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Role of Deficient DNA Mismatch Repair Status in Patients With Stage III Colon Cancer Treated With FOLFOX Adjuvant Chemotherapy

A Pooled Analysis From 2 Randomized Clinical Trials

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IMPORTANCE The prognostic impact of DNA mismatch repair (MMR) status in stage III colon cancer patients receiving FOLFOX (folinic acid, fluorouracil, and oxaliplatin) adjuvant chemotherapy remains controversial.

OBJECTIVE To determine the association of MMR status with disease-free survival (DFS) in patients with stage III colon cancer treated with FOLFOX.

DESIGN, SETTING, AND PARTICIPANTS The evaluated biomarkers for MMR status were determined from prospectively collected tumor blocks from patients treated with FOLFOX in 2 open-label, phase 3 randomized clinical trials: NCCTG N0147 and PETACC8. The studies were conducted in general community practices, private practices, and institutional practices in the United States and Europe. All participants had stage III colon adenocarcinoma. They were enrolled in NCCTG N0147 from February 2004 to November 2009 and in PETACC8 from December 2005 to November 2009.

INTERVENTIONS Patients in the clinical trials were randomly assigned to receive 6 months of chemotherapy with FOLFOX or FOLFOX plus cetuximab. Only those patients treated with FOLFOX alone were included in the present study.

MAIN OUTCOMES AND MEASURES Association of MMR status with DFS was analyzed using a stratified Cox proportional hazards model. Multivariable models were adjusted for age, sex, tumor grade, pT/pN stage, tumor location, ECOG (Eastern Cooperative Oncology Group) performance status, and *BRAF* V600E mutational status.

RESULTS Among 2636 patients with stage III colon cancer treated with FOLFOX, MMR status was available for 2501. Of these, 252 (10.1%) showed deficient MMR status (dMMR; 134 women, 118 men; median age, 59 years), while 2249 (89.9%) showed proficient MMR status (pMMR; 1020 women, 1229 men; median age, 59 years). The 3-year DFS rates in the dMMR and pMMR groups were 75.6% and 74.4%, respectively. By multivariate analysis, patients with dMMR phenotype had significantly longer DFS than those with pMMR (adjusted hazard ratio, 0.73; 95% CI, 0.54-0.97; $P = .03$).

CONCLUSIONS AND RELEVANCE The deficient MMR phenotype remains a favorable prognostic factor in patients with stage III colon cancer receiving FOLFOX adjuvant chemotherapy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00079274 for the NCCTG N0147 trial and EudraCT identifier: 2005-003463-23 for the PETACC8 trial.

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Supplemental content

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Adjuvant trials have demonstrated that adding oxaliplatin to fluorouracil is associated with improvement in survival of patients with stage III colon cancer, thereby establishing FOLFOX (folinic acid, fluorouracil, and oxaliplatin) as the current standard of care.[1] A subset of colorectal cancer (CRC) displays a microsatellite instability (MSI) phenotype that is the consequence of deficient DNA mismatch repair (dMMR), due either to a germline mutation in an MMR gene, producing Lynch syndrome, or, more commonly, to epigenetic inactivation of the *MLH1* gene (OMIM 120436) in sporadic cases.[2] Somatic mutations in *BRAF* V600E are enriched in sporadic dMMR subtypes in contrast to a low frequency in CRCs overall.[3]

While most studies have found that patients with dMMR (vs proficient MMR [pMMR]) tumors have a more favorable stage-adjusted prognosis,[4] other studies have not detected a significant difference in clinical outcome[5] or have suggested that any favorable prognostic effect of dMMR is limited to patients with earlier-stage tumors.[6] Furthermore, studies have shown that dMMR tumors may not benefit from fluorouracil-based adjuvant chemotherapy.[4] However, the impact of MMR status remains controversial in the era of the standard FOLFOX adjuvant chemotherapy.

In a pooled analysis, we examined the association of MMR status with disease-free survival (DFS) in patients with stage III colon cancer treated with FOLFOX from 2 phase 3 randomized clinical trials: the trial of the North Central Cancer Treatment Group (NCCTG, now part of the Alliance for Clinical Trials in Oncology) N0147[7] (Supplement 1) and the PETACC8 trial (Supplement 2).[8]

Key Points

Question What is the role of deficient DNA mismatch repair (MMR) in stage III colon cancer in the era of standard FOLFOX (folinic acid, fluorouracil, and oxaliplatin) adjuvant chemotherapy?

Findings This pooled multivariable analysis of data from 2 randomized clinical trials revealed that deficient vs proficient MMR was significantly associated with longer disease-free survival in patients with stage III colon cancer who were treated with FOLFOX alone.

Meanings Future clinical trials in the adjuvant setting should consider MMR status as an important stratification factor.

