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Assessment of Mismatch Repair Gene Expression in Colorectal Carcinoma: A Two-Year Single-Center Study

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ABSTRACT

Background:*Mismatch repair MMR deficiency is a crucial biomarker in colorectal carcinoma (CRC) with the diagnosis, prognosis, and treatment significance of the MMR deficiency. MMR deficiency testing has become universally recommended to allow for Lynch syndrome screening and for the identification of the candidates for immune checkpoint inhibitor therapy. This study aims to evaluate the incidence of MMR protein expression in Iraqi patients with colorectal carcinoma and study their association with clinicopathological parameters.* ***Methods:*** *The retrospective cross-sectional study consisted of 34 patients histopathologically confirmed with primary colorectal carcinoma and these patients underwent surgical resection between January 2024 to December 2025 in Al-Warith International Cancer Institute, Karbala, Iraq. The immunohistochemistry expression for MLH1, PMS2, MSH2, and MSH6 genes were assessed using formalin-fixed, paraffin-embedded tissue sections. The correlation between the MMR and clinicopathological factors was analyzed using Fisher's exact test or Fisher-Freeman-Halton exact test, as appropriate. Results: dMMR protein expression was identified in 4 out of 34 patients (11.8%), whereas 30 out of 34 patients (88.2%) showed proficient MMR expression. The most frequent MMR protein deficiency pattern was the MLH1/PMS2 deficiency, while the second most frequent was the MSH2/MSH6 deficiency, and only 1 out of 34 patients had MSH6 deficiency alone. There was a statistically significant correlation between dMMR expression and the location of the tumor (P = 0.009) and tumor grade (P = 0.035). No correlation was found between MMR protein expression and age, sex, cancer staging, histological type or lymph node involvement. No statistically significant correlation was observed with age, sex, tumor staging, histological type, or lymph node involvement.* ***Conclusion:*** *The incidence of dMMR in the studied Iraqi population was comparable to that proposed in earlier regional and international studies. Despite the existence of a relationship between the site of the tumor and its grade, it is necessary to mention that these findings should be taken into account with reservation due to the small number of participants and need for further validation.*

Keywords: Colorectal carcinoma, Mismatch repair (MMR), Gene expression, Microsatellite instability (MSI), Immunohistochemistry, Biomarkers, Tumor pathology

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INTRODUCTION

Colorectal carcinoma (CRC) is one of the three most prevalent tumor kinds worldwide. In 2020, the number of recorded cases was roughly 1.9 million. CRC commonly affects those 65 to 74 years of age. It ranks as the second most common contributor to tumor-related mortalities [1]. Only 5–10% of colorectal carcinomas are thought to be inherited, but

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incidental colon cancers tend to be more prevalent. Hereditary nonpolyposis colorectal cancer (HNPCC), a highly prevalent inherited cancer of the colon, is caused by microsatellite instability (MMR) (DNA mismatch repair genes) [2,3]. Mismatch repair proteins are nuclear kinases that are essential for detecting and correcting mistakes, remove insertion-deletion circuits and base-base disparities that arise in multiply cells during DNA replication process [4]. At least five distinct MMR proteins, including MSH2, MLH1, MSH6, PMS1, and PMS2, are needed to accomplish this. MMR gene mutation or silencing is demonstrated by molecular research, however, analyses using immunohistochemistry reveal whether gene expression of proteins is present or not [5]. Changes in the span of neutral, repeating microsatellite motifs across the entire genome are the main contributors of microsatellite instability (MSI) [6,7].

Colorectal cancers (CRCs) who exhibit inefficient mismatch repair (dMMR) along with elevated microsatellite instability (MSI-H) constitute a distinct subset of malignancies. Microsatellite stable (MSS) and competent mismatch repair (pMMR) CRCs have different genetic, clinical and pathological features than MSI-H/dMMR CRCs [8]. Because MSI-H CRC has certain clinical characteristics (being younger age, right-sided placement, mucinous or signet ring morphology, and heavy lymphocytic infiltration), cautious assessment of tumor histological features may assist in recognize them in alongside with IHC identification of MMR protein. This is despite the fact that the PCR-mediated amplification method of microsatellite cycles is still the premier method for detecting MSI, but it is not relevant in habitual histopathology clinics in our nation due to financial issues [7]. Therapeutic responses for MSI-H/dMMR and pMMR/MSS CRCs are varying due to their distinct an etiology, clinical and pathological features [9].

