Prognostic Value of Mismatch Repair Genes for Patients With Colorectal Cancer: Meta-Analysis

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Abstract
DNA mismatch repair was proposed to play a pivotal role in the development and prognosis of colorectal cancer. However, the prognostic value of mismatch repair on colorectal cancer is still unknown. The PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched. The articles about mismatch repair (including hMLH1, hMSH2, hMSH3, hMSH6, hPMSH1, and hPMSH2) deficiency for the prognosis of patients with colorectal cancer were included in the study. The hazard ratio and its 95% confidence interval were used to measure the impact of mismatch repair deficiency on survival time. Twenty-one articles were included. The combined hazard ratio for mismatch repair deficiency on overall survival was 0.59 (95% confidence interval: 0.50-0.69) and that on disease-free survival was 0.57 (95% confidence interval: 0.43-0.75). In subgroup analysis, there were a significant association between overall survival and mismatch repair deficiency in Asian studies (hazard ratio: 0.67; 95% confidence interval: 0.50-0.91) and Western studies (hazard ratio: 0.56; 95% confidence interval: 0.46-0.67). For disease-free survival, the hazard ratios in Asian studies and Western studies were 0.55 (95% confidence interval: 0.38-0.81) and 0.62 (95% confidence interval: 0.50-0.78), respectively. Our meta-analysis indicated that mismatch repair could be used to evaluate the prognosis of patients with colorectal cancer.

Keywords
DNA mismatch repair (MMR), prognosis, colorectal cancer, meta-analysis, overall survival, disease-free survival

Abbreviations
CI, confidence interval; CRC, colorectal cancer; DNA, deoxyribonucleic acid; DFS, disease-free survival; HR, hazard ratio; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; OS, overall survival; PCR, polymerase chain reaction; TS, thymidylate synthase.

Introduction
Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with an estimated 1.4 million cases and 693,900 deaths occurring in 2012. Molecular markers for the biological behavior and prognosis of CRC were extensively studied; among these markers, DNA mismatch repair (MMR) was proposed to play a pivotal role in the development and prognosis of CRC.

Approximately 10% to 20% of sporadic CRC is associated with impaired function of DNA MMR genes. Mismatch repair...
Meta-Analyses (PRISMA) statement.19 Two reviewers (JTH and XLC) independently searched the following databases from their inceptions to June 1st, 2017: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The search terms included the following:

1. “colorectal cancer” OR “colon cancer” OR “rectal cancer”
2. “mismatch repair gene” OR “hMLH1” OR “hMSH2” OR “hMSH3” OR “hMSH6” OR “hPMSH1” OR “hPMSH2” OR MMR
3. “prognosis” OR “prognoses” OR “prognostic” OR “predictive” OR “biomarker” OR “marker” OR “survival” OR “Cox” OR “Logrank” OR “Kaplan-Meier”

The search was not limited by language. The potentially relevant studies were manually reviewed in the relevant systematic reviews and meta-analysis. The relevant studies were also obtained by searching Google scholar with the search terms “colorectal cancer, colon cancer, or rectal cancer,” “mismatch repair gene,” and “prognosis, predictive, or survive.”

**Inclusion Criteria**

The inclusion criteria included the following: (1) patients who were diagnosed with primary CRC (including colon cancer, or rectal cancer) were included. Patients exhibiting different clinical stages, histological types, or treatment methods were all included; (2) the expression of MMR genes was measured using PCR, immunohistochemistry (IHC), or enzyme-linked immunosorbent assay in the CRC tissue; (3) the association between MMR with patient prognosis was investigated, and the hazard ratio (HR), its 95% confidence interval (CI), or the relevant information were provided; and (4) a full paper was published. When the same team reported several studies from the same patients, the most recent study was included. Studies published in the abstract were excluded.

