VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer

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See accompanying editorials on page 3207 and 3210

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Submitted November 17, 2009; accepted February 26, 2010; published online ahead of print at www.jco.org on May 24, 2010.

Supported by the North Central Cancer Treatment Group through Grant No. C25224 from the National Cancer Institute.

National Cancer Institute and North Central Cancer Treatment Group had a role in approving the design and conduct of the study but had no role in the collection, management, analysis, or interpretation of the data nor in the preparation, review, or approval of the manuscript.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2820-3219/$20.00

DOI: 10.1200/JCO.2009.27.1825

ABSTRACT

Purpose
Prior reports have indicated that patients with colon cancer who demonstrate high-level microsatellite instability (MSI-H) or defective DNA mismatch repair (dMMR) have improved survival and receive no benefit from fluorouracil (FU) -based adjuvant therapy compared with patients who have microsatellite-stable or proficient mismatch repair (pMMR) tumors. We examined MMR status as a predictor of adjuvant therapy benefit in patients with stages II and III colon cancer.

Methods
MSI assay or immunohistochemistry for MMR proteins were performed on 457 patients who were previously randomly assigned to FU-based therapy (either FU + levamisole or FU + leucovorin; n = 229) versus no postsurgical treatment (n = 228). Data were subsequently pooled with data from a previous analysis. The primary end point was disease-free survival (DFS).

Results
Overall, 70 (15%) of 457 patients exhibited dMMR. Adjuvant therapy significantly improved DFS (hazard ratio [HR], 0.67; 95% CI, 0.48 to 0.93; $P = .02$) in patients with pMMR tumors. Patients with dMMR tumors receiving FU had no improvement in DFS (HR, 1.10; 95% CI, 0.42 to 2.91; $P = .85$) compared with those randomly assigned to surgery alone. In the pooled data set of 1,027 patients (n = 165 with dMMR), these findings were maintained; in patients with stage II disease and with dMMR tumors, treatment was associated with reduced overall survival (HR, 2.95; 95% CI, 1.02 to 8.54; $P = .04$).

Conclusion
Patient stratification by MMR status may provide a more tailored approach to colon cancer adjuvant therapy. These data support MMR status assessment for patients being considered for FU therapy alone and consideration of MMR status in treatment decision making.

J Clin Oncol 28:3219-3226. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Colorectal cancer (CRC) is diagnosed in approximately 145,000 individuals annually in the United States. Since the early 1990s, adjuvant therapy with fluorouracil (FU) and levamisole, and later with leucovorin, has been standard of care for patients with stage III and selected stage II colon cancers.[1-4] Adding oxaliplatin to FU-based therapy additionally improves disease-free and overall survival in patients with stage III disease[5,6]; however, no overall survival benefit in unselected patients with stage II disease is present from adding oxaliplatin.[7]

Pathologic tumor staging remains the key determinant of CRC prognosis and treatment. However, considerable stage-independent outcome variability is observed that likely reflects molecular heterogeneity, which underscores the need for robust prognostic and predictive markers. Although the majority of CRCs develop via a chromosomal instability pathway, approximately 15% have defective DNA mismatch repair (MMR).[8] Defective MMR (dMMR) has frequently been measured by either the presence of microsatellite instability (MSI)[9] or by testing for loss of the protein products for genes involved in DNA mismatch repair, most commonly *MLH1*, *MSH2*, *MSH6*, and *PMS2*. CRCs with dMMR have distinctive features that include proximal colon predominance, poor differentiation and/or mucinous histology, intra- and peritumoral

lymphocytic infiltration, and diploid DNA content.[9-11] High-level MSI (MSI-H) and loss of protein expression of MLHl and MSH2 are highly concordant,[12-14] and *MLH1* and *MSH2* provide similar prognostic ability to MSI.[15]

Numerous retrospective studies, including a meta-analysis, have shown that patients with dMMR CRC have improved stage-independent survival relative to patients with proficient mismatch repair (pMMR).[9,10,16-19] In addition, a predictive role for MMR has been demonstrated by using data from randomized clinical trials of FU-based therapy versus surgery-only control.[20] In these trials, treatment benefit differed by MSI status ($P = .01$), and patients with MSI-H who were treated with FU-based therapy had a trend toward inferior outcomes compared with surgery-alone controls. In contrast, other studies have reported that patients with MSI-H tumors had similar outcomes with chemotherapy[21] or appeared to receive a greater benefit from FU-based adjuvant treatment.[22,23] The contradictory results were based on studies in which patients were not randomly assigned to FU-based treatment versus control, thus allowing for selection bias, shifts in patient populations, or any of the many other pitfalls inherent in nonrandomized comparisons.

