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PROGNOSTIC AND PREDICTIVE ROLES OF DNA MISMATCH REPAIR STATUS IN COLON CANCER PATIENTS TREATED WITH OXALIPLATIN-BASED CHEMOTHERAPY: A RETROSPECTIVE STUDY

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This study aims to evaluated the prognostic and predictive roles of DNA mismatch repair status in colon cancer patients treated with oxaliplatin-based chemotherapy. From 2005 to 2008, patients who underwent curative surgical resection for high-risk stage II or stage III colon cancer were recruited in this study. These patients had been received oxaliplatin-based chemotherapy. A total 324 patients were included (41.7% at stage II and 58.3% at stage III), and 59 patients (18.2%) exhibited mismatch repair-deficient (dMMR). The prognostic analysis revealed an increase in disease-free survival (DFS) for dMMR patients versus proficient MMR (pMMR) patients (81.4% versus 64.2%, P = 0.009), and overall survival (OS) (86.4% versus 69.1%, P = 0.004). Among the 82 patients who did not receive adjuvant therapy, the 5-year DFS was significantly higher in patients with dMMR (81.3%) than in patients with pMMR (49.7%, P = 0.040). In the multivariate models, dMMR was independently associated with improved DFS (HR = 2.171, 95% CI: 1.108 – 4.253, P = 0.024) and OS (HR = 2.521, 95% CI: 1.190 – 5.339, P = 0.016). In the predictive analysis, it was observed that the benefit of treatment significantly differed according to the DNA MMR status (P = 0.020). Compared with surgery alone, oxaliplatin-based adjuvant chemotherapy improved the 5-year DFS (69.9% versus 56.2%, P = 0.024) among patients with pMMR in the multivariable analysis (HR = 0.794, 95% CI = 0.646 – 0.976, P = 0.029). In contrast, the oxaliplatin-based chemotherapy in the group with dMMR had no benefit in DFS (83.1% versus 81.8%, HR 1.040, 95% CI: 0.276 – 3.922, P = 0.954). Patients with dMMR colon cancer are associated with improved survival rates, compared with pMMR colon cancer. MMR status is an independent prognostic biomarker for DFS in patients with high-risk stage II and stage III colon cancer. Oxaliplatin-based adjuvant chemotherapy mainly benefits patients with pMMR, but may not benefit patients with tumors exhibiting dMMR.

Key words: *colorectal cancer, oxaliplatin-based chemotherapy, oxaliplatin-based chemotherapy, DNA mismatch repair, mismatch repair-deficient, prognosis, predictive biomarker*

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second most commonly diagnosed cancer in females, with an estimated occurrence of 1.4 million cases and 693,900 deaths in 2012 (1). About 70% of malignant tumors are related to lifestyle and environmental factors, and better knowledge of their significance might reduce the prevalence of CRC (2). In China, the incidence of CRC is rapidly increasing, and it is now ranked fifth among all malignancies of morbidity and mortality (3). The main prognostic factor for survival and relapse after resection of nonmetastatic CRC is the pathologic tumor stage. Adjuvant chemotherapy based on 5-fluorouracil (5-Fu) has been shown to reduce the risk of recurrence and prolong survival in patients with stage III colon cancer in the 1990s. Oxaliplatin-based chemotherapy has been the standard adjuvant treatment for stage III colon cancer patients when several clinical trials demonstrated improved disease-free survival (DFS) and overall survival (OS) (4). At same time, oxaliplatin-based chemotherapy is also recommended for stage II patients with high-risk features.

Evidence has shown that microsatellite instability (MSI) is a marker of a more favorable outcome, and a predictive biomarker of 5-Fu-based adjuvant benefit (5). No benefit in DFS from 5-Fu-based adjuvant treatment was observed for patients with mismatch repair-deficient (dMMR), while the treatment was beneficial for patients with proficient MMR (pMMR) tumors (6). In contrast, other studies have suggested that patients with dMMR tumors derive a similar or even greater benefit from 5-Fu-based adjuvant treatment, when compared to patients with pMMR tumors (7). Since the fluoropyrimidine-oxaliplatin combination is presently the standard adjuvant chemotherapy for patients with high-risk stage II and stage III colon cancer, it is important to explore the predictive role of MMR status in oxaliplatin-based chemotherapy. However, few studies were conducted on Chinese patients.

