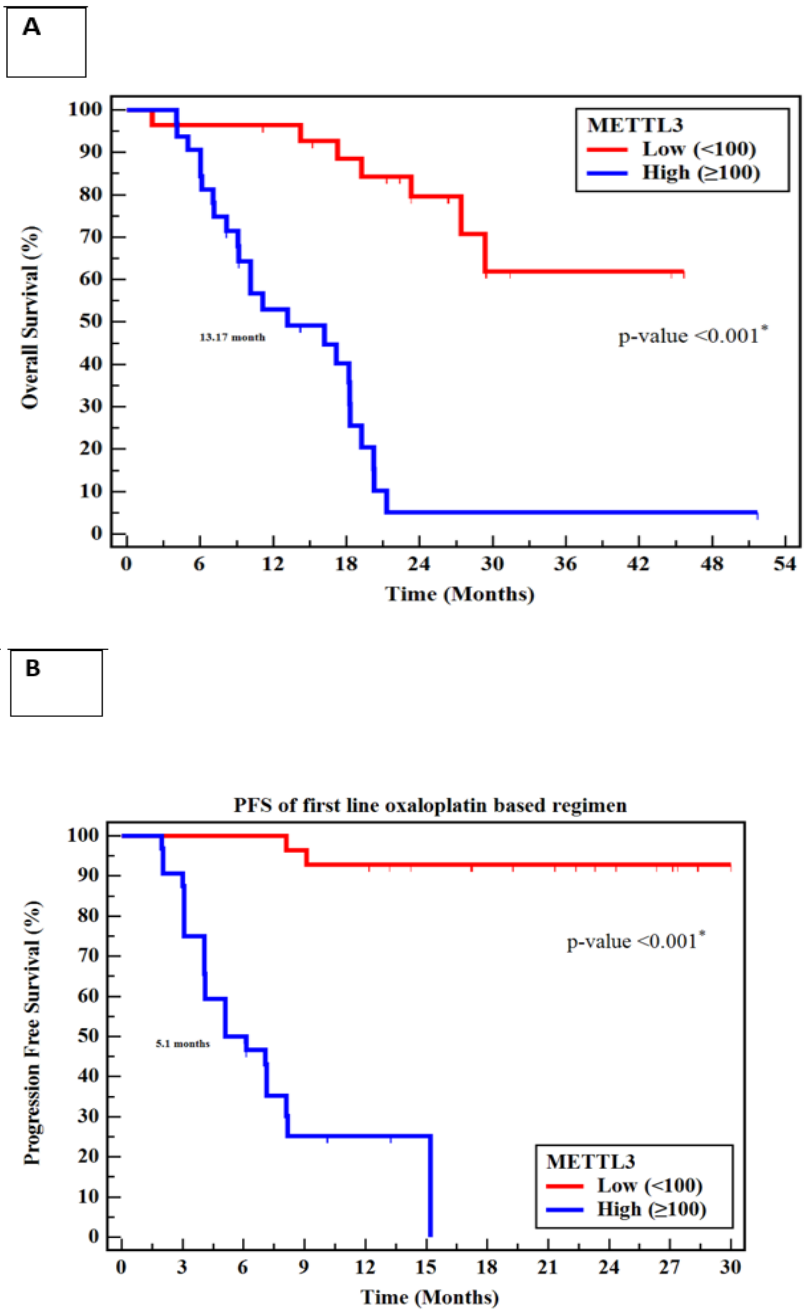


Figure 3. Patient's Survival According to *METTL3* Expression: A) OS, B) PFS.

METTL3 expression than in those with low expression.

However, our findings disagreed with Deng et al. [13], who reported that *METTL3* suppresses CRC cell proliferation, migration, and invasion via p38/ERK signaling. These contradictory conclusions may be due to differences in modification sites, various m6A-binding writers, and multiple downstream targets activated by *METTL3* in the cell.

A crossover study showed similar efficacy of FOLFOX and FOLFIRI in mCRC, with comparable response and survival after switching at progression [39]. However, many patients with metastatic disease exhibit varying levels of treatment resistance, demonstrating notable interindividual variability in therapeutic efficacy. These observations highlight the importance of identifying biomarkers to select the chemotherapy regimen most likely to provide a response.

