Microsatellite Instability and Colorectal Cancer Prognosis

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Abstract

Purpose: Many studies have evaluated the role of high levels of microsatellite instability (MSI) as a prognostic marker and predictor of the response to chemotherapy in colorectal cancer (CRC); however, the results are not conclusive. The aim of this study was to analyze the prognostic significance of high levels of MSI (MSI-H) in CRC patients in relation to fluorouracil-based chemotherapy.

Experimental Design: In three different institutions, 1,263 patients with CRC were tested for the presence of MSI, and CRC-specific survival was then analyzed in relation to MSI status, chemotherapy, and other clinical and pathologic variables.

Results: Two hundred and fifty-six tumors were MSI-H (20.3%): these were more frequently at a less advanced stage, right-sided, poorly differentiated, with mucinous phenotype, and expansive growth pattern than microsatellite stable carcinomas. Univariate and multivariate analyses of 5-year–specific survival revealed stage, tumor location, grade of differentiation, MSI, gender, and age as significant prognostic factors. The prognostic advantage of MSI tumors was particularly evident in stages II and III in which chemotherapy did not significantly affect the survival of MSI-H patients. Finally, we analyzed survival in MSI-H patients in relation to the presence of mismatch repair gene mutations. MSI-H patients with hereditary non–polyposis colorectal cancer showed a better prognosis as compared with sporadic MSI-H; however, in multivariate analysis, this difference disappeared.

Conclusions: The type of genomic instability could influence the prognosis of CRC, in particular in stages II and III. Fluorouracil-based chemotherapy does not seem to improve survival among MSI-H patients. The survival benefit for patients with hereditary non–polyposis colorectal cancer is mainly determined by younger age and less advanced stage as compared with sporadic MSI-H counterpart.

Colorectal cancer develops through different genetic pathways. The most common is characterized by the involvement of *APC*, *p53*, and *k-ras* genes, by *18q* allelic loss, and by aneuploid DNA content. These tumors are believed to have followed the chromosomal instability pathway and familial adenomatous polyposis represents the hereditary syndrome dealing with these genetic changes (1).

On the other hand, 15% to 20% of sporadic and most hereditary non–polyposis colorectal cancer tumors follow the so-called MIN pathway due to the loss of proficiency of the DNA mismatch repair system (MMR). These tumors are characterized by a near-diploid DNA content, DNA microsatellite instability (MSI), and the frequent involvement of *TGFBR2*, *BAX*, and, in sporadic cases, *BRAF* genes (2). Beyond genetic changes, pathologic features are substantially different in these tumors as compared with those following the chromosomal instability pathway: MSI tumors are in fact more frequently right-sided and poorly differentiated, and more often display unusual histologic type (mucinous and medullary), and marked peritumoral and intratumoral lymphocytic infiltration. Finally, MSI colorectal carcinomas have been associated with a more favorable clinical outcome (3).

Another important difference between tumors of the chromosomal instability and MIN phenotype concerns the sensibility to diverse chemotherapeutic agents. Since the early 1990s, 5-fluorouracil (5-FU) is the mainstay of chemotherapeutic

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Table 1. Main features of colorectal cancer patients included in the study, according to their MSI status (MSI-H versus MSS)

	Total	MSI-H	MSS	*P*
Patients	1,263	256	1,007	
Gender				
Male	669	123	546	0.07
Female	594	133	461	
Mean age (y ± SD)		63.4 ± 14.3	65.9 ± 16.0	0.06
Cancer site				
Right colon	535	205	330	
Left colon	469	32	437	<0.0001
Rectum	257	17	240	
Stage				
I	126	17	109	
II	491	120	371	0.01
III	461	88	374	
IV	184	31	153	
Histologic type				
Adenocarcinoma	1,052	158	804	<0.0001
Mucinous carcinoma	211	98	113	
Grade				
Well/moderately differentiated	991	144	847	<0.0001
Poorly differentiated	271	112	160	
Growth pattern				
Expansive	797	198	599	<0.001
Infiltrating	454	53	401	
5-FU therapy				
Treated	363	65	298	0.19
Untreated	900	191	709	

NOTE: The differences between the two groups were evaluated using the *t* test for continuous variables, and the χ^2 analysis for categorical values. Statistical significance was set at $P < 0.05$.

treatment of colorectal cancer. Almost all adjuvant chemotherapy regimens involves the use of 5-FU, typically in combination with levamisole or leucovorin. In particular, 5-FU-based adjuvant chemotherapy has been shown to improve survival in patients with stage III colon cancer (4) and among patients with stages II and III rectal cancer (5). During the past 5 years, the efficacy of new drugs, i.e., irinotecan and oxaliplatin (6, 7), have revolutionized the therapy of advanced colorectal cancer. Phase III clinical studies have recently shown a further advantage in stage III colorectal cancer patients who undergo adjuvant treatment with oxaliplatin-based regimens (8). Previous reports regarding *in vitro* models of MMR-deficient colorectal cancer cells indicated a reduced sensitivity to 5-FU and to a variety of clinically important drugs, due in part to the fact that the MMR system can recognize and bind to various types of adducts in DNA as well as to mismatches (9).

