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Deficient mismatch repair as a prognostic marker in stage II colon cancer patients

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ABSTRACT

Background: A number of reports have evaluated the relationship between deficient DNA mismatch repair (dMMR) and colorectal cancer prognosis. Unfortunately, the exact prognostic role of dMMR has not been clearly established due to contradictory results. This study aims to determine the prognostic impact of dMRR in stage II colon cancer patients only. The appropriate identification of high-risk stage II colon cancers is of paramount importance in the selection of patients who may benefit from adjuvant treatment after surgery.

Methods: Four hundred and fifty-two patients with curative resection of stage II colon cancer were included. Hospital records were used as data source, providing clinical, surgical, pathology, oncology and follow-up information for statistical analysis focusing on overall survival (OS) and time to progression (TTP). Mismatch repair status was determined by immunohistochemistry. Patient survival was followed-up for a mean of 77·35 months.

Results: dMMR was detected in 93 of 452 patients (20·6%). No impact on overall survival (Log-Rank, p = 0·583, 95% CI 0·76–1·67). However, the hazard ratio 0·50 for TTP was highly significant (Log-Rank, p = 0·012, 95% CI 0·28–0·87) in patients with dMMR compared with those with mismatch repair proficient tumours (pMMR).

Conclusions: Patients with dMMR tumours have a lower risk for recurrence compared to those with pMMR tumours, but this finding did not correlate to better overall survival.

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Introduction

Colorectal cancer (CRC) remains a significant healthcare problem world-wide, being the third most common cancer and the fourth most frequent cause of cancer death [1,2]. Among genetic aberrations involved in CRC carcinogenesis, deficient mismatched repair (dMMR) is one of the major pathways. Mismatch repair plays a critical role in the repair of errors that occur spontaneously during DNA replication, such as single base mismatches, short insertions or deletions. dMMR increases mutation frequency in an affected cell approximately 1000 times, leading to microsatellite instability (MSI) through the accumulation of short repetitive DNA sequences called microsatellites. Tumours with dMMR are characterised by high mutation rates that lead to the presence of neoantigens on the cell membrane, allowing the host immune system to develop an effective immunological response. The finding of dMMR is the basis for selection of tumours for novel treatments that attack immunologic checkpoints [3].

Approximately 15% of all CRCs display MSI as a molecular phenotype. In Lynch Syndrome MSI is caused by a germ-line mutation in one of the MMR genes (mostly in MLH1 or MSH2, less frequently in MSH6, PMS2 or EPCAM). Sporadic CRCs with MSI are primarily caused by epigenetic silencing of MLH1. Both forms of MSI colon cancers are characterised by poor differentiation,

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presence of tumour-infiltrating lymphocytes, proximal colon location and associated with female gender and age [4]. The remaining 85% of CRCs develop from the chromosomal instability (microsatellite-stable) pathway, characterised by aneuploidy, allelic losses, amplifications and translocations [5]. The prognostic value of dMMR has been addressed in several studies and systematic reviews, providing contradictory results with respect to overall survival or disease-free survival [6–10]. A major problem of many recent studies has been rather poor methodologic quality such as small sample size, mixed patient populations (CRC stages I-IV evaluated together), heterogeneity of underlying disease (colon vs. rectal cancer), under-reporting of many important clinical variables such as age and gender distribution, adjuvant treatment, and non-standardised statistical endpoints. Because of these shortcomings, a new study on strictly selected stage II colon cancer patients is warranted if we are to clarify the exact impact of dMMR in this population.

The ability to accurately identify high-risk stage II CRC subgroups would allow selection of patients that may to benefit from adjuvant chemotherapy. The present study investigates the potential prognostic value of dMMR status in a cohort of strictly selected stage II patients only.