To provide an independent validation of the findings of Ribic et al,[20] we established an international collaboration to test the hypothesis that patients whose tumors exhibit dMMR do not benefit from FU-based chemotherapy. Because this is specifically a predictive-factor hypothesis, data from randomized, clinical trials of FU-based treatment versus no-treatment control were required.[24] On the basis of the clinical importance of the question, we pursued the current collaboration to test specimens from all available patients, acknowledging that the low prevalence of dMMR rendered only modest power to detect a statistically significant finding for an interaction effect.[25]

METHODS

Patients

Patients with pathologically confirmed stage II or III colon cancer previously enrolled onto five completed, randomized clinical trials (Federation Francophone de la Cancerologie Digestive [FFCD] 8802, North Central Cancer Treatment Group [NCCTG] 78-48-52, NCCTG 87-46-51, Intergroup [INT] 0035, and Gruppo Italiano Valutazione Interventi in Oncologia [GIVIO]) testing FU with levamisole or leucovorin versus surgery alone as control were enrolled.[1,26-28] All patients who had tissue specimens available but whose specimens had not been used in the previous MSI-based analysis[20] were included. Median follow-up on living patients was 6.1 years. All original clinical trials were approved by the local institutional review boards of each participating site. The protocol for this pooled analysis was approved by the Mayo Clinic Institutional Review Board.

We subsequently present results combining these 507 patients with data from patients from four of five of these same clinical trials that had been used in the previous analyses,[20] as well as patients from one additional completed trial used in the previous analysis (ie, National Cancer Institute Clinical Trials Group study NCI-CTG C-03).[27] This data pooling was deemed appropriate, as all trials randomly assigned patients to surgery-alone control versus FU with levamisole or leucovorin.

MMR Status Determination

MMR status was performed by MSI testing in the GIVIO study (N = 183). MMR status was assessed by using immunohistochemistry (IHC) for all other trials in the new patient cohort. The dMMR was defined by the presence of either high-level MSI (MSI-H) or by loss of protein expression for *MLH1* or *MSH2*. Proficient MMR (pMMR) was defined by the presence of either microsatellite stable/low-level microsatellite instability or the presence of normal protein expressions for both *MLHI* and *MSH2*.

Immunohistochemical Analysis

For patients enrolled on protocols 784852, 874651, and INT0035, formalin-fixed, paraffin-embedded, 5-μm sections were stained by using the Biotek Solutions buffer and Biotek Solutions DAB detection kits (Ventana Medical Systems, Tucson, AZ) and the Tech Mate 500 (Ventana) automated immunohistochemical stainer according to manufacturer's instructions. Staining was performed by using antibodies to *MLH1* (clone G168-728, 1/250; Pharmingen, San Diego, CA) and *MSH2* (clone FE11, 1/50; Oncogene Research Products, Cambridge, MA). For patients enrolled on FFCD 8802, the identical staining was performed for *MLH1*; for *MSH2*, the G219-1129 1/200 BD Pharmingen antibody was used. Protein expression was defined as abnormal (or absent) when nuclear staining of tumor cells was absent in the presence of positive staining in surrounding cells.

MSI Analysis

Extracted DNA from specimens from the GIVIO trial, and for all patients included from the report by Ribic et al,[20] were amplified by polymerase chain reaction by using two to 11 microsatellite markers, as described previously.[16] Tumor samples were classified as displaying high-frequency MSI (instability at $\geq$ 30% of loci screened), low-frequency MSI (instability at $<$ 30% of loci screened), or microsatellite stability (stability at all loci tested). Because extensive data indicate that tumors with low frequency are biologically similar to those exhibiting MSS, these two molecular phenotypes were grouped as MSS.[17]

Fifty-three samples from the GIVIO trial did not have corresponding normal tissue. These samples were analyzed with the BAT25 and BAT26 markers, as previously described.[17] No specimen exhibited instability at only one of these two mononucleotide markers.

