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Review

Microsatellite Instability and Survival in Stage II Colorectal Cancer: A Systematic Review and Meta-analysis

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Abstract. *Background/Aim: About 15-20% of colorectal cancers (CRCs) have deficiency in a mismatch repair (MMR) protein. MMR has a high level of microsatellite instability (MSI-H). We have conducted this review and meta-analysis to determine the prognostic role of MSI-H status in stage II CRC. Materials and Methods: We searched PubMed, EMBASE, The Cochrane Library, Web of Science, and SCOPUS for studies reporting data on overall survival (OS) and disease-free or relapse-free survival (DFS or RFS) for MSI-H compared to microsatellite stable (MSS) CRC. Results: A total of 39 studies were analysed, including 12,110 patients. MSI-H status was associated with a significantly reduced risk of death (HR=0.64, 95%CI=0.52-0.8, p<0.01) and relapse (HR=0.59, 95%CI=0.45-0.77, p<0.01) in stage II CRC. Conclusion: MSI-H represents an important prognostic determinant in stage II CRC and may be considered when estimating the risk of recurrence in stage II CRC.*

Stage II colorectal cancer (CRC) is usually associated with a good prognosis; five-year overall survival (OS) rates range from 75 to 87.5% (1). However, the administration of postoperative 5-fluorouracil (5-FU)-based chemotherapy in this group of patients remains controversial, since it has been shown that survival gain generally does not exceed 5% (2). Several prognostic factors have been evaluated in order to identify a high-risk stage II CRC subgroup, for which adjuvant chemotherapy would have a better indication. High-risk features include an inadequate sampling of lymph nodes (less than 12), extension of primary tumor (pT4), poor differentiation (grade 3), acute onset of the disease with obstruction or perforation, lymph-vascular and perineural invasion, and close, indeterminate or positive resection margins (3).

Recently, microsatellite instability status (MSI) has been identified as a reliable prognostic indicator in stage II CRC, with an additional role in predicting the lack of benefit of 5-FU-based adjuvant chemotherapy (4-6). These data have been replicated in the large randomized phase III Quick and Simple and Reliable (QUASAR) trial, where 2,291 patients with stage II CRC were randomized to receive adjuvant chemotherapy with 5-FU and folinic acid or to undergo observation. An analysis performed on these patients found a prognostic role for MMR status, even if it was not shown to be predictive of any benefit from adjuvant chemotherapy (6).

Although a number of molecular markers of outcome in CRC has been proposed (BRAF/KRAS), there has been no clear consensus about their role in early stage CRC. Despite that a series of studies have investigated the relationship between MSI status and survival in CRC patients, they often included mixed populations of early (stage II-III) and advanced CRCs (stages IV).

The aim of our study was to evaluate the prognostic significance of MMR status in stage II CRC by analyzing all the available data coming from prospective and retrospective studies.

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Key Words: Colorectal cancer, microsatellite instability, meta-analysis, prognosis, stage II, review.

Materials and Methods

We performed this systematic review and meta-analysis in accordance with the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.

Search strategy. References for this systematic review and meta-analysis were identified through searches of PubMed, the Cochrane Library, SCOPUS, Web of Science, and EMBASE from inception to September 2019. Searches included the terms: (colon OR colorectal) and (cancer OR carcinoma) and (MMR OR MSI OR microsatellite instability OR replication error OR mismatch repair) and (stage 2 OR stage II) and (hazard ratio). Manual selection of relevant studies was also carried out based on the related articles function. The citation lists of all retrieved articles were analyzed to identify other potentially relevant reports.

Inclusion criteria and data extraction. Published studies were eligible if survival was analyzed in CRC cases stratified by MSI status by either genotyping or immunohistochemistry. In fact, MSI status can be assessed using a panel of five microsatellite biomarkers. The instability of two or more of these five microsatellite loci (>30%) was defined as high-frequency MSI (MSI-H), whereas instability of one or no marker characterized as low-frequency MSI (MSI-L) or stable microsatellite status (MSS) (7). An alternative method of MMR status evaluation is the analysis of MMR gene protein products (MLH1, MSH2, MSH6, and PMS2) using immunohistochemical (IHC) staining. Tumors that yielded negative staining results for at least one of the 4 MMR proteins, were classified as dMMR tumors, and all others were classified as pMMR tumors. Assignment of MSI status into corresponding groups (MSI-H or MSI-low or MSS) was performed using data provided in each contributing study. The primary outcome of interest was overall survival (OS), and the secondary endpoint was disease-free survival (DFS). Only studies providing at least one piece of information on survival were included. In cases of overlapping and duplicated data sets, only the most recent data sets were taken into consideration. Only studies published in the English language and in peer-review journals were included. Data from review articles, case reports, abstracts, and letters were not included. Two authors (FP and MC) conducted the search and identification independently, and the selection of an article was reached by consensus with a third author (GT). The following information was extracted from each report by the two authors independently: author/year of publication, country, patient number, type of study, rate of MSI tumors, adjuvant therapy exposure (rate), type of MSI evaluation method, BRAF status, survival data available, and type of analysis.

