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REVIEW

Rate of dissemination and prognosis in early and advanced stage colorectal cancer based on microsatellite instability status: systematic review and meta-analysis

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Abstract

Introduction For the past two decades, microsatellite instability (MSI) has been reported as a robust clinical biomarker associated with survival advantage attributed to its immunogenicity. However, MSI is also associated with high-risk adverse pathological features (poorly differentiated, mucinous, signet cell, higher grade) and exhibits a double-edged sword phenomenon. We performed a systematic review and meta-analysis to evaluate the rate of dissemination and the prognosis of early and advanced stage colorectal cancer based on MSI status.

Methods A systematic literature search of original studies was performed on Ovid searching MEDLINE, Embase, Cochrane Database of Systematic Reviews, American College of Physicians ACP Journal Club, Database of Abstracts of Reviews of Effects DARE, Clinical Trials databases from inception of database to June 2019. Colorectal cancer, microsatellite instability, genomic instability and DNA mismatch repair were used as key words or MeSH terms. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed. Data were pooled using a random-effects model with odds ratio (OR) as the effect size. Statistical analysis was performed using RevMan ver 5.3 Cochrane Collaboration.

Results From 5288 studies, 136 met the inclusion criteria (n = 92,035; MSI-H 11,746 (13%)). Overall, MSI-H was associated with improved OS (OR, 0.81; 95% CI 0.73–0.90), DFS (OR, 0.73; 95% CI 0.66–0.81) and DSS (OR, 0.69; 95% CI 0.52–0.90). Importantly, MSI-H had a protective effect against dissemination with a significantly lower rate of lymph node and distant metastases. By stage, the protective effect of MSI-H in terms of OS and DFS was observed clearly in stage II and stage III. Survival in stage I CRC was excellent irrespective of MSI status. In stage IV CRC, without immunotherapy, MSI-H was not associated with any survival benefit.

Conclusions MSI-H CRC was associated with an overall survival benefit with a lower rate of dissemination. Survival benefit was clearly evident in both stage II and III CRC, but MSI-H was neither a robust prognostic marker in stage I nor stage IV CRC without immunotherapy.

Keywords Microsatellite instability · DNA mismatch repair · Genomic instability · Colorectal cancer · Lynch syndrome · Sporadic cancer · Survival · Prognosis

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Introduction

Microsatellite instability (MSI) is a widely used biomarker in colorectal cancer (CRC). It is present in approximately 15% of CRCs. Currently, high MSI (MSI-H) status is used to identify patients for Lynch syndrome testing, to select patients with high-risk stage II CRC with adverse features for adjuvant treatment, to select stage IV CRC for immunotherapy and to guide prognosis. While its utility to identify Lynch syndrome is becoming universal, and it has increasingly been used to guide adjuvant therapy in high-risk stage II CRC and immunotherapy in stage IV CRCs, its utility as a robust biomarker of survival has not been widely adopted in clinical practice.

This is despite existing literature strongly supporting MSI as a robust biomarker of prognosis in CRC. Level 1 evidence thus far have reported that MSI status is useful in guiding prognosis in CRC patients, with MSI-H associated with enhanced survival [1, 2]. Furthermore, from tumour microenvironment studies, it is widely known that MSI-H is associated with immunogenicity, with MSI-H associated with increased tumour infiltrating lymphocytes (TILs) [3–7] and TILs has been associated with better prognosis [3, 8–17], decreased risk of lymph node metastases [18, 19] and distant metastases [20]. With two landmark meta-analyses reporting overall survival benefit associated with MSI [1, 2] and tumour biology and microenvironment studies demonstrating the immunogenicity of MSI-H CRCs, it may be difficult to understand why has MSI not been embraced universally as a robust clinical biomarker to guide prognosis in CRC.

This raises the question of whether the reported survival advantage conferred by MSI in the literature is observed in clinical practice. Closer inspection of the level 1 evidence reveals that a large majority of studies included in these meta-analyses [1, 2] have reported differences that were not statistically significant or only marginally significant.

While there is no doubt that MSI-H CRCs are immunogenic, MSI-H appears to exhibit a double-edged sword phenomenon. MSI-H CRCs are associated with an abundance of frameshift specific neo-peptides that, on one hand, is associated with the generation of the immune response [21–23]. On the other, MSI-H is also a marker of significantly more mutations. MSI-H CRCs are associated with poor differentiation [18, 24], larger diameter and increased likelihood to be higher grade, poorly differentiated or mucinous [25–27]. Several studies have reported that MSI-H may also be associated with an increased risk of locoregional recurrence after resection [28], increased risk of synchronous tumours [29, 30] and metachronous CRC [31]. Recent studies, including our own, have questioned the utility of MSI status as a universal clinical biomarker of enhanced survival [32].

In order to assess if MSI truly has any benefit, this meta-analysis examines the rate of dissemination associated with MSI-H CRCs. It also evaluates if MSI-H has a protective effect only in early stage, or if it maintains a survival benefit in advanced stage CRCs when it has already disseminated. To the best of our knowledge, this is the first meta-analysis to have reported on the rate of dissemination and prognosis in early and advanced stage colorectal cancer based on MSI status. This meta-analysis also updates the existing literature on overall prognosis in MSI-H CRC and provides the most precise insight into the clinical value of MSI to date.

Methods

Search strategy

The present study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines to investigate the association between MSI status, stage, age and prognosis in patients with colorectal cancer. Electronic databases were searched including MEDLINE, Embase, Cochrane Database of Systematic Reviews, American College of Physicians ACP Journal Club, Database of Abstracts of Reviews of Effects DARE, Clinical Trials databases from inception of database to July 2017, and this was updated in June 2019. To provide the most encompassing search strategy, we combined the terms microsatellite instability, DNA mismatch repair and colorectal cancer as either key words or MeSH terms (eTable 1 in the Supplement). The reference list of the included studies was reviewed to identify additional relevant studies that met inclusion criteria.

Selection criteria

Eligible studies that included CRC patients with survival outcomes presented by MSI status were considered for inclusion. Studies with cohorts reporting on MSI status in colorectal cancer either confirmed by immunohistochemistry (IHC), a range of mononucleotide and dinucleotide MSI markers in various combinations, and by both use of nucleotide markers and IHC, with at least 50 patients, ≥ 4 in each comparator group, and reporting on survival outcomes (OS, DFS, DSS). The status of adjuvant therapy was not an exclusion criteria. Studies evaluating the role of advancements in immunotherapy in CRC were excluded. We have previously reported on the potential role of immunotherapy in CRC [33]. Randomised controlled trials, non-randomised trials, prospective and retrospective cohort studies were considered. Studies that reported a hazard ratio (HR) or odds ratio (OR) on OS, DFS, DSS based on MSI status were included. Where HR was not reported, HR was estimated from published time-to-event analyses based on the technique reported by Tierney et al. Studies where HR/OR was not reported on extractible were excluded. Exclusion criteria were non-comparative studies, case reports, abstract studies, studies with fewer than 50 patients (≤ 4 in each group) and studies where method of MSI status assignment was not provided. Studies reporting specifically on Lynch syndrome were excluded. Several studies combined MSI-L with MSS and these were included. Studies with overlapping populations were excluded unless the studies reported on different stages or on different survival outcomes. In this case, these studies were included for systematic review and only included where reporting on different stage or outcome categories.

Data extraction, quality appraisal and risk of bias

Article titles and abstracts were screened by J.T. and K.P. independently, with inclusion for full-text review where there was a consensus between J.T and K.P. Where articles were identified for inclusion by only one investigator, these were discussed and resolved by consensus to determine if the study met inclusion criteria. Where full texts were not available or only conference abstracts were available, these were excluded from the meta-analysis. Articles were appraised using a standard protocol. Data extracted included OS, DFS, DSS, mean age (median if mean not available) of cohort based on MSI-H status, age index (MSI-H CRC age/MSS CRC age), stage (including number of patients with MSI-H in each stage), percentage of cohort with MSI-H, MSS, proximal (right) vs. distal (left) CRC, rectal cancer and where reported, percentage of cohort with BRAF mutation. Stratified and non-stratified OS, DFS and DSS were reported. HR and OR reported by the studies were used when available. In several studies, the HR was estimated from published time-to-event-analysis using the technique by Tierney et al. Where HR/OR was not available or estimable for one of OS, DFS, DSS, these studies were excluded from analysis. Quality appraisal of studies was assessed using the Newcastle-Ottawa scale for risk of bias assessment. The Newcastle-Ottawa scale was chosen over the Cochrane Collaboration risk of bias assessment tool as majority of the studies were non-RCTs, and of the RCTs included, majority were secondary analysis of MSI status data rather than MSI status being the primary endpoint.

Statistical analysis

Odds ratio (ORs) were used as summary statistics. We used a random-effects model. χ^2 test was used to evaluate the heterogeneity between trials. The I^2 statistic was used to estimate the variation across studies owing to heterogeneity rather than chance. Values greater than 50% were considered significant heterogeneity. For I^2 values > 50%, methodological and extractible clinical factors were examined to assess reasons for heterogeneity, but specific analyses were not possible due to raw data not being available. All p values were 2-sided, and statistical significance was set at $p < 0.05$. Statistical analysis was performed using Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. For relevant stage data, analysis was performed on STATA (Stata MP, version 15; StataCorp LP).

Results

Search results

A total of 5288 studies were identified through electronic database searches. After inclusion of 18 studies identified by additional sources and exclusion of duplicates, 3739 potentially relevant articles were retrieved. After applying the selection criteria, 136 articles were included for qualitative and quantitative synthesis (Fig. 1). Detailed study baseline stage characteristics have been summarised in Table 1, and risk of bias assessment in eTable 2 in the Supplement. Majority of studies included were cohort studies (non-RCTs), and the included RCTs reported MSI status in subset analysis rather than as a primary endpoint.

Baseline patient characteristics

There was a total of 92,035 patients included (MSI-H 11746 (13%)). Of the studies which reported a mean age, the mean age ranged from 41.3 to 74 for MSI-H group, 43.5 to 70.4 for the MSS group. Thirteen studies reported a mean (or median where mean not available) age < 60, 31 studies reported a mean age ≥ 60 for their MSI-H CRC cohort. Percentage of BRAF mutation within the cohort of MSI-H CRC was reported in 34 studies. The range was 14–72%.

Rate of dissemination (lymph node and distant metastasis)

A total of 118 of the 136 studies (MSI = 8681) included in this meta-analysis had stage-specific data. A total of 4393 (51%) patients were stage I/II, 3676 (42%) stage III and 616 (7%) stage IV CRC. However, this data included studies reporting on single stage, early (I/II) or advanced (III, IV) CRC as well as all stages. The likelihood of progression cannot be estimated with the inclusion of studies which reported specifically on early or advanced or single stage CRC, as this would skew the data due to selection bias.

To determine the likelihood of disease progression (lymph node metastases ± distant metastases) associated with MSI, only studies which included at least stage II and III CRC in their study cohort were pooled for stage data. A total of 77 studies (MSI = 6134) included at least stage II and III CRC patients. A total of 3692 (60%) patients were stage I/II, 2179 (36%) stage III and 263 (4%) stage IV. The ratio of early stage (I/II): advanced stage (III/IV) was 60%:40%.