Many studies have been addressed in order to evaluate the role of MSI as a prognostic marker in colorectal cancer and also as a predictor of the benefit from 5-FU-based treatment (10–24). Controversial data have been reported (11–15, 18, 20, 21, 23), thus, leaving an area of uncertainty on the usefulness of this biomolecular marker in clinical practice. Based on these reports, we have analyzed the prognostic significance of MSI in a large cohort of colorectal cancer patients in relation to 5-FU-based chemotherapeutic treatment.

Materials and Methods

We collected data on 1,263 consecutive patients with colorectal cancer, diagnosed from 1978 to 2002, who underwent MSI analysis in biomolecular laboratories from three different Italian institutions (University of Ferrara, University of Modena, and University of Verona). Patients from Modena and Verona were addressed to MSI analysis in the context of population-based biomolecular screening for hereditary non–polyposis colorectal cancer or for clinical suspicion of the presence of hereditary colorectal cancer syndromes. Patients from Ferrara were included in large prospective studies evaluating prognostic molecular markers in colorectal cancer. Informed consent was obtained from all the patients, or their relatives, under study. Patients were included in the study only if pathologic material was available and if their chemotherapeutic regimen was known. In these three centers, adjuvant chemotherapy was not administered routinely to patients until 1991. This allowed the inclusion of several patients who did not receive adjuvant chemotherapy. Furthermore, in the three centers in the study period, adjuvant chemotherapeutic regimens in stage II and III were all 5-FU-based whereas other agents, such as irinotecan or oxaliplatin,

were reserved for more advanced disease. This gave us the opportunity to analyze the interaction between MSI and chemotherapy in a homogeneous way avoiding the biases due to the use of different chemotherapeutic agents. Stage (according to the International Union Against Cancer tumor-node-metastasis staging system), grade of differentiation, histologic type, and location of cancers, patient age, gender, and use of chemotherapy were derived from clinical charts and from the archives of each hospital institution. The diagnosis of hereditary non–polyposis colorectal cancer was made on a biomolecular basis, thus, considering only patients with a constitutional mutation in one of the MMR genes as affected by the disease. Follow-up data were retrieved from the computerized archive of health care services of the respective institutions and confirmed by death certificates, clinical charts, and histology report reviews, direct interviews with the patients, with their relatives, or their practitioners.

DNA extraction and microsatellite analysis. DNA was extracted from formalin-fixed, paraffin-embedded tissues of each patient's colorectal tumor and the surrounding normal mucosa. Each area was identified on a reference H&E-stained slide and then microdissected by using a surgical scalpel blade, ascertaining the presence of adequate neoplastic tissue. The dissected specimen was deparaffinized in a microfuge tube with xylene, and then DNA was extracted according to a standard procedure (25). In one institution (University of Ferrara), DNA was obtained from fresh/frozen tissue specimens, as previously reported (18). For determination of MSI, we used the National Cancer Institute–recommended panel of five microsatellite markers (BAT25, BAT26, D5S346, D2S123, and D17S250; ref. 26) plus one additional mononucleotide marker (BAT40; ref. 27) to classify the tumor as MSI-high (MSI-H, the presence of at least two markers showing novel alleles compared with normal tissue), MSI-low (defined as one marker with a novel allele), or microsatellite stable (no marker with novel alleles). Because of the similarities of MSI-low and microsatellite stable tumors, these two groups were considered together as non–MSI-high tumors (MSS group). MSI analysis was conducted through the use of sequence analyzers (Beckman or ABI PRISM377, Applied Biosystems). In most MSI-H cases, immunohistochemical expression of MMR proteins (MLH1, MSH2, and MSH6) was analyzed as previously reported (25, 28). Constitutional mutations in MMR genes were searched through direct sequencing on DNA extracted from blood lymphocytes (25).