Statistical analysis. The association of MSI with OS and DFS was derived as a weighted average of study-specific estimates of the hazard ratio (HR), using inverse variance weights. The logHR and the corresponding variance were used as data points for pooling purposes. If data was only presented as survival curves, rates of survival were extracted at specified times to reconstruct the HR estimate and its variance, under the assumption that the rate of patients censored was constant during the study follow-up, according to the method described by Parmar *et al*. (8). HRs obtained according to multivariate analysis were used when provided. Otherwise, values derived from univariate analysis were considered. Each covariate tested in the multivariate analysis resulted to be significantly associated with the outcome of interest in the univariate analysis. By convention, an observed HR of <1 implied better survival for MSI cancers.

The percentage variability of the pooled HR attributable to heterogeneity among studies was quantified using the I^2 statistic and Cochran's Q statistics (9). Summary data from published studies was pooled using fixed-, and when heterogeneity was high ($p<0.05$ or $I^2>50\%$), random-effects models. Evidence of publication bias was examined by constructing funnel plots of HRs (Begg's test). Publication bias was also formally assessed by the Egger method (10). Sensitivity analysis for OS analysis was performed according to the race of participants (Asiatic *vs*. non-Asiatic), type of MSI evaluation (IHC *vs*. biomarkers), year of publication (before 2008 *vs*. 2008-2017), quality (high *vs*. low quality papers), type of analysis (uni- *vs*. multi-variate analysis), number of patients (above *vs*. below median number), type of study (trial *vs*. retrospective series), and rate of adjuvant chemotherapy.

We used the Newcastle-Ottawa Scale (NOS) for the risk of bias assessment (11). This scale assesses the likelihood of bias in three domains: 1) selection of the study groups; 2) comparability of groups; and 3) ascertainment of exposure and outcome. Studies with scores ≥7 were considered as having a low risk of bias, scores of 4-6 as having a moderate risk of bias, and scores <4 as having a high risk of bias. We assessed that follow-up was adequate if the median follow-up was more than five years.

Data was entered into the Comprehensive Meta-Analysis software v 3.3.070 (November 20th, 2014) and Review Manager (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

A total of 1,304 potentially relevant citations were reviewed (Figure 1). Ultimately, 39 studies (12-51) published from 1999 to 2019, reporting the prognostic value of MSI status in stage II CRC were analyzed, with a median follow up of 68.5 months. The total number of patients included was 12,110 ranging from 31 to 1,436 patients per study (median=213). Median age was 65.5 years. The major characteristics are shown in Table I.

In n=32 publications, a retrospective analysis of stage II CRC patients was presented; n=6 were retrospective analyses of phase III trials; and n=1 was a prospective series. According to race, most patients were of non-Asiatic origin (n=35) and the remaining publications (n=4) included Asian subjects. MSI status was diagnosed in 21% of CRC cases analyzed in the included studies (range 6-57.5%). In the n=2 studies, it was not reported. The analysis was performed with IHC detection in n=15 studies and with the biomarker method in n=22, while in one, both methods were used. In the article by Hansen *et al*., the method of MSI evaluation was not reported. Delivery of adjuvant chemotherapy was 19.5% (range=0-100%). In n=7 publications data about adjuvant chemotherapy was unknown.

The quality of paper expressed by the NOS scale ranged from five to nine, with 75% including studies of high quality (NOS scale scores from seven to nine).