Only 43 studies (MSI = 3150) included patients with I, II, III, IV or II, III, IV CRC. A total of 1928 (61%) patients

Table 1 Study characteristics of included studies (studies reporting on different stages or different survival outcomes (OS, DFS, DSS) on overlapping cohort included; duplicate data excluded)

First author	Stage I	Stage II	Stage III	Stage IV	*n*	MSI-H	% MSI-H	MSS
Alex 2017 (IV) [52]				41	125	41	33%	84
Aparicio 2013 (I, II, III, IV) [53]	4	26	18	3	231	52	23%	179
Andrici 2016 (I, II, III, IV) [54]	14	47	32	2	264	95	36%	169
Bae 2015 (IV) [55]					1133	89	8%	1044
Banerjea 2009 (I, II, III) [56]	1	12	3		91	16	18%	75
Barault 2008 (NS) [57]					554	77	14%	477
Barrasa Shaw 2009 (I, II, III, IV) [58]	2	2	1	1	75	6	7%	69
Benatti 2005 (I, II, III, IV) [59]	17	120	88	31	1263	256	20%	1007
Bertagnolli 2011 (II, III) [60]		199	131		1852	330	18%	1515
Birgisson 2015 (II, III, IV) [61]		13	9	2	114	24	21%	90
Brenner 2012 (NS) [62]	1	3			58	4	7%	54
Carethers (II, III) [63]		22	14		204	36	18%	168
Chang, S 2006 (I, II, III, IV) [64]	4	8	4	3	213	19	9%	194
Chang, E 2006 (I, II, III) [65]	12	20	11		140	43	31%	97
Chouhan 2018 (III) [66]			95		686	95	14%	591
Curran 2000 (II) [67]		22			159	22	14%	137
Dahlin 2011 (NS) [14]					443	69	16%	374
Des Guetz 2010 (I, II, III) [68]		11	8		105	19	18%	86
Deschoolmeester 2008 (I, II, III) [69]	2	14	14		331	30	9%	301
De Weger 2011 (I, II, III) [70]					196	34	17%	162
Diep 2003 (I, II, III, IV) [71]	5	17	10	4	296	36	12%	239
Donada 2010 (II, III) [72]		3	4		55	7	13%	48
Drucker 2013 (III) [73]			18		159	18	11%	141
Du 2013 (I, II, III, IV) [74]	7	10	6		272	23	8%	249
Elsaleh 2001 (III) [75]			63		732	63	9%	669
Emterling 2004 (I, II, III, IV) [76]	3	25	22	7	438	59	13%	379
Eveno 2014 (IV) [77]				15	152	15	10%	137
Ferri 2013 (I, II, III) [78]	1	5	8		119	14	12%	105
Fujiyoshi 2017 (IV) [79]				15	401	15	4%	386
Gafa 2000 (I, II, III, IV) [80]	8	76	59	29	208	44	21%	164
Gavin 2012 (I, II, III) [81]		93	114		2299	207	12%	1589
Gervaz 2002 (II) [82]		21			88	21	24%	65
Ghanipour 2017 (II, III, IV) [83]		7	33	7	313	47	15%	266
Gkekas 2019 (II) [84]		93			452	93	21%	359
Gryfe 2000 (I, II, III, IV) [85]	14	46	27	15	587	102	17%	485
Guidoboni 2001 (II, III) [86]		27	20		109	47	43%	48
Gupta 2010 (NS) [87]					111	11	10%	100
Hartman 2013 (II, III, IV) [88]		13	8	2	53	23	43%	30
Hemminki 2000 (III) [89]			11		95	11	12%	84
Hong 2012 (I, II, III, IV) [90]	17	55	28	6	1125	106	9%	938
Hu 2016 (I, II, III, IV) [91]	3	20	6	1	401	30	7%	371
Hutchins 2011 (II, III) [92]		205	10		2131	218	10%	1913
Hveem 2014 (I, II, III) [93]					579	87	15%	452
Imai 2015 (I, II, III, IV) [94]		17	18		156	35		121
Iachetta 2016 (II) [95]		15			118	15	13%	103
Jensen 2009 (II, III, IV) [96]		6	34	3	311	43	14%	268
Johannsdottir 1999 (I, II, III) [97]		24	22		197	47	24%	150
Jover 2009 (I, II, III, IV) [98]	5	38	22	11	754	76	10%	678

Table 1 (continued)

First author	Stage I	Stage II	Stage III	Stage IV	*n*	MSI-H	% MSI-H	MSS
Jung 2016 (I, II, III, IV) [99]	3	29	19	5	176	56	32%	120
Kakar 2004 (I, II, III, IV) [100]	2	48	19	3	248	72	29%	176
Kalady 2012 (NS) [101]					475	76	16%	399
Kang 2015 (I) [102]	10				125	10	8%	115
Kang 2011 (II, III) [103]		30	11		564	41	7%	523
Kazama 2007 (I, II, III, IV) [18]	2	6	2	2	53	12	23%	41
Kevans 2011 (II) [104]		30			258	30	12%	228
Kim, J.E. 2017 (III) [105]			50		598	50	8%	548
Kim, C.G. 2016 (I, II, III) [106]	56	138	67		2940	261	9%	2679
Kim, J.E. 2015 (II) [107]		126			860	126	15%	734
Kim, S.T. 2010 (II, III) [108]		3	9		134	12	9%	122
Kim, G.P. 2007 (II, III) [109]		48	50		542	98	18%	444
Kim, S.H. 2013 (III) [110]			26		394	26	7%	368
Kim, J.E. 2011 (IV) [111]				23	197	23	12%	174
Klingbiel 2015 (II, III) [112]		86	104		1254	190	15%	1064
Korphaisarn 2015 (I, II, III) [113]	7	8	16		208	31	15%	177
Lamberti 2008 (I, II, III, IV) [19]	11	25	10	5	395	52	13%	343
Lanza 2002 (I, II, III, IV) [114]	10	69	43	10	305	132	43%	173
Lanza 2006 (II, III) [115]		73	41		718	114	16%	604
Lee 2015 (I, II, III, IV) [116]	26	70	75	27	2819	198	7%	2621
Li 2017 (NS) [117]					2233	232	10%	2001
Liang 2002 (IV) [118]					228	52	23%	176
Lim 2004 (I, II, III, IV) [119]	2	11	9	1	248	23	9%	225
Lin 2014 (I, II, III, IV) [120]	10	71	31	15	1063	127	12%	936
Lin 2012 (I, II, III, IV) [121]	6	33	17	4	709	60	8%	649
Maccaroni 2015 (I, II, III, IV) [122]	11	12	9	1	64	22	34%	42
MacQuarrie 2012 (III) [123]			168		168	21	13%	147
Maestro 2007 (NS) [124]		12	8	4	314	24	8%	290
Malesci 2007 (I, II, III, IV) [35]	13	42	27	7	893	89	10%	804
Markovic 2012 (I, II, III, IV) [125]	1	9	8	1	155	19	12%	128
Meng 2007 (II, III) [126]		7	5		128	12	9%	88
Merok 2013 (I, II, III, IV) [127]	7	65	27	13	805	112	14%	693
Messerini 1999 (I, II, III) [128]	2	10	6		50	18	36%	32
Mohan 2016 (I, II, III, IV) [129]		103	32	3	1250	138	11%	1112
Mojarad 2016 (I, II, III) [130]	3	11	21		137	35	26%	102
Mouradov 2013 (II, III) [131]		104	68		1197	172	14%	1025
Nakaji 2017 (II, III) [132]		27	17		472	44	9%	428
Nash 2010 (I, II, III, IV) [133]	16	21	10	2	532	58	11%	420
Nehls 2009 (I, II, III) [134]		36	15		344	51	15%	293
Nopel-Dunneback 2014 (IV) [135]				14	204	14	7%	190
Nordholm-Carstensen 2015 (IV) [136]					6692	983	15%	5709
Ogino 2009 (I, II, III, IV) [137]	19	70	22	5	631	118	19%	513
Oh 2013 (III) [138]			16		127	16	13%	111
Ohrling 2010 (II, III) [139]		84	73		1006	157	16%	849
Ooki 2014 (III) [140]			15		405	15	4%	390
Parc 2004 (II) [141]		24			142	24	17%	118
Park 2010 (I, II, III, IV) [142]	2	21	11	1	318	36	11%	282
Phipps 2013 (NS) [143]					3285	461	14%	2824
Ribic 2003 (II, III) [144]		58	37		570	95	17%	475

Table 1 (continued)

First author	Stage I	Stage II	Stage III	Stage IV	*n*	MSI-H	% MSI-H	MSS
Rosty 2014 (NS) [145]					738	86	12%	652
Roth 2010 (II, III) [146]					1254	190	15%	1064
Salahshor 1999 (I, II, III) [147]	4	15	3		181	22	12%	152
Samowitz 2009 (NS) [148]					968	22		968
Samowitz 2001 (I, II, III, IV) [149]	44	68	53	14	1396	184	13%	1212
Sargent 2010 (II, III) [150]		44	26		457	70	15%	387
Saridaki 2010 (IV) [151]				22	144	22	15%	122
Shima 2011 (I, II, III, IV) [152]	32	87	26	10	1072	162	15%	910
Shin 2014 (II, III) [153]		15	5		245	20	8%	225
Sinicrope, F.A. 2015 (III) [154]			255		2720	255	9%	2465
Sinicrope, F.A. 2013 (III) [155]			*314*		*2580*	*314*	*12%*	*2266*
Sinicrope, F.A. 2006 (II, III) [156]		*35*	*60*		*528*	*95*	*18%*	*433*
Sinicrope, F.A. 2011 (II, III) [157]		164	180		2141	344	16%	1797
Slik 2017 (II) [158]		37			173	37	21%	136
Soreide 2009 (I, II, III) [28]	1	27	9		186	37	20%	149
Srdjan 2016 (II, III) [159]		9	12		125	21	17%	104
Sun 2014 (I, II, III, IV) [160]	8	33	59	10	404	110	27%	294
Taieb 2016 (III) [161]			177		1791	177	10%	1614
Tan 2018 (III) [162]			63		654	63	10%	591
Thomas 2015 (III) [163]			77		802	77	10%	725
Tian 2012 (II, III) [164]					1164	130	13%	903
Tikidzhieva 2012 (II, III) [165]		8	26		269	34	15%	189
Toh 2017 (I, II, III, IV) [32]	26	51	26	11	1009	114	11%	895
Toon 2014 (NS) [166]					1426	278	19%	1148
Touchefeu 2015 (II) [167]		50			187	50	27%	137
Tran 2011 (IV) [168]				40	350	40	11%	310
Turner 2015 (II) [169]		25			196	25	13%	171
Venderbosch 2014 (IV) [170]				153	3077	153	5%	2924
Vogelaar 2015 (II) [171]		43			186	43	23%	143
Wang 2003 (II) [172]		33			154	33	21%	121
Wangefjord 2013 (I, II, III, IV) [173]		54	18	5	515	77	15%	438
Ward 2005 (I, II, III, IV) [174]	24	61	23	7	835	115	14%	720
Watanabe 2001 (II, III) [175]					270	62	23%	208
Westra 2005 (III) [176]			44		273	44	16%	229
Wright 2000 (III) [177]			21		255	21	8%	234
Xiao 2013 (NS) [24]					1941	178	9%	1763
Yang 2015 (II) [178]		97			460	97	21%	363
Yoon 2011 (I, II, III, IV) [179]					2025	202	10%	1823
Zaanan 2011 (III) [180]			34		303	34	11%	269

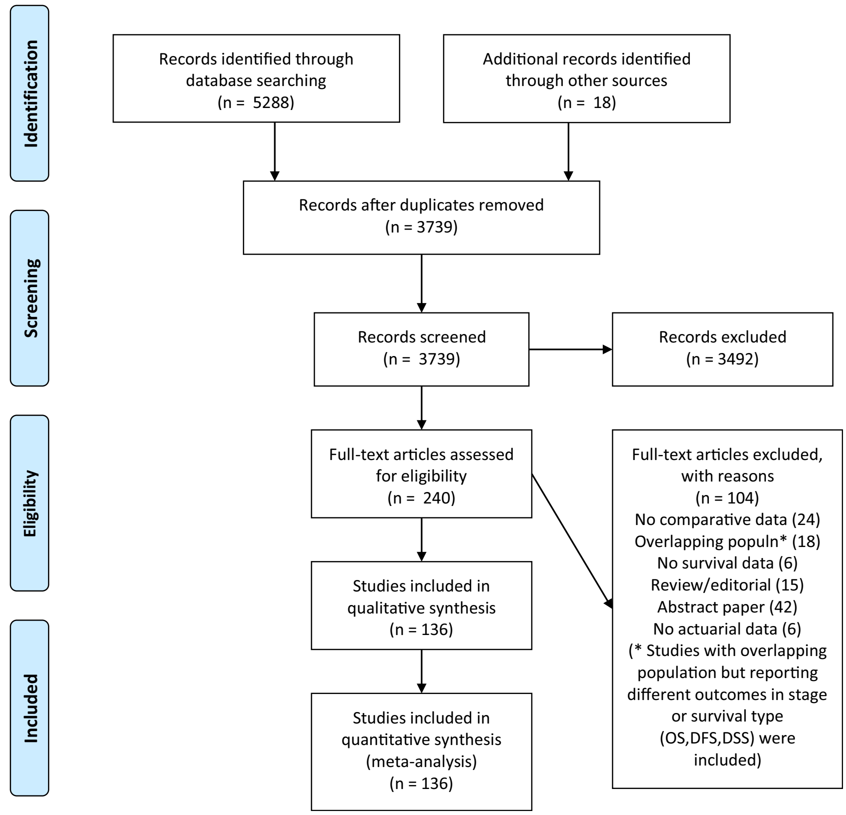
were stage I/II, 959 (30%) stage III and 263 (8%) stage IV CRC. The stage I/II:III/IV ratio was approximately 60%:40%.