Statistical analysis. Colorectal cancer (CRC)–specific survival was computed since the date of cancer diagnosis up to the date of death or end of follow-up (July 31, 2004). Patients who died due to causes unrelated to colorectal cancer were censored at the time of death, whereas patients who died within 1 month from surgical intervention were excluded from the analyses. For survival analyses, the following variables were assessed: age, sex, location of the tumor (colon versus rectum), tumor-node-metastasis stage, histologic type (adenocarcinoma versus mucinous carcinoma), grade of differentiation (well/moderate versus poor), use of 5-FU therapy, and MSI. Five-year survival analyses were done through a Cox proportional hazard function for both univariate and multivariate analyses and Kaplan-Meier curves were plotted. The Cox proportional hazard function

Table 2. Results of univariate and multivariate Cox regression analyses on 5-year–specific colorectal cancer survival of the whole sample

	Univariate analysis		Multivariate analysis	
	Hazard ratios for death (95% confidence interval)	*P*	Hazard ratios for death (95% confidence interval)	*P*
MSI				
MSS	1 ref.		1 ref.	
MSI-H	0.51 (0.39-0.67)	<0.0001	0.46 (0.31-0.68)	<0.001
Gender				
Male	1 ref.		1 ref.	
Female	0.67 (0.53-0.85)	<0.01	0.68 (0.53-0.87)	<0.001
Stage				
I	1 ref.		1 ref.	
II	4.62 (1.88-11.4)		5.51 (2.23-13.7)	
III	10.8 (4.43-26.3)	<0.0001	11.8 (4.84-28.9)	<0.001
IV	36.6 (14.0-95.6)		44.7 (17.1-117.1)	
Histologic type				
Adenocarcinoma	1 ref.		1 ref.	
Mucinous carcinoma	0.79 (0.56-1.14)	not significant	0.96 (0.66-1.40)	not significant
Grade				
Well/moderately differentiated	1 ref.		1 ref.	
Poorly differentiated	1.42 (1.07-1.89)	<0.01	1.62 (1.20-2.19)	<0.001
5-FU therapy				
Untreated	1 ref.		1 ref.	
Treated	1.10 (0.85-1.40)	not significant	0.87 (0.67-1.14)	not significant
Cancer site				
Colon	1 ref.		1 ref.	
Rectum	1.64 (1.28-2.12)	<0.001	1.63 (1.26-2.12)	<0.001
Age	1.016 (1.008-1.024)	<0.001	1.026 (1.016-1.037)	<0.001

NOTE: Patients that died within 1 month after surgical intervention were excluded.

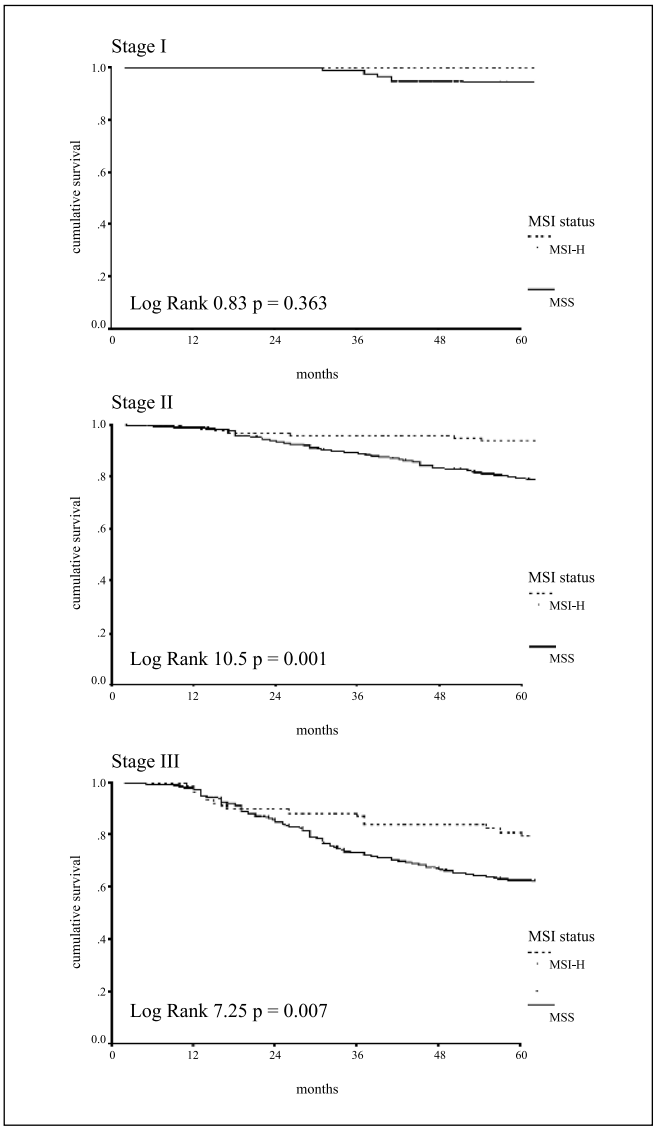

Fig. 1. Kaplan-Meier curves of 5-year – specific survival of patients affected by colorectal cancer in stages I, II, and III by MSI status.

allowed calculation of the relative risk ratio. Univariate and multivariate survival distributions were compared with the use of the log-rank test. Significance for all statistics were recorded if $P < 0.05$.