**Materials and Methods**

**Search Strategy**

A meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.19 Two reviewers (JTH and XLC) independently searched the following databases from their inceptions to June 1st, 2017: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The search terms included the following:

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heterogeneity, 50% was considered medium, and 75% was considered high. The sensitivity analysis were conducted by reestimating the pooled HR and omitting each study in turn to investigate the influence of each individual study on the overall meta-analysis summary estimate. Furthermore, subgroup analysis based on geographical regions (Asia, West [Europe and America]), different subtypes of gene (MMR, hMSH2, hMLH1), and different methods for detection of MMR (IHC, PCR) were performed to clarify the source of heterogeneity. In addition, the heterogeneity of the effect was discovered using meta-regression, including country, type of patient, sample size (≤200, and >200), test content, analysis method, subtype of gene, and therapy methods as covariates. Heterogeneity was defined as a $P \leq .05$. An observed HR >1 implied a worse prognosis in the high expression of MMR compared to the low expression of MMR. Publication bias and small study effects were assessed by Begg test and Egger test, with $P < .05$ considered to show significant publication bias. All of the calculations were performed by STATA version 12.0.

**Results**

The Characteristics of the Studies

A total of 849 studies met the inclusion criteria (Figure 1), of which 232 studies were excluded for duplicates, and 553 studies...
### Table 1. The Main Characteristics of the Included Studies.

| Author     | Year of Publication | Country | Time       | Patients          | Sample Size | Male | Mean of Age (range) | Stage | Surgery Treatment | Chemotherapy | Radiotherapy | Median Follow-Up Month (Range) |
|------------|---------------------|---------|------------|-------------------|-------------|------|--------------------|-------|------------------|--------------|--------------|-------------------------------|
| Bendardaf R| 2008                | Finland | 1996-2003  | CRC               | 73          | 46   | 57.9 (NR)          | II-IV | Partial           | All          | No patient   | 32.6 (NR)                                  |
| Cawkwell L | 1999                | UK      | NR         | CRC               | 101         | NR   | >50 (NR)           | NR    | NR               | NR           | NR           | 60.0 (NR)                                 |
| Huh JW     | 2016                | Korea   | NR         | Rectal cancer     | 209         | 136  | 56 (27-81)         | II, III| All              | All          | All          | 44 (2-87)                                 |
| Ide T      | 2008                | Japan   | 1999-2005  | CRC               | 94          | 60   | 68.2 (40-87)       | I-IV  | All              | All          | NR           | 26.1 (NR)                                 |
| Jansson A  | 2003                | Sweden  | 1972-1996  | CRC               | 301         | NR   | 70 (34-94)         | I-IV  | All              | NR           | NR           | NR (NR)                                    |
| Jensen LH  | 2007                | Denmark | NR         | CRC               | 28          | 13   | 61 (49-74)         | III-IV| NR               | All          | NR           | 12.2 (6.7-20.2)                            |
| Jensen SA  | 2009                | Denmark | 1996-2003  | CRC               | 340         | 159  | NR (NR)            | II-IV | NR               | All          | NR           | 6.1 (4.1-11.3)                            |
| Langner E  | 2010                | Poland  | NR         | CRC               | 75          | 45   | NR (NR)            | I-IV  | All              | NR           | NR           | NR (NR)                                    |
| Lanza G    | 2006                | Italy   | 1986-1995  | CRC               | 718         | 359  | 65 (27-85)         | II, III| Partial          | Most         | Partial      | 90.5 (63-144)                             |
| Ma J       | 2015                | China   | 2008-2011  | Colon cancer      | 184         | 111  | NR (NR)            | NR    | NR               | All          | NR           | 17.6 (7-36)                               |
| Park JW    | 2010                | Korea   | 2001-2003  | CRC               | 318         | 191  | 60.5 (27-87)       | I-IV  | All              | Partial      | NR           | 24.0 (NR)                                 |
| Pu C       | 2015                | China   | 2005-2008  | CRC               | 327         | 201  | NR (NR)            | I-IV  | NR               | Partial      | NR           | 24.0 (NR)                                 |
| Rau B      | 2003                | Germany | 1993-1999  | CRC               | 66          | 41   | 59 (39-74)         | NR    | NR               | All          | All          | 39.3 (11.3-83.4)                          |
| Russo A    | 2009                | Italy   | NR         | CRC               | 526         | 288  | 48 (20-88)         | I-IV  | NR               | NR           | NR           | 64 (6-383)                                |
| Sinicrope FA| 2006               | USA     | NR         | Colon cancer      | 528         | 274  | NR (NR)            | NR    | NR               | All          | NR           | NR (NR)                                    |
| Smyth EF   | 2004                | UK      | 1995-1998  | Colon cancer      | 111         | NR   | 72 (3990)          | I-IV  | All              | NR           | NR           | NR (NR)                                    |
| Sun Z      | 2014                | China   | 2009-2012  | CRC               | 404         | 233  | NR (NR)            | I-IV  | NR               | NR           | NR           | >36 (NR)                                  |
| Wang H     | 2014                | China   | 2005-2008  | CRC               | 327         | 201  | 58.7 (2581)        | I-IV  | NR               | NR           | NR           | 60.0 (NR)                                 |
| Wang JB    | 2016                | China   | 2011-2012  | Colon cancer      | 90          | 58   | NR (NR)            | II, III| Partial          | All          | NR           | 27 (5-35)                                 |
| Wang Y     | 2014                | China   | NR         | CRC               | 433         | 254  | 58.6 (2482)        | I-IV  | All              | Partial      | Partial      | 52 (1-87)                                 |
| Wu HW      | 2013                | China   | 2004-2006  | CRC               | 87          | 56   | 59 (35-82)         | I-III | All              | NR           | NR           | 60.0 (NR)                                 |