Given that MSI-H/dMMR CRCs tend to be more immunogenic and respond more effectively to immune therapy than pMMR/MSS CRCs, this is particularly relevant for immune checkpoint blocking [10–12]. Numerous clinical trials assessing the benefits of neoadjuvant immunotherapy in individuals with initial stages of disease have been initiated as a result of the discovery that MSI-H/dMMR may be a biochemical indicator for the effectiveness of immune therapy for those with colorectal cancer [13]. Numerous ongoing studies are also looking into the effectiveness of immunotherapy when combined with complementary therapies (such as chemotherapeutic agents and radiation) [14–17].

Neoadjuvant immunotherapy, either by itself or in conjunction with other treatment modalities, may offer patients with early-stage colorectal cancer (CRC), particularly those with MSI-H/dMMR CRC, novel approaches to therapy [18]. Microsatellite instability (MSI) and mismatch repair (MMR) detection rates in medical settings are still insufficient, particularly among populations at greatest risk, in spite of the significance of MSI-H/dMMR and pMMR/MSS state in therapeutic decisions [19,20]. With deficient MSI and MMR essays many patients with MSI-H/dMMR CRC may prohibited from being identified as candidates for immunotherapy [21,22]. Failing to differentiate both MSI-H/dMMR and pMMR/MSS CRCs could also result in disparities in CRC diagnostic and predictive properties due to variations in their epidemiological, genetic, morphological and histological aspects [23]. This study aims to assess the incidence of mismatch repair proteins (MMR) expression in patients with colorectal carcinoma in Karbala province and their relation to the clinicopathological parameters as age, sex, histological subtypes, T stages, grades, location of the tumor and lymph-nodes involvement.

MATERIALS AND METHODS

The cross-sectional retrospective study involved 34 consecutive eligible patients diagnosed with primary colorectal carcinoma by histopathology and operated on during the period from January 2024 to December 2025 at Al-Warith International Cancer Institute in Karbala, Iraq. Even though the duration of this study was for two years, the patients involved in this study were those fulfilling all the predefined inclusion criteria including complete clinicopathological information, availability of adequate formalin fixed paraffin embedded tissues and no neoadjuvant therapy prior to

surgery. The histopathological diagnosis of all cases was confirmed by two pathologists. Five 5 µm-thick slices were extracted from paraffin embedded tissue blocks, all of them have been examined with IHC for MMR proteins, while the first had been treated with hematoxylin and eosin stain.

For immunohistochemical analysis of Mismatch repair proteins, four monoclonal antibodies were used to detect MMR proteins [MSH6 (Clone: EP49), MSH2 (Clone: RED2), MLH1 (Clone: GM011) and PMS2(EP51)) Rabbit Monoclonal Antibodies-Pathnsitu Biotechnologies] expression on tissue sections according to CAP regulations, any nuclear staining, whether evenly or unevenly distributed, is regarded as "proficient no lack of expression", whereas just the total lack of nuclear staining is recognized as " deficient-loss of expression", assuming the internal checks are valid. [20] Whenever nuclear staining for the minimum of a single protein was absent, the tumor was classified as dMMR. Positive internal checks included cells from stromal tissues, lymphocytes, and nearby native colonic epithelium as seen in Fig.1A-E and Fig.2 [7]. accordingly, all cases then were classified as MMR proteins proficient or MMR proteins deficient and the percentage of each class was evaluated. Additionally, the percentage of immunohistochemical expression of each MMR protein (MSH6, MSH2, MLH1, and PMS2) was assessed separately for all cases.

Inclusion criteria:

Patients with histopathologically evaluated with primary colorectal carcinoma who underwent surgical resection between January 2024 to December 2025 were included in this study. Only those patients with complete clinical and pathological information and having adequate formalin-fixed paraffin-embedded tissues were considered for immunohistochemical staining.

Exclusion criteria:

In case of clinicopathological information was not available or incomplete, tissue blocks were unavailable or unsuitable for immunohistochemical examination, or the surgical samples were obtained after neoadjuvant chemotherapy or radiotherapy, the samples excluded from the study.