Materials and methods

Study population

Patients included in this study were treated between 1995 and 2012 at two surgical departments in northern Sweden (one regional and one university hospital) and three university hospitals in the Czech Republic. Inclusion criteria were: i) histologically confirmed colon cancer; ii) curative R0 resection of the primary tumour and lymphadenectomy; iii) pathologically confirmed stage II disease according to the 2002 American Joint on Committee on Cancer (AJCC) TNM classification; iv) necessary demographic data and data regarding the course of the disease; and v) follow-up over a minimum of 5 years [11]. Adjuvant treatment with chemotherapy was allowed but was not mandatory. Exclusion criteria were: i) patients younger than 18 years; and ii) patients with tumour in the rectosigmoid junction and rectum. Unscheduled resection performed during the same admission as diagnosis of the primary tumour was classified as acute surgery. Collected data included demographic information, stage at diagnosis, histological type, differentiation grade, number of lymph nodes examined, vascular and lymphatic invasion, perineural involvement, localisation of the primary tumour, type and duration of adjuvant chemotherapy (oxaliplatin-based, bolus and infusion of 5-fluorouracil, other). The following parameters were used to describe the course of the disease: date of diagnosis; date of surgery; date and site of relapse; and date and cause of death. The last date of follow-up was either the date of death or the last date of contact. Information was mostly obtained through a retrospective search of the hospital records, and for the small number of patients who died, from the National Death Registers in Sweden and the Czech Republic. The study was approved by the Regional Ethics Review Board in Umea University (registration number: 2014/371–31).

Determination of MMR status

Proficiency or deficiency of the MMR system (pMMR and dMMR) was determined by immunohistochemical (IHC) analysis of the protein products of genes involved in DNA MMR. To achieve highest sensitivity, antibodies against all four key MMR proteins (MLH1, MSH2, PMS2 and MSH6) were used to explore the proficiency of the MMR system. The loss of expression of one or more of these proteins indicated deficient MMR [12]. Interpretation of immunohistochemistry results took into account the dependent expression of specific MMR protein heterodimers MSH2/MSH6 and MLH1/PMS2 [13,14].

For patients included from the three university hospitals in the Czech Republic and the regional hospital in Sweden the immunohistochemistry assay was performed as follows: Formalin-fixed, paraffin-embedded tissue was cut into 4-6 μm-thick slices and placed on positively charged glass slides. After deparaffination and rehydration in xylene and ethanol, antigen retrieval in Dako target retrieval solution pH 9 was performed for 40 min at 96 °C. After incubation with the primary antibodies, the Dako visualisation system (DAKO EnVision™+ System, HRP) was applied according to the manufacturer's instructions. For patients from the University hospital in Umea, immunohistochemistry was performed in a similar way but using another semiautomatic immunostaining machine, Ventana (Roche) and reagents used were according to the manufacturer's recommendations [15]. In all cases, internal positive control cells (crypt epithelium, lymphoid aggregates or stromal fibroblasts) were evaluated for comparison prior to tumour tissue assessment. Specimens with no internal positive control were excluded from further evaluation. Only nuclear staining was considered positive. A negative stain result was defined as less than 1% staining of the tumour cell nucleus. Tumours that yielded at least one negative stain were considered to be MMR-protein deficient.

For patients from the Chech Republic and the regional hospital in Sweden, BRAF mutation testing was carried out using Cobas® 4800 BRAF V600 Mutation Test (Roche). Besides the most common mutation V600E (c.1799 T > A) the test can also detect mutations V600K (c.1798_1799delGTinsAA) and V600D (c.1799_1800delTGinsAT). Analytical sensitivity of the assay is approximately 5%. For cases from Umea University Hospital, BRAF was instead detected by a BRAF V600E mutation-specific Taqman allelic discrimination assay (reagents from Applied Biosystems) [16]. In all cases, DNA for analysis was extracted from formalin-fixed, paraffin-embedded (FFPE) specimens either by the DNA Sample Preparation Kit (Roche) or QIAamp® DNA FFPE Tissue Kit (Qiagen), with macrodissection when necessary [17,18]. Percentage of neoplastic cells present in a sample was estimated by a pathologist.

Statistical analyses

Analyses were performed with SAS software IBM version 25.0. The Pearson x^2 test (Fisher exact test if expected numbers in the contingency table were below 5) was used to compare categorical variables, and the Wilcoxon rank sum test was used to compare continuous variables between groups. Survival curves were estimated using the Kaplan-Meier method and compared by mean of the log rank test. The Cox proportional hazards regression model was used for univariate and multivariate analyses. Covariates that were significantly associated with overall survival and those with a p value < 0.2 in the univariate test were included in the multivariate model. All statistical tests were performed as two-sided at a significance level of 0.05 (5%) with 95% confidence intervals.