Abbreviations: CRC, colorectal cancer; NR, not report.
were excluded by reviewing the titles and abstracts. The full texts of the remaining 64 studies were obtained for review. Eventually, 21 studies were included in the meta-analysis.9-18,21-31

The characteristics of the included studies are shown in Table 1. Twenty-one studies contained a total of 5340 patients with CRC. All the studies were published from 1999 to 2016.
Of the 21 studies, 15 studies reported OS and 10 reported DFS (Table 2).

**Meta-Analysis for OS**

Fifteen studies of MMR for OS in patients with CRC were included in the meta-analysis. There was no significant heterogeneity across 15 studies with OS ($I^2 = 32.0\%$, $P = 0.113$; Figure 2). The combined HR of the 15 studies was 0.59 (95% CI: 0.50-0.69; Figure 2).Mismatch ratio was significantly associated with improved prognosis in Asian studies (HR: 0.67; 95% CI: 0.50-0.91; Figure 3) and western studies (HR: 0.56; 95% CI: 0.46-0.67; Figure 3). The HR was 0.58 (95% CI: 0.45-0.75) for MMR as a marker in 10 studies, 0.29 (95% CI: 0.10-0.87) for hMLH1 as a marker in one study, and 0.48 (95% CI: 0.30-0.77) for hMSH2 as a marker in 4 studies (Table 3; Figure 3). When the subgroups were analyzed based on the test method, the combined HRs for IHC and PCR were 0.51 (95% CI: 0.42-0.62) and 0.74 (95% CI: 0.57-0.96), respectively (Figure 3).

**Meta-Analysis for DFS**

In a pooled analysis of 10 DFS studies, deficient MMR was associated with a better prognosis for CRC (HR: 0.62; 95% CI: 0.44-0.88; Figure 4). There was significant heterogeneity across 10 studies with DFS ($I^2 = 66.5\%$, $P = .001$). A meta-regression was performed to explore the source of heterogeneity.
The results showed that all the variables were not related with the heterogeneity (Table 4). The tested content was nearly significant ($P = .077$). In addition, Bendardaf study included 73 patients, and thymidylate synthase (TS) and MMR expressions were assessed for each patient. Its HR was calculated by comparing 18 patients with both high TS and MMR expression with 27 patients with both low TS and MMR, while other patients with low MMR and high TS or high MMR and low TS were excluded. This may result in significant heterogeneity between Bendardaf study and other studies ($P = .001$). Thus, Bendardaf study was excluded in subgroup analysis.

The combined HRs for studies without Bendardaf study were 0.57 (95\% CI: 0.50-0.73; $I^2 = 48.0\%$, $P = .052$). The HRs of deficient MMR on DFS in Asian studies or western studies were 0.62 (95\% CI: 0.50-0.91) and 0.55 (95\% CI: 0.38-0.81) for hMLH1 as a marker in 2 studies, and 0.72 (95\% CI: 0.52-1.00) for hMSH2 as a marker in 3 studies (Table 3; Figure 5). When the subgroups were analyzed based on the test method, the combined HRs for IHC and PCR were 0.62 (95\% CI: 0.51-0.76) and 0.06 (95\% CI: 0.01-0.30), respectively (Figure 5).