From both analyses, the ratio of early:advanced CRC was approximately 60:40%—i.e. more early than advanced CRC associated with MSI-H.

Overall prognosis

Overall, 96 studies provided OS pooled data with OS overall estimate of OR, 0.81; 95% CI, 0.73–0.90, $p < 0.00001$; $I^2 = 70\%$ (refer to Fig. 2). Sixty studies provided DFS data with DFS overall estimate of OR, 0.73; 95%

Fig. 1 PRISMA flowchart of search strategy for present systematic review



CI, 0.66–0.81, $p < 0.00001$; $I^2 = 71\%$ (Fig. 3). Twenty-nine studies provided DSS data with DSS overall estimate of 0.69; 95% CI 0.52–0.90, $p = 0.007$; $I^2 = 69\%$ (Fig. 4). Overall, MSI-H was associated with better OS, DFS and DSS.

Prognosis in early and late stage

For stage I, results from 4 studies showed no difference in OS between stage I MSI-H and MSS CRC: OS (OR, 1.33; 95% CI 0.41–4.39; $p = 0.63$; $I^2 = 11\%$). Two studies were suitable for pooling to provide DFS data (OR, 0.41; 95% CI 0.17–1.00; $p = 0.05$; $I^2 = 0\%$). Two studies reported on DSS (OR, 0.59; 0.27–1.33; $p = 0.08$; $I^2 = 0\%$). There was not a statistically significant difference in OS, DFS and DSS in stage I CRC. It was unclear whether this was partly due to the sparsity of data available on MSI status in stage I CRC, but survival was excellent irrespective of MSI status in stage I CRC.

For stage II CRC, 26 studies provided OS data. The estimate for OS for stage II CRC was OR, 0.56; 95% CI 0.36–0.89; $p = 0.01$; $I^2 = 93\%$. Twenty studies provided DFS data for stage II CRC (OR, 0.59; $p < 0.0001$; 95% CI 0.46–0.76; $I^2 = 60\%$). Only four studies reported on stage II CRC DSS (OR, 0.55; 95% CI 0.23–1.34; $p = 0.19$; $I^2 = 47\%$). For DSS, there was a trend to benefit but this was statistically insignificant and this was likely due to the limited data available for DSS in stage II CRC. Both the estimates for OS and DFS demonstrated a survival advantage for stage II MSI-H CRC.

23 studies provided OS data with the OS for stage III CRC estimated to be OR, 0.74; 0.60–0.91; $p = 0.005$; $I^2 = 57\%$). Nineteen studies reported on DFS in stage III CRC. The estimate for DFS in stage III CRC was OR, 0.71 (95% CI 0.63–0.80; $p < 0.00001$; $I^2 = 0\%$). For DSS, there was limited data with significant heterogeneity with only 7 studies reporting this outcome for stage III CRC. This showed no difference in DSS between the MSI-H and MSS CRC (OR, 1.09; 0.76–1.55; $p = 0.64$; $I^2 = 52\%$). Both the estimates for OS and DFS reported a statistically significant survival benefit for stage III MSI-H CRC.

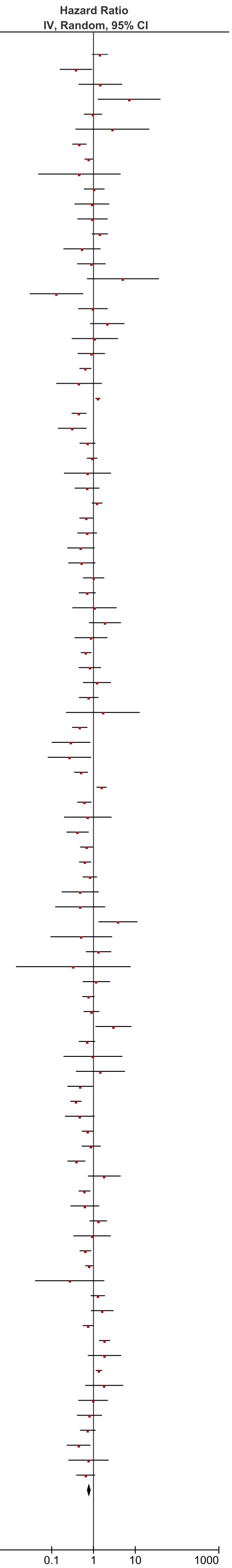
Eleven studies reported no difference in OS between stage IV MSI-H and MSS CRC (OR, 1.05; 95% CI 0.81–1.36; $p = 0.70$; $I^2 = 68\%$). Only three studies reported on DFS in stage IV CRC. The estimate for DFS was OR, 0.63; 95% CI 0.32–1.22; $p = 0.17$; $I^2 = 71\%$). Three studies reported data for DSS in stage IV CRC with no statistically significant difference between the two groups (OR, 0.75; 95% CI 0.41–1.38; $p = 0.35$; $I^2 = 0$). There was no benefit in OS, DFS nor DSS in stage IV CRC based on MSI status.

While studies on immunotherapy trials were excluded in this present meta-analysis (as not within the scope of this meta-analysis), we have previously performed a systematic review of immunotherapy for stage IV metastatic CRC which demonstrated a survival advantage with immunotherapy for

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.4.5 Any Stage				
Alex 2017 (IV)	0.350657	0.226353	1.4%	1.42 [0.91, 2.21]
Aparicio 2013 (I,II,III,IV)	-0.96758	0.45441	0.8%	0.38 [0.16, 0.93]
Bae 2015 (IV)	0.378436	0.61276	0.5%	1.46 [0.44, 4.85]
Banerjea 2009 (I, II, III)	1.965713	0.881922	0.3%	7.14 [1.27, 40.22]
Barault 2008 (NS)	-0.03046	0.256089	1.3%	0.97 [0.59, 1.60]
Barrasa 2009 (I,II,III,IV)	1.040277	1.037604	0.2%	2.83 [0.37, 21.63]
Benatti 2005 (I,II,III,IV)	-0.77653	0.200388	1.5%	0.46 [0.31, 0.68]
Bertagnolli 2011 (II,III)	-0.26136	0.118326	1.8%	0.77 [0.61, 0.97]
Brenner 2012 (I,II,III,IV)	-0.77653	1.159004	0.2%	0.46 [0.05, 4.46]
Carathers 2004 (II,III)	0.039221	0.290136	1.2%	1.04 [0.59, 1.84]
Chang 2006 (I,II,III, IV)	-0.09431	0.486858	0.7%	0.91 [0.35, 2.36]
Curran 2000 (II)	-0.05129329	0.42508298	0.8%	0.95 [0.41, 2.19]
Des Guetz 2017 (IV)	0.350657	0.226353	1.4%	1.42 [0.91, 2.21]
Deschoolmeester 2008 (I,II,III)	-0.63488	0.521937	0.6%	0.53 [0.19, 1.47]
Diep 2003 (I,II,III,IV)	-0.11653	0.400416	0.9%	0.89 [0.41, 1.95]
Drucker 2013 (III)	1.6227489	1.0120342	0.2%	5.07 [0.70, 36.83]
Elsaleh 2001 (III)	-2.04022	0.751132	0.4%	0.13 [0.03, 0.57]
Emterling 2004 (I,II,III,IV)	-0.03046	0.416436	0.9%	0.97 [0.43, 2.19]
Evertson 2003 (NS)	0.760806	0.481954	0.7%	2.14 [0.83, 5.50]
Ferri 2003 (I,II,III)	0.076961	0.652354	0.5%	1.08 [0.30, 3.88]
Fujiyoshi 2017 (IV)	-0.11429	0.383693	0.9%	0.89 [0.42, 1.89]
Gavin 2012 (I,II,III)	-0.44629	0.168366	1.6%	0.64 [0.46, 0.89]
Gervaz 2002 (II)	-0.79851	0.639777	0.5%	0.45 [0.13, 1.58]
Gkekas 2019 (II)	0.24686	0.070258	1.9%	1.28 [1.12, 1.47]
Gryfe 2000 (I,II,III,IV)	-0.79851	0.208753	1.5%	0.45 [0.30, 0.68]
Guidoboni 2001 (II,III)	-1.17118	0.403176	0.9%	0.31 [0.14, 0.68]
Gupta 2010 (NS)	-0.3285	0.223334	1.4%	0.72 [0.46, 1.12]
Hansen 2014 (II)	-0.0715	0.1492	1.7%	0.93 [0.69, 1.25]
Hartman 2013 (II,III,IV)	-0.3285	0.662055	0.5%	0.72 [0.20, 2.64]
Hong 2012 (I,II,III,IV)	-0.35667	0.348121	1.0%	0.70 [0.35, 1.38]
Hu 2016 (I,II,III,IV)	0.201307	0.148982	1.7%	1.22 [0.91, 1.64]
Hveem 2014 (II (I,II,III))	-0.4005	0.1919	1.5%	0.67 [0.46, 0.98]
Imai 2015 (I,II,III,IV)	-0.34814	0.275795	1.3%	0.71 [0.41, 1.21]
Jensen 2009 (II,III,IV)	-0.69315	0.383693	0.9%	0.50 [0.24, 1.06]
Johannsdottir 1999 (I,II,III)	-0.64245	0.380269	0.9%	0.53 [0.25, 1.11]
Kakar 2004 (I,II,III,IV)	0.007968	0.298535	1.2%	1.01 [0.56, 1.81]
Kalady 2012 (NS)	-0.34249	0.238508	1.4%	0.71 [0.44, 1.13]
Kazama 2007 (I,II,III,IV)	0.058269	0.623405	0.5%	1.06 [0.31, 3.60]
Kevans 2011 (II)	0.631272	0.450455	0.8%	1.88 [0.78, 4.55]
Kim 2017 (III)	-0.13697	0.463168	0.8%	0.87 [0.35, 2.16]
Kim, C.G. 2016 (I,II,III)	-0.40947	0.149659	1.7%	0.66 [0.50, 0.89]
Kim, G.P. 2007 (II,III)	-0.19845	0.312869	1.1%	0.82 [0.44, 1.51]
Kim, J.E. 2011 (IV)	0.19062	0.394592	0.9%	1.21 [0.56, 2.62]
Kim, J.E. 2015 (II)	-0.26266	0.274127	1.3%	0.77 [0.45, 1.32]
Kim, S.T. 2010 (II,III)	0.518794	1.036227	0.2%	1.68 [0.22, 12.80]
Klingbiel 2015 (II,III)	-0.75502	0.214969	1.5%	0.47 [0.31, 0.72]
Korphaisarn 2015 (I,II,III)	-1.23787	0.542916	0.6%	0.29 [0.10, 0.84]
Krajewska 2015 (II)	-1.32426	0.610987	0.5%	0.27 [0.08, 0.88]
Lamberti 2008 (I,II,III,IV)	-0.68518	0.193622	1.5%	0.50 [0.34, 0.74]
Li 2017 (NS)	0.444686	0.142141	1.7%	1.56 [1.18, 2.06]
Liang 2002 (IV)	-0.50253	0.198579	1.5%	0.60 [0.41, 0.89]
Lim 2004 (I,II,III,IV)	-0.31471	0.667703	0.5%	0.73 [0.20, 2.70]
Lin 2012 (I,II,III,IV)	-0.87467	0.312718	1.1%	0.42 [0.23, 0.77]
Lin 2014 (I,II,III,IV)	-0.37688	0.183654	1.6%	0.69 [0.48, 0.98]
Maccaroni 2015 (I,II,III,IV)	-0.46204	0.168366	1.6%	0.63 [0.45, 0.88]
Macquarrie 2012 (III)	-0.19845	0.201137	1.5%	0.82 [0.55, 1.22]
Maestro 2007 (NS)	-0.73397	0.518959	0.7%	0.48 [0.17, 1.33]
Meng 2007 (II,III)	-0.73396918	0.7028169	0.4%	0.48 [0.12, 1.90]
Messerini 1999 (I,II,III)	1.348073	0.54833	0.6%	3.85 [1.31, 11.28]
Mojarad 2016 (I,II,III)	-0.66943	0.865563	0.3%	0.51 [0.09, 2.79]
Nakaji 2017 (II,III)	0.277632	0.356825	1.0%	1.32 [0.66, 2.66]
Nehls 2009 (I,II,III)	-1.10866	1.611653	0.1%	0.33 [0.01, 7.77]
Nopel-Dunneback 2014 (IV)	0.157004	0.385257	0.9%	1.17 [0.55, 2.49]
Nordholm-Carstensen 2015 (IV)	-0.27444	0.172055	1.6%	0.76 [0.54, 1.06]
Ogino 2009 (I,II,III,IV)	-0.11653	0.221125	1.4%	0.89 [0.58, 1.37]
Oh 2013 (III)	1.098612	0.504697	0.7%	3.00 [1.12, 8.07]
Ohrling 2010 (II,III)	-0.35667	0.231184	1.4%	0.70 [0.44, 1.10]
Parc 2004 (II)	-0.03046	0.82803	0.3%	0.97 [0.19, 4.92]
Park 2010 (I,II,III,IV)	0.385262	0.688582	0.4%	1.47 [0.38, 5.67]
Phipps 2013 (Distal colon)	-0.73397	0.358907	1.0%	0.48 [0.24, 0.97]
Phipps 2013 (Proximal colon)	-0.96758	0.157918	1.7%	0.38 [0.28, 0.52]
Phipps 2013 (Rectum)	-0.75502	0.415384	0.9%	0.47 [0.21, 1.06]
Ribic 2003 (II,III)	-0.3285	0.159395	1.6%	0.72 [0.53, 0.98]
Rosty 2014 (NS)	-0.12783	0.268547	1.3%	0.88 [0.52, 1.49]
Roth 2010 (II,III)	-0.94161	0.250212	1.3%	0.39 [0.24, 0.64]
Salahshor 1999 (I,II,III)	0.593327	0.460552	0.8%	1.81 [0.73, 4.46]
Samowitz 2001 (I,II,III,IV)	-0.4943	0.165226	1.6%	0.61 [0.44, 0.84]
Sargent 2010 (II,III)	-0.47804	0.405045	0.9%	0.62 [0.28, 1.37]
Saridaki 2010 (IV)	0.262364	0.246194	1.3%	1.30 [0.80, 2.11]
Sasaki 2016 (III)	-0.07257	0.524605	0.6%	0.93 [0.33, 2.60]
Shima 2011 (I,II,III,IV)	-0.44629	0.16288	1.6%	0.64 [0.47, 0.88]
Sinicrope, F.A. 2011 (II,III)	-0.23572	0.111285	1.8%	0.79 [0.64, 0.98]
Slik 2017 (II)	-1.3093	0.9743	0.2%	0.27 [0.04, 1.82]
Taieb 2016 (III)	0.239017	0.200867	1.5%	1.27 [0.86, 1.88]
Tikidzhieva 2012 (II,III)	0.476234	0.319582	1.1%	1.61 [0.86, 3.01]
Toon 2014 (NS)	-0.30111	0.149946	1.7%	0.74 [0.55, 0.99]
Tran 2011 (IV)	0.609766	0.155308	1.7%	1.84 [1.36, 2.49]
Turner 2015 (II)	0.604316	0.468472	0.7%	1.83 [0.73, 4.58]
Venderbosch 2014 (IV)	0.300105	0.09031	1.8%	1.35 [1.13, 1.61]
Vogelaar 2015 (II)	0.587787	0.53573	0.6%	1.80 [0.63, 5.14]
Wang 2003 (II)	-0.0202	0.415167	0.9%	0.98 [0.43, 2.21]
Ward 2005 (I,II,III,IV)	-0.22314	0.353647	1.0%	0.80 [0.40, 1.60]
Watanabe 2001 (III (II,III))	-0.31061	0.218576	1.4%	0.73 [0.48, 1.13]
Wright 2000 (III)	-0.82098	0.333458	1.1%	0.44 [0.23, 0.85]
Xiao 2014 (NS)	-0.27444	0.563895	0.6%	0.76 [0.25, 2.30]
Yoon 2011 (I,II,III,IV)	-0.43078	0.26452	1.3%	0.65 [0.39, 1.09]
Subtotal (95% CI)			**100.0%**	**0.81 [0.73, 0.90]**