Statistical Methods

The primary end point for the study was disease-free survival (DFS), defined as the time from random assignment to death or recurrence of disease,

Table 1. Patient Baseline and Clinical Characteristics

	Patient Group (N = 457)				
	pMMR (n = 387)		dMMR (n = 70)		
Variable	No.	%	No.	%	*P*
Study					.4499
784852	46	90.2	5	9.8	
874651	28	87.5	4	12.5	
FFCD 8802	96	80.7	23	19.3	
GIVIO	153	83.6	30	16.4	
INT 0035	64	88.9	8	11.1	
Age, years					.6415
$<$ 50	52	88.1	7	11.9	
50-60	95	81.2	22	18.8	
60-70	167	85.6	28	14.4	
$\geq$ 70	73	84.9	13	15.1	
Stage					.0063
II	174	79.8	44	20.2	
III	213	89.1	26	10.9	
Grade					.0022
Missing	7		3		
Low	340	87.2	50	12.8	
High	40	70.2	17	29.8	
Treatment status					.6058
Control	191	83.8	37	16.2	
Treated	196	85.6	33	14.4	

Abbreviations: dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair; FFCD, Federation Francophone de la Cancerologie Digestive; GIVIO, Gruppo Italiano Valutazione Interventi in Oncologia; INT, Intergroup.

Table 2. DFS and OS by MMR and Treatment Status in Univariate and Multivariate Models Adjusted for Stage, Sex, and Age

MMR and Treatment Status	No. of Patients (N = 457)	DFS 5-Year Rate (%)	DFS Univariate HR	DFS Univariate 95% CI	DFS Univariate P	DFS Multivariate HR	DFS Multivariate 95% CI	DFS Multivariate P	OS 5-Year Rate (%)	OS Univariate HR	OS Univariate 95% CI	OS Univariate P	OS Multivariate HR	OS Multivariate 95% CI	OS Multivariate P
Untreated	228														
dMMR	37	76	0.46	0.22 to 0.95	.03	0.58	0.26 to 1.28	.17	81	0.51	0.24 to 1.10	.06	0.62	0.28 to 1.37	.24
pMMR	191	53							62						
Treated	229														
dMMR	33	71	0.90	0.44 to 1.82	.77	0.76	0.36 to 1.63	.48	75	0.73	0.35 to 1.54	.41	0.58	0.26 to 1.30	.19
pMMR	196	64							71						
dMMR	70														
Untreated	37	76	1.44	0.55 to 3.81	0.46	1.39	0.46 to 4.15	.56	81	1.19	0.43 to 3.27	.74	1.04	0.32 to 3.35	.95
Treated	33	72							75						
pMMR	387														
Untreated	191	53	0.67	0.49 to 0.93	.02	0.67	0.48 to 0.93	.02	62	0.75	0.54 to 1.05	.09	0.76	0.54 to 1.06	.11
Treated	196	64							71						

Abbreviations: DFS, disease-free survival; OS, overall survival; MMR, DNA mismatch repair; HR, hazard ratio; dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.

whichever occurred first. Overall survival (OS) was the secondary end point. Formal statistical power calculations were not performed, as the goal of this collaboration was to test every available specimen, acknowledging that the scarcity of tissue and the relatively low prevalence of dMMR limited the power available for analyses. Because of inconsistent long-term follow-up between studies, patients without an event were censored on their date of last follow-up, or at 5 years for DFS and 8 years for OS. Cox proportional hazards regression models, stratified by the original protocol, which adjusted analyses for stage, tumor grade, and patient age, were used to compute *P* values, hazard ratios (HRs), and 95% CIs. Among patients with dMMR tumors, there were an inadequate number of events to allow extensive multivariate or stratified models; thus, these models were not stratified and were adjusted only for patient stage. Two-sided *P* values of less than .05 were designated as statistically significant; because of the nature of these analyses as confirmatory to hypotheses previously generated by Ribic et al,[20] these values were not adjusted for multiple comparisons. The primary analyses were conducted in the patients that were not used in previous analyses, and the by-stage and pooled data set analyses were secondary analyses.