This study found that *METTL3* overexpression was associated with a lower response to OXA-based therapy (P = .001), consistent with Huo et al. [40]. This is because *METTL3* mediates resistance of CRC to chemotherapy, for example, by enhancing m6A modification of Sec62 mRNA and increasing its affinity for β-catenin in the Wnt pathway [41].

In conclusion, our findings revealed that elevated METTl3 expression, as determined by IHC, was associated with lower response, survival in mCRC patients treated with oxaliplatin-based regimens as the first-line treatment. Moreover, *METTL3* IHC expression may serve as an independent prognostic factor in metastatic CRC,

suggesting that it may be a promising target for therapeutic approaches in CRC and other malignancies.

Limitations: Limitations, particularly related to the sample size, which was constrained by the limited availability of *METTL3* antibody kits and restricted financial support. Therefore, we recommend further research on *METTL3* expression in mCRC patients using larger sample sizes. In addition, *METTL3* expression should be evaluated using alternative methods, as real-time polymerase chain reaction (RT-PCR) which could provide additional insights, it would require more resources and might not be feasible within the study's constraints because of funding limitations.

Author Contribution Statement

Marwa Saber and Fatma Zakaria were responsible for analyzing and interpreting all data. Sally Salah conducted the histopathological examination of samples. Hanan El-Tyb and Ashraf Zedan played key roles in drafting the manuscript.

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Funding statement

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Approval

This study was submitted in partial fulfillment of the requirements for the M.D. degree in Medical Oncology by Marwa Saber, Assistant Lecturer of Medical Oncology, SECI.

Ethical Approval

Regarding ethical considerations, this study was approved by the Institutional Ethical Committee of South Egypt Cancer Institute, and its Institutional Review Board (IRB) approval number is IORG0006563-623. The drugs were supplied either by treatment decisions at state expense or by health insurance

Data Availability

For direct communication with the corresponding author, with approval from the co-authors.

Study Registration

This study was not a clinical trial, guideline, or meta-analysis and was therefore not registered in any clinical trial or systematic review registry.

Conflict of Interest

No conflicts of interest to disclose

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63. https://doi.org/10.3322/caac.21834
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L. GLOBOCAN 2022: Egypt fact sheet. Global Cancer Observatory; 2024. Available from: https://gcoiarcwhoint.
3. Vatandoust S, Price TJ, Karapetis CS. Colorectal cancer: Metastases to a single organ. World J Gastroenterol. 2015;21(41):11767. https://doi.org/10.3748/wjg.v21.i41.11767
4. Sawicki T, Ruszkowska M, Danielewicz A, Niedźwiedzka E, Arłukowicz T, Przybyłowicz KE. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Cancers. 2021;13(9):2025. https://doi.org/10.3390/cancers13092025
5. Dienstmann R, Salazar R, Tabernero J. Molecular subtypes and the evolution of treatment decisions in metastatic colorectal cancer. Am Soc Clin Oncol Educ Book. 2018;38(38):231-8. https://doi.org/10.1200/EDBK_200929
6. Ogunwobi OO, Mahmood F, Akingboye A. Biomarkers in colorectal cancer: current research and future prospects. Int J Mol Sci. 2020;21(15):5311. https://doi.org/10.3390/ijms21155311
7. Sun Y, Gong W, Zhang S. *METTL3* promotes colorectal cancer progression through activating JAK1/STAT3 signaling pathway. Cell Death Dis. 2023;14(11):765. https://doi.org/10.1038/s41419-023-06287-w
8. Liu X, Liu L, Dong Z, Li J, Yu Y, Chen X, et al. Expression patterns and prognostic value of m6A-related genes in colorectal cancer. Am J Transl Res. 2019;11(7):3972.
9. Liu K, Gao Y, Gan K, Wu Y, Xu B, Zhang L, et al. Prognostic roles of N6-methyladenosine *METTL3* in different cancers: a system review and meta-analysis. Cancer Control. 2021;28:1073274821997455. https://doi.org/10.1177/1073274821997455
10. Li T, Hu PS, Zuo Z, Lin JF, Li X, Wu QN, et al. *METTL3* facilitates tumor progression via an m6A-IGF2BP2-dependent mechanism in colorectal carcinoma. Molecular cancer. 2019;18(1):112. https://doi.org/10.1186/s12943-019-1038-7
11. Alkhizzi B, Khan MI, Al-Ghafari A, Choudhry H. Upregulation of circular and linear *METTL3* and USP3 in colorectal cancer. Oncol Lett. 2021;22(3):675. https://doi.org/10.3892/ol.2021.12936
12. Zhang J, Cheng X, Wang J, Huang Y, Yuan J, Guo D. Gene signature and prognostic merit of M6a regulators in colorectal cancer. Exp Biol Med (Maywood). 2020;245(15):1344-54. https://doi.org/10.1177/1535370220936145
13. Deng R, Cheng Y, Ye S, Zhang J, Huang R, Li P, et al. m6A methyltransferase *METTL3* suppresses colorectal cancer proliferation and migration through p38/ERK pathways. Onco Targets Ther. 2019:4391-402. https://doi.org/10.2147/OTT.S201052
14. Amatu A, Mauri G, Tosi F, Bencardino K, Bonazzina E, Gori V, et al. Efficacy of retreatment with oxaliplatin-based regimens in metastatic colorectal cancer patients: the RETROX-CRC retrospective study. Cancers. 2022;14(5):1197. https://doi.org/10.3390/cancers14051197
15. Su W, Che L, Liao W, Huang H. The RNA m6A writer *METTL3* in tumor microenvironment: emerging roles and therapeutic implications. Front Immunol. 2024;15:1335774. https://doi.org/10.3389/fimmu.2024.1335774
16. Weiser MR. AJCC 8th edition: colorectal cancer. Ann Surg Oncol. 2018;25(6):1454-5. https://doi.org/10.1245/s10434-018-6462-1
17. Dettmeyer RB. Forensic histopathology: fundamentals and perspectives. Springer; 2018 May. https://doi.org/10.1007/978-3-319-77997-3
18. Li H, Liu Z, Wang H. Expression and clinical