Methods

Study Population

This pooled analysis included all patient participants in the NCCTG N0147[7] and PETACC8[8] adjuvant randomized phase 3 trials who had signed biological informed consent and whose tumor blocks of resected stage III colon adenocarcinoma were available for analysis. Patients were randomized after surgery to receive 6 months of adjuvant FOLFOX therapy with or without cetuximab, as described previously.[7,8] The present study is restricted to patients treated with FOLFOX alone, since the cetuximab did not improve efficacy in adjuvant setting.[7,8] The NCCTG N0147 trial (NCT00079274) enrolled participants between February 2004 and November 2009; the PETACC8 trial (EudraCT 2005-003463-23) enrolled participants between December 2005 and November 2009. The molecular analysis was centralized at the Mayo Clinic, Rochester, Minnesota, for the NCCTG N0147 trial, and at the European Georges Pompidou Hospital, Paris, France, for the PETACC8 trial.

MMR Status Determination

Mismatch repair (MMR) tumor status was determined by immunohistochemical analysis (IHC) or by MSI testing when IHC findings were indeterminate, as previously described for each trial.[9,10] Tumors with a dMMR phenotype were defined as showing loss of expression of 1 or more MMR proteins by IHC or exhibiting high-level tumor DNA MSI on MSI testing by polymerase chain reaction (PCR). Proficient MMR phenotype tumors were defined as showing intact MMR protein expression on IHC or microsatellite-stable or low-level MSI status on MSI testing.

DNA Extraction and Mutation Analysis

Tumor DNA was extracted from formalin-fixed, paraffin-embedded tissue specimens containing more than 50% tumor cells using the QIAamp DNA Mini Kit (Qiagen). Testing for the *BRAF* V600E hotspot exon 15 mutation (c.1799T>A/p.V600E) and *KRAS* exon 2 mutation was performed as described previously.[9,10]

Statistical Analysis

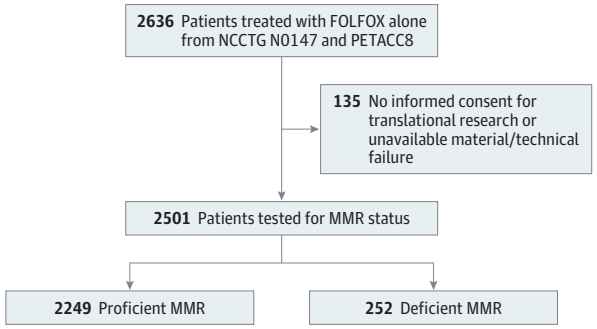
Biomarker status data were analyzed with investigators blinded to patient outcomes. We defined DFS as the time between randomization and local or metastatic recurrence, or death from any cause, whichever occurred first.

For comparisons of baseline characteristics, categorical factors were analyzed with χ^2 tests, and continuous factors were compared with Wilcoxon rank-sum tests. A stratified Cox regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) and to calculate *P* values for candidate prognostic factors.

Thereafter, multivariable analyses were performed on MMR phenotype adjusted for patient age, sex, tumor grade, ECOG (Eastern Cooperative Oncology Group) performance status, pT/pN stage, primary tumor location, and *BRAF* V600E mutational status. Survival curves were estimated with the Kaplan-Meier method and adjusted for the reported covariates.[11] Discriminatory accuracy was tested using the Harrell concordance index. The Harrell *c* index was used to estimate the proportion of correct predictions. The Harrell *c* index ranges from 0.5 (no discrimination) to 1 (perfect discrimination).

Two-sided *P* values are reported; $P < .05$ was considered statistically significant. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc), on a data set locked on June 2015. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center.

Figure 1. Participant Enrollment Flowchart



Included are participants in the NCCTG N0147[7] and PETACC8[8] phase 3 trials evaluating the impact of mismatch repair (MMR) phenotype in patients with stage III colon cancer treated with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) adjuvant chemotherapy.

Results

Patients

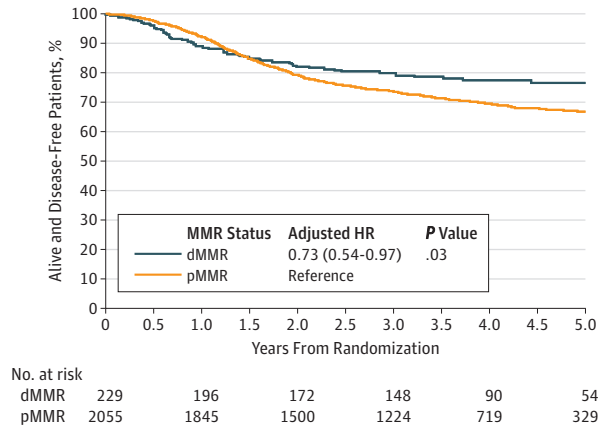
Among 2636 patients with stage III colon cancer treated with FOLFOX alone in the NCCTG N0147 (n = 1669)[7] and PETACC8[8] (n = 967) adjuvant therapy trials, MMR status was available for 2501 patients. Among this study population, 10.1% (252 of 2501) of tumors showed a dMMR phenotype (**Figure 1**). Consistent with prior studies, and with all supporting data reported in the **Table**, dMMR vs pMMR was significantly associated with older age, female sex, higher T stage, higher tumor grade, and proximal location.[4] As expected, mutations of *BRAF* V600E were more often associated with dMMR (36.9%) than with pMMR (6.3%) tumors ($P < .001$) (Table).[6,12] The overall median follow-up was 4.0 years (interquartile range, 3.3-5.0 years).