RESULTS

Patient Characteristics and Associations With MMR Status

Tumor tissue was available on 507 patients; MMR status was successfully determined in 457 (90%) of these patients. The rates of dMMR were consistent among the five trials; overall, 70 patients (15%) exhibited dMMR (Table 1). Patients with dMMR tumors were more likely to be stage II ($P = .006$) and to have poorly differentiated tumors ($P = .002$). After adjustment for originating clinical trial, stage, and treatment arm, the DFS and OS outcomes for the 457 patients with MMR results did not differ from the complete patient cohorts enrolled onto the original clinical trials.

MMR Status As a Prognostic Marker

In univariate models in patients treated with surgery alone, dMMR status was associated with improved DFS (HR, 0.46; 95% CI, 0.22 to 0.95; $P = .03$) and a trend toward improved OS (HR, 0.51; 95% CI, 0.24 to 1.10; $P = .06$). These trends remained but were not significant in multivariate models (DFS multivariate: HR,= 0.58; 95% CI, 0.26 to 1.28; $P = .17$; OS multivariate: HR, 0.62; 95% CI, 0.28 to 1.37; $P = .24$; Table 2). No association was observed between MMR status and outcome in patients treated with FU-based chemotherapy (DFS: HR, 0.90; 95% CI, 0.44 to 1.82; $P = .77$; OS: HR, 0.73; 95% CI, 0.35 to 1.54; $P = .41$).

MMR Status As a Predictive Marker

No benefit in DFS from FU-based treatment was observed for patients with dMMR status (multivariate DFS: HR, 1.39; 95% CI, 0.46 to 4.15; $P = .56$), whereas treatment was of benefit in patients with pMMR tumors (multivariate DFS: HR, 0.67; 95% CI, 0.48 to 0.93; $P = .02$; Table 2). Inadequate sample size prohibited a by-stage analysis in patients with dMMR tumors. In patients with stage III disease and pMMR tumors, a clear DFS benefit from treatment was observed (HR, 0.56; 95% CI, 0.37 to 0.83; $P = .004$). No DFS benefit from treatment was present in patients with stage II disease and

Table 3. Demographics and Overall Outcome in the Two Data Sets

Variable	Data Set (N = 1,027) Current (n = 457) No.	Current %	Ribic[20] (n = 570) No.	Ribic %
Stage				
II	218	47.7	312	54.7
III	239	52.3	258	45.3
Treatment				
Surgery alone	228	49.9	287	50.4
FU	229	50.1	283	49.6
MMR status				
pMMR	387	84.7	475	83.3
dMMR	70	15.3	95	16.7
5-year OS, %	68		73	

Abbreviations: FU, fluorouracil; MMR, DNA mismatch repair; pMMR, proficient DNA mismatch repair; dMMR, defective DNA mismatch repair; OS, overall survival.

Table 4. DFS and OS by MMR and Treatment Status in Univariate and Multivariate Models Adjusted for Stage, Sex, and Age in the Pooled Data Set

MMR and Treatment Status	No. of Patients (N = 1,027)	DFS							OS						
		5-Year Rate (%)	Univariate			Multivariate			5-Year Rate (%)	Univariate			Multivariate		
			HR	95% CI	*P*	HR	95% CI	*P*		HR	95% CI	*P*	HR	95% CI	*P*
Untreated	515														
dMMR	79	80	0.41	0.24 to 0.70	.001	0.51	0.29 to 0.89	.009	85	0.42	0.24 to 0.72	.001	0.47	0.26 to 0.83	.004
pMMR	436	56							66						
Treated	512														
dMMR	86	70	0.98	0.64 to 1.51	0.93	0.79	0.49 to 1.25	.30	73	0.95	0.62 to 1.48	.83	0.78	0.49 to 1.24	.28
pMMR	426	67							74						
dMMR	165														
Untreated	79	80	1.61	0.84 to 3.10	.15	1.53	0.78 to 3.04	.22	85	1.58	0.81 to 3.09	.18	1.56	0.77 to 3.16	.21
Treated	86	70							73						
pMMR	862														
Untreated	436	56	0.69	0.55 to 0.86	.001	0.70	0.56 to 0.88	.002	66	0.73	0.58 to 0.91	.006	0.74	0.59 to 0.94	.01
Treated	426	67							74						