Due to evolving standards, the prospective evaluation of the predictive effect of MMR status on surgery alone and oxaliplatin-based adjuvant chemotherapy remains quite difficult. Hence, the investigators took advantage of the practice patients. The present study was conducted to assess the predictive significance of MMR status in high-risk stage II and stage III patients who received surgery alone and oxaliplatin-based adjuvant chemotherapy.

MATERIALS AND METHODS

Study population

The present trial was a retrospective study. Between January 2005 and December 2008, patients with colon cancer were included in the present study. The Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences approved the retrospective study.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients definitely diagnosed with colon cancer; (2) patients > 18 years old; (3) patients treated with oxaliplatin-based chemotherapy.

Exclusion criteria: (1) patients with unavailable immunohistochemical (IHC) analysis results; (2) the quality of the immunostaining was considered unsatisfactory; (3) patients treated with 5-Fu alone adjuvant chemotherapy; (4) patients at stage II, but without high risk factors (T4, poorly differentiated histology, lymphatic/vascular invasion, localized perforation, or close, obstruction, < 12 lymph nodes examined, perineural invasion, indeterminate, or positive margins); (5) patients with rectal cancer, abdominopelvic radiotherapy, severe complications, changing regimens, multi-primary cancer, or familial adenomatous polyposis.

Data collection

The specific procedures used for the inclusion of patients are presented in *Fig. 1*. The present retrospective study included 324 consecutive patients with histologically confirmed high-risk stage II or stage III colon cancer and available tumor specimens, who received curative surgical resection, followed by eight weeks of oxaliplatin-based adjuvant chemotherapy or surgery alone, from January 2005 to December 2008. For all adjuvant treatment patients, the chemotherapy was started at the Cancer Institute and Hospital, Chinese Academy of Medical Sciences, and further follow-ups were conducted.