Statistical analyses: Statistical analyses of the data were done using IBM SPSS Statistics (Version 16; IBM Corporation, Armonk, New York, USA). Descriptive statistics for categorical variables are defined as frequency and percentage. Since only four patients were found with dMMR protein expression, many contingency tables had fewer than five as the expected cell count. Thus, Fisher's Exact Test was used for 2 × 2 contingency table while Fisher-Freeman-Halton Exact Test was used for contingency tables that exceed 2 × 2. All statistical tests were two-sided and statistical significance level was set at $P < 0.05$.

RESULTS

The current study involving 34 patients diagnosed with colorectal carcinoma. The mean age (47.9 ± 15.7 years) and a range of (13-71 years). Of all cases, there were 19 (55.9%) males and 15 (44.1%) females. All the patients were grouped into two categories, those younger than fifty years were 18 (52.9%) and those who are older forming 16 (47.1%). Concerning the location of the malignancy, most of the tumors were recto sigmoidal 27 (79.4%), 5 (14.7%) cases detected on the descending colon with 2 (5.8%) on the ascending part.

Regarding the histopathological type of malignant neoplasm, Mucinous adenocarcinoma was detected in 3 (8.8%) of total sample, while non mucinous type was seen in the majority of the cases 31 (91.2%). In the majority of cases the tumor invades the muscularis propria to the peri colorectal tissues (T3) 17 (50%) followed by those that invades through the visceral peritoneum (T4) 12 (35.3%), show no lymph node metastasis 14 (41.2%) followed by those with metastasis in 1-3 regional LN (N1) 13 (38.2%) and of intermediate grade (GII) 26 (76.5%). The clinic-pathological characteristics of the collected sample were presented in Table 1.

Table 1: The Clinic-Pathological Parameters of Patients with Colorectal Carcinoma.

Clinic-pathological parameters		Number	Percentage
Age	< 50	18	52.9%
	> 50	16	47.1%
Sex	Males	19	55.9%
	Females	15	44.1%
Location	Recto-sigmoid	27	79.4%
	Ascending colon	2	5.8%
	Descending colon	5	14.7%
Histological type	Mucinous AC*	3	8.8%
	Non mucinous AC*	31	91.2%
T* stage	T1	0	0%
	T2	5	14.7%
	T3	17	50%
	T4	12	35.3%
Tumor grades	G1 (well differentiated)	5	14.7%
	G2 (Moderately differentiated)	26	76.5%
	G3 (Poorly differentiated)	3	8.8%
LN involvement	N0	14	41.2%
	N1	13	38.2%
	N2	7	20.6%

AC*: adenocarcinoma, T*: tumor size

For the total cases, mismatch repair proteins expression was examined by immunohistochemistry and was detected to be proficient (nuclear staining, whether evenly or unevenly distributed) in 30 (88.2%) cases and deficient with total loss of nuclear staining in 4 (11.8%) cases. The rates of expression of each of four proteins MLH1, PMS2, MSH2 and MSH6 sequentially were as 32 (94.1%) proficient, 2 (5.9%) deficient for each of MLH1 and PMS2 with 33 (97.1%) proficient, 1 (2.9%) deficient for MSH2 and 32 (94.1%) proficient, 2 (5.9%) deficient for MSH6 as seen in Table 2.

Table 3 shows the relationships of the MMR protein expression with the clinical-pathological parameters of the patients with colorectal carcinoma. On the basis of exact Fisher/Fisher-Freeman-Halton tests, there were significant relationships between the lack of MMR proteins expression and tumor site (P = 0.0094) and tumor grade (P = 0.0351). Specifically, 3/4 dMMR cases (75%) were found in the descending colon. Similarly, out of the total four dMMR cases, 2 cases (50%) were Grade 1 (well-differentiated) tumors. However, there was no statistical significance between the MMR status and the variables including age (P = 0.105), sex (P = 0.613), histology (P = 1.000), T-stage (P = 1.000), or LN involvement (P = 0.829). The correlations of expression pattern of individual MMR proteins are shown in Table4. Concurrent loss of MLH1 and PMS2 was found in 2/4 dMMR cancers, and there was a statistically significant correlation between the expressions of MLH1 and PMS2 (P = 0.001). On the other hand, there were no statistically significant correlations between MLH1-deficiency and MSH2-deficiency (P = 0.8) or MSH6-deficiency (P = 0.7).