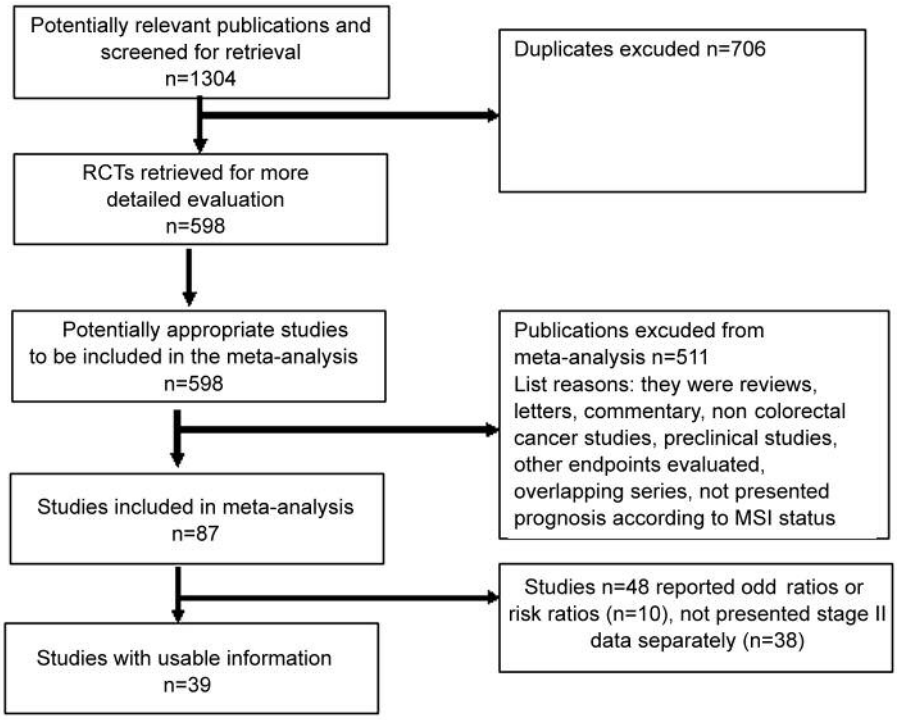

Figure 1. *Literature search flow diagram.*

Meta-analysis of overall survival. Because the heterogeneity test showed a moderate level of heterogeneity (I^2=58%, p<0.01) between studies, a random-effects model was used for analysis. A pooled HR of 0.64 (95%CI=0.52-0.8, p<0.01) from n=27 studies showed that patients with MSI CRC were associated with a reduced risk of death (Figure 2). In n=3 studies, HRs were calculated from survival curves because they were not provided by the authors. After exclusion of the least (47) and most favorable (38) HRs the final result did not change significantly.

Meta-analysis of disease-free or relapse-free survival. Because the heterogeneity test showed a moderate level of heterogeneity (I^2=57%, p<0.01) between studies, a random-effects model was used even for this analysis. A pooled HR of 0.59 (95%CI=0.45-0.77, p<0.01) from n=27 studies showed that patients with MSI CRC were associated with a reduced risk of relapse (Figure 3). In n=8 publications, other endpoints were used for time-to-event analysis of relapse. Only in n=1 study HR was calculated from survival curves because was not provided by authors. After exclusion of the least (35) and most favorable (37) HRs the final result did not change significantly.

Subgroup analysis and meta-regression for overall survival analysis. The subgroup analysis (Table II), performed according to the number of patients (above or below the calculated median number), showed that in the largest studies (>213 subjects) the effect size was inferior compared to the smallest studies (<190 subjects): HR=0.69 (95%CI=0.53-0.88) and 0.51 (95%CI=0.40-0.66) respectively (p=0.11 for subgroups difference). Analysis according to race (Asian *vs*. non-Asian race of included patients) led to a significant effect on OS for Asian studies but with only n=3 studies with this origin (p for difference=0.038). According to the type of MSI analysis for biomarkers evaluation, when either a polymerase chain reaction or IHC method were used, the positive association of MSI status with survival was significant, even if a deeper association was found with the former (HR=0.51, 95%CI=0.4-0.65; p<0.001 *vs*. HR=0.77, 95%CI=0.60-0.99; p=0.044: p for difference=0.006). Since only one publication was of prospective nature in the OS analysis, subgroup analysis according to types of studies was not performed. Meta-regression showed that the effect size did not depend on the rate of adjuvant chemotherapy (p=0.14).

Under the random effects model, the pooled HR obtained from both multivariate and univariate HRs were not significantly different: 0.67 (95%CI=0.55-0.82; p<0.001) and 0.57 (95%CI=0.41-0.81, p=0.002; p for difference=0.44). On the contrary, significance was maintained only in high quality (HR=0.61, 95%CI=0.48-0.74; p<0.001) but not in low quality studies (HR=0.62, 95%CI=0.34-1.16; p for difference=0.96). Finally, in more