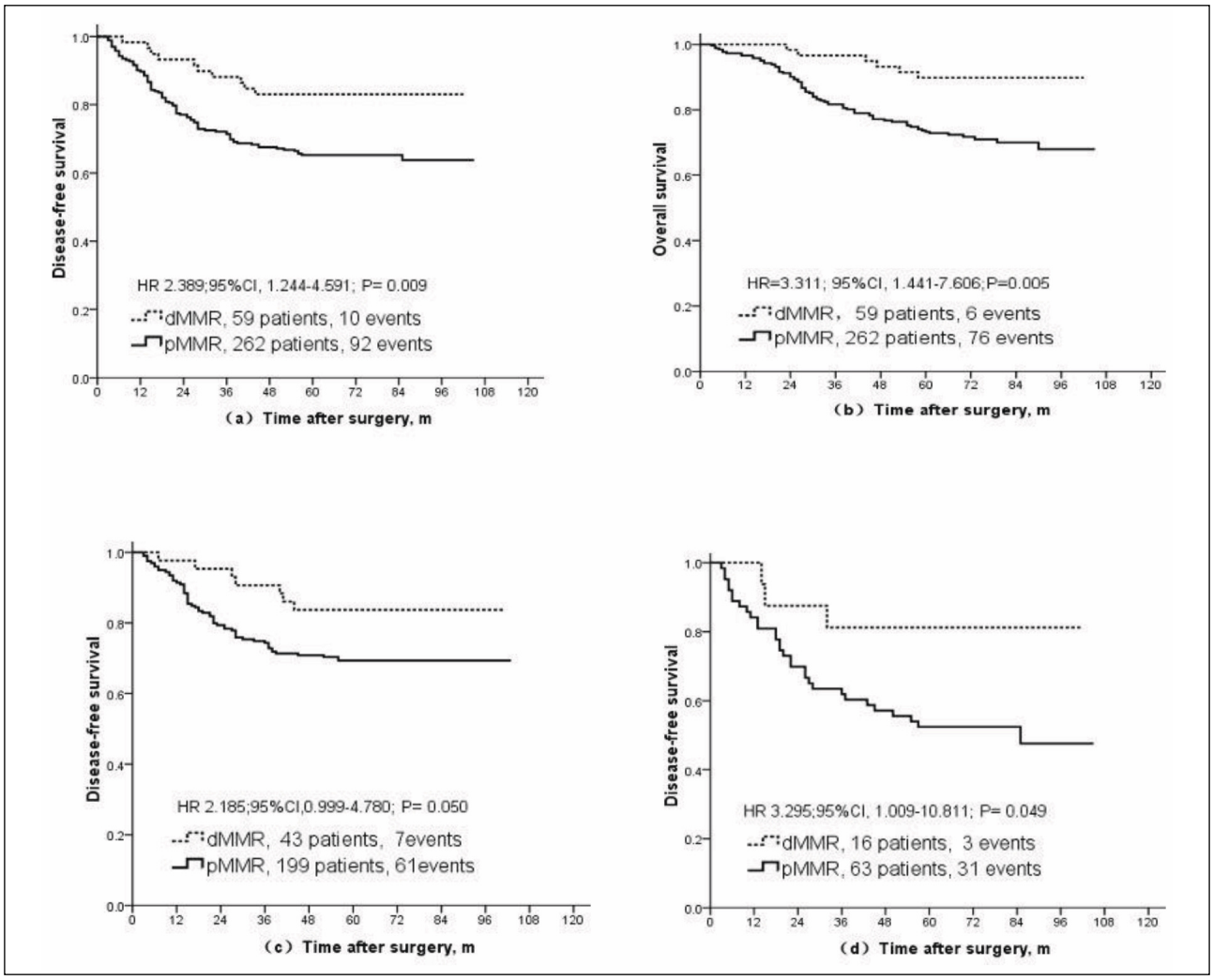

Fig. 1. (a): Kaplan-Meier disease free survival (DFS) and (b): overall survival (OS) curves according to mismatch repair (MMR) status in 321 patients; (c): Kaplan-Meier DFS survival curves according to MMR status in group of oxaliplatin-based chemotherapy; (d): Kaplan-Meier DFS survival curves according to MMR status in group of surgery-alone.

Treatment and follow-up

The oxaliplatin-based treatment group received mFOLFOX6 (85 mg/m^2 of oxaliplatin, infused for two hours, day one; 200 mg/m^2 of CF, intravenously (i.v.), two hours, day one; 400 mg/m^2 of 5-Fu, i.v., and subsequently with continuous infusion of 2400 mg/m^2 for 46 hours, day 1 – 2, *q2w* × 12) or XELOX (85 mg/m^2 of oxaliplatin, infused for two hours, day one; 1000 mg/m^2 of Xeloda, twice a day, *per os (*p.o.*)*, day 1 – 14, *q3w* × 8) regimen treatments. After the surgery, tumor recurrence was detected by physical examination, serum carcinoembryonic antigen (CEA) assay, and abdominal and thoracic imaging every 3 – 6 months for three years, every six months for the following two years, and annually thereafter. The duration of follow-up was defined as the time between surgery and disease recurrence, death, or last hospital contact (scheduled follow-up or telephone contact). The cutoff date for this analysis was June 2013.

Mismatch repair (MMR) status determination

Tumor MMR status was determined by IHC analysis. Defective MMR status was defined as loss of tumor MLH1, MSH2, MSH6, or PMS2 protein expression. Proficient MMR status was defined as normal tumor MLH1, MSH2, MSH6, and PMS2 protein expression.

Immunohistochemical analysis

The paraffin tissue blocks were stored in room temperature. Blocks of formalin-fixed, paraffin-embedded adenocarcinoma tissue that comprised of an area of normal colonic mucosa adjacent to the tumor were selected for each case. The grade of differentiation was determined according to the World Health Organization criteria. Four-µm sections cut from the paraffin-embedded tissue samples were placed onto silane-treated Superfrost slides and left to dry at 37°C overnight. Then, these slides were deparaffinized in xylene and rehydrated in pure ethanol, and endogenous peroxidase was blocked using 3% hydrogen peroxide in methanol for 30 minutes. Before the immunostaining, antigen retrieval was performed by immersing the sections in citrate buffer (pH 8.0). Then, the sections were incubated for 15 minutes at room temperature with antibodies to MLH1 (dilution 1/100 clone ES 05, Dako, Denmark), MSH2 (dilution 1/100, clone FE11, Dako, Denmark), MSH6 (dilution 1/100 clone EP49, Dako, Denmark). and PMS2 (dilution 1/100 clone EP51, Dako, Denmark). The intensity of the immunostaining for MLH1/MSH2/MSH6/PMS2 was reviewed and scored according to the location of the cytoplasmic membrane, with or without a positive nucleus. The protein expression was considered negative when there was a complete absence of nuclear staining of neoplastic cells. The staining of adjacent lymphocytes, normal epithelial cells, endothelial cells, or fibroblasts was used as a positive control. The IHC assays were read by pathologists blinded to the clinical characteristic of patients, and discordant cases were reviewed by a supplementary pathologist to reach a consensus. Therefore, IHC result was not available to physicians at time of treatment decision.