Results

Of 1,263 patients included in the study, 700 were from Modena, 443 were from Ferrara and the remaining 120 were from Verona. Two hundred and fifty-six tumors from our cohort were MSI-H (20.3%) and the remaining 1,007 were included in the MSS group. MSI-H tumors were more frequently located in the right colon and at less advanced tumor-node-metastasis stage. Furthermore, MSI-H tumors more often displayed poor differentiation, mucinous phenotype, and expansive pattern of growth than MSS carcinomas. We found no significant differences between patients with MSI-H and MSS tumors for 5-FU treatment, age, and gender (Table 1)

Among MSI-H colorectal cancer patients, 162 underwent MMR gene sequence analysis, which showed 57 pathogenic mutations: 34 were in the *hMLH1* gene, 22 were in the *hMSH2* gene, and 1 in the *hMSH6* gene.

One hundred and sixty-three patients with colorectal cancer did not undergo radical surgery (4 in stage II, 6 in stage III, and 153 in stage IV), they were then excluded from the survival analysis; an additional 12 patients were also excluded following death within 1 month from surgical intervention. During the follow-up period (mean time, 64.0 months), there were 288 deaths due to colorectal cancer and 159 deaths due to causes unrelated to CRC. A Cox proportional hazard model for univariate analyses of 5-year–specific survival (Table 2) revealed stage, tumor location, grade of differentiation, MSI, gender, and age as significant prognostic factors. We found no differences in CRC-specific survival on the basis of the use of 5-FU chemotherapy. Cox regression multivariate analysis confirmed the independent effects of stage, grade, MSI, age, and gender on 5-year colorectal cancer–specific survival (Table 2).

We then compared the effect on prognosis of MSI status in each stage. We found statistically significant differences in survival for stages II and III only (Fig. 1). In stage IV, we separately analyzed both overall patients (Fig. 2A) and only those treated surgically with curative intent (Fig. 2B). Similarly, the same results were obtained when colon and rectal cancer were analyzed separately (data not shown).

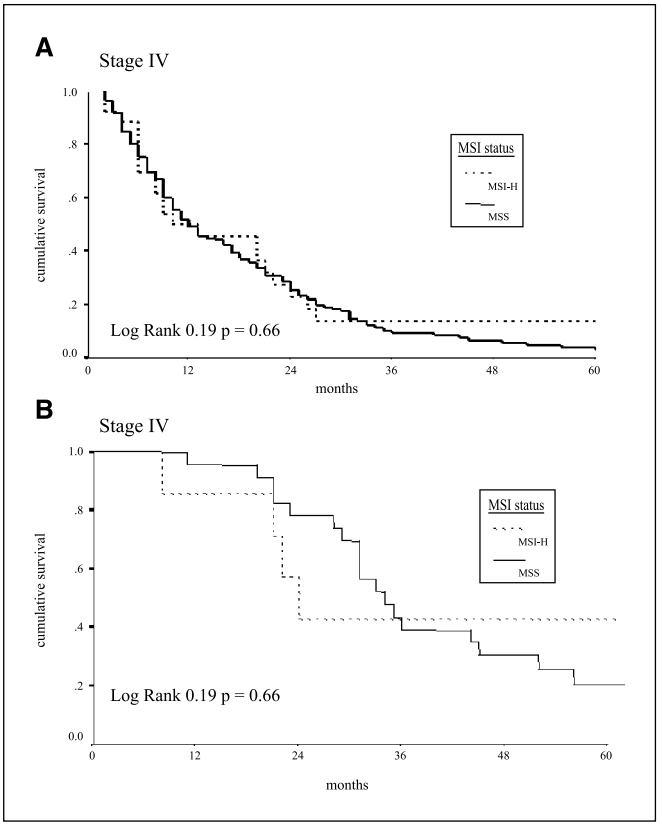

Fig. 2. Kaplan-Meier curves of 5-year – specific survival of patients affected by colorectal cancer in stage IV by MSI status. *A,* all 172 stage IV patients surviving >1 month were analyzed. *B,* only patients who underwent surgery with curative intent were considered.