Abbreviations: DFS, disease-free survival; OS, overall survival; MMR, DNA mismatch repair; HR, hazard ratio; dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.

pMMR tumors (HR, 1.01; 95% CI, 0.56 to 1.83; $P = .98$). An interaction test between MMR status and treatment efficacy from the multivariate stratified Cox model for DFS was not significant ($P = .18$). All findings were consistent in terms of direction of association and statistical significance for the OS end point (data not shown).

Pooled Data

On the basis of strongly consistent findings in the 457 patients with the findings of our previous report,[20] the two data sets were combined to facilitate by-stage and multivariate analyses. Patient demographics and overall outcomes were similar in the two data sets (Table 3).

MMR Status As a Prognostic Marker in the Pooled Data

In the pooled data set, MMR status was a significant prognostic marker (Table 4; Fig 1). In patients not treated with FU-based therapy, dMMR status was associated with improved DFS (HR, 0.51; 95% CI, 0.29 to 0.89; $P = .009$) and OS (HR, 0.47; 95% CI, 0.26 to 0.83; $P = .004$; Fig 1A). No association was observed between MMR status and outcome in FU-treated patients (DFS: HR, 0.79; 95% CI, 0.49 to 1.25; $P = .30$; OS: HR, 0.78; 95% CI, 0.49 to 1.24; $P = .28$; Fig 1B).

MMR Status As a Predictive Marker in the Pooled Data

No benefit from treatment was observed in the pooled data set for patients with either stage II (Fig 2A; HR, 2.30; 95% CI, 0.85 to 6.24; $P = .09$) or stage III (Fig 2B; HR, 1.01; 95% CI, 0.41 to 2.51; $P = .98$) disease with dMMR (Table 4). No treatment benefit was present in patients with pMMR and stage II disease (HR, 0.84; 95% CI, 0.57 to 1.24; $P = .38$; Fig 2C). In patients with stage III disease and pMMR tumors (Fig 2D), a benefit from treatment was observed (HR, 0.64; $P = .001$). The interaction test between MMR status and treatment efficacy for DFS was significant ($P = .04$), which indicated that the effect of treatment differs by MMR status. All findings were consistent for the OS end point, with one exception. For the OS end point, there

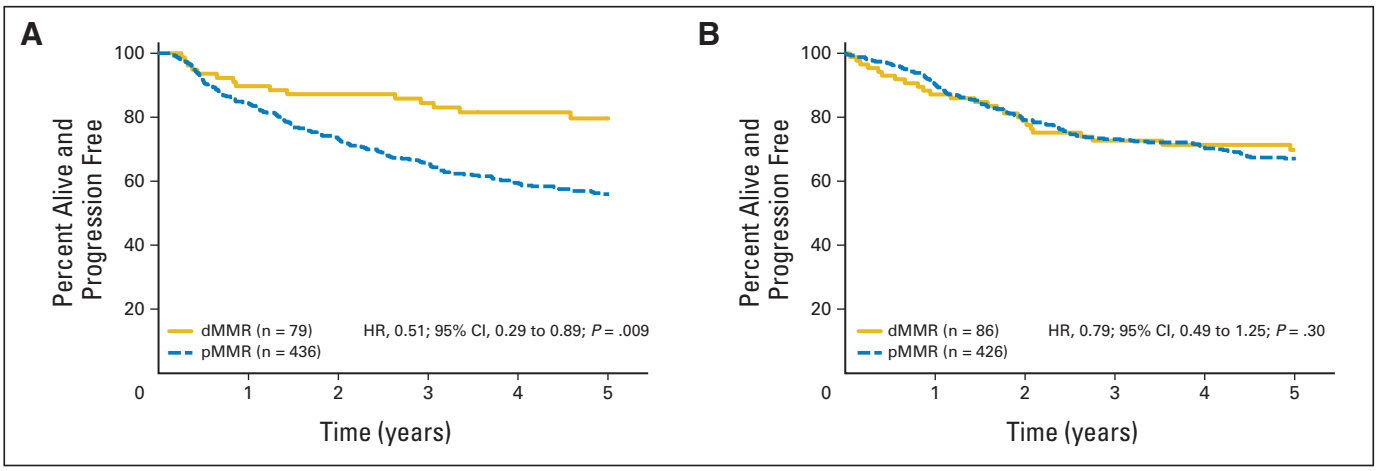

Fig 1. (A) Disease-free survival (DFS) in untreated patients by DNA mismatch repair (MMR) status. (B) DFS in treated patients by MMR. dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.

