Systematic review

Meta-analysis of microsatellite instability in relation to clinicopathological characteristics and overall survival in gastric cancer

K. Polom[1,6], L. Marano[2], D. Marrelli[1], R. De Luca[3], G. Roviello[4,5], V. Savelli[1], P. Tan[7] and F. Roviello[1]

[1]Department General Surgery and Surgical Oncology, University of Siena, Siena, [2]General, Minimally Invasive and Robotic Surgery, Department of Surgery, San Matteo degli Infermi Hospital, Spoleto, [3]Department of Surgical Oncology, National Cancer Research Centre–Istituto Tumori G. Paolo II, Bari, and [4]Department of Oncology, Medical Oncology Unit, San Donato Hospital, Arezzo, and [5]Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy, [6]Department of Surgical Oncology, Medical University of Gdansk, Gdansk, Poland, and [7]Cancer and Stem Cell Biology, Duke–National University of Singapore Graduate Medical School, Genome Institute of Singapore, Cancer Science Institute of Singapore, National University of Singapore, and Cellular and Molecular Research, National Cancer Centre, Singapore

Correspondence to: Dr K. Polom, Department of General Surgery and Surgical Oncology, University of Siena, Viale Bracci 16, 53-100, Siena, Italy (e-mail: polom.karol@gmail.com)

Background: **Several associations between microsatellite instability (MSI) and other clinicopathological factors have been reported in gastric cancer, but the results have been ambiguous. This systematic review and meta-analysis investigated the relationship between MSI and overall survival and clinicopathological characteristics of patients with gastric cancer.**

Methods: **A systematic literature search of the PubMed, Cochrane and Ovid databases until 31 January 2016 was performed in accordance with the PRISMA statement. The articles were screened independently according to PICO (population, intervention, comparator, outcome) eligibility criteria. All eligible articles were evaluated independently by two reviewers for risk of bias according to the Quality In Prognosis Study tool.**

Results: **Overall, 48 studies with a total of 18 612 patients were included. MSI was found in 9·2 per cent of patients (1718 of 18 612), and was associated with female sex (odds ratio (OR) 1·57, 95 per cent c.i. 1·31 to 1·89; $P < 0·001$), older age (OR 1·58, 2·20 to 1·13; $P < 0·001$), intestinal Laurén histological type (OR 2·23, 1·94 to 2·57; $P < 0·001$), mid/lower gastric location (OR 0·38, 0·32 to 0·44; $P < 0·001$), lack of lymph node metastases (OR 0·70, 0·57 to 0·86, $P < 0·001$) and TNM stage I–II (OR 1·77, 1·47 to 2·13; $P < 0·001$). The pooled hazard ratio for overall survival of patients with MSI *versus* those with non-MSI gastric cancer from 21 studies was 0·69 (95 per cent c.i. 0·56 to 0·86; $P < 0·001$).**

Conclusion: **MSI in gastric cancer was associated with good overall survival, reflected in several favourable clinicopathological tumour characteristics.**

Paper accepted 6 July 2017

Published online 1 November 2017 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10663

Introduction

Gastric cancer is still one of the most common neoplasms worldwide and is generally associated with poor prognosis[1]. Treatment outcomes may be improved by implementing tailored therapy[2]. Optimal treatment of patients with gastric cancer also entails identifying predictors of disease prognosis. Current prognostic factors used in clinical practice include tumour location, disease staging and pathological classifications, such as those of Laurén or the WHO. Two separate genomic and molecular classifications of gastric cancer have been proposed, by The Cancer Genome Atlas (TCGA) in the USA and the Asian Cancer Research Group in Korea/Singapore[3,4]. Both classifications may serve as a guide for better understanding the biology and behaviour of this complex disease. Notably, both of these new classifications identified microsatellite instability (MSI) as a separate subgroup of gastric cancer.