Overall Survival was defined as the time from the date of surgery to death from any cause. For patients still alive at the end of follow-up, the date of last contact was used as censoring date. Time to progression was defined as the time from the date of surgery to the date of first relapse. Thus, patients without relapse and those with non-cancer-related death were censored and excluded from analysis.

Results

Study characteristics

Of 475 curatively operated patients, 452 were available for statistical analysis (Fig. 1). A total of 324 patients had a resection between January 2002 and December 2012 and were followed until at least the end of 2017, and 128 patients had a resection between January 1995 and December 2003 and were followed until the end of 2012. Median follow up was 77·35 months (79·83 for pMMR and 67·63 for dMMR). Clinical characteristics of the 452 patients and pathological data are shown in Table 1.

dMMR was found in 93 of 452 specimens (20·6%). Associations between MMR status and other variables are shown in Table 1. The interpretation of continuous variables has been simplified by categorisation in all tables. Mean age at diagnosis was 67·8 years and patients were dichotomised at 70 years-of-age (44·5% ≥ 70). The splenic flexure was considered the border between right and left colonic tumours (46·5% right tumours) and was included as left colon [19].

Mutation analysis of pathogenic mutations *BRAF* V600E(K) was carried out in 166 cases. Patients were not further screened for the presence of hereditary cancer syndromes. Sixty-two operations were unscheduled (14%). A minimum of twelve lymph nodes sampled from the surgical specimen and examined was considered to be optimal, but only 46% of specimens achieved this goal [20]. Apart from colon cancer-specific death, other causes of death were recorded such as surgical complications, oncological complications, as well as non-cancer-related and other cancer-related deaths (Table 1).

Overall survival data

One hundred and sixty-two patients (35·80%) died during the study period. Of these, 12 patients with dMMR died due to relapse of their colon cancer. Another 14 patients with a dMMR tumour died of other causes during the follow−up period. There was no significant association in the univariable model between dMMR and overall survival (Log-Rank, p = 0·583, 95% CI 0·76–1·67; Wilcoxon p = 0·263, 95% CI 0·55–1·16; HR 1·28, 95% CI 0·82–1·08, p = 0·323) (Fig. 2, Table 2). The multivariable model adjusted for variables that had a significant association with OS or a p value < 0·2 revealed a significant impact of dMMR. Covariates with a statistically significant association with overall survival were: acute surgery, age over 70 years, less than 12 lymph nodes found in the surgical specimen and the administration of adjuvant treatment. Stepwise removal of non-significant variables in the multivariable model led to loss of dMMR significance when the covariates of acute surgery and number of lymph nodes were removed.