Table 3. Results of multivariate Cox regression analyses on 5-year–specific survival of patients with stage II and III colorectal cancer

	No.	Hazard ratios for death (95% confidence interval)	*P*
MSI			
MSS	720	1 ref.	
MSI-H	206	0.40 (0.25-0.63)	<0.001
Gender			
Male	483	1 ref.	
Female	443	0.71 (0.55-0.94)	<0.001
Stage			
II	477	1 ref.	
III	449	2.07 (1.56-2.74)	<0.001
Histologic type			
Adenocarcinoma	759	1 ref.	
Mucinous carcinoma	167	0.80 (0.53-1.21)	not significant
Grade			
Well/moderately differentiated	738	1 ref.	
Poorly differentiated	188	1.91 (1.39-2.64)	<0.001
5-FU therapy			
Untreated	622	1 ref.	
Treated	304	0.78 (0.57-1.07)	not significant
Cancer site			
Colon	753	1 ref.	
Rectum	173	1.67 (1.24-2.24)	<0.001
Age		1.03 (1.02-1.04)	<0.001

NOTE: Patients that died within 1 month from surgical intervention and those that did not undergo radical surgery were excluded.

For further analyses, we focused our attention on the effect of 5-FU-based adjuvant chemotherapy in patients with MSI-H and MSS stages II and III tumors. Initially, we used Cox regression model to calculate hazard ratio in multivariate analysis of stages II and III colorectal cancer survival (Table 3). Six variables were shown to be significant in the model: MSI, tumor-node-metastasis stage, grade of differentiation, tumor site, patient's gender, and age. In this cohort, the use of 5-FU-based treatment was not a significant factor for survival. Patients with MSI-H tumors were less likely to die compared with those whose cancer was MSS (hazard ratio, 0.40). Stage III patients had a 2.07-fold higher risk of death than stage II patients, whereas female patients had a 0.71-fold risk with respect to men. Older patients had an increased risk for death (relative risk of 1.03 per year of age), and finally, rectal cancer showed a worse prognosis (hazard ratio, 1.67) in our cohort (Table 3). We then analyzed the effect of chemotherapy separately considering MSI-H and MSS CRC patients. We found no difference in survival among patients whose tumor was MSI-H, irrespective of whether they received 5-FU-based chemotherapy (for those receiving 5-FU therapy: hazard ratio, 0.55; 95% confidence intervals, 0.20-1.69). The same results were found when adjusting for stage (Fig. 3). Even patients with MSS colorectal cancer in stages II and III, when considered as a whole, did not seem to take survival advantage from 5-FU therapy. This also held true in stage II disease, whereas in stage III, we observed a significant survival advantage for patients receiving 5-FU therapy (Fig. 4).

Finally, among patients affected by MSI-H colorectal cancer, 162 were analyzed both for the immunohistochemical expression of MMR proteins (i.e., MLH1, MSH2, and MSH6) and for the presence of germ line MMR gene mutations, which were detected in 57 patients (Table 4). The remaining 105 cases were considered to be sporadic MSI-H. In univariate analysis, we found a significant survival advantage for MSI-H colorectal cancer patients who were carriers of MMR gene mutations as compared with those who were sporadic (Fig. 5). However, in multivariate analysis, classification of tumors as sporadic or hereditary was not selected as an independent prognostic variable (Table 5).

Discussion

Several studies have been addressed to analyze the role of MSI in colorectal cancer prognosis (10–24). Although many authors have reported a better outcome for MSI cases (19–23), the estimates of the prognostic values of this biomolecular marker have varied considerably (10–17), probably owing to the different sample sizes and to the different threshold markers used to assign MSI in each published investigation. To avoid these biases, we conducted our analysis on a very large series of CRC, to our knowledge, one of the largest ever published. Furthermore, we decided

to define MSI using the panel of five markers proposed in the Bethesda guidelines, which should represent a uniform tool for MSI detection, plus BAT40, which is a highly sensitive and specific mononucleotide marker for the identification of MSI (27).

The results of our study clearly show that the type of genomic instability independently influences the clinical outcome of patients with colorectal cancer. In particular, we found differences in survival between patients with MSI-H and MSS tumors in the whole series of cases and, separately, in colon and rectal cancers. The prognostic advantage conferred by the presence of MSI was most evident in stage II and III disease. This confirms the recent results of a systematic review by Popat et al., which was conducted on a large majority of articles published regarding MSI status and