Heterogeneity: Tau² = 0.13; Chi² = 320.85, df = 95 (P < 0.00001); I² = 70%

Test for overall effect: Z = 4.06 (P < 0.0001)



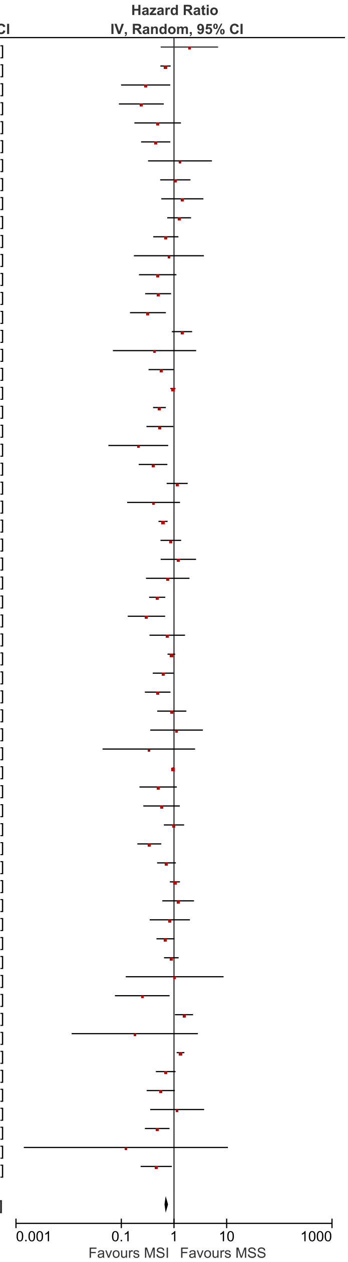
Test for subgroup differences: Not applicable

Fig. 2 Forest plot of overall survival (OS) (any stage) based on MSI Status

Fig. 3 Forest plot of disease-free survival (DFS) (any stage) based on MSI Status

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Barrasa 2009 (I,II,III,IV)	0.672944	0.640648	0.5%	1.96 [0.56, 6.88]
Bertagnolli 2011 (II,III)	-0.37106	0.114034	3.5%	0.69 [0.55, 0.86]
Birgisson 2015 (II,III)	-1.23787	0.548919	0.7%	0.29 [0.10, 0.85]
Birgisson 2015 (IV)	-1.42712	0.500423	0.8%	0.24 [0.09, 0.64]
Chang 2006 (I,II,III, IV)	-0.71335	0.519613	0.8%	0.49 [0.18, 1.36]
De Weger 2011 (I,II,III)	-0.79851	0.325585	1.5%	0.45 [0.24, 0.85]
Des Gruetz 2010 (I,II,III)	0.262364	0.712716	0.5%	1.30 [0.32, 5.26]
Deschoolmeester 2008 (I,II,III)	0.058269	0.338109	1.5%	1.06 [0.55, 2.06]
Drucker 2013 (III)	0.3646431	0.4691609	0.9%	1.44 [0.57, 3.61]
Du 2013 (I,II,III,IV)	0.225541	0.265677	2.0%	1.25 [0.74, 2.11]
Eveno 2014 (IV)	-0.35667	0.280258	1.8%	0.70 [0.40, 1.21]
Ferri 2003 (I,II,III)	-0.22314	0.780681	0.4%	0.80 [0.17, 3.69]
Gafa 2000 (I,II,III,IV)	-0.71335	0.417757	1.1%	0.49 [0.22, 1.11]
Gkekas 2019 (II)	-0.69315	0.28921	1.8%	0.50 [0.28, 0.88]
Guidoboni 2001 (II,III)	-1.13943	0.400157	1.2%	0.32 [0.15, 0.70]
Hansen 2014 (II)	0.3507	0.2259	2.3%	1.42 [0.91, 2.21]
Hemminki 2000 (III)	-0.85097	0.928684	0.3%	0.43 [0.07, 2.64]
Hong 2012 (I,II,III,IV)	-0.56212	0.280258	1.8%	0.57 [0.33, 0.99]
Hu 2016 (I,II,III,IV)	-0.04814	0.056724	4.0%	0.95 [0.85, 1.07]
Hutchins 2011 (II,III)	-0.63488	0.142759	3.2%	0.53 [0.40, 0.70]
Hveem 2014 (II (I,II,III))	-0.6162	0.2999	1.7%	0.54 [0.30, 0.97]
Iachetta 2016 (II)	-1.56064775	0.66708158	0.5%	0.21 [0.06, 0.78]
Jensen 2009 (II,III,IV)	-0.91629	0.319582	1.6%	0.40 [0.21, 0.75]
Jover 2009 (I,II,III,IV)	0.139762	0.234446	2.2%	1.15 [0.73, 1.82]
Kang 2011(II,III)	-0.8916	0.589379	0.6%	0.41 [0.13, 1.30]
Kim, C.G. 2016 (I,II,III)	-0.47965	0.101081	3.6%	0.62 [0.51, 0.75]
Kim, J.E. 2015 (II)	-0.13926	0.23005	2.3%	0.87 [0.55, 1.37]
Kim, S.H. 2013 (III)	0.1906204	0.3945924	1.2%	1.21 [0.56, 2.62]
Kim, S.T. 2010 (II,III)	-0.27444	0.484837	0.9%	0.76 [0.29, 1.97]
Klingbiel 2015 (II,III)	-0.73397	0.180547	2.8%	0.48 [0.34, 0.68]
Korphaisarn 2015 (I,II,III)	-1.20397	0.417284	1.1%	0.30 [0.13, 0.68]
Lin 2012 (I,II,III,IV)	-0.29437	0.396033	1.2%	0.75 [0.34, 1.62]
Markovic 2012 (I,II,III,IV)	-0.11653	0.084806	3.8%	0.89 [0.75, 1.05]
Merok 2013 (I,II,III,IV)	-0.47	0.233104	2.2%	0.63 [0.40, 0.99]
Mouradov 2013 (II,III)	-0.71335	0.286261	1.8%	0.49 [0.28, 0.86]
Nakaji 2017 (II,III)	-0.09541	0.324876	1.5%	0.91 [0.48, 1.72]
Oh 2013 (III)	0.113329	0.586892	0.6%	1.12 [0.35, 3.54]
Ooki 2014 (III)	-1.09961	1.032203	0.2%	0.33 [0.04, 2.52]
Parc 2004 (II)	-0.04082	0.015949	4.2%	0.96 [0.93, 0.99]
Roth 2010 (II,III)	-0.69315	0.416504	1.1%	0.50 [0.22, 1.13]
Sargent 2010 (II,III)	-0.54473	0.406616	1.1%	0.58 [0.26, 1.29]
Saridaki 2010 (IV)	0	0.226353	2.3%	1.00 [0.64, 1.56]
Shima 2011 (I,II,III,IV)	-1.07881	0.267173	1.9%	0.34 [0.20, 0.57]
Sinicrope, F.A. 2006 (II,III)	-0.3285	0.209221	2.5%	0.72 [0.48, 1.08]
Sinicrope, F.A. 2013 (III)	0.039221	0.112493	3.5%	1.04 [0.83, 1.30]
Soreide 2009 (I,II,III)	0.182322	0.353647	1.4%	1.20 [0.60, 2.40]
Srdjan 2016 (II,III)	-0.18272	0.448306	1.0%	0.83 [0.35, 2.01]
Sun 2014 (I,II,III,IV)	-0.37397	0.200186	2.5%	0.69 [0.46, 1.02]
Taieb 2016 (III)	-0.11653	0.162703	2.9%	0.89 [0.65, 1.22]
Tan 2018 (III)	0.029559	1.090691	0.2%	1.03 [0.12, 8.73]
Tian 2012 (II,III)	-1.38629	0.609871	0.6%	0.25 [0.08, 0.83]
Toh 2017 (I,II,III,IV)	0.438255	0.202472	2.5%	1.55 [1.04, 2.31]
Turner 2015 (II)	-1.7148	1.407513	0.1%	0.18 [0.01, 2.84]
Venderbosch 2014 (IV)	0.285179	0.08616	3.8%	1.33 [1.12, 1.57]
Watanabe 2001 (III (II,III))	-0.36241	0.219027	2.4%	0.70 [0.45, 1.07]
Westra 2005 (III)	-0.57982	0.313828	1.6%	0.56 [0.30, 1.04]
Xiao 2014 (NS)	0.139762	0.60157	0.6%	1.15 [0.35, 3.74]
Yoon 2011 (I,II,III,IV)	-0.73397	0.274111	1.9%	0.48 [0.28, 0.82]
Yoon 2015 (NS)	-2.10373	2.275848	0.0%	0.12 [0.00, 10.56]
Zaanan 2011 (III)	-0.77653	0.348415	1.4%	0.46 [0.23, 0.91]
Total (95% CI)			**100.0%**	**0.73 [0.66, 0.81]**

Heterogeneity: Tau² = 0.06; Chi² = 204.01, df = 59 (P < 0.00001); I² = 71%
Test for overall effect: Z = 6.24 (P < 0.00001)



MSI-H CRC [33] and results from this present meta-analysis on stage IV metastatic CRC as well as the potential role of immunotherapy in stage IV MSI-H CRC will be discussed in the discussion.