Time to progression

The association between dMMR and decreased risk for relapse

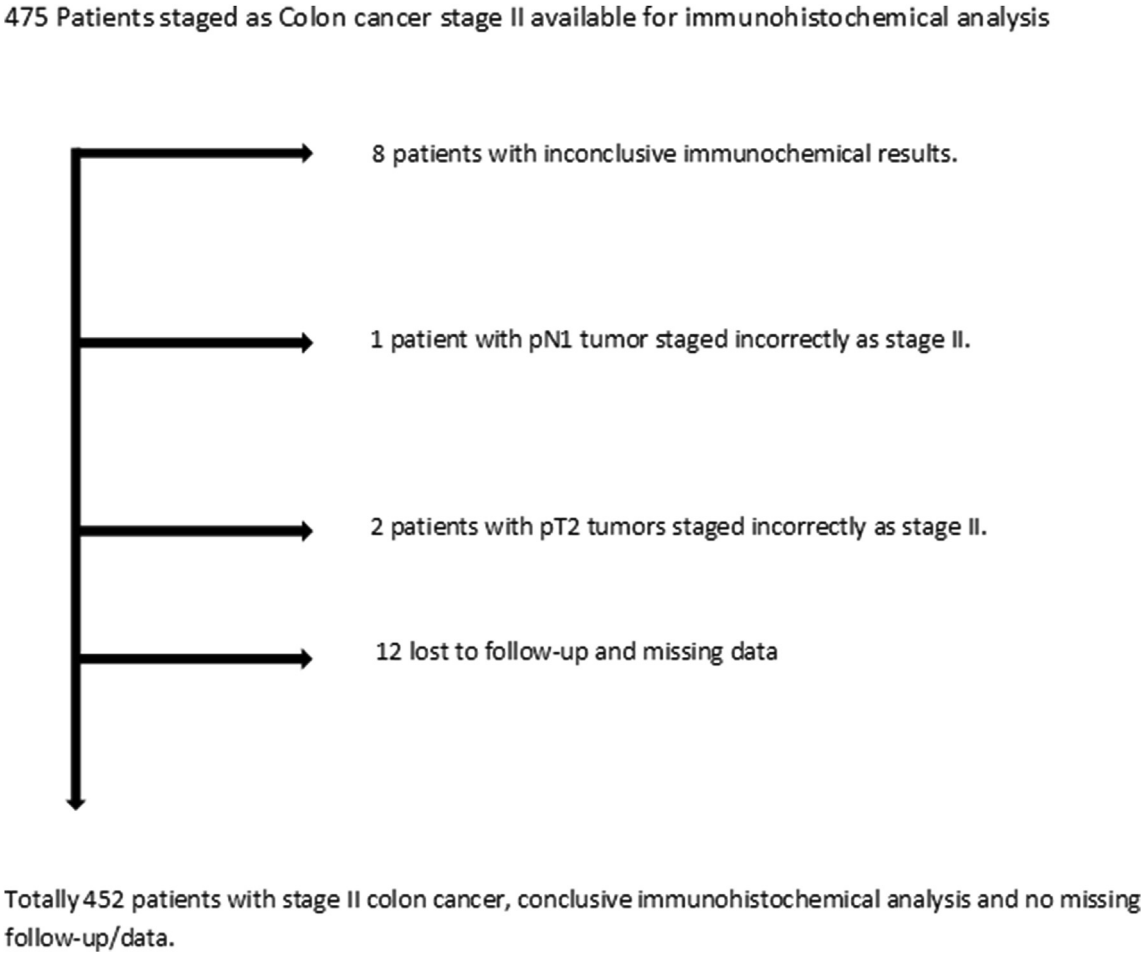

Fig. 1. Details of the included and excluded patients.

Table 1
Clinical and pathological characteristics of cohort of patients studied.

	Deficient MMR		Proficient MMR	
	No.	Per cent [1)]	No.	Per cent [1)]
Age (years)				
<70	42	9·3	209	46.2
≥70	51	11·3	150	33·2
Median	69·4		67·5	
Mean	71·5		66·9	
Range	28–97		29–88	
Median follow up	67·63		79·83	
Gender				
Male	39	8·6	165	36·5
Female	54	11·55	194	43·3
Tumour site				
Right Colon	74	16·4	136	30·1
Left Colon	19	4·2	223	50·67
Acute surgery				
No	85	18·8	305	67·5
Yes	8	1·8	54	11·9
Vascular invasion				
Yes	8	1·8	31	6·7
No	68	15·0	272	61·2
Not determined	17	3·8	56	12·4
Perineural invasion				
Yes	7	1·5	26	5·9
No	59	13·0	237	52·4
Not determined	27	6·0	96	21·2
Lymphatic invasion				
Yes	7	1·5	29	6·4
No	39	8·8	155	34·3
Not determined	47	10·4	175	38·7
T stage				
T3	88	19·5	324	71·5
T4	5	1·1	35	7·9
Lymph nodes examined				
<12	10	2·2	94	20·8
≥12	53	11·7	155	34·3
Not determined	30	6·6	110	24·3
Tumour Type				
Adenocarcinoma	69	15·3	337	74·8
Mucinous	22	4·9	22	4·9
Other				
Not determined	2	0·4	0	0·0
Differentiation grade				
1	8	8·2	40	8·8
2	42	9·3	258	57·1
3	41	9·2	59	13·0
4	0	0·0	1	0·2
1 + 2	50	11·1	298	65·9
3 + 4	41	9·1	60	13·3
Not determined	2	0·4	1	0·2
Adjuvant chemotherapy				
Yes	22	4·9	90	19·9
No	69	15·3	266	58·9
Unknown	2	0·4	3	0·7
Relapse				
Yes	14	3·1	112	24·8
No	79	17·5	247	54·6
Cause of death				
Colon cancer progress	12	2·65	59	13·0
Surgical complication	0	0·0	1	0·2
Oncological complication	0	0·0	0	0·0
Non cancer-related death	14	3·1	55	12·2
Second primary cancer	2	0·4	1	0·2
Unknown	0	0·0	18	4·0