Table I. *Characteristics of included studies.*

Author	Year	Type of study	N° of pts	Median follow up (months)	Median age (years)	Country
Aparicio	2013	Retrospective	91	14.8	NA	France
Curran	1999	Retrospective	159	94.8	69.7	Ireland
De Weger	2011	Retrospective (phase III study)	117	180	NA	The Netherlands
Deschoolmeester	2008	Retrospective	130	NA	64.5	Belgium
Donada	2010	Retrospective	31	91.2	NA	Italy
Gray	2011	Retrospective (phase III study)	1436	NA	NA	UK
Gryfe	2000	Retrospective	173	86.4	43	Canada
Guidoboni	2001	Retrospective	55	74	NA	Italy
Hansen	2014	Retrospective	554	NA	74	Denmark
Hveem	2014	Retrospective	278	69	74	Norway
Kevans	2011	Retrospective	258	NA	70.6	Ireland
Kim	2015	Retrospective	860	60.3	61	Korea
Klingbiel	2014	Retrospective (phase III study)	395	69.1	57.5	Europe
Kopetz	2015	Retrospective	416	81	67	International
Krajewska	2015	Retrospective	106	66	55	Korea
Lanza	2006	Retrospective	393	90.5	66	Italy
Maak	2013	Retrospective	132	101	65	Germany
Malesci	2007	Retrospective	246	52	65	Italy
Marcker Espersen	2016	Retrospective	144	92	73	Denmark
Nazemalhosseini Mojarad	2016	Retrospective	73	60.2	NA	Iran
Niedzwiecki	2016	Retrospective (phase III study)	393	97.2	64	USA
Nitsche	2012	Retrospective	232	97	66	Germany
Ozawa	2014	Retrospective	164	69	68	Japan
Park	2003	Retrospective	142	42	67.7	France
Roth	2010	Retrospective (phase III study)	409	68	NA	Europe
Salazar	2011	Retrospective	114	65	68.5	Europe
Samowitz	2001	Retrospective	402	62	NA	USA
Sargent	2011	Retrospective	241	60	74	USA
Shin	2014	Retrospective	115	38	61	Korea
Sinicrope	2011	Retrospective (phase III trials)	778	96	62	International
Slik	2017	Retrospective	173	57	NA	Finland/Libya
Tian	2012	Retrospective	263	NA	NA	Europe
Touchefeu	2016	Retrospective	195	>36	73.4	France
Turner	2015	Prospective series	396	61.2	NA	Australia
Vogelaar	2015	Retrospective	186	NA	NA	The Netherlands
Wang	2003	Retrospective	154	75	NA	Australia
Yang	2015	Retrospective	460	41.5	64.5	China
Zhang	2013	Retrospective	735	66	NA	China

NA: Not available; pts: patients.

recent studies (2008-2017) HR for OS was 0.65 (95%CI=0.5-0.85; p=0.002) and it was 0.54 in older studies (95%CI=0.43-0.68; p<0.001; p for difference=0.29).

The funnel plot (p=0.21; Figure 4) and Egger test (p=0.11) for OS did not indicate the existence of obvious publication bias. Also, trim and fill analysis did not change the pooled estimates of the meta-analysis (HR=0.64; 95%CI=0.52-0.78).

Discussion

Patients with stage II CRC have a disease-free survival of approximately 80% with surgery alone, but 20% recur within five years and those patients potentially require adjuvant treatment after colectomy (51). Common prognostic factors such as pT stage, grade, number of lymph nodes removed, and emergency surgery can discriminate high-risk patients, although the OS benefit with fluoropyrimidine-based chemotherapy in stage II disease is at best 5%. But neither the QUASAR study nor the previous Cochrane meta-analyses were able to confirm a survival benefit in stage II disease (2, 51). Conversely the prognostic role of MSI status split by stage has not systematically evaluated in previous meta-analysis, in particular for stage II CRC. Within this scenario, we aimed to discover and validate potential prognostic factors able to discriminate patients, with