The publication bias was not significant (OS, $P = .113$; DFS, $P = .210$). However, one study was out of the reference line in the DFS group indicated that there might be publication bias for DFS (Figure 6).

| Table 3. The Results of the Meta-Analysis. |
|-------------------------------------------|
| Number of Studies | Patients | HR (95\% CI) | Heterogeneity ($I^2, P$) |
|---------------------|----------|--------------|--------------------------|
| Overall survival    |          |              |                          |
| All                 | 15       | 4146         | 0.59 (0.50-0.69)         | 32.0\%, 0.113 |
| Asian               | 5        | 1352         | 0.67 (0.50-0.91)         | 50.4\%, 0.089 |
| Western             | 10       | 2794         | 0.56 (0.46-0.67)         | 20.9\%, 0.251 |
| Gene                |          |              |                          |
| MMR                 | 10       | 3539         | 0.58 (0.45-0.75)$^a$     | 47.3\%, 0.047 |
| hMSH2               | 4        | 496          | 0.48 (0.30-0.77)         | 0.0\%, 0.805 |
| hMLH1               | 1        | 111          | 0.29 (0.10-0.87)         | NR           |
| Test method         |          |              |                          |
| IHC                 | 11       | 3084         | 0.51 (0.42-0.62)         | 9.7\%, 0.351 |
| PCR                 | 4        | 1062         | 0.74 (0.57-0.96)         | 33.4\%, 0.212 |
| Disease-free survival |        |              |                          |
| All                 | 10       | 2312         | 0.62 (0.44-0.88)         | 66.5\%, 0.001 |
| All$^b$             | 9        | 2239         | 0.57 (0.43-0.75)         | 48.0\%, 0.052 |
| Asian               | 6        | 1305         | 0.62 (0.50-0.78)$^a$     | 61.9\%, 0.022 |
| Western             | 3        | 934          | 0.55 (0.38-0.81)         | 0.0\%, 0.373 |
| Gene                |          |              |                          |
| MMR                 | 4        | 1456         | 0.61 (0.47-0.79)         | 0.0\%, 0.493 |
| hMLH1               | 2        | 421          | 0.32 (0.17-0.58)$^a$     | 79.2\%, 0.028 |
| hMSH2               | 3        | 362          | 0.72 (0.52-1.00)         | 25.5\%, 0.261 |
| Test method         |          |              |                          |
| IHC                 | 8        | 2145         | 0.62 (0.51-0.76)         | 5.3\%, 0.389 |
| PCR                 | 1        | 94           | 0.06 (0.01-0.30)         | NR           |

Abbreviations: IHC, immunohistochemistry; NR: not report; MMR, mismatch repair; PCR, polymerase chain reaction.

$^a$Results from random-effect model.

$^b$Bendardaf study was excluded, which was also excluded in subgroup analysis.

Figure 4. Forest plot for the association between MMR expression and DFS in CRC. CRC indicates colorectal cancer; DFS, disease-free survival; MMR; mismatch repair.
Discussion

Our pooled results from all the eligible studies showed that the HR was 0.59 for OS and 0.62 for DFS, with all showing statistically significant associations between MMR and CRC. The results indicated that deficient MMR was associated with better OS and DFS in the patients with CRC. Meanwhile, subgroup analysis of the different regions (Western and Asia) MMR showed consistent results. In addition, no obvious publication bias was determined by Begg test. These analyses enhanced the reliability of this meta-analysis.
Mismatch repairs are a group of enzymes that can recognize and repair mismatched base pairs during DNA replication, including hMLH1, hMSH2, hMSH3, hMSH6, hPMSH1, and hPMSH2, which are considered critical proteins for the formation of MSI.\(^7\)\(^{,14}\)\(^\text{-}^{16}\)\(^,^{17}\)\(^\text{-}^{19}\)\(^\text{-}^{23}\)\(^,^{28}\)\(^\text{-}^{35}\) Mismatch repairs, along with MSI, are proposed to be useful markers in CRC. Approximately 90\% hereditary nonpolyposis CRC and 10\% to 20\% of sporadic CRC demonstrate MSI.\(^32\) The vast majority of CRC with MSI is caused by aberrant hMLH1 expression (70\% to 95\%), while others primarily result from the inactivation of hMSH2 and hMSH6. Additionally, in sporadic CRC, approximately 95\% deficient hMLH1 expression is due to hypermethylation of the hMLH1 promoter.\(^33\)\(^,^{34}\)