Left colon includes splenic flexure and descending colon. [1)] Given if applicable.

or colon cancer-specific death was highly significant (TTP: HR 0·50, 95% CI 0·28–0·87, p = 0·012) (Fig. 3). Other covariates that were found to have statistical significance for TTP were tumour localisation (HR 0·62, 95% CI 0·43–0·91, p = 0·013) and vascular invasion (HR 3·18, 95% CI 1·74–5·81, p = 0·001). Vascular invasion was the only covariate to retain significance in the multivariable model of the significant covariates and variables with a p value < 0·2 in the univariate analysis. Stepwise removal of non-significant covariates in the multivariable model had no effect on the association between dMMR and TTP, and the significant association with vascular invasion was independent of any removal (Table 3).

Discussion

In the present study, no significant association between dMMR and overall survival was found in patients operated with curative resection for stage II colon cancer. In contrast, dMMR was shown to be a strong prognostic factor for reduced risk for relapse and CRC-specific death. These findings are particularly important in the field of colon cancer treatment.

This failure to document a statistically relevant association between OS and TTP is largely attributable to the relatively good prognosis for stage II patients after surgery [21]. It is well known that microsatellite-instable CRC tumours are generally diagnosed in older patients and mainly in the group of patients with sporadic MSI with epigenetic silencing of the MLH1 gene. This may explain why overall survival is not primarily affected by microsatellite status but more on non-CRC-related deaths that occur more frequently in older patients. Our study supports this hypothesis. We found a higher mean age at diagnosis in patients with an dMMR tumour (26%, p = 0·009) (Appendix S1, supporting information). One might expect that dMMR linked to Lynch Syndrome should decrease the average age of these patients, but on the other hand it is well-known that sporadic colon cancer is more common among elderly patients [22,23], which may counteract and override the effect of hereditary tumours. Most authors do not report on family history or results of genetic testing for hereditary colorectal cancer syndromes. Studies reporting these data describe non-significant differences in age distribution between dMMR and pMMR cohorts [9,24].

Analysis of time to progression shows that dMMR is a strong prognostic factor in colon cancer stage II, regarding relapse and colon cancer-specific death. This implies that dMMR status is likely to be useful in clinical decision-making regarding postoperative adjuvant treatment even if there are studies there its significance is being affected by the plethora of other variables. This observation concurs well with our recent meta-analysis of 19 clinical trials specifically carried out on patients with stage II colon cancer [25]. Patient outcome did not differ significantly between patients with dMMR tumours and those with pMMR tumours (95% CI 0·33–1·65). On the other hand, in an earlier meta-analysis published by Guastadisegni, better overall survival and disease-free survival was found in dMMR patients (HR 0.60, 95% CI 0·53–0·69), but this result is difficult to extrapolate for stage II disease due to heterogeneity of staging in the source data [26].

The strength of this study is that it includes strictly selected stage II colon cancer patients only. All surviving patients were followed for at least 5 years after their colon resection, and the loss to follow-up was minimal. The requirement of at least 10 times as many events as independent variables was satisfied in all multivariate analyses. Furthermore the requirement of 420 patients to avoid type II statistical errors was satisfied.

This study was conducted on a population-based cohort where the only selection bias was the date of diagnosis and the stage of colon cancer. Thus, this cohort reflects the normal clinical situation where the proportion of patients with dMMR (around twenty per cent) compares well with the numbers found in previous meta-analyses (Guastadisegni 17% [26], Ribic 17% [9] and Webber 15% [27]) and is in concordance with our recent meta-analysis [25]. Adjuvant treatment was given to 25% of the patients in this study, a figure that also reflects current treatment recommendations.