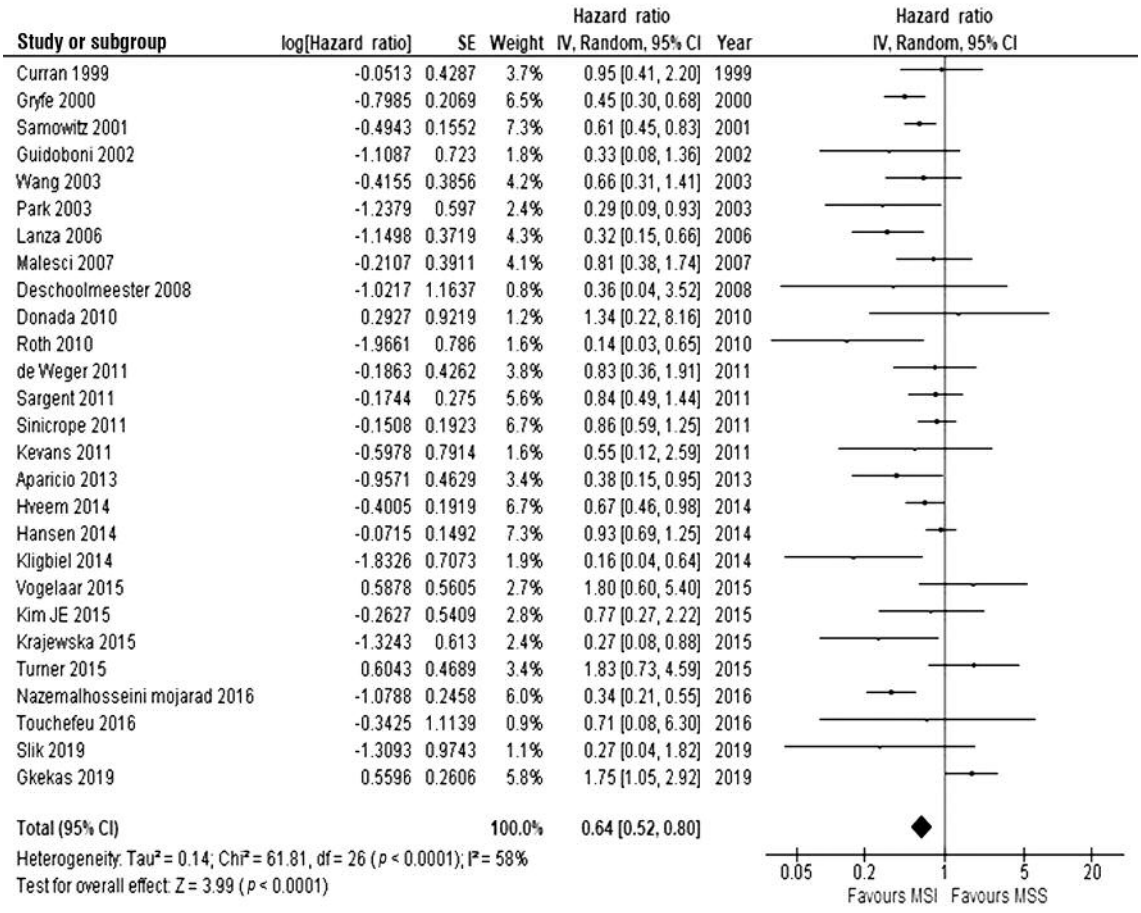

Figure 2. *Meta-analysis of overall survival for MSI vs. MSS colorectal cancer.*

significant risk of recurrence, who may need postoperative therapy after resection.

Previous systematic review and meta-analysis that have evaluated MSI status and survival did not split and analyze stage II CRC separately from more advanced disease stages. In our meta-analysis, including more than 11,000 patients and 38 studies, we can confirm that MSI status, evaluated by molecular or IHC testing, is a significant and favorable prognostic factor for both survival and relapse in stage II CRC. Compared to MSS CRCs, patients with MSI have a 40% reduced risk of death and recurrence and the benefit in OS is independent of other prognostic factors according to multivariate analysis and the receipt of chemotherapy.

Deficiency of MMR proteins (dMMR status) is common in Lynch syndrome and is present in about 15-20% of sporadic cancers (52). Functional impairment of the DNA MMR system results in the accumulation of insertion/deletion lesions at loci of DNA repeat sequences termed microsatellites, thereby producing a phenotype known as MSI. Some molecular markers such as MSI also have a side prevalence. Overall MSI-H status and BRAF mutation (more frequently detected in sporadic MSI CRC) are more frequently diagnosed in proximal CRC (53). In these patients, better prognosis associated with MSI status is not attenuated by *BRAF* mutations (54). *BRAF* mutations were frequently seen also in sessile serrate adenoma pathway and in sporadic MSI-H CRC, both of which were associated with DNA methylation (55). Analyzing CRCs for MSI and dMMR status with IHC staining has become a useful strategy for identifying patients who should undergo genetic evaluation for Lynch syndrome and for deciding which patients could withhold adjuvant chemotherapy, because of a more favorable prognosis associated with the MSI status (56). Published systematic reviews and meta-analysis in all stages of disease showed that MSI CRCs are associated with better OS compared to MSS ones (35-40% of reduced risk) (57). Also, in MSI CRCs, there is evidence for an inferior benefit associated with adjuvant chemotherapy compared to MSS tumors (58). The role of *BRAF* mutations was presented only in 8 studies of this meta-analysis (range=7.9-56.7%), but only in 2 studies MSI status was confirmed to be an independent positive predictor of OS