In this meta-analysis, some studies defined negative hMLH1 or hMSH2 expression as MMR deficiency, and they demonstrated a significantly longer OS for patients with deficient MMR.\(^7\)\(^,^{14}\)\(^,^{16}\)\(^,^{17}\)\(^\text{-}^{23}\)\(^,^{28}\)\(^,^{35}\) Some studies defined deficient hMLH1 (or hMSH2) expression as deficient MMR and demonstrated the same result for OS.\(^11\)\(^-^{13}\)\(^,^{24}\)\(^,^{26}\) Four studies showed longer DFS in the patients with CRC with deficient hMLH1 or hMSH2.\(^14\)\(^-^{16}\)\(^,^{28}\) However, Bendardaf et al suggested that deficient MMR demonstrated a shorter DFS. This inconsistency could be explained by combining with other genes (TS) and distinctive clinic features indicating that CRC with deficient MMR is apt to display marked peritumoral and intratumoral lymphocytic infiltration.\(^36\)\(^-^{39}\) To summarize, these results suggest that detection of both hMLH1 and hMSH2 could be used to identify most MMR and could be useful methods to evaluate OS for patients with CRC. However, further studies are required to confirm the relationship between MMR and DFS because of significant heterogeneity.

The prognosis of CRC is strongly associated with tumor stage, tumor site, and treatment. MMR-deficient CRC exhibit distinct clinical and pathological features, including proximal location and early tumor stage.\(^38\)\(^,^{40}\) Further, Scarpa et al reported that CRC with MMR deficiency exhibited a higher CD80 expression and CD8+ and Th1 T-cell infiltration.\(^41\) In vitro silencing of hMSH2, hMLH1, and hMSH6 significantly increased the CD80+ cell rate. These results suggest an enhanced immune surveillance mechanism in the presence of MMR deficiency,\(^41\) which may explain the improved OS and DFS for patients with CRC with MMR deficiency. These reports might explain our observations that deficient MMR was associated with better prognosis of patients with CRC. However, MMR-deficient CRC shows poor differentiation and mucinous histology, and strong preclinical and clinical evidence suggests a possible resistance to 5-FU in these tumors. Thus, further studies are required to explore the underlying mechanism of MMR deficiency and better CRC prognosis.

There are 2 broadly accepted methods for aberrant MMR detection including MSI testing by PCR and MMR protein expression analysis by IHC. It has been shown that the results of MMR protein expression by IHC are concordant with DNA-based MSI testing, with a favorable sensitivity and a dramatic specificity.\(^42\) Immunohistochemistry is commonly used as an alternative test when a molecular laboratory is not available.\(^43\) In addition, IHC for MMR is cost-effective and simple, which can determine the specific protein of MMR.\(^43\) In this meta-analysis, most studies adopted the methods of IHC for the detection of aberrant MMR. The subgroup of IHC demonstrated that deficient MMR was a protective factor for the prognosis of CRC, which could predict a longer OS and DFS. As a result, the detection of aberrant MMR by IHC could be a promising method to assess the prognosis of CRC.

There were several limitations in our study. First, the detection of MMR is different among the studies; however, most studies adopted IHC to determine the expression of MMR, and the results were consistent. Second, the definition of aberrant MMR is inconsistent; some studies considered aberrant MMR as negative MMR expression, some selected negative hMLH1 expression alone or negative hMSH2 expression alone, and 2 studies selected negative expression of hMLH1, hMSH2, hMSH6, and hPMS2. This may result in significant heterogeneity among these studies. Third, there is significant heterogeneity among the DFS studies. Although we investigated the influence of each individual study on the overall estimate and conducted a meta-regression and subgroup analysis according to geographical regions and different detection methods, the heterogeneity remained significant in some subgroup analysis and could not be clearly classified. Fourth, some studies did not mention certain vital data, especially the follow-up information, such as studies by Langner E, Jansson A, and Smyth EF, which may influence the reliability of the statistical analysis.

### Conclusion

In summary, our pooled results indicated that deficient MMR was associated with a better OS and DFS for the CRC patients. However, large well-designed studies with a uniform method of MMR detection are required to confirm these results.