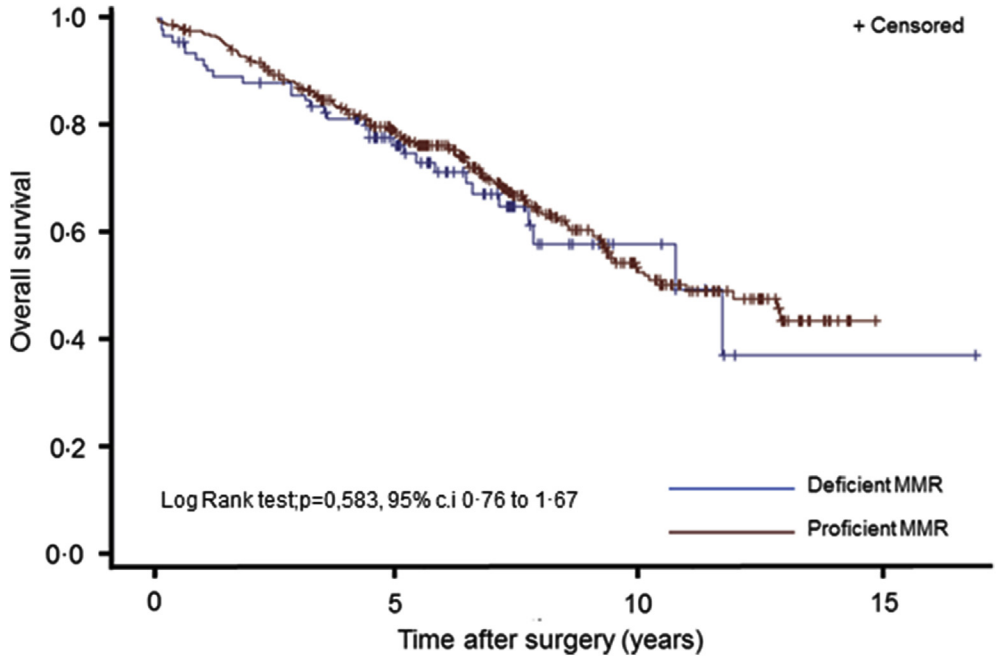

Fig. 2. Overall survival of 452 colon cancer stage II patientsafter curative resections acording to MMR status. Log Rank Test ; p = 0.583.

The dMMR rate was significantly higher in women (58% vs 42%, p = 0.044) (Table 1), (Appendix S1, supporting information). Previous studies have not reported any difference in the male to female ratio [9,22] apart from the CALGB 9581 clinical trial, where a higher proportion dMMR cases among men was reported (male: female ratio 55:45, p = 0.002) [28] and a series of unselected dMMR colorectal tumours displayed opposite results [29].

Stage II colon cancer remains primarily a surgical disease. According to a recent analysis of 164 688 patients recorded and followed in the SEER database, 10-year overall survival reached 71.2% for patients who received adjuvant chemotherapy vs. 50.3% who did not [30]. Chemotherapy was associated with an increase in median survival from 7.0-years to 13.2-years. Survival benefit was described across all patient subgroups. Adjuvant chemotherapy is generally not given to low-risk patients but is reserved for the approximately 20% of patients with a high-risk tumour. Consensually, these tumours are defined as those presenting with ileus, T4 tumours, poorly differentiated tumours without dMMR, tumours with vascular and lymphatic invasion, and perforating tumours. A further indication for adjuvant treatment is inadequate lymphadenectomy [30]. In our study 25% of stage II CC has been administered adjuvant chemotherapy which reflects the modern trend in oncology, even if a higher amount of these patients had less than 12 lymph nodes removed at the time of surgery. There are two main reasons why adjuvant chemotherapy has been omitted in these patients with less than 12 examined lymph nodes. First of all, a large proportion of them, were older patients without other risk factors. The age alone and shorter life expectancy of this population was an important factor that decreased potential benefits of adjuvant treatment. Secondly, it must be emphasized that the concept "12 + lymph nodes as indication of adjuvant chemotherapy" was introduced at the end of the first decade of this century, when surgery of the most of our retrospectively included patients have been already performed [31].