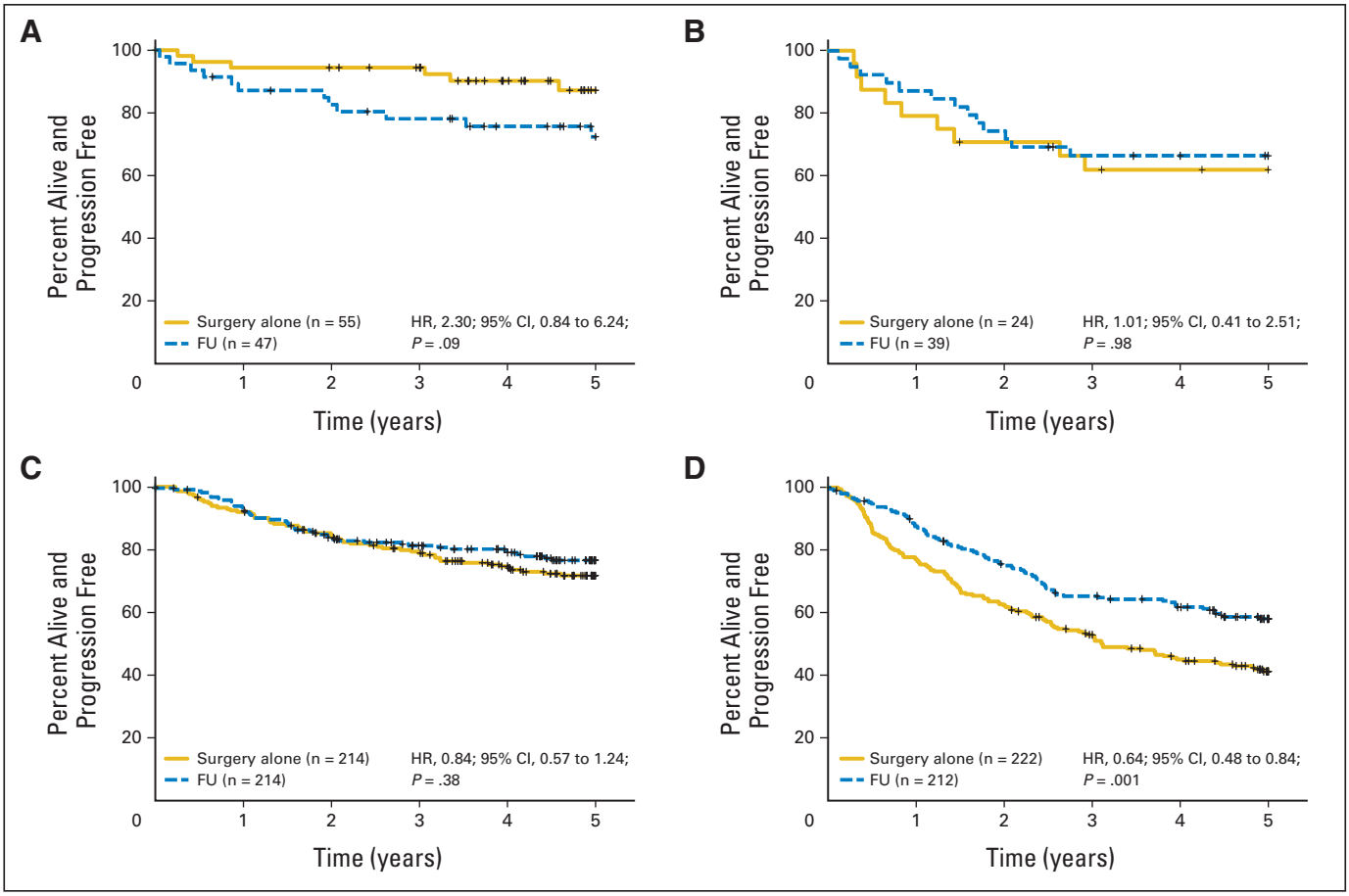

Fig 2. (A) Disease-free survival (DFS) in patients with stage II disease and defective DNA mismatch repair (dMMR) by treatment status. (B) DFS in patients with stage III disease and dMMR by treatment status. (C) DFS in patients with stage II disease and proficient MMR (pMMR) by treatment status. (D) DFS in patients with stage III disease and pMMR by treatment status. HR, hazard ratio; FU, fluorouracil.

was a statistically significant decreased OS in patients with stage II disease and dMMR tumors who were treated compared with patients in the surgery-alone control (HR, 2.95; 95% CI, 1.02 to 8.54; $P = .04$).

DISCUSSION

Adjuvant fluoropyrimidine-based therapy in patients with stage III colon carcinoma is the standard of care worldwide; however, it remains controversial for patients with stage II disease. An American Society of Clinical Oncology (ASCO) panel in 2004 concluded that routine administration of adjuvant therapy in stage II colon cancers was not recommended.[29] Pooled analyses have demonstrated a modest 2% to 4% benefit in 5-year DFS for FU-based adjuvant therapy in stage II colon cancer,[29,30] findings which were verified in the recent QUASAR (Quick and Simple and Reliable) study (5-year OS, 80.3% for chemotherapy, 77.4% for observation; HR, 0.83; $P = .02$).[31] The QUASAR data, coupled with updated results from the MOSAIC (Multicenter International Study of Oxaliplation/5FU-LV in the Adjuvant Treatment of Colon Cancer) trial demonstrating no benefit for adding oxaliplatin to FU/leucovorin in unselected patients with stage II disease[7] or even high-risk patients with stage II disease,[32] support single-agent, fluoropyrimidine-based therapy as the preferred therapy for a patient with stage II disease in whom chemotherapy is deemed appropriate.