The OS, DFS and DSS by stage has been summarised in Table 2 and forest plot analysis of OS, DFS and DSS (overall and by stage) has been provided in Figs. 5, 6 and 7.

Other factors influencing prognosis

Age (< 60/≥ 60) Studies were divided into two subgroups (< 60/≥ 60) based on the mean age of the MSI-H cohort. In studies where a mean age was not reported, the median age was used. Thirteen studies reported a mean or median age < 60, 31 studies reported a mean or median age ≥ 60. There was a statistically significant benefit in OS associated with MSI-H status in studies with mean/median age < 60 (OR, 0.69; 95% CI 0.58–0.84; p = 0.0002; I^2 = 37%). However, where the mean/median age was ≥ 60, there was trend to better OS, but was not statistically significant (OR, 0.84; 95% CI 0.70–1.02; p = 0.07; I^2 = 74%) (refer to eFigure 1). In this meta-analysis, the survival benefit conferred by MSI status was greatest in younger cohorts where the median (mean) age of the cohort was < 60.

BRAF status Percentage of BRAF mutation within the cohort of MSI-H CRC was reported in 34 studies. The range was 14–72%. The data were not statistically significant but there was a

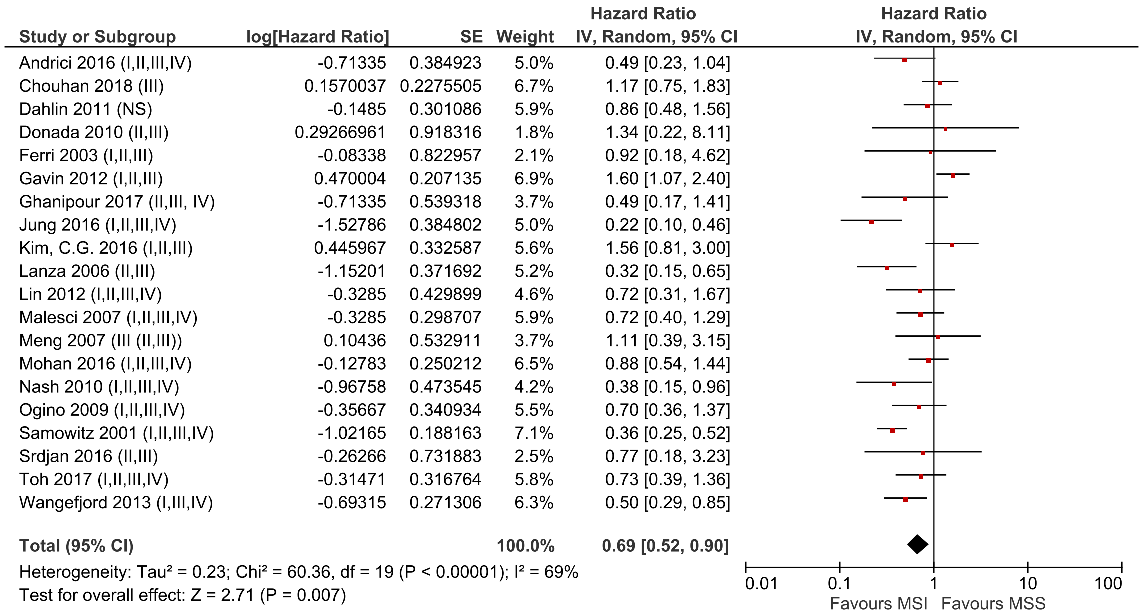


Fig. 4 Forest plot of disease specific survival (DSS) (any stage) based on MSI Status

trend to better OS and DFS with studies reporting a lower percentage of BRAF mutation in the MSI-H cohort.

High grade/mucinous/signet cell/poor differentiation High grade CRC was reported specifically in eight studies (mucinous $n = 3$, signet cell $n = 2$, poor differentiation $n = 3$). With the limited data available, a survival benefit associated with MSI-H was not detected in high grade, poorly differentiated CRC that were mucinous or with signet cell (OR 0.91; 95% CI 0.64–1.28; $p = 0.58$; $I^2 = 28\%$).

Sidedness and rectum MSI-H status in both right and left side colon cancers were associated with improved OS (Right: OR, 0.39; 95% CI 0.30–0.51; $p < 0.00001$; $I^2 = 0\%$; Left: OR. 0.40; 95% CI 0.30–0.53; $p < 0.00001$; $I^2 = 0\%$). An analysis comparing percentage of right (proximal) and left (distal) colon cancer with OS showed no difference in OS between right and left side in patients with MSI-H colon cancer. The survival benefit associated with MSI-H was statistically significant for both right and left colon.

Table 2 Survival (OS, DFS and DSS) based on MSI status (MSI-H vs. MSS) based on stage

	OS	DFS	DSS
Stage I	1.33 (0.41–4.39)	0.41 (0.17–1.00)	0.59 (0.27–1.33)
Stage II	**0.56 (0.36–0.89)**	**0.59 (0.46–0.76)**	0.55 (0.23–1.34)
Stage III	**0.74 (0.60–0.91)**	**0.71 (0.63–0.80**	1.09 (0.76–1.55)
Stage IV	1.05 (0.81–1.36)	0.63 (0.32–1.22)	0.75 (0.41–1.38)
All stages	**0.81 (0.73–0.90)**	**0.73 (0.66–0.81)**	**0.69 (0.52–0.90)**

Bold values - statistically significant difference in survival based on MSI status

The findings for rectal cancer was based on limited studies and was not statistically significant (OR, 0.93; 95% CI 0.35–2.49; $p = 0.88$; $I^2 = 75\%$).

Only a limited number of studies were available for analysis on other factors influencing prognosis, and these results must be interpreted carefully.

Publication bias

Funnel plot analysis was produced for OS, DFS and DSS (overall, early and advanced stage). (refer to Figs. 8, 9, 10, 11, 12 and 13). There was no significant funnel plot asymmetry and publication bias was not significant.

Discussion

Level 1 evidence to date has reported better survival associated with MSI-H in CRC [1, 2]. In 2010, Guastadisegni et al. concluded that patients with stage I-IV MSI-H CRC appear to have better survival and better outcome found in terms of OS, DSS and DFS [2]. However, the survival advantage observed in clinical practice with this CRC phenotype has not been as robust and comprehensive as that reported in the above meta-analyses. This present meta-analysis attempts to explain differences between the evidence in the existing literature and in clinical practice.

Rate of dissemination (lymph node and distant metastasis)

This meta-analysis demonstrated that MSI-H was associated with a lower incidence of disease progression to lymph

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.5.1 Stage I				
Kang 2015 (I)	-0.71367	0.994541	20.5%	0.49 [0.07, 3.44]
Kim, C.G. 2016 (I (I,II,III))	-0.92382	0.504405	79.5%	0.40 [0.15, 1.07]
Subtotal (95% CI)			**100.0%**	**0.41 [0.17, 1.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%				
Test for overall effect: Z = 1.96 (P = 0.05)				
1.5.2 Stage II				
Bertagnolli 2011 (II (II,III))	-0.43078	0.16288	9.2%	0.65 [0.47, 0.89]
De Weger 2011 (II (I,II,III))	-0.84397	0.437449	4.8%	0.43 [0.18, 1.01]
Deschoolmeester 2008 (II (I, II, III))	0.09531	0.756973	2.3%	1.10 [0.25, 4.85]
Gkekas 2019 (II)	-0.69315	0.28921	7.0%	0.50 [0.28, 0.88]
Guidoboni 2001 (II (II,III))	-1.46968	0.799871	2.1%	0.23 [0.05, 1.10]
Hansen 2014 (II)	0.3507	0.2259	8.1%	1.42 [0.91, 2.21]
Hutchins 2011 (II)	-0.82098	0.213622	8.3%	0.44 [0.29, 0.67]
Hveem 2014 (II (I,II,III))	-0.6162	0.2999	6.8%	0.54 [0.30, 0.97]
Iachetta 2016 (II)	-1.56064775	0.66708158	2.8%	0.21 [0.06, 0.78]
Kim, C.G. 2016 (II (I,II,III))	-0.34814	0.14515	9.4%	0.71 [0.53, 0.94]
Kim, J.E. 2015 (II)	-0.13926	0.23005	8.0%	0.87 [0.55, 1.37]
Klingbiel 2015 (II (II,III))	-1.34707	0.477501	4.3%	0.26 [0.10, 0.66]
Merok 2013 (II (I,II,III,IV))	-0.7032	0.342833	6.1%	0.49 [0.25, 0.97]
Roth 2010 (II (II,III))	-1.30933	0.503592	4.1%	0.27 [0.10, 0.72]
Shin 2014 (II (II,III))	1.386294	0.693947	2.6%	4.00 [1.03, 15.59]
Tian 2012 (II (II,III))	-1.38629	0.609871	3.2%	0.25 [0.08, 0.83]
Touchefeu 2015 (II)	-0.28768	1.109765	1.2%	0.75 [0.09, 6.60]
Turner 2015 (II)	-1.7148	1.407513	0.8%	0.18 [0.01, 2.84]
Vogelaar 2015 (II)	0.470004	0.438176	4.8%	1.60 [0.68, 3.78]
Yang 2015 (II)	-1.07587	0.485116	4.3%	0.34 [0.13, 0.88]
Subtotal (95% CI)			**100.0%**	**0.59 [0.46, 0.76]**
Heterogeneity: Tau² = 0.15; Chi² = 47.87, df = 19 (P = 0.0003); I² = 60%				
Test for overall effect: Z = 4.10 (P < 0.0001)				
1.5.3 Stage III				
Aparicio 2013 (III (I,II,III,IV))	-0.67334	0.622307	1.0%	0.51 [0.15, 1.73]
Bertagnolli 2011 (III (II,III))	-0.19845	0.156935	15.9%	0.82 [0.60, 1.12]
De Weger 2011 (III (I,II,III))	-0.51083	0.560516	1.2%	0.60 [0.20, 1.80]
Deschoolmeester 2008 (III (I,II,III))	0.09531018	1.34146342	0.2%	1.10 [0.08, 15.25]
Drucker 2013 (III)	0.3646431	0.4691609	1.8%	1.44 [0.57, 3.61]
Guidoboni 2001(III (II,III))	-1.04982	0.471831	1.8%	0.35 [0.14, 0.88]
Jensen 2009 (III (II,III,IV))	-0.69315	0.280258	5.0%	0.50 [0.29, 0.87]
Kim 2017 (III)	-0.51416	0.418779	2.2%	0.60 [0.26, 1.36]
Kim, C.G. 2016 (III (I,II,III))	-0.35525	0.147504	18.0%	0.70 [0.53, 0.94]
Kim, S.H. 2013 (III)	0.1906204	0.3945924	2.5%	1.21 [0.56, 2.62]
Klingbiel 2015 (III (II,III))	-0.40048	0.19553	10.3%	0.67 [0.46, 0.98]
Oh 2013 (III)	0.113329	0.586892	1.1%	1.12 [0.35, 3.54]
Ooki 2014 (III)	-1.09961	1.032203	0.4%	0.33 [0.04, 2.52]
Roth 2010 (III (II,III))	-0.52763	0.222774	7.9%	0.59 [0.38, 0.91]
Taieb 2016 (III)	-0.11653	0.162703	14.8%	0.89 [0.65, 1.22]
Tan 2018 (III)	0.029559	1.090691	0.3%	1.03 [0.12, 8.73]
Watanabe 2001 (III (II,III))	-0.36241	0.219027	8.2%	0.70 [0.45, 1.07]
Westra 2005 (III)	-0.57982	0.313828	4.0%	0.56 [0.30, 1.04]
Zaanan 2011 (III)	-0.77653	0.348415	3.2%	0.46 [0.23, 0.91]
Subtotal (95% CI)			**100.0%**	**0.71 [0.63, 0.80]**
Heterogeneity: Tau² = 0.00; Chi² = 15.50, df = 18 (P = 0.63); I² = 0%				
Test for overall effect: Z = 5.47 (P < 0.00001)				
1.5.4 Stage IV				
Birgisson 2015 (IV)	-1.42712	0.500423	23.5%	0.24 [0.09, 0.64]
Eveno 2014 (IV)	-0.35667	0.280258	36.5%	0.70 [0.40, 1.21]
Saridaki 2010 (IV)	0	0.226353	40.0%	1.00 [0.64, 1.56]
Subtotal (95% CI)			**100.0%**	**0.63 [0.32, 1.22]**
Heterogeneity: Tau² = 0.23; Chi² = 6.86, df = 2 (P = 0.03); I² = 71%				
Test for overall effect: Z = 1.38 (P = 0.17)				