significance of *METTL3* in colorectal cancer. Medicine. 2023;102(37):e34658. https://doi.org/10.1097/MD.0000000000034658
19. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1). https://doi.org/10.3322/caac.21763
20. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken J, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386-422. https://doi.org/10.1093/annonc/mdw235
21. Xu Y, Song M, Hong Z, Chen W, Zhang Q, Zhou J, et al. The N6-methyladenosine *METTL3* regulates tumorigenesis and glycolysis by mediating m6A methylation of the tumor suppressor LATS1 in breast cancer. J Exp Clin Cancer Res. 2023;42(1):10. https://doi.org/10.1186/s13046-022-02581-1
22. Zheng W, Dong X, Zhao Y, Wang S, Jiang H, Zhang M, et al. Multiple functions and mechanisms underlying the role of *METTL3* in human cancers. Front Oncol. 2019;9:1403. https://doi.org/10.3389/fonc.2019.01403
23. Yaeger R, Chatila WK, Lipsyc MD, Hechtman JF, Cercek A, Sanchez-Vega F, et al. Clinical sequencing defines the genomic landscape of metastatic colorectal cancer. Cancer cell. 2018;33(1):125-36. e3. https://doi.org/10.1016/j.ccell.2017.12.004
24. Zhao BS, Roundtree IA, He C. Post-transcriptional gene regulation by mRNA modifications. Nat Rev Mol Cell Biol. 2017;18(1):31-42. https://doi.org/10.1038/nrm.2016.132
25. Pan J, Liu F, Xiao X, Xu R, Dai L, Zhu M, et al. *METTL3* promotes colorectal carcinoma progression by regulating the m6A–CRB3–Hippo axis. J Exp Clin Cancer Res. 2022;41(1):19. https://doi.org/10.1186/s13046-021-02227-8.
26. Guo Y, Heng Y, Chen H, Huang Q, Wu C, Tao L, et al. Prognostic values of *METTL3* and its roles in Tumor Immune Microenvironment in Pan-cancer. J Clin Med. 2022;12(1):155. https://doi.org/10.3390/jcm12010155
27. Missiaglia E, Jacobs B, D'ario G, Di Narzo A, Soneson C, Budinska E, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol. 2014;25(10):1995-2001. https://doi.org/10.1093/annonc/mdu275
28. Xiu J, Brody J, Parrish C, Samuels M, Cordes L, Michel E, et al. Comparison of molecular and genomic features of primary colorectal carcinomas and their matched metastases. J Clin Oncol. 2017;35((15_suppl)):3501-9.
29. Colloca G, Venturino A, Guarneri D. Different variables predict the outcome of patients with synchronous versus metachronous metastases of colorectal cancer. Clin Transl Oncol. 2020;22(8):1399-406. https://doi.org/10.1007/s12094-019-02277-7
30. Tang J, Huang M, Peng H, He J, Gong L, Yang M, et al. *METTL3*-mediated Hsa_circ_0000390 downregulation enhances the proliferation, migration, and invasion of colorectal cancer cells by increasing Notch1 expression. Hum Cell. 2023;36(2):703-11. https://doi.org/10.1007/s13577-022-00835-w