There was a statistically significant correlation between the MSH2 and MSH6 deficiency (P = 0.001), as both MSH2 and MSH6 deficient in one of the cancers. Overall, among the four dMMR tumors, two cases exhibited concurrent loss of MLH1/PMS2, one MSH2/MSH6 co-deficient, and one MSH6 deficient as indicated in Table 4.

Table 2: Immuno-Histochemical Expression of MMR Proteins in Colorectal Carcinoma.

MMR proteins		Number	Percentage
Total - MMR	Proficient	30	88.2%
	Deficient	4	11.8%
MLH1	Proficient	32	94.1%
	Deficient	2	5.9%
PMS2	Proficient	32	94.1%
	Deficient	2	5.9%
MSH2	Proficient	33	97.1%
	Deficient	1	2.9%
MSH6	Proficient	32	94.1%
	Deficient	2	5.9%

Table 3: Association between MMR proteins expression and clinicopathological features of the studied patients

Clinicopathological characteristic	Category	Proficient, n (%) (n = 30)	Deficient, n (%) (n = 4)	Original χ^2 P value	Exact P value*
Age	<50 years	14 (46.7)	4 (100.0)	0.040	0.105
	>50 years	16 (53.3)	0 (0.0)		
Sex	Male	16 (53.3)	3 (75.0)	0.400	0.613
	Female	14 (46.7)	1 (25.0)		
Tumor location	Rectosigmoid	26 (86.7)	1 (25.0)	0.004	**0.009**
	Ascending colon	2 (6.7)	0 (0.0)		
	Descending colon	2 (6.7)	3 (75.0)		
Histological type	Mucinous adenocarcinoma	3 (10.0)	0 (0.0)	0.500	1.000
	Non-mucinous adenocarcinoma	27 (90.0)	4 (100.0)		
T stage	T1	0 (0.0)	0 (0.0)	0.600	1.000
	T2	5 (16.7)	0 (0.0)		
	T3	15 (50.0)	2 (50.0)		
	T4	10 (33.3)	2 (50.0)		
Tumor grade	G1, well differentiated	3 (10.0)	2 (50.0)	0.030	**0.033**
	G2, moderately differentiated	25 (83.3)	1 (25.0)		
	G3, poorly differentiated	2 (6.7)	1 (25.0)		
Lymph node involvement	N0	13 (43.3)	1 (25.0)	0.700	0.821
	N1	11 (36.7)	2 (50.0)		
	N2	6 (20.0)	1 (25.0)		

*Exact p-values were calculated using Fisher's exact test for 2 × 2 tables and the Fisher–Freeman–Halton exact test for tables with more than two categories. Values in bold are statistically significant at $P < 0.05$.

Table 4: The Statistical Association Between MMR Proteins

MMR proteins		MLH1		P value
		Proficient	Deficient	
PMS2	Proficient	32	0	**0.001***
	Deficient	0	2	
MSH2	Proficient	31	2	0.8
	Deficient	1	0	
MSH6	Proficient	30	2	0.7
	Deficient	2	0	
		MSH2		**0.001***
		Proficient	Deficient	
MSH6	Proficient	32	0	
	Deficient	1	1	

*significant statistical relation, P-value <0.05

DISCUSSION

In the current study, expression of Mismatch Repair (MMR) proteins was evaluated in a cohort of Iraqi patients diagnosed with colorectal carcinoma, along with their correlation with clinicopathological parameters. Deficiency in MMR (dMMR) was noted in 11.8% of the samples, which is similar to the findings in previous studies from the Middle Eastern population and other populations [24]. There were significant correlations between dMMR and the location of the tumors and tumor grades but there were no correlations with age, gender, type of histology, T stages, or lymph nodes.

The mean age of the patients in the current study was 47.9 ± 15.7 years old, and more than half of the subjects were less than 50 years old. The mean age was lower compared to those data reported in Western countries where colorectal carcinoma typically occurs after 60 years of age [25,26]. Indeed, our findings were generally consistent with other findings in the Iraqi literature, as well as in other neighboring Middle Eastern countries [27,28]. However, since there was no significant association between the age of patients and the presence of dMMR using Fisher's Exact test, our results did not support an independent relationship between younger age and MMR deficiency in this cohort. There was also a predominance male frequency accounting 55.9% of the study subjects. This is consistent with previous regional and international studies as well as the recognized modest male predominance of colorectal carcinoma [29,30]. There was no statistically significant correlation found between the sex of the patients and their MMR status.