Test for subgroup differences: Chi² = 2.96, df = 3 (P = 0.40), I² = 0%

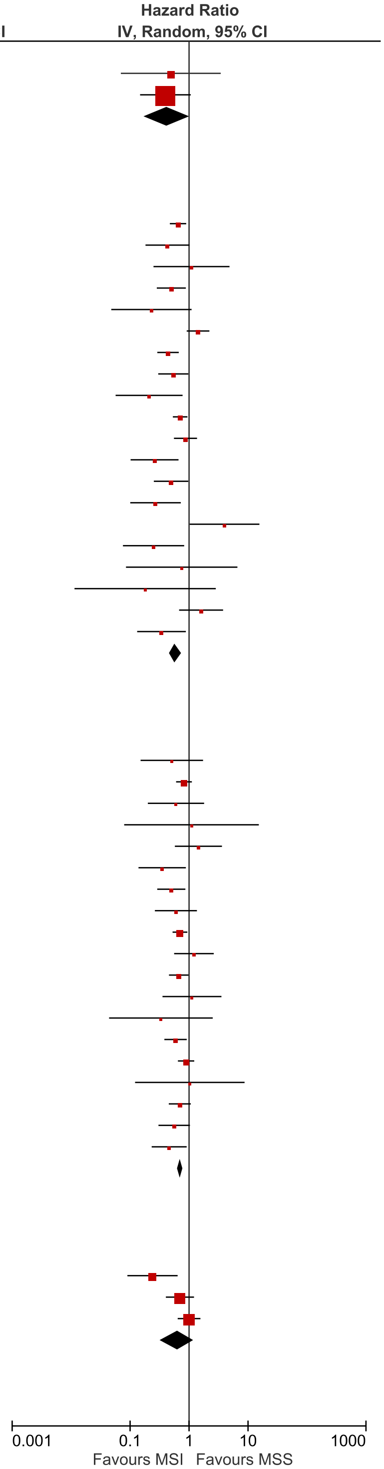


Fig. 5 Forest plot of overall survival (OS) (stage-by-stage analysis) based on MSI Status

node and distant metastases. From examining studies reporting on at least stage II and III CRC patients as well as stage I/II/III/IV or II/III/IV, the ratio of early (I/II): late (III/IV) MSI-H CRC from appropriate studies was 60%:40% (ratio 1.5) respectively—i.e. more MSI-H CRC was detected and managed at early stage.

In comparison, CRC statistics from the 2010–2016 National Cancer Institute Surveillance, Epidemiology and End Results (SEER) data reports localised disease (I/II 38%), regional (III 35%) and distant (IV 22%) metastases (unknown in 4%) associated with CRC [34]. The stage I/II:III/IV ratio based on 2010–2016 SEER data was

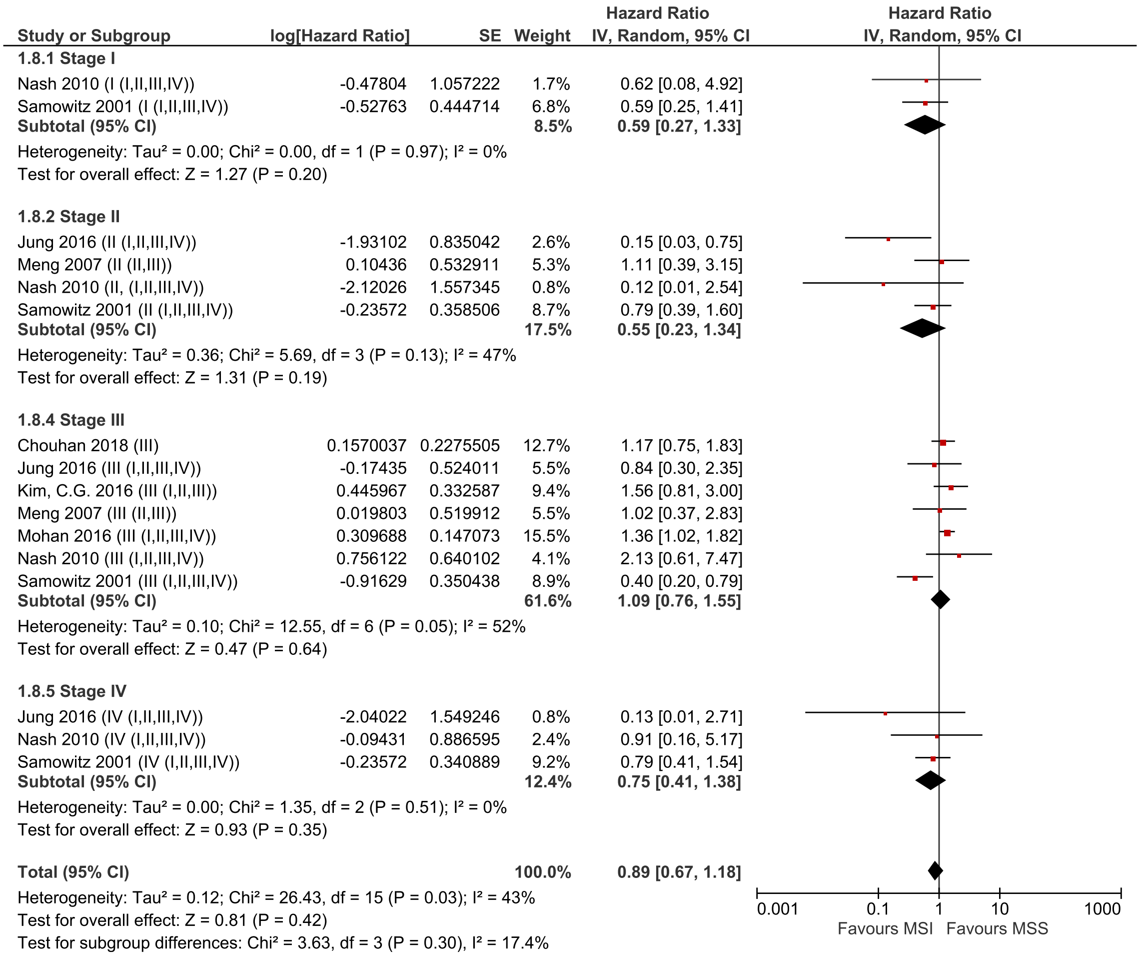


Fig. 6 Forest plot of disease-free survival (DFS) (stage-by-stage analysis) based on MSI Status

40%:60% (ratio 0.67)—i.e. more CRC of any phenotype detected at advanced stage (refer to Table 3).

The ratio of early to advanced cancer for MSI-H CRC was approximately double the ratio from the SEER data, demonstrating a lower incidence of progression to lymph node and distant metastases with MSI-H CRC when compared to an international database reporting on all phenotypes of CRC. There was significantly less progression to stage IV disease in MSI-H CRC. This finding of decreased likelihood of dissemination in MSI-H CRC is similar to findings from studies such as by Malesci et al. [35] which demonstrated an association between MSI-H and decreased risk of dissemination of cancer.

Overall prognosis and prognosis in early and late stage

This meta-analysis demonstrated an overall benefit in terms of OS, DFS and DSS. The protective effect of MSI-H was observed most clearly in stage II and III with better OS and DFS demonstrated in stage II and III CRC. There was not in a survival benefit in stage I (excellent survival irrespective of MSI status) and nor in stage IV CRC (without immunotherapy). Better DFS in stage II and III reported in this meta-analysis was consistent with the current literature reporting lower risk of relapse [35].

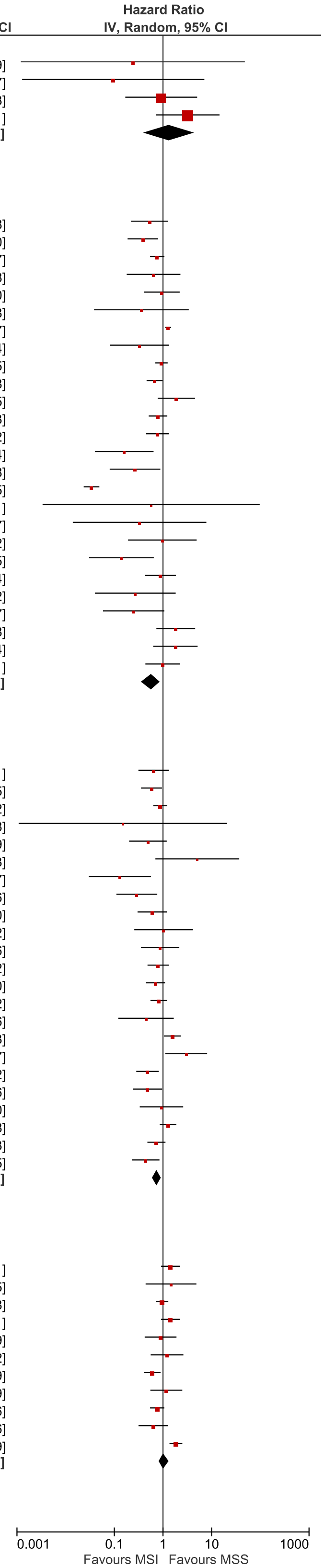
The lack of benefit in stage I may be explained by the overall excellent prognosis in stage I CRC for both MSI-H and MSS, but also may be partly due to the limited studies reporting on stage I MSI-H CRC. The lack of benefit in stage IV CRC (without immunotherapy) may be explained by the phenomenon of TILs exhaustion [33, 36]. Results from immunotherapy trials in metastatic MSI-H CRCs have been promising [33], but not within the scope of this meta-analysis. We have, however, previously reported on the benefits of immunotherapy on metastatic stage IV CRC [33] and the findings of this meta-analysis thus underscores the importance of immunotherapy for metastatic stage IV CRC, as without it, stage IV MSI-H CRC appeared to have lost its immunogenicity.