Statistical analysis

The SPSS 20.0 software (IBM, Chicago, USA) was used to conduct the statistical analysis. All analysis was carried out with a bilateral alpha type 1 error of 5%. Data were described in frequency (percentage), or means and medians (range). The X^2 and Wilcoxon rank-sum tests were used to test for any association between the MMR status and other clinicopathologic variables. Fisher exact test was used to compare the distribution of qualitative and ordinal variables. The primary endpoint was DFS, which was defined as the time between the date of surgery and first event (local or distant disease recurrence or death from any cause, whichever occurred first). Patients who were alive and relapse-free at last contact were censored at the last follow-up date. OS was defined as the time elapsed from the date of surgery until death (all cause). Surviving patients were censored on the last follow-up date. The distributions of OS and DFS were estimated using the Kaplan-Meier methodology. The median follow-up and 95% confidence interval (CI) were calculated using the reverse Kaplan-Meier method. Univariate and multivariate COX proportional hazard regression models were used to estimate the heart rate and 95% CI. The DFS and OS curves of the groups of patients who received surgery alone and oxaliplatin-based adjuvant treatment were compared, according to the tumor MMR status. A multivariate Cox model was constructed. The multivariate Cox analysis included all relevant clinical variables, regardless of the univariate Cox P-value, namely, age, gender and differentiation grade. Two-sided P-values of < 0.05 were considered statistically significant.

RESULTS

General characteristics

A total of 324 patients were included in this study. The median age of these patients was 60 years old (range: 18 – 83 years old). These patients received either surgery alone (n = 82), or surgery plus oxaliplatin-based adjuvant chemotherapy (n = 242) (*Table 1*). Among there participants, fifty-nine patients (18.2%) had dMMR tumors. Among the 43 patients with loss of MLH1 and/or PMS2 protein expression, five patients had a confirmed Lynch syndrome or a positive family history, according to the revised Bethesda Guidelines, 30 patients had no suggestive family history, and there was no information about the family history for the remaining three patients. Among the 16 patients with loss of MSH2 and/or MSH6 protein expression, 14 patients had a positive family history, while there was no information on the family history for the remaining two patients. Among the 18 patients with suspected germline tumors, two patients had recurrence and died. Besides, patients with dMMR tumors were younger than patients with pMMR tumors. All other characteristics were well-balanced between the MMR tumor groups.

Adjuvant chemotherapy

Adjuvant chemotherapy was administered in 63.7% (n = 86/135) and 82.5% (n = 156/189) of patients with stage II and stage III colon cancer, respectively. The mean number of adjuvant chemotherapy cycles was 10.2 and 6.9 in the FOLFOX and XELOX treatment groups, respectively.

The relationship between mismatch repair status and survival

At the end of the follow-up period, 82 patients with pMMR tumors and eight patients with dMMR tumors died. The 5-year OS rate was 86.8% for patients with dMMR tumors and 68.8% for patients with pMMR (HR: 2.738, 95% CI: 1.324 – 5.662, P = 0.007). For the DFS analysis, 95 patients with pMMR tumors and 11 patients with dMMR relapsed or died. The 5-year DFS rate was 80.9% for patients with dMMR tumors and 63.2% for patients with pMMR tumors (HR: 2.236, 95% CI: 1.197 – 4.175, P = 0.012). Among the 82 patients who did not receive adjuvant therapy, the 5-DFS was significantly higher in patients with dMMR tumors (81.3%) than in patients with pMMR

Table 1. Demographic and pathological characteristics of the study population.

	Surgery-alone (n = 79) No. of patients (%)	**Oxaliplatin-based chemotherapy** (n = 242) No. of patients (%)	**P-value**
Age			< 0.001
Mean	69.0	55.8	-
Range	30 – 83	23 – 82	-
≥ 65	58 (73.4%)	65 (26.9%)	-
Gender	-	-	0.596
Male	46 (58.2%)	150 (62.0%)	-
Female	33 (41.8%)	92 (38.0%)	-
Tumor location	-	-	0.540
Proximal	38 (48.1%)	126 (52.1%)	-
Distal	41 (51.9%)	116 (47.9%)	-
Differentiation	-	-	0.562
Well/moderate	60 (75.9%)	175 (72.3%)	-
Poor	19 (24.1%)	67 (37.3%)	-
Stage	-	-	< 0.001
Stage II	47 (59.5%)	88 (36.4%)	-
Stage III	32 (40.5%)	154 (63.6%)	-
MMR Status	-	-	0.738
dMMR	16 (20.2%)	43 (17.8%)	-
pMMR	63 (79.8%)	199 (82.2%)	-