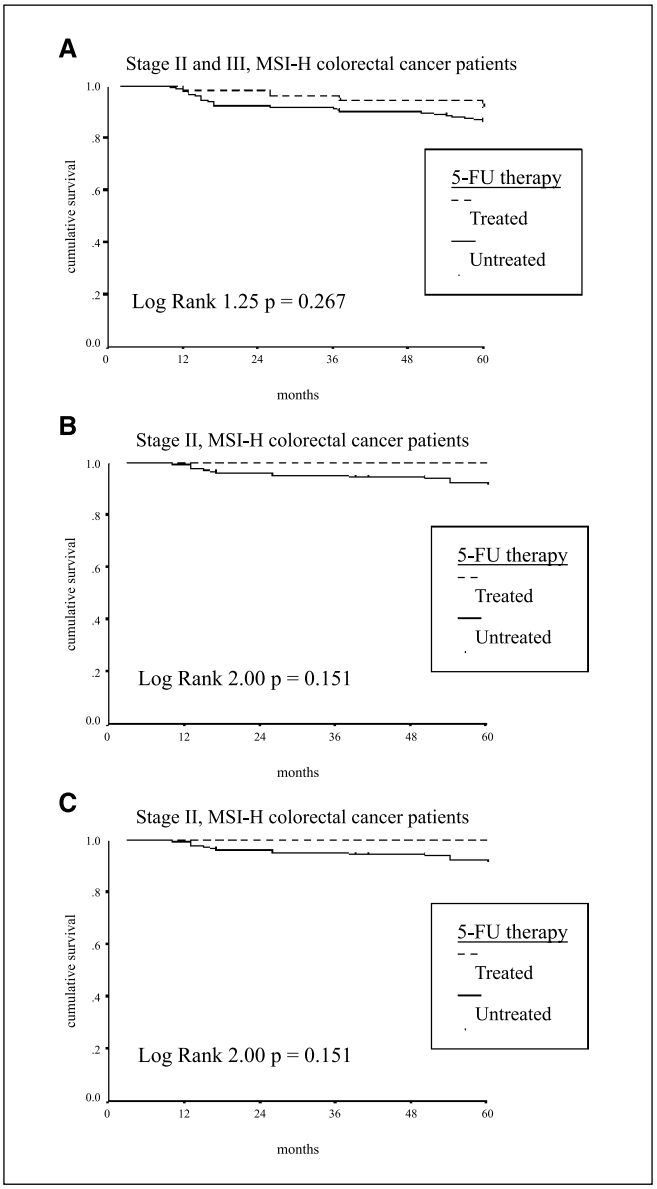

Fig. 3. Kaplan-Meier curves of 5-year – specific survival of patients affected by MSI-H colorectal cancer according to the use of 5-FU-based adjuvant chemotherapy. *A,* patients in stage II and III are considered altogether, whereas patients in stage II (*B*) and stage III (*C*) were analyzed separately.