In terms of DSS, there was better prognosis overall. However, by stage, there was no statistically significant survival advantage. This was likely due to the limited studies available reporting on DSS by stage rather than a true effect. It is important to understand that DSS censor patients who

Fig. 7 Forest plot of disease specific survival (DSS) (stage-by-stage analysis) based on MSI Status

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 Stage I				
Benatti 2005 (I (I,II,III,IV))	-1.42712	2.703159	4.9%	0.24 [0.00, 47.99]
Chang 2006 (I (I,II,III,IV))	-2.35388	2.198916	7.4%	0.09 [0.00, 7.07]
Kim, C.G. 2016 (I (I,II,III))	-0.08447	0.867298	39.6%	0.92 [0.17, 5.03]
Samowitz 2001 (I (I,II,III,IV))	1.174647	0.765451	48.2%	3.24 [0.72, 14.51]
Subtotal (95% CI)			**100.0%**	**1.33 [0.41, 4.39]**
Heterogeneity: Tau² = 0.18; Chi² = 3.36, df = 3 (P = 0.34); I² = 11%				
Test for overall effect: Z = 0.48 (P = 0.63)				
1.1.2 Stage II				
Aparicio 2013 (II (I,II,III,IV))	-0.63488	0.449232	4.3%	0.53 [0.22, 1.28]
Benatti (II (I,II,III,IV))	-0.95192	0.368871	4.5%	0.39 [0.19, 0.80]
Bertagnolli 2011 (II (II,III))	-0.27444	0.17445	5.0%	0.76 [0.54, 1.07]
Chang 2006 (II (I,II,III,IV))	-0.44629	0.647697	3.6%	0.64 [0.18, 2.28]
Curran 2000 (II)	-0.0513	0.4287	4.3%	0.95 [0.41, 2.20]
Deschoolmeester 2008 (II (I, II, III))	-1.02165	1.142901	2.3%	0.36 [0.04, 3.38]
Gkekas 2019 (II)	0.24686	0.070258	5.1%	1.28 [1.12, 1.47]
Guidoboni 2001 (II (II,III))	-1.10866	0.713203	3.4%	0.33 [0.08, 1.34]
Hansen 2014 (II)	-0.0715	0.1492	5.0%	0.93 [0.69, 1.25]
Hveem 2014 (II (I,II,III))	-0.4005	0.1919	4.9%	0.67 [0.46, 0.98]
Kevans 2011 (II)	0.631272	0.450455	4.3%	1.88 [0.78, 4.55]
Kim, C.G. 2016 (II (I,II,III))	-0.23572	0.224166	4.9%	0.79 [0.51, 1.23]
Kim, J.E. 2015 (II)	-0.26266	0.274127	4.8%	0.77 [0.45, 1.32]
Klingbiel 2015 (II (II,III))	-1.83258	0.707293	3.4%	0.16 [0.04, 0.64]
Krajewska 2015 (II)	-1.32426	0.610987	3.8%	0.27 [0.08, 0.88]
Meng 2007 (II (II,III))	-3.38139475	0.1888889	4.9%	0.03 [0.02, 0.05]
Mojarad 2016 (II (I,II,III))	-0.56212	2.619864	0.7%	0.57 [0.00, 96.81]
Nehls 2009 (II (I,II,III))	-1.10866	1.611653	1.5%	0.33 [0.01, 7.77]
Parc 2004 (II)	-0.03046	0.82803	3.1%	0.97 [0.19, 4.92]
Roth 2010 (II (II,III))	-1.96611	0.780681	3.2%	0.14 [0.03, 0.65]
Samowitz 2001 (II (I,II,III,IV))	-0.11878	0.372234	4.5%	0.89 [0.43, 1.84]
Slik 2017 (II)	-1.3093	0.9743	2.7%	0.27 [0.04, 1.82]
Touchefeu 2015 (II)	-1.38629	0.739691	3.3%	0.25 [0.06, 1.07]
Turner 2015 (II)	0.604316	0.468472	4.2%	1.83 [0.73, 4.58]
Vogelaar 2015 (II)	0.587787	0.53573	4.0%	1.80 [0.63, 5.14]
Wang 2003 (II)	-0.0202	0.415167	4.4%	0.98 [0.43, 2.21]
Subtotal (95% CI)			**100.0%**	**0.56 [0.36, 0.89]**
Heterogeneity: Tau² = 1.05; Chi² = 360.17, df = 25 (P < 0.00001); I² = 93%				
Test for overall effect: Z = 2.48 (P = 0.01)				
1.1.3 Stage III				
Aparicio 2013 (III (I,II,III,IV))	-0.44629	0.365701	4.4%	0.64 [0.31, 1.31]
Benatti 2005 (III (I,II,III,IV))	-0.54473	0.252263	6.1%	0.58 [0.35, 0.95]
Bertagnolli 2011 (III (II,III))	-0.12783	0.168593	7.5%	0.88 [0.63, 1.22]
Chang 2006 (III, (I,II,III,IV))	-1.89712	2.515986	0.2%	0.15 [0.00, 20.78]
Deschoolmeester 2008 (III (I,II,III))	-0.713349	0.453703	3.5%	0.49 [0.20, 1.19]
Drucker 2013 (III)	1.6227489	1.0120342	1.0%	5.07 [0.70, 36.83]
Elsaleh 2001 (III)	-2.04022	0.751132	1.7%	0.13 [0.03, 0.57]
Guidoboni 2001(III (II,III))	-1.23787	0.493071	3.1%	0.29 [0.11, 0.76]
Jensen 2009 (III (II,III,IV))	-0.51083	0.353647	4.6%	0.60 [0.30, 1.20]
Kakar 2005 (III (II,III,IV))	0.029559	0.707906	1.8%	1.03 [0.26, 4.12]
Kim 2017 (III)	-0.13697	0.463168	3.4%	0.87 [0.35, 2.16]
Kim, C.G. 2016 (III (I,II,III))	-0.22941	0.257093	6.0%	0.80 [0.48, 1.32]
Klingbiel 2015 (III (II,III))	-0.35667	0.231418	6.4%	0.70 [0.44, 1.10]
Macquarrie 2012 (III)	-0.19845	0.201137	6.9%	0.82 [0.55, 1.22]
Meng 2007 (III (II,III))	-0.80296205	0.66865667	2.0%	0.45 [0.12, 1.66]
Mohan 2016 (III (I,II,III,IV))	0.444686	0.205777	6.9%	1.56 [1.04, 2.33]
Oh 2013 (III)	1.098612	0.504697	3.0%	3.00 [1.12, 8.07]
Roth 2010 (III (II,III))	-0.73397	0.270981	5.8%	0.48 [0.28, 0.82]
Samowitz 2001 (III (I,II,III,IV))	-0.73397	0.353647	4.6%	0.48 [0.24, 0.96]
Sasaki 2016 (III)	-0.07257	0.524605	2.9%	0.93 [0.33, 2.60]
Taieb 2016 (III)	0.239017	0.200867	6.9%	1.27 [0.86, 1.88]
Watanabe 2001 (III (II,III))	-0.31061	0.218576	6.6%	0.73 [0.48, 1.13]
Wright 2000 (III)	-0.82098	0.333458	4.8%	0.44 [0.23, 0.85]
Subtotal (95% CI)			**100.0%**	**0.74 [0.60, 0.91]**
Heterogeneity: Tau² = 0.12; Chi² = 51.04, df = 22 (P = 0.0004); I² = 57%				
Test for overall effect: Z = 2.80 (P = 0.005)				
1.1.4 Stage IV				
Alex 2017 (IV)	0.350657	0.226353	10.5%	1.42 [0.91, 2.21]
Bae 2015 (IV)	0.378436	0.61276	3.5%	1.46 [0.44, 4.85]
Benatti 2005 (IV (I,II,III,IV))	-0.04082	0.148762	12.7%	0.96 [0.72, 1.28]
Des Guetz 2017 (IV)	0.350657	0.226353	10.5%	1.42 [0.91, 2.21]
Fujiyoshi 2017 (IV)	-0.11429	0.383693	6.6%	0.89 [0.42, 1.89]
Kim, J.E. 2011 (IV)	0.19062	0.394592	6.4%	1.21 [0.56, 2.62]
Liang 2002 (IV)	-0.50253	0.198579	11.3%	0.60 [0.41, 0.89]
Nopel-Dunneback 2014 (IV)	0.157004	0.385257	6.6%	1.17 [0.55, 2.49]
Nordholm-Carstensen 2015 (IV)	-0.27444	0.172055	12.1%	0.76 [0.54, 1.06]
Samowitz 2001 (IV (I,II,III,IV))	-0.46204	0.354458	7.2%	0.63 [0.31, 1.26]
Tran 2011 (IV)	0.609766	0.155308	12.6%	1.84 [1.36, 2.49]
Subtotal (95% CI)			**100.0%**	**1.05 [0.81, 1.36]**
Heterogeneity: Tau² = 0.11; Chi² = 30.90, df = 10 (P = 0.0006); I² = 68%				
Test for overall effect: Z = 0.38 (P = 0.70)				

Test for subgroup differences: Chi² = 7.76, df = 3 (P = 0.05), I² = 61.3%



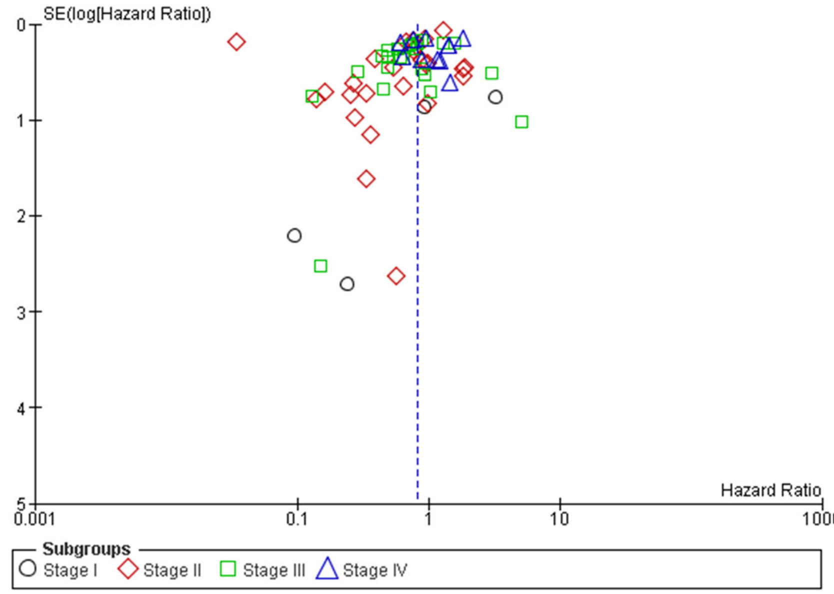


Fig. 8 Funnel plot for publication bias of meta-analysis of OS based on MSI status (MSI-H vs. MSS/MSI-L) stratified by stage

have died from causes other than the disease being studied. Deaths from other causes (competing causes of death) are removed (in the same way that people who are lost to follow-up are removed). Patients with sporadic MSI-H were older and thus more likely to die from other causes, and this may have partly contributed to DSS findings reported in this meta-analysis.

Other factors influencing prognosis

Age (< 60/≥ 60) Studies with a younger MSI-H CRC cohort (< 60) reported better OS associated with MSI. While this meta-analysis reported mainly on sporadic CRC, Lynch syndrome has traditionally been underdiagnosed and studies included in this meta-analysis may have included Lynch syndrome patients unknowingly (younger patients with BRAF wild type) as genetic testing may not have been performed in a large majority of cases. Patients with Lynch syndrome have a hereditary predisposition for colorectal cancer with early age of onset, with a median age of colorectal cancer diagnosis between the age of 40–50 years old. In a study by Schofield et al. looking at patients <60 years of age, 105/1344 patients had MSI-H. In these MSI-H cases, germline mutation in MMR associated with Lynch syndrome was estimated to be 89% (< 30 years), 83% (30–39), 68% (40–49) and 17% (50–59) [37]. A study by Stigliano et al. reported that the median age for diagnosis of a primary CRC was 61 years old whereas it was approximately 47 years for Lynch syndrome [38]. Within the literature, Lynch syndrome has been associated with better survival [38, 39]. This meta-analysis showed that

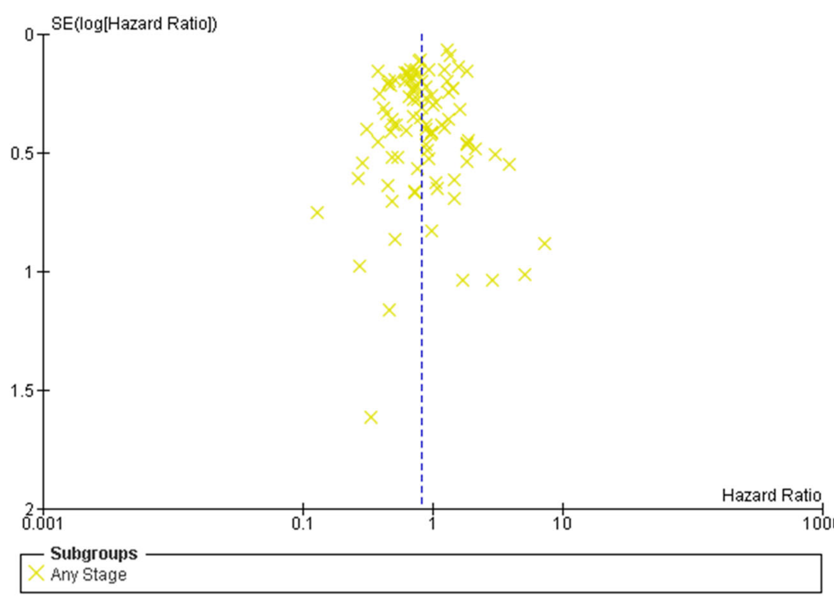


Fig. 9 Funnel plot for publication bias of meta-analysis of OS based on MSI status (MSI-H vs. MSS/MSI-L) not stratified by stage