### Authors’ Note

Jiang-tao Hou and Li-na Zhao equally contributed to the work. The study was approved by the ethics committees of Guangzhou University of Chinese Medicine.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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References
1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
2. Gelsomino F, Barbolini M, Spallanzani A, Pugliese G, Casinu S. The evolving role of microsatellite instability in colorectal cancer: a review. Cancer Treat Rev. 2016;51:19-26.
3. Zhang CM, Lv JF, Gong L, et al. Role of deficient mismatch repair in the personalized management of colorectal cancer. Int J Environ Res Public Health. 2016;13(9):892.
4. Popat S, Huhner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23(3):609-618.
5. Kerr DJ, Midgley R. Defective mismatch repair in colon cancer: a prognostic or predictive biomarker? J Clin Oncol. 2010;28(20):3210-3212.
6. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28(20):3219-3226.
7. Guastadisegni C, Colafranceschi M, Ottini L, Dogliotti E. Microsatellite instability as a marker of prognosis and response to therapy: a meta-analysis of colorectal cancer survival data. Eur J Cancer. 2010;46(15):2788-2798.
8. Ogino S, Goel A. Molecular classification and correlates in colorectal cancer. J Mol Diagn. 2008;10(1):13-27.
9. Aparicio T, Schischmanoff O, Poupardin C, et al. Deficient mismatch repair phenotype is a prognostic factor for colorectal cancer in elderly patients. Dig Liver Dis. 2013;45(3):245-250.
10. Russo A, Sala P, Alberici P, et al. Prognostic relevance of MLH1 and MSH2 mutations in hereditary non-polyposis colorectal cancer patients. Tumori. 2009;95(6):731-738.
11. Wu HW, Gao LD, Wei GH. hMSh2 and nm23 expression in sporadic colorectal cancer and its clinical significance. Asian Pac J Cancer Prev. 2013;14(3):1995-1998.
12. Rau B, Sturm I, Lage H, et al. Dynamic expression profile of p21WAF1/CIP1 and Ki-67 predicts survival in rectal carcinoma treated with preoperative radiochemotherapy. J Clin Oncol. 2003;21(18):3391-3401.
13. Langner E, Przybylowska K, Trzcinski R, et al. Loss of hMSH2 gene expression correlates with improved survival in patients with sporadic colorectal cancer. J Genet. 2010;89(1):101-104.
14. Ma J, Zhang Y, Shen H, et al. Association between mismatch repair gene and irinotecan-based chemotherapy in metastatic colon cancer. Tumour Biol. 2015;36(12):9599-9609.
15. Sun Z, Yu X, Wang H, Zhang S, Zhao Z, Xu R. Clinical significance of mismatch repair gene expression in sporadic colorectal cancer. Exp Ther Med. 2014;8(5):1416-1422.
16. Jensen SA, Vainer B, Kruhoffer M, Sorensen JB. Microsatellite instability in colorectal cancer and association with thymidylate synthase and dihydrofolate reductase expression. BMC Cancer. 2009;9:25.
17. Cawkwell L, Gray S, Murgatroyd H, et al. Choice of management strategy for colorectal cancer based on a diagnostic immunohistochemical test for defective mismatch repair. Gut. 1999;45(3):409-415.
18. Wang H, Sun Z, Ye L, et al. [hMSH2 aberrant expression in patients with sporadic colorectal cancer in Xinjiang]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2014;39(6):552-557.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009;339:b2535.
20. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
21. Pu C, Ren W, Sun Z, et al. Human mutL homolog 1 expression and prognostic significance of hMLH1/ hMSH2 gene mutations and hMLH1 promoter methylation in sporadic colorectal cancer. Med Oncol. 2014;31(7):39.
22. Park JW, Chang HI, Park S, et al. Absence of hMLH1 or hMSH2 expression as a stage-dependent prognostic factor in sporadic colorectal cancers. Ann Surg Oncol. 2010;17(11):2839-2846.
23. Smyth EF, Sharma A, Sivarajasingham N, Hartley J, Monson JR, Cawkwell L. Prognostic implications of hMLH1 and p53 immunohistochemical status in right-sided colon cancer. Dis Colon Rectum. 2004;47(12):2086-2091; discussion 2091-2.
24. Ide T, Kitajima Y, Ohtaka K, Mitsuno N, Nakafusa Y, Miyazaki K. Expression of the hMLH1 gene is a possible predictor for the clinical response to 5-fluorouracil after a surgical resection in colorectal cancer. Oncol Rep. 2008;19(6):1571-1576.
25. Jansson A, Armbman G, Zhang H, Sun XF. Combined deficiency of hMLH1, hMSH2, hMSH3 and hMSH6 is an independent prognostic factor in colorectal cancer. Int J Oncol. 2003;22(1):41-49.
26. Benardaf R, Lamllum H, Ristamaki R, Korkeila E, Syrjanen K. Expression of the hMLH1 gene is a possible predictor for the clinical response to 5-fluorouracil after a surgical resection in colorectal cancer. Oncol Rep. 2008;19(6):1571-1576.
27. Lasson A, Armbman G, Zhang H, Sun XF. Combined deficiency of hMLH1, hMSH2, hMSH3 and hMSH6 is an independent prognostic factor in colorectal cancer. Int J Oncol. 2003;22(1):41-49.
28. Bendiad R, Lamllum H, Ristamaki R, Korkeila E, Svrjanek K, Pyrhonen S. Thymidylate synthase and microsatellite instability in colorectal cancer: implications for disease free survival, treatment response and survival with metastases. Acta Oncol. 2008;47(6):1046-1053.
29. Sinicrope FA, Rego RL, Foster N, et al. Microsatellite instability accounts for tumor site-related differences in clinicopathologic variables and prognosis in human colon cancers. Am J Gastroenterol. 2006;101(12):2818-2825.
29. Jensen LH, Danenberg KD, Danenberg PV, Jakobsen A. Predictive value of MSH2 gene expression in colorectal cancer treated with capecitabine. *Clin Colorectal Cancer*. 2007;6(6):433-435.