The modest therapeutic benefit of FU-based therapy in patients with stage II disease emphasizes the need for prognostic and predictive markers to risk-stratify patients. Fundamental principles of clinical trials require that predictive marker validation be from trials that randomly assigned patients between the treatments for which the marker is purported to predict differential efficacy. To our knowledge, only the previous report of Ribic et al[20] and the current analysis meet this level of evidence.

Our findings in the independent data set assembled for this project are consistent and supportive of the findings of Ribic et al.[20] MMR status was a significant prognostic factor in untreated patients in univariate analysis. Although the prognostic effect was not maintained in multivariate models, the estimated HRs suggest a strong protective effect. The prognostic importance of dMMR has been additionally confirmed recently in two large studies of patients with stage II disease.[33,34] Regarding dMMR as a predictive factor, in multivariate models no benefit of treatment was observed in patients with dMMR tumors (HR, 1.39; $P = .56$).

The new data presented support MMR status as a clinically useful marker in patients being considered for fluoropyrimidine-based therapy, in particular in patients with sporadic stage II colon cancer. First, the favorable prognosis of patients with dMMR (v pMMR) colon

cancers supports a no–adjuvant-treatment approach, a strategy already implemented in the ongoing US Intergroup trial E5202. Second, the lack of benefit from FU-based chemotherapy in patients with dMMR tumors indicates that such patients should not receive FU-based adjuvant chemotherapy. A recommendation for observation can spare such patients treatment-related toxicities, expense, and reduced quality of life during chemotherapy.