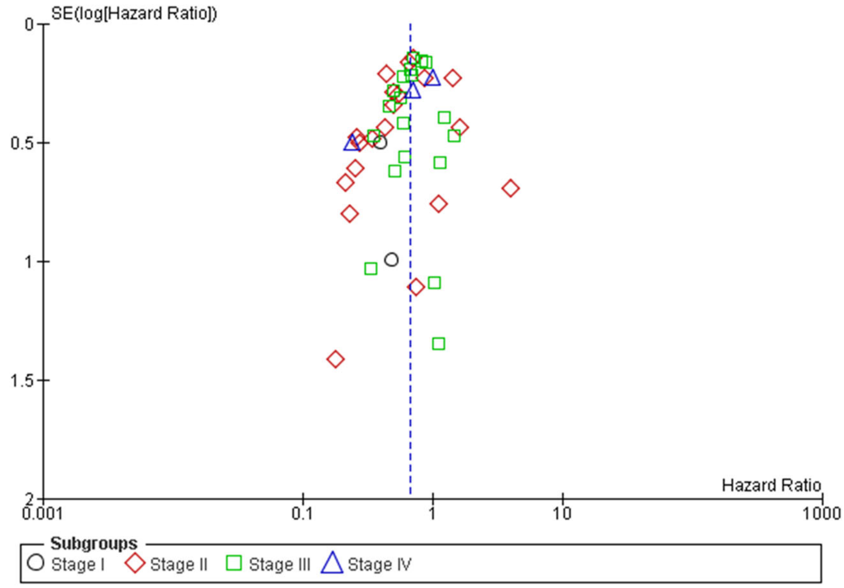


Fig. 10 Funnel plot for publication bias of meta-analysis of DFS based on MSI status (MSI-H vs. MSS/MSI-L) stratified by stage

younger patients with MSI-H CRC irrespective of Lynch syndrome diagnosis were associated with improved survival. It is unclear if this may be due to an underdiagnosis of Lynch syndrome patients in younger patients with MSI-H CRC.

BRAF status In this study, there was a trend to better OS and DFS in studies with a lower percentage of BRAF mutation within their MSI-H cohort. However, this was not statistically significant. This is in line with the current literature which suggests that BRAFV600E mutation is associated with worse prognosis in CRC. BRAFV600E testing is also a useful method for triaging MSI-H CRC patients for genetic testing for Lynch syndrome [40, 41]. The detection of BRAFV600E mutation in MSI-H CRC nearly always excludes Lynch syndrome. Absence of BRAF mutation in MSI-H CRC is associated with Lynch syndrome in approximately 60–70% [42]. As with age, it is unclear if the survival advantage of BRAF wild type in MSI-H CRC was influenced by an underdiagnosis of Lynch syndrome patients (which have a better prognosis) in the younger patients with MSI-H CRC.

High grade/poorly differentiated/mucinous Only eight studies included in our meta-analysis reported survival outcomes specifically on high grade (signet cell, mucinous and poor differentiation) MSI-H CRC. A subset analysis demonstrated no difference in OS between MSI-H and MSS in patients with high grade CRC. Within the current literature, it is unclear if high grade MSI-H CRC is associated with better survival as studies have reported a range of results [26, 43–45]. This meta-analysis did not find a survival advantage in high grade CRC based on MSI status; however, this result was based on a limited number of studies.

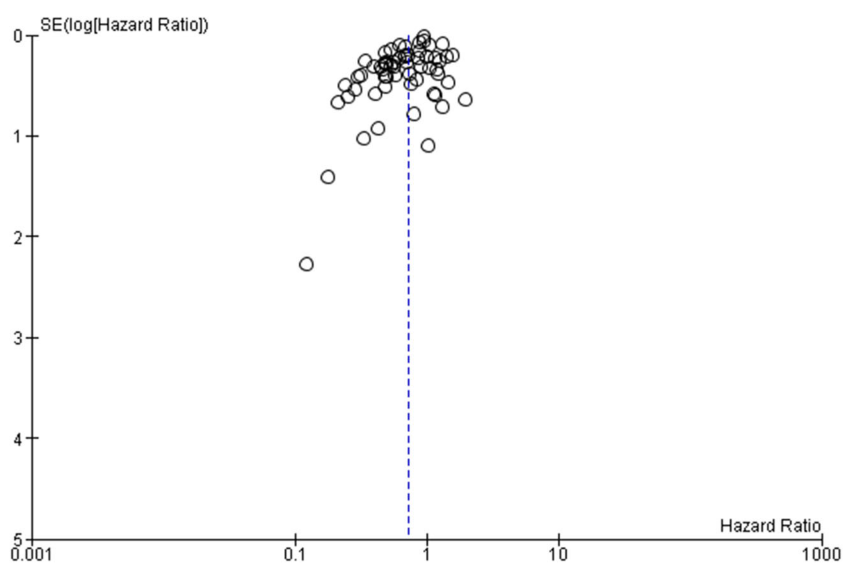


Fig. 11 Funnel plot for publication bias of meta-analysis of DFS based on MSI status (MSI-H vs. MSS/MSI-L) not stratified by stage

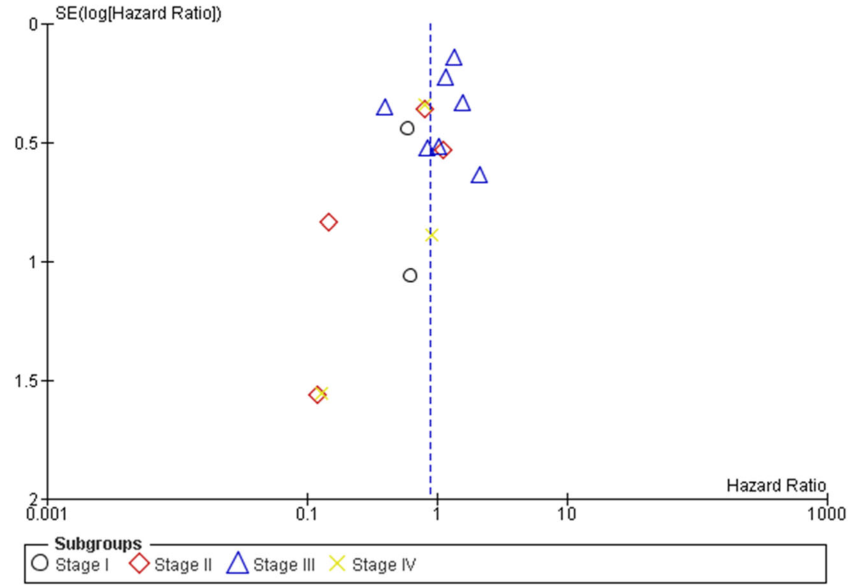


Fig. 12 Funnel plot for publication bias of meta-analysis of DSS based on MSI status (MSI-H vs. MSS/MSI-L) stratified by stage

Right colon/left colon/rectum MSI-H colon cancers are more likely to be right-sided when compared to MSS colon cancers [46]. Furthermore, LS cancers are also more likely to be right-sided (85% right-sided) than sporadic (57% right-sided) MSI-H CRC [38]. From this present meta-analysis, as well as the meta-analysis by Popat et al. and Guastadisegni et al. [1, 2], which have all reported improved OS with MSI-H CRC, it would be reasonable to assume that right-sided colon cancer would have better survival outcome than the left as a greater proportion are associated with MSI. However, recent studies [47–49] which includes a meta-analysis on right vs. left-sided colorectal cancer [49] as well as a Surveillance, Epidemiology and End Results (SEER) database analysis [48] have reported that survival outcome is better for left-sided than right-sided colon cancer. This meta-analysis showed better survival outcomes associated with MSI in both right and left colon cancer, but it does not explain why survival rates associated with left-sided cancers are better than right in general.

There were limited studies reporting on MSI status in rectal cancer. This meta-analysis did not show a survival benefit for MSI-H rectal cancers, but with the limited studies available, these results must be interpreted with caution. In any case, most rectal cancers are MSS. Within the current literature, there have been studies reporting both lower survival in MSI-H rectal cancer [50] as well as no difference [51].

Limitations

There were several limitations in this present meta-analysis. Firstly, there were only a limited number of studies reporting on stage I and IV, DSS and other factors influencing prognosis. Included studies were predominantly observational cohort

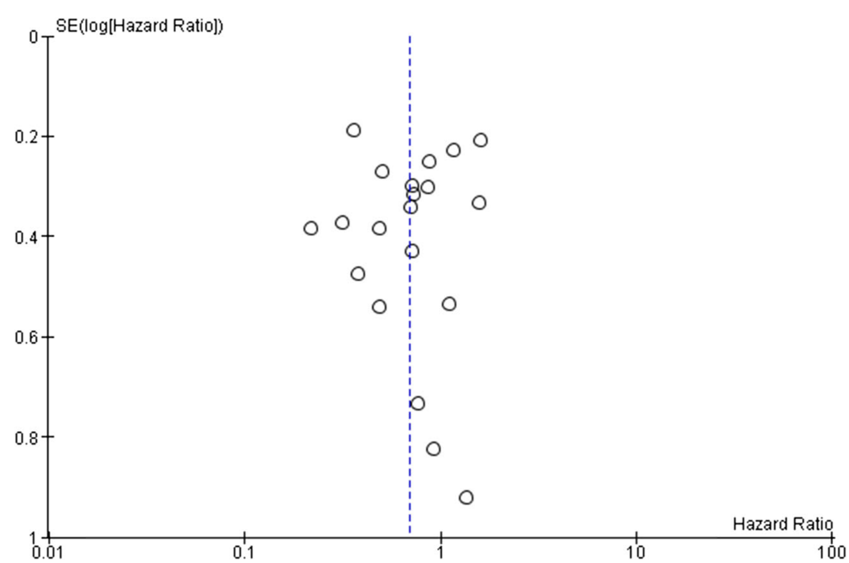


Fig. 13 Funnel plot for publication bias of meta-analysis of DSS based on MSI status (MSI-H vs. MSS/MSI-L) not stratified by stage

Table 3 Disease progression of MSI-H CRC compared to the National Cancer Institute Surveillance Epidemiology and End Results (SEER) program data

	Stage I/II (localised disease)	Stage III (lymph node metastases)	Stage IV (distant metastases)	Stage I/II:III ratio	Stage I/II:III/IV ratio
MSI-H CRC*	61%	30%	8%	2.03	1.61
NCI SEER data (2010–2016)—any phenotype CRC	38%	35%	22%	1.09	0.66

* Data based on 43 studies that have reported OS results in stage I-IV CRC and have been included in this present meta-analysis

studies and retrospective in nature and this contributed to the heterogeneity seen within this meta-analysis. There was insufficient data on genetic testing for Lynch syndrome to include in quantitative analysis, and it is likely that there was underreporting of Lynch syndrome in studies on MSI. Despite its limitations, this meta-analysis is the most comprehensive and largest meta-analysis on MSI status in CRC to date and provides valuable information on the rate of dissemination and prognosis of early and late stage CRC based on MSI status.

Conclusion

This meta-analysis has confirmed an overall protective effect associated with microsatellite instability with overall improved survival (OS, DFS, DSS). There was also a lower rate of dissemination to lymph node and distant metastases associated with MSI-H CRC. By stage, the survival benefit associated with MSI-H is greatest in stage II and III CRC. Stage I CRC has excellent prognosis irrespective of MSI status, and MSI-H was not associated with any survival advantage without immunotherapy in stage IV CRC which may be explained by a phenomenon known as TILs exhaustion in late stage. Survival benefit associated with MSI-H appeared to be enhanced in younger patients <60 and other factors such as BRAF status, grade and tumour location may influence survival associated with MSI-H, but these results were based on a limited number of studies and must be interpreted judiciously.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00384-021-03874-1.

Declarations

Conflict of interest The authors declare no competing interests.

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