Most tumors of the current study were located in the rectosigmoid region, whereas a small number of patients had an ascending colonic tumor. This predominance of distal tumors was in line with some other publications from Iraq [31]and the nearby countries [32]. At the same time, there was a statistically significant association between the presence of dMMR and tumor location. Most cases of dMMR tumors were localized in the descending colon. These findings do not match the previous reported results in which the pathologists showed the majority of dMMR colorectal carcinomas are located on the right side [9,33]. Given that only four dMMR tumors were identified in the present cohort, this finding should be interpreted cautiously because the subgroup analysis is susceptible to random variation and limited statistical power.

Non-mucinous adenocarcinoma represented the predominant histological subtype in the present cohort, whereas mucinous adenocarcinoma accounted for only a small proportion of cases. Although mucinous histology has frequently been associated with dMMR tumors in previous studies [34], no significant association was identified in the present investigation. This finding may reflect the limited number of dMMR cases and should be interpreted cautiously. Most Tumors were classified as T3 or T4, suggesting that the majority of cases presented with advanced cancer [35]. Likewise, the majority of patients had regional lymph node involvement. These observations in parallel with previous studies in Iraq and other countries and probably result from late diagnosis of the cancer in most patients due to the lack of colorectal cancer screening programs [36–38]. However, T stage and lymph node involvement did not have any significant relation to MMR status.

The majority of tumors were moderately differentiated Grade2. Although the presence of dMMR had a statistically significant relationship with the tumor grading, this is inconsistent with many of previous studies where the presence of dMMR had a relationship with poorly differentiated tumors [39]. Because this correlation was based on only 4 dMMR tumors, it should be interpreted cautiously. This observed distribution may reflect random variation resulting from the limited sample size rather than a true biological difference. Therefore, validation in larger sample size is required.

Taken all together, the prevalence of dMMR observed in this study (11.8%) is similar to the frequency of about 10-15% that is seen for sporadic colorectal carcinoma globally and is in agreement with other studies conducted in Iraq and surrounding countries [40,41]. The commonest loss of proteins observed in this study involved MLH1/PMS2 and MSH2/MSH6 loss occurring together while one patient had loss of only MSH6. This is in line with the function of the heterodimers and with what was reported in earlier studies [42,43].

Identification of dMMR tumors from a clinical point of view is important due to the diagnosis, prognosis, and treatment significance of the MMR deficiency. MMR deficiency testing has become universally recommended to allow for Lynch syndrome screening and to identify patients who may benefit from immune check point inhibitor therapy. MMR testing in all patients with colorectal carcinoma has become widely suggested for Lynch syndrome screening as well as the determination of candidates for immune checkpoint inhibitor therapy. While molecular diagnosis of MSI was not possible in the current study, immunohistochemical analysis still represents an easily affordable test, especially in resource-poor regions.

LIMITATIONS

This study has several limitations. First, a relatively small sample size, especially small dMMR cases (n = 4), decreased statistical power and made difficult detection of any other potential clinicopathological correlations; second, this study was retrospective in one center that might influence generalizability of results for other populations; third, MMR status determination was based on immunohistochemistry alone, without molecular confirmation of MSI status. Fourth, due to unavailability of MLH1 promoter methylation analysis and germline genetic analysis it was impossible to differentiate between sporadic dMMR tumors and those related to Lynch syndrome. Thus, the present findings should be interpreted with caution and validated in larger sample size, multicenter studies with molecular biology analyses.

CONCLUSION

The current study showed that deficient MMR protein expression was found in a subset of Iraqi population patients with colorectal carcinoma and was significantly associated with tumor grade and location. However, these findings should be interpreted carefully because of the relatively small sample size, and limited number of dMMR cases. Larger multicenter studies with molecular MSI testing and genetic analyses are important to validate these observations and further characterize the

clinicopathological significance of MMR deficiency in the Iraqi population.

ETHICAL APPROVAL

The study was approved by the ethical committee from Al-Warith International Cancer Institute, Karbala, Iraq, with approval ethical# WICI-SUMS00324. The study adhered to the ethical principles of the Helsinki Declaration. As per the current study, since it is a retrospective study involving only the existing anonymous archived formalin fixed paraffin embedded tissue samples, the requirement for informed consent was waived by the IRB.