Former studies suggest that dMMR tumours do not respond to adjuvant chemotherapy [32]. In our study 22 dMMR patients (4, 9%) received adjuvant chemotherapy and 5 of them experienced relapse during the study period. On the remainder group, 69 patients were treated only with surgery and 9 of them experienced relapse during the study period. Patient outcome did not differ significantly (p = 0·498).

Several attempts have been made to improve patient selection for adjuvant treatment to avoid unnecessary treatment. One of these strategies includes the determination of MMR system status. Recent clinical studies [4] as well as one meta-analysis [3] found dMMR to be a negative predictor for the efficacy of adjuvant chemotherapy. This would suggest that chemotherapy should be omitted in the treatment of dMMR patients that are otherwise conventionally classified as high-risk. However, other meta-analyses and retrospective studies on cohorts of patients participating in randomised clinical trials indicate a possible positive prognostic value of dMMR [9]. It must be said, however, that as far as stage II colon cancer is concerned, most studies to date do not allow estimation of the impact of dMMR on prognosis. This is because most base their results on data from mixed non-selected cohorts of patients including stages II and III disease, or colon and rectal cancers analysed together. Reports are sometimes biased by the selection of low-risk patients that have not received chemotherapy (mainly pT3 cohorts), while others present results from stage II colon cancers where all patients have received adjuvant treatment regardless of high-risk factors or not. Our meta-analysis was primarily based on carefully selected papers describing data on stage II colon cancer only, and, as already mentioned above, no significance of dMMR on overall survival has been reported [25].

Among the 452 patients in this study, no death could be attribued to postoperative oncological treatment, and only one death was due to surgical complications. These findings reflect the advances made in the quality of both treatments. Another important secondary finding was that there was no difference in survival rate between T3 and T4 tumours, despite the fact that this classification is used in routine clinical practice when deciding on adjuvant chemotherapy [27,28]. Our results also confirm the independent value of vascular invasion in prognosticating poor survival and high relapse rates [33].

Table 2
Univariable and multivariable analyses for Overall Survival in 452 patients with colon cancer stage II.

Variables	Univariable			Multivariable		
	HR	95% CI	p value	HR	95% CI	p value
Gender						
Male	1·00	0·60–1·13	0·230			
Female	0·82					
MMR status						
Proficient	1·00	0·82–1·80	0·323	1·00	1·05–2·93	0·033
Deficient	1·28			1·75		
BRAF						
Wild Type	1·00	0·78–2·04	0·455			
Mutation	1·28					
Acute surgery						
Yes	1·00	0·34–0·74	0·001	1·00	0·21–0·59	0·000
No	0·50			0·35		
Tumour location						
Left	1·00	0·81–1·51	0·507			
Right	1·11					
Age						
<70	1·00	1·57–2·95	0·000	1·00	1·23–2·82	0·000
≥70	2·15			1·87		
T stage						
T4	1·00	0·79–2·68	0·233			
T3	1·45					
Vascular Inv						
No	1·00	0·43–1·23	0·237			
Yes	1·27					
Perineural Inv						
No	1·00	0·40–1·23	0·265			
Yes	1·28					
Lymph Nodes examined						
≥12	1·00	0·93–2·06	0·106	1·00	0·97–2·20	0·073
<12	1·39			1·45		
Tumour Type						
Adenocarcinoma	1·00	0·75–2·17	0·376			
Mucinous	1·27					
Tumour Grade Differentiation						
1 + 2	1·00	0·58–1·22	0·363			
3 + 4	1·16					
Adjuvant Chemotherapy						
No	1·00	0·40–0·86	0·007	1·00	0·92–2·35	0·108
Yes	0·58			1·47		

Left colon includes splenic flexure and descending colon.