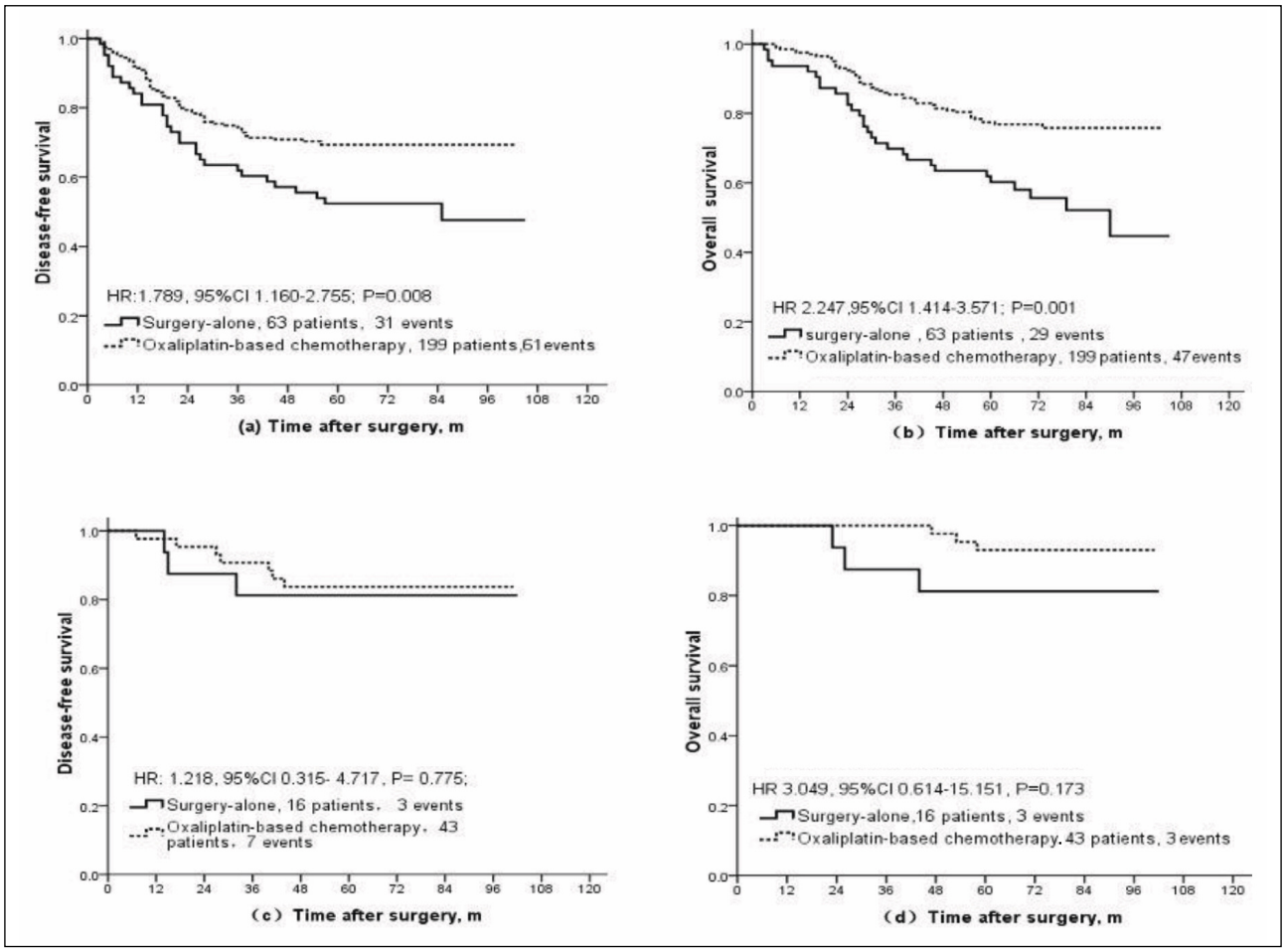

Fig. 2. Disease free survival (DFS) and overall survival (OS) according mismatch repair (MMR) status and treatment model. Kaplan-Meier DFS (a) and OS (b) survival curves according to treatment model in pMMR patients; Kaplan-Meier DFS (c) and OS (d) survival curves according to treatment model in dMMR patients.