CONFLICT OF INTEREST

The authors declare that they have no competing interests

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This research received no external funding.

DATA AVAILABILITY

The data set that analyzed and generated through the study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

R.A.A.A.; study design, data analyses, conceptualization, histopathological examination, manuscript drafting. S.A.H.A.; slides staining, data collection. M.F.; pathological examination, data collection, data analyses. S.J.; manuscript revision, statistical analyses and supervision. All authors reviewed and approved the final version of the manuscript.

REFERENCES

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Translational Oncology. 2021. doi:10.1016/j.tranon.2021.101174
2. Mohymen NA, Hanon BM, Mahommod AS. The Correlation between Microsatellite Instability and the Features of Sporadic Colorectal Cancer in Sample of Iraqi Patients. JOURNAL OF ADVANCES IN BIOTECHNOLOGY. 2014;4(1). doi:10.24297/jbt.v4i1.1632
3. Faghani M, Fakhrieh Asl S, Mansour-Ghanaei F, Aminian K, Tarang A, Seighalani R, et al. The correlation between microsatellite instability and the features of sporadic colorectal cancer in the north part of iran. Gastroenterol Res Pract. 2012. doi:10.1155/2012/756263
4. Mohammed DS, Hasan IA. Evaluation of immunohistochemical expression of mismatch repair genes product in colorectal carcinoma and its correlation with clinicopathological parameters in a sample of Iraqi patients. Indian J Pathol Microbiol. 2025;68(3). doi:10.4103/ijpm.ijpm_383_24
5. Ashktorab H, Brim H, Al-Riyami M, Date A, Al-Mawaly K, Kashoub M, et al. Sporadic colon cancer: Mismatch repair immunohistochemistry and microsatellite instability in Omani subjects. Dig Dis Sci. 2008;53(10). doi:10.1007/s10620-007-0189-3
6. Vink-Börger E, den Bakker M, Voorham R, van Nederveen F, Nagtegaal I. Mismatch repair deficiency: how reliable is the two-antibody approach? A national real-life study. Histopathology. 2024;85(4). doi:10.1111/his.15236
7. Hashmi AA, Ali R, Hussain ZF, Faridi N, Khan EY, Bakar SMA, et al. Mismatch repair deficiency screening in colorectal carcinoma by a four-antibody immunohistochemical panel in Pakistani population and its correlation with histopathological parameters. World J Surg Oncol. 2017;15(1). doi:10.1186/s12957-017-1158-8
8. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite Instability Testing and Its Role in the Management of Colorectal Cancer. Current Treatment Options in Oncology. 2015. doi:10.1007/s11864-015-0348-2
9. Jin Z, Sinicrope FA. Prognostic and predictive values of mismatch repair deficiency in non-metastatic colorectal cancer. Cancers (Basel). 2021;13(2). doi:10.3390/cancers13020300
10. Manz SM, Losa M, Fritsch R, Scharl M. Efficacy and side effects of immune