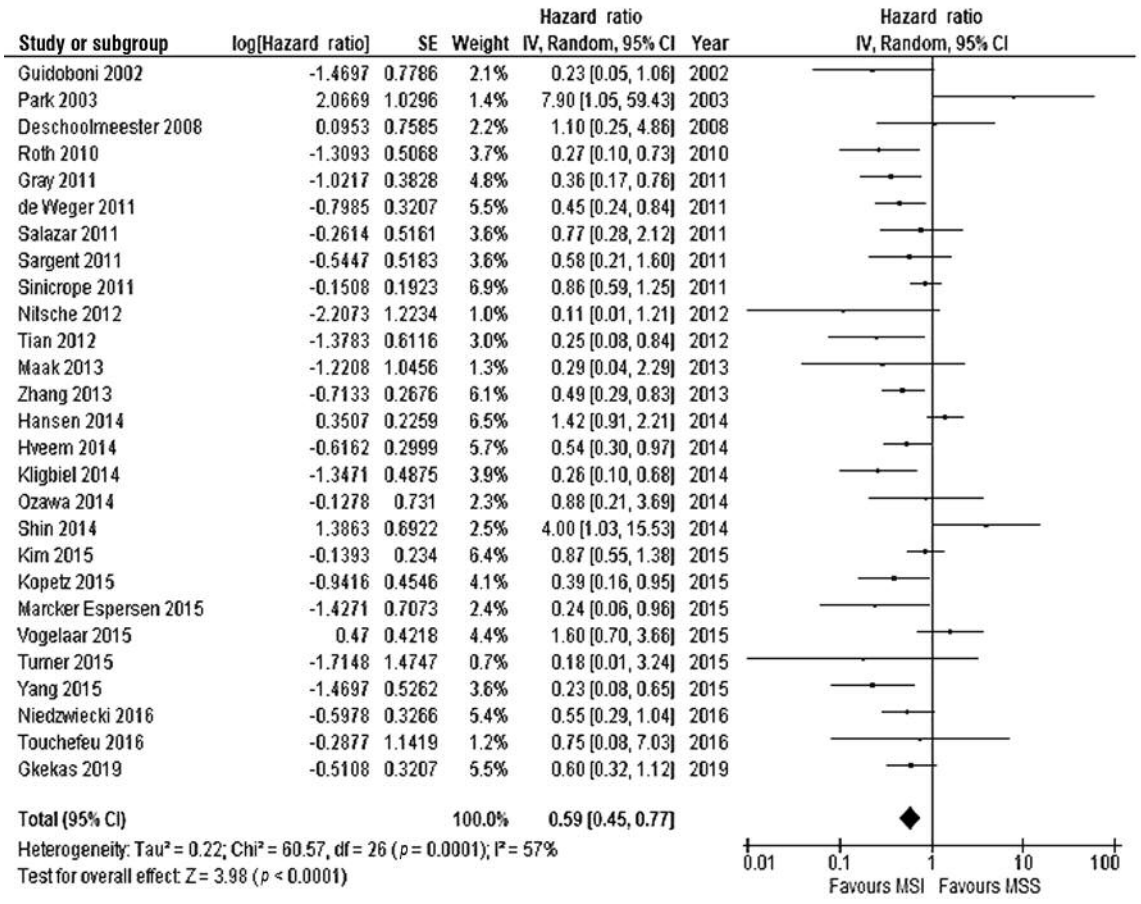

Figure 3. *Meta-analysis of disease-free survival for MSI vs. MSS colorectal cancer.*

with respect to *BRAF* mutations in the multivariate analysis. Overall, the role of *BRAF* mutations in early CRC is, however, still debated in MSI stage II CRC (59-61). Recently, CRC subtypes have been proposed based on distinct global gene expression profiles. One proposed molecular classification system suggests the presence of four unique clinically relevant molecular subtypes with distinguishing features. The CMS1 (MSI-like) subgroup contains most MSI-H tumors. The MSI-like subtype is also enriched for tumors with a CpG island methylator phenotype (CIMP) and mutations in the BRAF oncogene. This subgroup is associated with a good prognosis but this classification is not yet ready for incorporation into prognostic stratification in clinical practice.