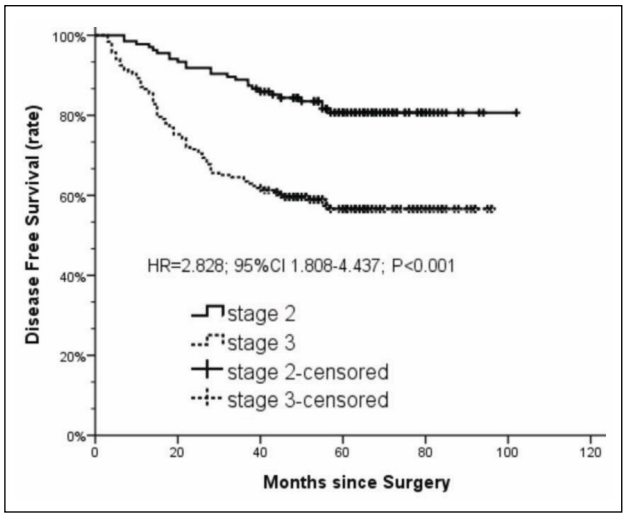

Fig. 3. Comparison of stage 2 and stage 3.

tumors (49.7%) (P = 0.040), and the 5-year OS not significantly higher in patients with dMMR tumors, when compared to patients with pMMR tumors (81.3% versus 56.1%, P = 0.059). The survival plots of the MMR status are presented in *Fig. 1*.

The benefit of oxaliplatin-based chemotherapy

The 5-year DFS of patients treated by mFOLFOX6/XELOX and surgery alone was 70.0% and 56.2%, respectively (HR: 1.589, 95% CI: 1.060 – 2.382, P = 0.025). The 5-year OS rate between oxaliplatin-based chemotherapy and surgery alone was 75.5% and 61.9%, respectively (HR: 1.846, 95% CI: 1.199 – 2.844, P = 0.005), confirming that oxaliplatin-based adjuvant chemotherapy improves the prognosis of colon cancer. In stage III colon cancer, DFS and OS were longer in patients who received oxliplatin-based adjuvant chemotherapy (n = 156), when compared to patients treated with surgery alone (n = 33), in the survival analysis (62.2% versus 33.3%, P < 0.001; 68.6% versus 39.4%, P < 0.001). In high-risk stage II colon cancer, OS was longer in patients who received adjuvant chemotherapy (n = 86), when compared to patients treated with surgery alone (n = 49), in the survival analysis (89.5% versus 75.5%, P = 0.026), while DFS was not statistically and significantly longer (86.0% versus 73.5%, P = 0.079).

The relationship between the benefit of oxaliplatin-based chemotherapy and mismatch repair status

For patients with pMMR tumors, the 5-years DFS was significantly higher in oxaliplatin-based chemotherapy (67.8%), when compared to surgery alone (49.7%) (HR: 0.820, 95% CI: 0.683 – 0.984, P = 0.033). Furthermore, the OS was also higher in oxaliplatin-based chemotherapy (72.7%), when compared to surgery alone (56.7%) (HR: 0.781, 95% CI: 0.642 – 0.950, P = 0.014). For patients with dMMR tumors, oxaliplatin-based chemotherapy revealed no statistical significance in DFS or OS, when compared to surgery alone (DFS: 80.6% versus 81.3%, HR: 1.071, 95% CI: 0.580 – 1.979, P = 0.826; OS: 88.6% versus 81.3%, HR: 1.650, 95% CI: 0.394 – 6.919, P = 0.493). The survival plots of MMR status and treatment are presented in *Fig. 2*.

Univariate and multivariate analysis of disease-free survival

Among the variables analyzed in the univariate Cox model (age, gender, tumor location, differentiation grade, bowel obstruction, tumor stage, MMR and treatment model), merely age (< 65 versus ≥ 65: HR: 1.689, 95% CI: 1.154 – 2.472, P = 0.007), gender (males versus females: HR: 1.499, 95% CI: 1.023 – 2.195), tumor stage (stage II versus III: HR: 2.866, 95% CI: 1.829 – 4.491, P < 0.001), MMR status (dMMR versus pMMR: HR: 2.236, 95% CI: 1.197 – 4.175, P = 0.012), and treatment model (oxaliplatin-based adjuvant chemotherapy versus surgery alone: HR: 0.629, 95% CI: 0.420 – 0.943, P = 0.025) were significantly associated with improved DFS (*Table 2*). The multivariate analysis revealed that merely MMR status, tumor stage and treatment model retained a significant prognostic value for DFS (*Table 3*).