checkpoint inhibitors in the treatment of colorectal cancer. Therapeutic Advances in Gastroenterology. 2021. doi:10.1177/17562848211002018
11. Fan A, Wang B, Wang X, Nie Y, Fan D, Zhao X, et al. Immunotherapy in colorectal cancer: Current achievements and future perspective. International Journal of Biological Sciences. 2021. doi:10.7150/IJBS.64077
12. Ooki A, Shinozaki E, Yamaguchi K. Immunotherapy in Colorectal Cancer: Current and Future Strategies. Journal of the Anus, Rectum and Colon. 2021. doi:10.23922/jarc.2020-064
13. Chalabi M, Fanchi LF, Dijkstra KK, Van den Berg JG, Aalbers AG, Sikorska K, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med. 2020;26(4). doi:10.1038/s41591-020-0805-8
14. George TJ, Yothers G, Hong TS, Russell MM, You YN, Parker W, et al. NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC)—First experimental arm (EA) initial results. Journal of Clinical Oncology. 2019;37(15_suppl). doi:10.1200/jco.2019.37.15_suppl.3505
15. Salvatore L, Bensi M, Pietrantonio F, Boccaccino A, Barbara C, Auriemma A, et al. Phase II study of preoperative (PREOP) chemoradiotherapy (CTRT) plus avelumab (AVE) in patients (PTS) with locally advanced rectal cancer (LARC): The AVANA Study. Annals of Oncology. 2019;30. doi:10.1093/annonc/mdz246.139
16. Salvatore L, Bensi M, Corallo S, Bergamo F, Pellegrini I, Rasola C, et al. Phase II study of preoperative (PREOP) chemoradiotherapy (CTRT) plus avelumab (AVE) in patients (PTS) with locally advanced rectal cancer (LARC): The AVANA study. Journal of Clinical Oncology. 2021;39(15_suppl). doi:10.1200/jco.2021.39.15_suppl.3511
17. Inamori K, Togashi Y, Bando H, Tsukada Y, Fukuoka S, Suzuki A, et al. Translational research of VOLTAGE-A: Efficacy predictors of preoperative chemoradiotherapy and consolidation nivolumab in patients with both microsatellite stable and microsatellite instability-high locally advanced rectal cancer. Journal of Clinical Oncology. 2021;39(3_suppl). doi:10.1200/jco.2021.39.3_suppl.100
18. Mei WJ, Mi M, Qian J, Xiao N, Yuan Y, Ding PR. Clinicopathological characteristics of high microsatellite instability/mismatch repair-deficient colorectal cancer: A narrative review. Frontiers in Immunology. 2022. doi:10.3389/fimmu.2022.1019582
19. Thiebault Q, Defossez G, Karayan-Tapon L, Ingrand P, Silvain C, Tougeron D. Analysis of factors influencing molecular testing at diagnostic of colorectal cancer. BMC Cancer. 2017;17(1). doi:10.1186/s12885-017-3759-6
20. Shaikh T, Handorf EA, Meyer JE, Hall MJ, Esnaola NF. Mismatch repair deficiency testing in patients with colorectal cancer and nonadherence to testing guidelines in young adults. JAMA Oncol. 2018;4(2). doi:10.1001/jamaoncol.2017.3580
21. André T, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Annals of Oncology. 2022;33(10). doi:10.1016/j.annonc.2022.06.008
22. Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. Journal of Clinical Oncology.

2018;36(8). doi:10.1200/JCO.2017.76.9901
23. Evrard C, Tachon G, Randrian V, Karayan-Tapon L, Tougeron D. Microsatellite instability: Diagnosis, heterogeneity, discordance, and clinical impact in colorectal cancer. Cancers. 2019. doi:10.3390/cancers11101567
24. Elsayed I, Geraghty R, Mekki SO, Mohamedani AA, Ahern S, Salim OEH, et al. Evaluating utility and feasibility of mismatch repair testing of colorectal cancer patients in a low-middle-income country. Sci Rep. 2022;12(1). doi:10.1038/s41598-022-14644-6
25. Walker B, Jani CT, Liu W, Punjwani S, Kareff S, Ceglowski P, et al. Does a "Western Lifestyle" Confer a Higher Burden of Colorectal Cancer? A Comparison of EU15+ Countries versus Global Trends between 1990 and 2019. Cancers (Basel). 2024;16(12). doi:10.3390/cancers16122277
26. Marcellinaro R, Spoletini D, Grieco M, Avella P, Cappuccio M, Troiano R, et al. Colorectal Cancer: Current Updates and Future Perspectives. Journal of Clinical Medicine. 2024. doi:10.3390/jcm13010040
27. Farhad RM, Saleh ES, Alsammarraie AZ. Clinicopathological Features of Colorectal Cancer in the Iraqi Population Focusing on Age and Early-Onset of Malignancy: A Descriptive Cross-Sectional Study. Al-Rafidain Journal of Medical Sciences. 2023;5(3). doi:10.54133/ajms.v5i.158
28. Aldriwesh MG, Aljaian AR, Alorf KM, Bayounis MA, Alrayani YH, Philip W, et al. Comparative analysis of the clinical aspects of colorectal cancer in young adult and older adult patients in Saudi Arabia. Front Oncol. 2024;14. doi:10.3389/fonc.2024.1460636
29. Tsokkou S, Konstantinidis I, Papakonstantinou M, Chatzikomnitsa P, Liampou E, Toutziari E, et al. Sex Differences in Colorectal Cancer: Epidemiology, Risk Factors, and Clinical Outcomes. Journal of Clinical Medicine. 2025. doi:10.3390/jcm14155539
30. Purim O, Gordon N, Brenner B. Cancer of the colon and rectum: Potential effects of sex-age interactions on incidence and outcome. Medical Science Monitor. 2013;19(1). doi:10.12659/MSM.883842
31. Muhammed SH, Asad NM, Dewana AM, Ahmed BS, Al-Dabbagh A. Surgical and Oncological Outcome of Laparoscopic Resection of Colorectal Cancers: A Single-Center Experience. Cureus. 2024. doi:10.7759/cureus.58849
32. Al Zaabi A, Al Shehhi A, Sayed S, Al Adawi H, Al Faris F, Al Alyani O, et al. Early Onset Colorectal Cancer in Arabs, Are We Dealing with a Distinct Disease? Cancers (Basel). 2023;15(3). doi:10.3390/cancers15030889
33. Baran B, Mert Ozupek N, Yerli Tetik N, Acar E, Bekcioglu O, Baskin Y. Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. Gastroenterology Res. 2018;11(4). doi:10.14740/gr1062w
34. Luo C, Cen S, Ding G, Wu W. Mucinous colorectal adenocarcinoma: Clinical pathology and treatment options. Cancer Communications. 2019. doi:10.1186/s40880-019-0361-0
35. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging . CA Cancer J Clin. 2017;67(2). doi:10.3322/caac.21388
36. Ibrahem S, Ahmed H, Zangana S. Trends in colorectal cancer in Iraq over two decades: incidence, mortality, topography and morphology. Ann Saudi Med. 2022;42(4). doi:10.5144/0256-4947.2022.252
37. Hussain AMA, Lafta RK. Cancer trends in Iraq 2000–2016. Oman Med J. 2021;36(1). doi:10.5001/omj.2021.18