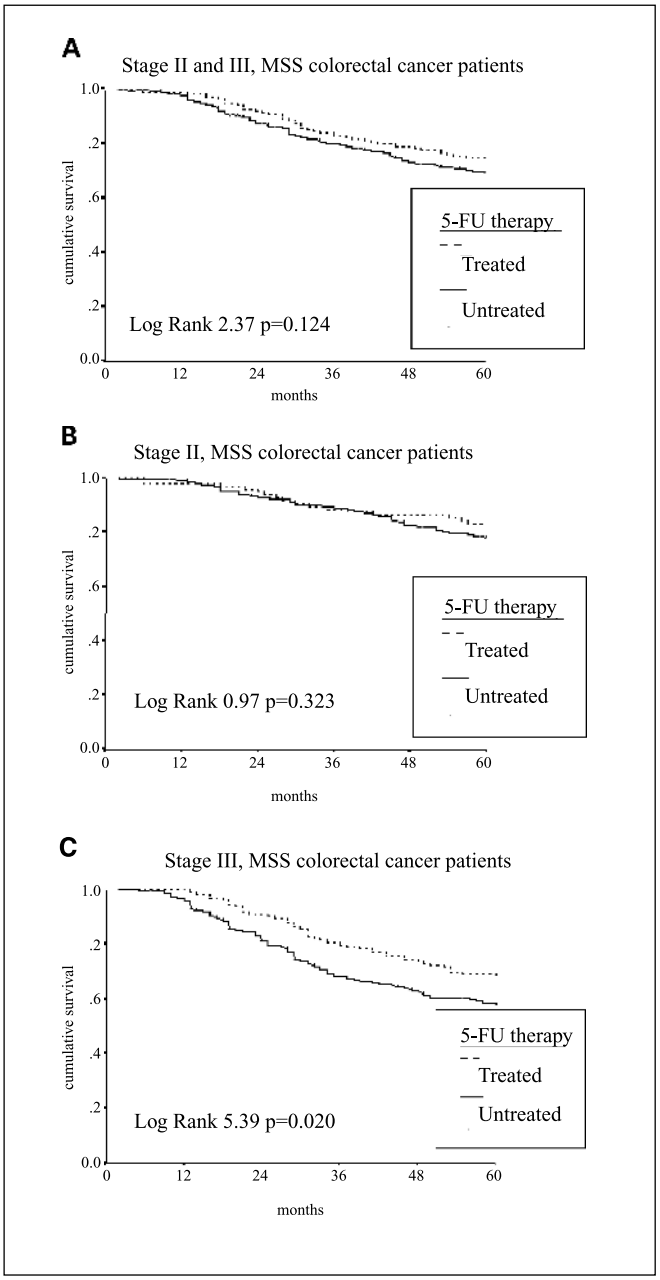

Fig. 4. Kaplan-Meier curves of 5-year – specific survival of patients affected by MSS colorectal cancer according to the use of 5-FU-based adjuvant chemotherapy. *A,* patients in stages II and III are considered altogether, whereas patients in stage II (*B*) and stage III (*C*) were analyzed separately.

CRC prognosis (29). In our series, even in stages I and IV, patients with MSI-H tumors showed a better prognosis, but the difference did not reach the level of statistical significance, probably owing to the low number of events (CRC-specific deaths) in stage I and because of the small number of MSI-H tumors in stage IV disease. The precise explanation for the prognostic advantage due to MSI is still not clearly established, even if intense lymphocytic infiltration, increased rate of apoptosis, and infrequent occurrence of allelic loss or mutation of *p53*, *DCC*, and *KRAS* in MMR-deficient colorectal cancer have been advocated to be responsible for their clinical behavior (19, 30–32).

Table 4. MMR gene mutations found in 57 patients affected by MSI-H colorectal cancer

Gene	Exon/Intron	Nucleotide change	Consequence	No. of patients with mutations
hMLH1 *	exon 19	InsT 2269-2270	protein elongation	15
hMLH1	intron 17	G → C, +5	splice defect	2
hMLH1	intron 13	G → T, +1	splice defect	1
hMLH1	exon 12	C → A 1367	protein truncated	1
hMLH1	exon 13	InsT 1542-1543	protein truncated	4
hMLH1	exon 13	C → T 1459	protein truncated	1
hMLH1	exon 9	Del AATG 727	protein truncated	2
hMLH1	exon 18	G → A 2041	change Ala → Thr	3
hMLH1	exon 17	Del GGGA 1953	protein truncated	3
hMSH2	exon 7	Del CCTA 1243	protein truncated	5
hMSH2	intron 5	A → T, +3	splice defect	4
hMSH2	exon 6	G → A 1034	protein truncated	3
hMSH2	exon 16	Del A 2647	protein truncated	2
hMSH2	exon 5	Del TT 880	protein truncated	3
hMSH2	exon 12	Del AAT 1786	loss of Asn	2
hMSH2	exon 14	Ins A 2362-2363	protein truncated	2
hMSH2	exon 13	C → T 2131	protein truncated	3
hMSH6	exon 4	Del A 2647	protein truncated	1

NOTE: For each mutation, we reported the gene involved, the site (exon/intron), and the type of mutation (nucleotide change), the consequence on protein synthesis, and the number of patients carrying each mutation.
*Mutation in *hMLH1*, exon 19 (insT) is a founder mutation which originated in the area of Modena and Reggio Emilia, identified in four apparently unrelated families (see ref. 36).

A further aim of our study was to evaluate the influence of MSI status on the response to chemotherapy. The mainstay of chemotherapy in colorectal cancer is represented by fluoropyrimidines. Data derived from *in vitro* studies have shown a certain resistance of MMR-deficient colorectal cancer cells to the use of 5-FU (9): the lack of MMR might allow cell-incorporated 5-FU to cause harmful effects to DNA synthesis and replication, but with no recognition by the dysfunctional MMR system and no inhibition of cell growth. On the other hand, a competent MMR system may trigger a cell death program and might be operative in MSS colorectal tumors treated with 5-FU, making this agent more effective. Our results support the hypothesis that 5-FU-based chemotherapy does not seem to provide survival benefits among patients with MSI-H tumors, either in stage II or in stage III colon and rectal cancer. This is in accordance with the latest reports on this issue (23, 24) and reinforces the hypothesis that the use of 5-FU in patients with MSI-H tumors should be limited to avoid harmful side effects (e.g., stomatitis, nausea, diarrhea, alopecia, dermatitis, and neurologic symptoms) of unnecessary chemotherapeutic regimens. However, due to the fact that all these investigations are retrospective, we need caution in implementing these findings in clinical practice until prospective trials, considering MSI status as an indicator of prognosis, can give us more confident results. Furthermore, recent reports on the possibility of oxaliplatin's ability to overcome the drug resistance induced by MMR deficiency, as well as to the hypersensitivity of MSI-H tumors to irinotecan (8, 33), should be taken into account in future studies, considering the different responses to different chemotherapeutic agents.