30. Wang JB, Ma DL, Li JY, Sun QD, Liu YE. Association between expression of DNA mismatch repair genes and clinical features and prognosis of patients with radical resection of colon cancer. *Genet Mol Res*. 2016;15(3).

31. Huh JW, Kim HC, Kim SH, et al. Mismatch repair gene expression as a predictor of tumor responses in patients with rectal cancer treated with preoperative chemoradiation. *Medicine (Baltimore)*. 2016;95(3):e2582.

32. Strate LL, Syngal S. Hereditary colorectal cancer syndromes. *Cancer Causes Control*. 2005;16(3):201-213.

33. Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer*. 2009;100(2):266-273.

34. Devaud N, Gallinger S. Chemotherapy of MMR-deficient colorectal cancer. *Fam Cancer*. 2013;12(2):301-306.

35. Lanza G, Gafa R, Santini A, Maestri I, Guerzoni L, Cavazzini L. Immunohistochemical test for MLH1 and MSH2 expression predicts clinical outcome in stage II and III colorectal cancer patients. *J Clin Oncol*. 2006;24(15):2359-2367.

36. Jass JR, Do KA, Simms LA, et al. Morphology of sporadic colorectal cancer with DNA replication errors. *Gut*. 1998;42(5):673-679.

37. Gafa R, Maestri I, Matteuzzi M, et al. Sporadic colorectal adenocarcinomas with high-frequency microsatellite instability. *Cancer*. 2000;89(10):2025-2037.

38. Ward R, Meagher A, Tomlinson I, et al. Microsatellite instability and the clinicopathological features of sporadic colorectal cancer. *Gut*. 2001;48(6):821-829.

39. Hawkins NJ, Tomlinson I, Meagher A, Ward RL. Microsatellite-stable diploid carcinoma: a biologically distinct and aggressive subset of sporadic colorectal cancer. *Br J Cancer*. 2001;84(2):232-236.

40. Zeinalian M, Hashemzadeh-Chaleshti M, Salehi R, Kazemi M, Emami MH. Tumor microsatellite instability and clinicopathologic features in Iranian colorectal cancer patients at risk for Lynch syndrome. *J Res Med Sci*. 2015;20(2):154-160.

41. Scarpa M, Ruffolo C, Canal F, et al. Mismatch repair gene defects in sporadic colorectal cancer enhance immune surveillance. *Oncotarget*. 2015;6(41):43472-43482.

42. Lindor NM, Burgart LJ, Leontovich O, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. *J Clin Oncol*. 2002;20(4):1043-1048.

43. Zhang X, Li J. Era of universal testing of microsatellite instability in colorectal cancer. *World J Gastrointest Oncol*. 2013;5(2):12-19.