Clinical follow-up results

The mean follow-up period was 70.3 and 67.0 months for the surgery alone group and oxaliplatin-based adjuvant treatment group, respectively (median: 69 and 65 months, respectively). The 5-year DFS and OS was 66.4% and 72.1%, respectively.

DISCUSSION

Chronic inflammation is linked to pathogenesis of colon cancer (8). One of the risk factors is infestation of the digestive tract with pathogenic bacteria since bacterial lipopolysaccharides (LPS). The previous study explored the role of oxidative DNA damage in damaged colonic mucosa and repair of DNA process in experimental animal model of inflammation induced by LPS (9).

It is unlikely that tumors with distinct MMR status would respond similarly to chemotherapeutic agents that damage the DNA. Given that the combination of a fluoropyrimidine with oxaliplatin is the present standard of care, it may be unethical to compare surgery alone versus oxaliplatin-based chemotherapy as an adjuvant treatment. Hence, a retrospective study was conducted to determine whether MMR status could serve as a predictor of survival benefit with oxaliplatin-based chemotherapy. The median follow-up in the present study was 67.5 months, which was sufficient to compare the DFS and OS in the dMMR and pMMR groups.

The present results in patients with stage II or stage III colon cancer confirm the previous reports on the survival benefit for patients with dMMR tumors (10). In the univariate and multivariate analysis, dMMR was associated with improved five-year DFS in patients with stage II or stage III colon cancer. When analyzing the overall population, it was confirmed that patients who received oxaliplatin-based chemotherapy experienced a longer DFS and OS, when compared with patients who received surgery alone. These results were consistent with the result of the MOSAIC and National Surgical Adjuvant Breast and Bowel Project C-07 trials (11, 12). In the present retrospective study, the efficacy of treatment by surgery alone or with oxaliplatin-based chemotherapy in patient subsets were further evaluated.

However, these present findings contrast with an unselected case series of patients with stage III colon cancer, which demonstrated a significant association between the increased duration of survival and patients with dMMR tumors receiving oxaliplatin-based chemotherapy. However, this nonrandomized study has the potential for bias. For example, patients with dMMR tumors, who did not receive oxaliplatin chemotherapy, were 18.6 years older than those who received oxaliplatin-based chemotherapy, in terms of median age. Increasing age has been demonstrated to be significantly and independently associated with poor outcome in patients with CRC, after adjusting for the MMR status of the tumor (13).

Table 2. Univariate analyses between covariates of interest and disease-free survival.

	n	Events	HR	95%CI	P
Age, years	-	-	-	-	-
< 65	198	52	1 [R]	-	-
≥ 65	123	50	1.739	1.179 – 2.565	0.005
Sex	-	-	-	-	-
Male	196	55	1 [R]	-	-
Female	125	47	1.436	0.972 – 2.119	0.069
Tumor location	-	-	-	-	-
-Proximal	164	56	1 [R]	-	-
Distal	157	46	0.846	0.574 – 1.253	0.407
Differentiation grade	-	-	-	-	-
Well/moderate	235	70	1 [R]	-	-
Poor	86	32	1.397	0.919 – 2.123	0.117
Stage	-	-	-	-	-
Stage II	135	25	1 [R]	-	-
Stage III	186	77	2.735	1.741 – 4.296	< 0.001
Treatment model	-	-	-	-	-
Surgery alone	79	34	1 [R]	-	-
Oxaliplain-based chemotherapy	242	68	0.597	0.396 – 0.902	0.014
MMR status	-	-	-	-	-
dMMR	59	10	1 [R]	-	-
pMMR	262	92	2.389	1.244 – 4.591	0.009

R, reference.