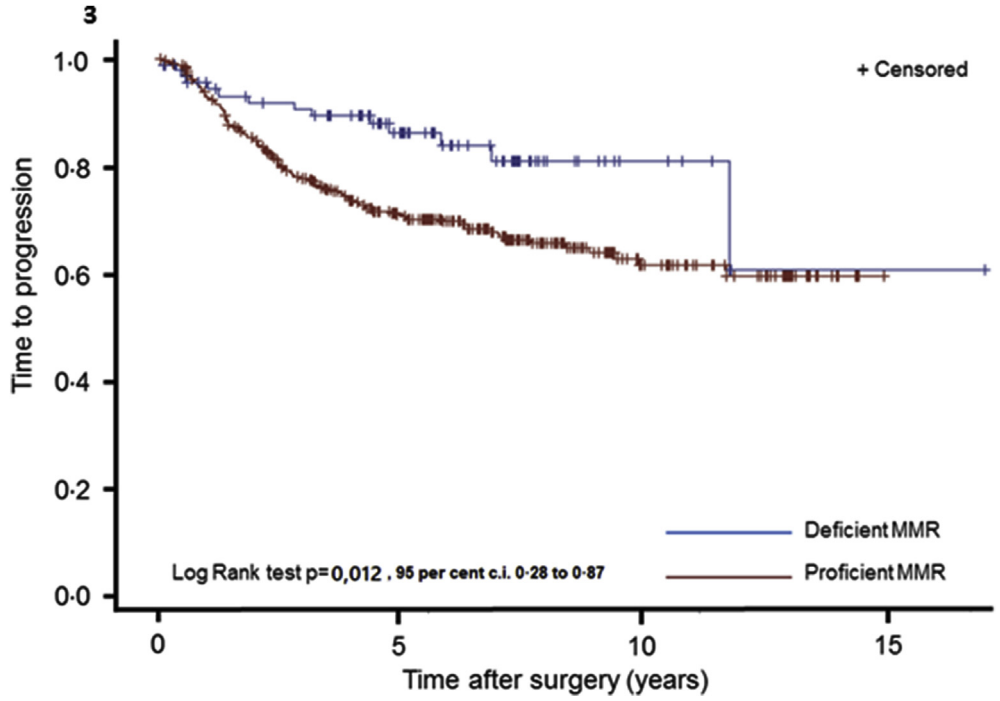

Fig. 3. Time to progression of 452 colon cancer stage II patients after curative resections according to MMR status. Log Rank Test ; p = 0.012.

Table 3
Univariable and multivariable analyses for TTP in 452 patients with colon cancer stage II.

Variables	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Gender						
Male	1·00	0·71–1·48	0·864			
Female	1·03					
MMR status						
Preficient	1·00	0·28–0·89	0·019	1·00	0·32–1·11	0·104
Deficient	0·50			0·60		
BRAF						
Wild Type	1·00	0·34–1·78	0·552			
Mutation	0·78					
Acute surgery						
Yes	1·00	0·58–1·34	0·465			
No	0·84					
Tumour location						
Left	1·00	0·43–0·91	0·013	1·00	0·47–1·10	0·125
Right	0·62			0·71		
Age						
⟨70	1·00	0·53–1·10	0·141	1·00	0·56–1·27	0·404
≥70	0·78			0·83		
T stage						
T4	1·00	0·54–1·72	0·897			
T3	0·96					
Vascular Inv.						
No	1·00	1·74–5·81	0·000	1·00	1·77–5·84	0·000
Yes	3·18			3·18		
Perineural Inv.						
No	1·00	0·49–2·13	0·940			
Yes	1·03					
Lymph Nodes examined						
≥12	1·00	0·61–1·38	0·678			
<12	0·92					
Tumour Type						
Adenocarcinoma	1·00	0·29–1·36	0·236			
Mucinous	0·63					
Tumour Grade Differentiation						
1 + 2	1·00	0·77–1·99	0·378			
3 + 4	1·24					
Adjuvant chemotherapy						
No	1.00	0·81–1·76	0·375			
Yes	1·19					

Left colon includes splenic flexure and descending colon.

Conclusion

In the present study dMMR was not found to have prognostic value in stage II colon cancer patients with respect to overall and disease-free survival. However, we noticed a significantly lower relapse rate in patients with a dMMR tumour.

Disclosure

The authors declare no conflict of interest.

Aknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.05.023.

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