31. Wang Y, Hong Z, Song J, Zhong P, Lin L. *METTL3* promotes drug resistance to oxaliplatin in gastric cancer cells through DNA repair pathway. Front Pharmacol. 2023;14:1257410. https://doi.org/10.3389/fphar.2023.1257410
32. Pan J, Huang T, Deng Z, Zou C. Roles and therapeutic implications of m6A modification in cancer immunotherapy. Front Immunol. 2023;14:1132601. https://doi.org/10.3389/fimmu.2023.1132601
33. Liao J-N, Ni W-J, Wu P-H, Yang Y-D, Yang Y, Long W, et al. Switching from messenger RNAs to noncoding RNAs, *METTL3* is a novel colorectal cancer diagnosis and treatment target. World J Gastrointest Oncol. 2025;17(5):104076. https://doi.org/10.4251/wjgo.v17.i5.104076
34. Yue B, Song C, Yang L, Cui R, Cheng X, Zhang Z, et al. *METTL3*-mediated N6-methyladenosine modification is critical for epithelial-mesenchymal transition and metastasis of gastric cancer. Mol cancer. 2019;18(1):142. https://doi.org/10.1186/s12943-019-1065-4
35. Alarcón CR, Goodarzi H, Lee H, Liu X, Tavazoie S, Tavazoie SF. HNRNPA2B1 is a mediator of m6A-dependent nuclear RNA processing events. Cell. 2015;162(6):1299-308. https://doi.org/10.1016/j.cell.2015.08.011
36. Lin YT, Wu KJ. Epigenetic regulation of epithelial-mesenchymal transition: focusing on hypoxia and TGF-β signaling. J Biomed Sci. 2020;27(1):39. https://doi.org/10.1186/s12929-020-00632-3
37. Ouyang D, Hong T, Fu M, Li Y, Zeng L, Chen Q, et al. *METTL3* depletion contributes to tumour progression and drug resistance via N6 methyladenosine-dependent mechanism in HR+ HER2—breast cancer. Breast Cancer Res. 2023;25(1):19. https://doi.org/10.1186/s13058-022-01598-w
38. Yao M-D, Jiang Q, Ma Y, Liu C, Zhu C-Y, Sun Y-N, et al. Role of *METTL3*-dependent N6-methyladenosine mRNA modification in the promotion of angiogenesis. Mol Ther. 2020;28(10):2191-202. https://doi.org/10.1016/j.ymthe.2020.07.022
39. Neugut AI, Lin A, Raab GT, Hillyer GC, Keller D, O'Neil DS, et al. FOLFOX and FOLFIRI use in stage IV colon cancer: analysis of SEER-medicare data. Clin Colorectal Cancer. 2019;18(2):133-40. https://doi.org/10.1016/j.clcc.2019.01.005
40. Huo M, Gao Z, Wang G, Hou Z, Zheng J. Huaier promotes sensitivity of colorectal cancer to oxaliplatin by inhibiting *METTL3* to regulate the Wnt/β-catenin signaling pathway. Oncol Rep. 2024;53(1):7. https://doi.org/10.3892/or.2024.8840
41. Liu Y, Leslie PL, Zhang Y. Life and death decision-making by p53 and implications for cancer immunotherapy. Trends Cancer. 2021;7(3):226-39. https://doi.org/10.1016/j.trecan.2020.10.005