Table 3. Multivariate analyses between covariates of interest and disease-free survival.

	n	Events	HR	95%CI	P
Age, y	-	-	-	-	-
< 65	198	52	1 [R]	-	-
≥ 65	123	50	1.400	0.891 – 2.202	0.145
Sex	-	-	-	-	-
Male	196	55	1 [R]	-	-
Female	125	47	1.377	0.930 – 2.039	0.110
Tumor location	-	-	-	-	-
Proximal	164	56	1 [R]	-	-
Distal	157	46	0.849	0.568 – 1.269	0.425
Differentiation grade	-	-	-	-	-
Well/moderate	235	70	1 [R]	-	-
Poor	86	32	1.406	0.916 – 2.150	0.118
Stage	-	-	-	-	-
Stage II	135	25	1 [R]	-	-
Stage III	186	77	3.101	1.934 – 4.973	< 0.001
Treatment model	-	-	-	-	-
Surgery alone	79	34	1 [R]	-	-
Oxaliplain-based chemotherapy	242	68	0.497	0.306 – 0.809	0.005
MMR status	-	-	-	-	-
dMMR	59	10	1 [R]	-	-
pMMR	262	92	2.171	1.108 – 4.253	0.024

R, reference.

To date, there is very limited data on the prognostic/predictive impact of MMR on the chemosensitivity to oxliplatin, and the results remain controversial (14). The study conducted by Zaanan *et al*. enrolled 233 stage III colon cancer patients into two treatments (15) (FL chemotherapy in 124 patients, and FOLFOX chemotherapy in 109 cases), and the 3-year DFS revealed no statistical difference in pMMR patients between the two groups. However, there was a DFS benefit for dMMR patients. Another

two studies revealed that the MMR status was not predictive for oxaliplatin benefits. Li P *et al*. reported an analysis of 255 unselected patients with stage III colon cancer treated by FL or oxaliplatin-based chemotherapy (16).

The present study revealed that oxaliplatin-based chemotherapy may not be beneficial for patients with dMMR. A possible biological explanation for the efficacy of oxaliplatin on tumors is the induction of an antitumor immune response, which has been shown to induce the immunogenic death of colon cancer cells (17, 18). It is noteworthy in this aspect that tumor-infiltrating lymphocytes are particularly abundant in patients with dMMR tumors.

However, these present results were inconsistent with the result of the AGEO study, which mostly contained patients with dMMR colon cancer to overcame the problem of insufficient sample. The study revealed that patients treated with oxaliplatin-based chemotherapy had a statistically and significantly longer DFS, when compared to patients treated with surgery alone. In the subgroup analysis, DFS was longer in patients who received adjuvant oxaliplatin-based chemotherapy, when compared patients treated with surgery alone only in stage III. Furthermore, patients a significantly older age would more likely have a coexisting disease, which is an important reason why some patients are not offered adjuvant treatment. In the present study, the mean age was 62 and 53 years old, respectively, which was significantly lower than that in the AGEO study. Therefore, these present results were less affected by age. In other studies, such as the study conducted by Zaanan *et al*. (15), it was reported that patients with dMMR benefited from oxliplatin-based chemotherapy, when compared with 5Fu-based adjuvant treatment. However, 5-Fu-based chemotherapy may reduce the decreased survival in patients with dMMR. Hence, it is important to compare surgery alone and oxliplatin-based chemotherapy according MMR status.

The present study revealed that MMR status was associated with the benefit of adjuvant oxaliplatin-based chemotherapy in patients with high-risk stage II or stage III colon cancer (19-22). Therefore, oxaliplatin-based chemotherapy is not the best choice for patients with dMMR, especially in patients with Lynch syndrome and stage II dMMR tumors. A recent study on pembrolizumab confirmed that MMR-deficient tumors were more responsive to PD-1 blockade, when compared to MMR-proficient tumors (23, 27). Therefore, there is a need to carry out further studies, including PD-1, in order to determine the optimal adjuvant treatment for patients with dMMTR. The previous study provided an insight on the small-molecule protein inhibitors into mechanism of inhibition of carcinogenesis by blocking the Akt1-FAK interaction responsible for cancer cell adhesion and metastasis (25). Adjuvant colon cancer trials using immunotherapy checkpoint inhibitors is needed to explore further.

There were some limitations in the present study. First, the present trial was merely a retrospective study, and not a randomized controlled trial. Second, the present study was a single-center trial, and the sample size was limited. Third, there was a need to observe the long-term clinical prognosis. Fourth, data are not contemporary, and given that the model showed stage II and II as affecting survival, we should perform the survival analysis by stage II and stage III.

We concluded that patients with dMMR colon cancer are associated with improved survival rates, when compared to patients with pMMR colon cancer. MMR status is an independent prognostic biomarker for DFS in patients with high-risk stage II and stage III colon cancer. Oxaliplatin-based adjuvant chemotherapy mainly benefited patients with pMMR tumors, but this may not benefit patients with tumors exhibiting dMMR.

Conflict of interests: None declared.

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