38. Shamseddine A, Chehade L, Al Mahmasani L, Charafeddine M. Colorectal Cancer Screening in the Middle East: What, Why, Who, When, and How? American Society of Clinical Oncology Educational Book. 2023;(43). doi:10.1200/edbk_390520
39. Mulet-Margalef N, Linares J, Badia-Ramentol J, Jimeno M, Sanz Monte C, Manzano Mozo JL, et al. Challenges and Therapeutic Opportunities in the dMMR/MSI-H Colorectal Cancer Landscape. Cancers. 2023. doi:10.3390/cancers15041022
40. Ibrahim T, Saer-Ghorra C, Trak-Smayra V, Nadiri S, Yazbeck C, Baz M, et al. Molecular characteristics of colorectal cancer in a Middle Eastern population in a single institution. Ann Saudi Med. 2018;38(4). doi:10.5144/0256-4947.2018.251
41. Jung J, Kang Y, Lee YJ, Kim E, Ahn B, Lee E, et al. Comparison of the mismatch repair system between primary and metastatic colorectal cancers using immunohistochemistry. J Pathol Transl Med. 2017;51(2). doi:10.4132/jptm.2016.12.09
42. Risbey C, Fielder T, Steffens D, Shin JS, Solomon M. Patterns of DNA mismatch repair protein expression for primary and recurrent colorectal cancer at an advanced surgical unit: A retrospective audit. Colorectal Disease. 2023;25(3). doi:10.1111/codi.16391
43. Grillo F, Paudice M, Gambella A, Bozzano S, Sciallero S, Puccini A, et al. Evaluating mismatch repair deficiency in colorectal cancer biopsy specimens. Histochem Cell Biol. 2023;160(2). doi:10.1007/s00418-023-02202-8

Figure1: Conventional colonic adenocarcinoma, (A) from 53 years old female, grade II, (H &E, X10). The pictures show proficient Miss Match Repair (MMR) status by immunohistochemistry with intact nuclear expression of MLH1 (B), PMS2 (C), MSH2 (D) and MSH6 (E).

Figure2: Colonic adenocarcinoma, (A) from 57 years old male, grade III, (H &E, X10). The pictures show deficient Mis-Match Repair (MMR) status by immunohistochemistry with lost nuclear expression of MLH1 (B), PMS2 (C), retained nuclear expression MSH2 (D) and MSH6 (E).