Recent publications have highlighted MSI testing as relatively underused in the early stages of disease. In an analysis of 152,993 adults including 17,218 younger adult patients with CRC, only 28.2% and 43.1% underwent MMR testing, respectively (62). Older age, uninsured, recto-sigmoid, and nonsurgical cases were those associated with no receipt of testing. Similar data have been reported by Thiebault *et al.* in 1,269 CRCs cases, where MSI status was evaluated only in 10.9% (63). Instead, MSI status has recently gained relevance for treatment strategies in an advanced setting, where immunotherapy has provided evidence of activity in pretreated MSI CRCs. In fact, in a phase 2 study, Overman *et al.* have observed an overall response rate of 31% in 74 MSI CRC patients, with eight cases having responses lasting 12 months or longer (64).

Standardization of MMR status testing and a general implementation in the current clinical practice are of noteworthy importance. Diagnosis of MSI is realized *via* PCR amplification of specific microsatellite repeats. The standard diagnostic method for MSI, advocated by the National Cancer Institute, involves PCR analyses of tumor and normal tissues using five microsatellite markers, two for mononucleotide repeats (BAT26 and BAT25) and three for dinucleotide repeats (D2S123, D5S346, and D17S250) (65, 66). There is, however, evidence that IHC analysis is a simple and more available method representing a good surrogate for MSI status. Recently, the American Society for Clinical Pathology (ASCP), College of

Table II. *MSI status and outcome data available in the included studies*.

Author	Year	MSI-H (%)	BRAF mutation (%)	Adjuvant ct (%)	MSI-H evaluation		DFS or RFS	OS	Type of analysis	Quality of paper
					Biomarkers	IHC				
Aparicio	2013	28.5	NA	7	≥3/5		NA	√	UVA	6
Curran	1999	14	NA	0	≥2/4		NA	√	UVA	9
De Weger	2011	17	NA	50[#]	≥2/5		√ (RFI)	√	UVA	8
Deschoolmeester	2008	12.4	NA	NA		x	√	√	MVA	5
Donada	2010	9.6	NA	100	≥3/5		NA	√	MVA	7
Gray	2011	14	NA	56		x	√	NA	MVA	7
Gryfe	2000	26.5	NA	NA	≥2/5		NA	√	UVA	7
Guidoboni	2001	57.5	NA	12.7	≥2/5		√	√	MVA	7
Hansen	2014	29	NA	0	NA		√	√	MVA	6
Hveem	2014	19	NA	0	≥2/5		√	√	MVA	9
Kevans	2011	12	NA	0		x	NA	√	UVA	5
Kim	2015	14.7	NA	85.8		x	√	√	MVA	8
Klingbiel	2014	21.8	50	100	≥3/10		√	√	UVA	9
Kopetz	2015	19.2	NA	29.8	≥2/5	x	√ (ROR)	NA	UVA	9
Krajewska	2015	21	NA	0	≥2/6		NA	√	UVA	9
Lanza	2006	18.5	NA	18.1	≥30%		NA	√ (CSS)	MVA	9
Maak	2013	23.5	NA	2.2	≥2/5		√ (DMFS)	NA	UVA	9
Malesci	2007	17	56.7**	46		x	NA	√	UVA	7
Marcker Espersen	2016	22.9	NA	0		x	√	NA	MVA	8
Nazemalhosseini Mojarad	2016	31.4	NA	NA	≥2/5		NA	√	UVA	6
Niedzwiecki	2016	26	NA	49		x	√ (RFI)	NA	MVA	9
Nitsche	2012	26	15	NA	≥2/5		√ (DMFS)	NA	MVA	8
Ozawa	2014	NA	NA	NA		x	√	NA	UVA	8
Park	2003	17	NA	0		x	√	√	UVA	7
Roth	2010	21	7.9^	100	≥3/10		√	√	MVA	9
Salazar	2011	18	11	NA		x	√	NA	UVA	9
Samowitz	2001	15	NA	NA	≥2/5		NA	√	MVA	8
Sargent	2011	31.5	NA	0		x	√ (TTR)	√	MVA	9
Shin	2014	13	NA	87.5	≥2/5		√	NA	MVA	6
Sinicrope	2011	21.1	NA	50		x	√	√	MVA	9
Slik	2017	21	15^	30		x	√	√	MVA	7
Tian	2012	30	11.7	20	≥2/5*	x	√ (DMFS)	NA	UVA	5
Touchefeu	2016	27	NA	19	≥2/5		√	√	MVA	6
Turner	2015	6	NA	22		x	√ (RFS)	√	UVA	8
Vogelaar	2015	23	19	0	1/1		√	√	UVA	5
Wang	2003	21	NA	<5%	1/1		NA	√	UVA	7
Yang	2015	21	NA	56	≥2/5		√	NA	MVA	6
Zhang	2013	14.6	NA	33		x	√	NA	MVA	9

*Analysis was performed with IHC and biomarker analysis in the 2 cohorts analysed; RFS: relapse-free survival; RFI: relapse-free interval; UVA: univariate analysis; MVA: multivariate analysis; ROR: risk of relapse; [#]adjuvant immunotherapy; NA: not available; ^outcome according to MSI status analysed independent of BRAF status; **in sporadic MSI colorectal cancer.