Table. Demographic and Clinicopathologic Characteristics of Stage III Colon Cancer Patients Treated With FOLFOX Arm From NCCTG N0147 and PETACC8 Trials

Characteristic	MMR Status, No (%) dMMR (n = 252)	pMMR (n = 2249)	*P* Value
Age, y			
Median	59.0	59.0	
<70	208 (82.5)	1977 (87.9)	.01
≥70	44 (17.5)	272 (12.1)	
Sex			.02
Female	134 (53.2)	1020 (45.4)	
Male	118 (46.8)	1229 (54.6)	
ECOG PS			.42
0	192 (78.0)	1773 (79.8)	
1	54 (22.0)	439 (19.8)	
≥2	0 (0.0)	10 (0.5)	
pT stage			.01
pT1-pT2	19 (7.5)	310 (13.8)	
pT3	185 (73.4)	1598 (71.1)	
pT4	48 (19.0)	341 (15.2)	
pN stage			.27
pN1	160 (63.5)	1347 (59.9)	
pN2	92 (36.5)	902 (40.1)	
Tumor grade			<.001
High	121 (48.4)	439 (19.6)	
Low	129 (51.6)	1800 (80.4)	
Tumor site			<.001
Proximal	213 (86.2)	896 (40.5)	
Distal	34 (13.8)	1314 (59.5)	
KRAS exon 2 status			<.001
Wild-type	192 (77.1)	1289 (57.9)	
Mutated	57 (22.9)	937 (42.1)	
BRAF V600E status			<.001
Wild-type	152 (63.1)	1994 (93.7)	
Mutated	89 (36.9)	133 (6.3)	

Abbreviations: dMMR, deficient MMR; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, Mismatch Repair; pMMR, proficient MMR.

Figure 2. Disease-Free Survival



Disease-free survival by MMR phenotype, deficient (dMMR) vs proficient (pMMR), in patients with stage III colon cancer treated with adjuvant FOLFOX (folinic acid, fluorouracil, and oxaliplatin). Survival curves and hazard ratio (HR) with 95% confidence intervals (CIs) are adjusted for age, sex, tumor grade, ECOG (Eastern Cooperative Oncology Group) performance status, pT/pN stage, primary tumor location, and *BRAF* V600E mutational status.

Association of MMR Status and Clinical Outcome

In this study population of patients with stage III colon cancer treated with FOLFOX, there were 701 recurrences and 415 deaths. The 3-year DFS rates in dMMR and pMMR tumors were 75.6% and 74.4%, respectively. In multivariate analysis that included *BRAF* V600E mutational status, compared with the pMMR group, patients with dMMR tumor had a significantly longer DFS (adjusted HR, 0.73; 95% CI, 0.54-0.97; $P = .03$) (Harrell *c* index, 0.67; 95% CI, 0.64-0.70) (**Figure 2**).

Discussion

In the era of FOLFOX adjuvant chemotherapy, the first data concerning the impact of MMR status came from retrospective studies suggesting that the addition of oxaliplatin to fluorouracil may confer survival benefit for patients with stage III dMMR colon cancer.[13,14] Thereafter, post hoc analyses of patients with stage II and III colon cancer (n = 1796) from NSABP-C07 (comparing fluorouracil with and without oxaliplatin) and NSABP-C08 (comparing FOLFOX with and without bevacizumab) trials suggested that the benefit of adding oxaliplatin to fluorouracil was independent of MMR status.[12] Similarly, the analysis of MMR status in patients with stage II and III colon cancer (n = 1008) from the MOSAIC trial suggested that patients with both dMMR and pMMR tumors had a survival benefit from FOLFOX compared with fluorouracil alone, although the number of dMMR tumors analyzed was limited.[15]

In the present pooled analysis of patients with stage III colon cancer treated with FOLFOX in 2 adjuvant trials, we found that the dMMR phenotype was a favorable prognostic factor. Although the Harrell *c* index is of marginal clinical utility (<0.70), our study has several strengths that include prospective tissue biospecimen collection and uniform tumor stage (III only) and treatment of patients enrolled in large recent randomized studies. Our report represents the largest study to date evaluating the relationship of MMR status with clinical outcome for FOLFOX adjuvant treatment. The relatively low benefit in terms of 3-year DFS rates (75.6% vs 74.4%) associated with a significant decrease in the risk of recurrence in multivariate analysis (HR, 0.74) is related to the fact that our study is a post hoc and unplanned analysis with imbalanced subgroups of patients (Table). Therefore, the unadjusted analysis highlights a survival benefit that may appear to be low but is actually clinically meaningful based on multivariate analysis that adjusts the results on clinical and pathological characteristics of these two groups.

Limitations

The main study limitation is the lack of mature follow-up to assess the overall survival.

Conclusions

In conclusion, this large pooled analysis showed that dMMR is a favorable prognostic factor in patients with stage III colon cancer treated with FOLFOX adjuvant chemotherapy. Future clinical trials in the adjuvant setting should consider this molecular characteristic as an important stratification factor.

ARTICLE INFORMATION

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