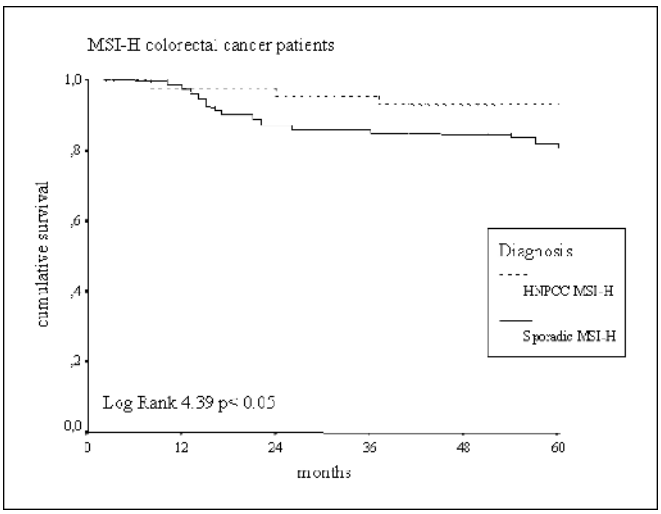

Fig. 5. Kaplan-Meier curves of 5-year – specific survival of patients affected by MSI-H colorectal cancer according to the diagnosis of hereditary non – polyposis colorectal cancer or sporadic MSI-H.

Finally, the most original feature of our report is represented by the comparison of disease-specific survival between patients with hereditary and sporadic MSI-H tumors. Recent publications have shown that sporadic and hereditary MSI-H colorectal cancers differ in terms of pathologic features and underlying molecular alterations, i.e., Cp-G methylation status, *BRAF* (34) and *B-catenin* gene mutations (35). This could also lead to the hypothesis that there are different clinical courses between the two variants of MSI-H colorectal cancers. The results of our study indicate that the survival benefit for patients with hereditary non – polyposis

Table 5. Results of univariate and multivariate Cox regression analyses on 5-year–specific survival of 57 patients affected by hereditary non–polyposis colorectal cancer and 105 patients affected by sporadic MSI-H colorectal cancer

	No.	Univariate analysis		Multivariate analysis	
		Hazard ratios for death (95% confidence interval)	*P*	Hazard ratios for death (95% confidence interval)	*P*
Diagnosis					
Sporadic MSI-H	105	1 ref.		1 ref.	
Hereditary non–polyposis colorectal cancer MSI-H	57	0.22 (0.05-0.93)	0.03	0.76 (0.13-4.48)	not significant
Gender					
Male	86	1 ref.		1 ref.	
Female	76	0.74 (0.32-1.70)	not significant	0.54 (0.22-1.33)	not significant
Stage					
I/II	83	1 ref.		1 ref.	
III/IV	79	5.36 (2.11-13.6)	<0.001	5.28 (2.08-15.4)	<0.001
Histologic type					
Adenocarcinoma	112	1 ref.		1 ref.	
Mucinous carcinoma	50	0.71 (0.33-1.51)	not significant	0.62 (0.24-2.35)	not significant
Grade					
Well/moderately differentiated	107	1 ref.		1 ref.	
Poorly differentiated	54	1.68 (0.71-3.97)	not significant	2.42 (0.97-6.07)	not significant
5-FU therapy					
Untreated	112	1 ref.		1 ref.	
Treated	50	0.42 (0.13-1.41)	not significant	0.39 (0.11-1.40)	not significant
Cancer site					
Colon	146	1 ref.		1 ref.	
Rectum	14	1.64 (0.54-4.68)	not significant	3.23 (0.98-10.6)	not significant
Age		1.04 (1.01-1.07)	<0.001	1.04 (1.01-1.07)	<0.001

NOTE: Colorectal cancer stages were dichotomized in stages I and II versus stages II and IV.

colorectal cancer is mainly determined by younger age and less advanced tumor stage as compared with the sporadic MSI-H counterpart.

In summary, our study indicates that MSI testing of colorectal cancers should be used more commonly in clinical practice to give important prognostic information. The presence of MSI-H seems to carry the same prognostic advantage in patients with inherited mutations of MMR genes and in patients with sporadic tumors. In agreement with other recent retrospective analyses, 5-FU-based adjuvant chemotherapy does not seem to significantly improve disease-specific survival among patients with MSI-H stages II and III colorectal cancers. This last finding, which needs to be further confirmed in studies comprising a large number of patients treated with 5-FU-based adjuvant therapy, should be taken into account when tailoring 5-FU treatment in patients affected by colorectal cancer in these stages, especially in those who are more prone to be affected by chemotherapeutic side effects.

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