American Pathologists (CAP), Association for Molecular Pathology (AMP), and the American Society of Clinical Oncology (ASCO) implemented evidence-based guidelines for biomarker testing in CRC (67). They stated that clinicians should order MMR status testing in patients with CRC for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification. In our meta-analysis, the OS advantage of MSI status was larger in studies where molecular analysis was performed by using established microsatellite markers, even if the panel of biomarkers was slightly different in various studies.

Our analysis has some intrinsic limitations. Firstly, we observed notable heterogeneity due to retrospective nature of the study, and the inclusion of relatively different populations. We took this into account with a random effect model analysis and with subgroup analysis and meta-regression. A significant difference was observed for the type of MMR evaluation (biomarker *vs*. IHC analysis) and quality/size of publications. Secondly, this meta-analysis was based on published data

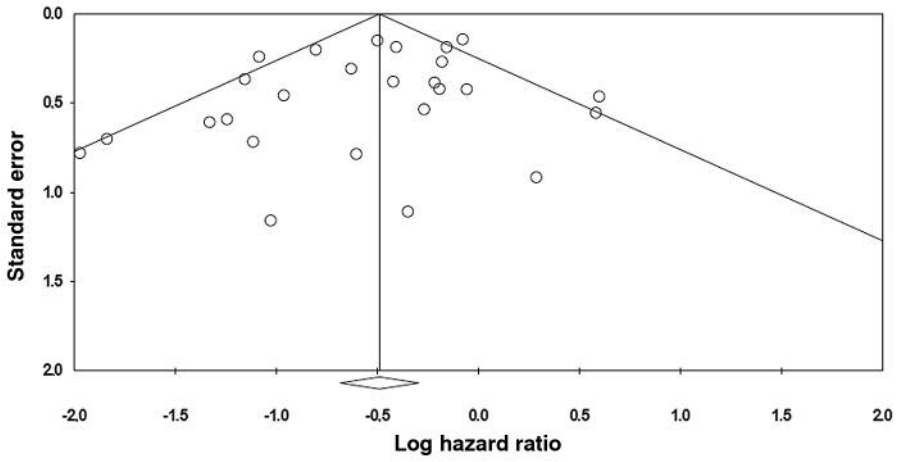

Figure 4. *Funnel plot for publication bias in overall survival analysis.*

instead of individual patient data. Thirdly, analysis was not performed according to different side (right *vs*. left CRC), pT stage (pT4 *vs*. pT3), and for colon *vs*. rectal cancers, even if the latter was the minority. Finally, our results address the prognostic and not the predictive role of MSI status in stage II CRC. The strength of our analysis is represented by the overall number of patients included (more than 12,000 of CRC subjects from 39 studies), the independent prognostic significance of MSI status according to multivariate analysis, and the lack of significant and obvious biases with funnel plot and Egger's test. So, this is the first and largest meta-analysis of published studies that establishes the prognostic significance of MSI status in stage II CRC and indicates the need for implementing it in current practice for all resected patients. The current 2017 National Comprehensive Cancer Network practice guidelines suggest detection of MSI status for all patients with stage II disease and patients with no other high-risk features or pT4 stage, which indicates no adjuvant treatment (68). Similar suggestions are offered by the 2013 European Society of Medical Oncology guidelines for early CRC where it is stated that MSI/MMR may be useful for identifying a small subset of stage II patients who are at a very low risk of recurrence and in whom the benefits of chemotherapy are very unlikely (69). While other prognostic factors such as gene signatures and CDX2 are developing, but are still not entirely implemented in clinical practice, we can affirm that in stage II CRC patients that are MSI/dMMR, there is 40% less risk of death and relapse. In these cases, if other adverse prognostic factors are excluded, adjuvant chemotherapy could be discussed and may be avoided by MSI stage II CRC patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

FP, MG, GT: Concept, design, statistical analysis and final review; MC, AC, AV, AG: Data collection; EP, DC, LT, SB: Final review and approval.

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