Our data do not support pMMR as a sole risk factor to recommend adjuvant treatment for patients with stage II disease. MSS and MSI-L tumors comprise the majority (80% to 85%) of colorectal cancers at all stages. In patients with pMMR tumors, decisions regarding adjuvant therapy should be based on other factors that indicate a high-risk patient, such as a T4 tumor, tumor perforation, bowel obstruction, poor differentiation, venous invasion, or fewer than 12 lymph nodes examined.[5]

Although the presence of dMMR appears to be an important predictive marker for stage II colon cancer, there are several cautionary notes. Patients in this analysis were drawn from multiple clinical trials conducted between 20 and 30 years ago in multiple countries. However, we felt the need to obtain data from the scarce trials that included a randomly assigned surgery-alone control arm outweighed this limitation. Second, although the current study and others[35,36] provide substantial evidence that patients with dMMR colon cancers do not benefit from adjuvant FU/leucovorin, the current standard adjuvant therapy for stage III disease is infusional fluorouracil, leucovorin, and oxaliplatin. Preliminary data suggests that adding either oxaliplatin or irinotecan to FU/leucovorin may overcome the resistance observed to FU/leucovorin in patients with dMMR[37,38]; however, this requires confirmation in samples from randomized trials. Thus available data do not justify excluding patients with stage III disease and dMMR tumors from infusional fluorouracil, leucovorin, and oxaliplatin chemotherapy.

The molecular etiology of tumors involving dMMR is heterogeneous, involving several different genes and numerous mechanisms of gene inactivation, including epigenetic, somatic and germline alterations. Among sporadic colon cancer, the vast majority of occurrences with dMMR are due to inactivation of *MLH1* (approximately 95%), and *MSH2* and *MSH6* account for a much smaller percentage (approximately 5% and less than 1%, respectively).[39] For *MLH1*, the most common mechanism (approximately 90%) of gene inactivation is promoter hypermethylation.[40] In this series, tissue was inadequate to allow hypermethylation and/or *BRAF* testing. However, as the vast majority of clinical trials represent unselected patients, the majority of dMMR occurrences will almost certainly be due to loss of *MLH1* from promoter hypermethylation. Thus, the results derived from these trials primarily reflect the biology of sporadic *MLH1* occurrences. Because dMMR tumors arising from other mechanisms represent a small subset of patients, we are not able to determine the prognostic and/or predictive value of MMR status in such patients. A final caution recognizes that, although greater than 1,000 occurrences were obtained for this pooled analysis, the absolute number of dMMR occurrences remains modest. To our knowledge, a single, large trial—the QUASAR study[31]—remains possibly available to additionally confirm these findings[30]; analyses of the predictive value of dMMR in that study are of interest.

Several hypotheses have been proposed to provide biologic mechanism(s) by which FU-based adjuvant chemotherapy does not benefit patients with dMMR. Possibilities include an antitumor immune response characterized by the lymphocytic infiltrate characteristic of dMMR tumors,[41] which may be abrogated by the immunosuppressive effects of chemotherapy. In vitro studies have predicted differential efficacy of FU between dMMR versus pMMR tumors.[42,43] A final hypothesis relates to the role of MMR systems in the removal of FU from DNA, whereby the absence of MMR may reduce repair DNA synthesis and thus attenuate the FU effect.[44] The biologic question of whether FU-based adjuvant chemotherapy is of no benefit or is actually harmful in patients with dMMR tumors is not conclusively addressed by this study; however, neither possibility supports adjuvant treatment for such patients.

Extensive research is ongoing to identify multigene signature panels that are prognostic, predictive, or both in patients with stages II and III colon cancer.[34,45-48] The relative utility of dMMR as a single test versus these multigene panels remains unknown; an initial report suggests that, for one panel, the two methods provide independent prognostic ability.[34] It seems likely that MMR status may ultimately become integrated into a multigene panel.

In conclusion, this prospectively specified analysis of data from randomized, clinical trials provides independent, supportive evidence of the following: dMMR colon cancers have a favorable stage-adjusted prognosis compared with the majority of colon cancers; and patients with dMMR colon cancers do not benefit from FU-based adjuvant therapy. These findings support the conclusion that average-risk patients with colon cancer who are considered for FU-based adjuvant therapy should have the tumor MMR status assessed to inform the likelihood of patient benefit of chemotherapy. Our conclusions are restricted to patients being considered for single-agent, fluoropyrimidine-based therapy (ie, patients with stage II disease), and the conclusions provide guidance as to who should not be treated (ie, the dMMR subset). We believe that dMMR status in the setting of stage II disease should be considered a clinically useful marker of tumor biology and represents an additional step in individualized cancer therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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