For gastric cancer, the incidence of MSI varies between countries, ranging from 5·6 to 33·3 per cent[5,6]. Associations between MSI and other clinical and pathological factors have been reported, but with ambiguous results[4,7–14].

However, with the new molecular classifications of gastric cancer, it seems that MSI is one of the most robust subgroups of gastric cancer. The aim of this study was to review currently available data on MSI in gastric cancer, in order to assess its role in prognosis, and its relationship with other clinical and pathological factors that may influence gastric cancer treatment.

Methods

Literature search

This systematic review with meta-analysis was performed in accordance with the PRISMA statement[15] and the *Cochrane Handbook for Systematic Reviews of Interventions*[16]. A literature search was undertaken in PubMed, Cochrane and Ovid databases for all articles published up to January 2016 with the Medical Subject Headings (MeSH) and keywords 'microsatellite instability', 'microsatellite repeats', 'mismatch repair', 'replication error', 'stomach neoplasms', 'stomach carcinoma', 'stomach adenocarcinoma', 'stomach tumor', 'gastric carcinoma', 'gastric adenocarcinoma', 'gastric tumor' and 'gastric cancer'. The search was carried out independently by two investigators. The keywords were used in all 66 possible combinations to obtain the maximum number of articles.

Article selection

The articles were screened for the presence of the following defined eligibility criteria according to the PICO (population, intervention, comparator, outcome) format[17]. The population comprised patients with a diagnosis of gastric cancer who underwent surgical treatment without neoadjuvant therapy. Two groups for comparison were defined, based on MSI status (with more than 1 MSI marker tested). In the present analysis, subjects included in the MSI group were those with MSI-high status, whereas the microsatellite stable (MSS) group included those with either MSS or MSI-low status. The outcome of interest was overall survival. Only studies published in full text were included. Experimental studies in animal models, single case reports, technical reports, reviews, abstracts, editorials and studies in languages other than English were excluded.

Data extraction

Data were extracted by two authors, who independently reviewed and screened all eligible studies for content according to the inclusion criteria above. Data recorded included: study design, study setting (single centre or multicentre), country of origin, year of publication, sample size, demographic features, clinicopathological characteristics, total number of patients assessed in survival analysis, total number of markers and number of mononucleotides used to estimate MSI status, threshold used to assign MSI, proportion of MSI tumours, median or mean duration of follow-up, MSI and MSS groups for estimation of the pooled hazard ratio (HR), and overall survival outcomes.

Summary outcome measures

The primary outcome was influence of MSI status on the overall survival of patients with gastric cancer. Associations between demographic features as well as clinicopathological characteristics and MSI status were investigated as a secondary analysis.

Quality assessment

All eligible articles were evaluated independently by two reviewers for risk of bias according to the Quality In Prognosis Study (QUIPS) tool[18]. Risk of bias was scored as low, moderate or high for each domain, based on answers to three to six questions, for six items: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis. A final grading of low risk of bias was assigned when three or more of the six items were considered to be of high methodological quality; risk of bias was considered high when three or more of the six items were deemed to be of low methodological quality. Otherwise a moderate risk of bias was assigned.

Statistical analysis

Comprehensive Meta-Analysis software version 3.3.070 (Biostat, Englewood, New Jersey, USA) was used for meta-analysis. In pooled analyses of associations between various demographic and clinicopathological variables and MSI status, effect sizes were calculated as odds ratios (ORs) with 95 per cent confidence intervals. The HR and 95 per cent c.i. for overall survival were retrieved from each article where possible; otherwise the value was estimated according to the method of Tierney and colleagues[19] using Plot Digitizer version 2.5.1 (http://plotdigitizer.sourceforge.net/). The pooled HR was estimated in meta-analysis.

Between-study heterogeneity was explored using the Higgins I^2 measure[20]. I^2 values of around 25, 50 and 75 per cent were considered to represent low, moderate and high heterogeneity respectively. When the I^2 value exceeded 50 per cent, the effect size for each study was calculated

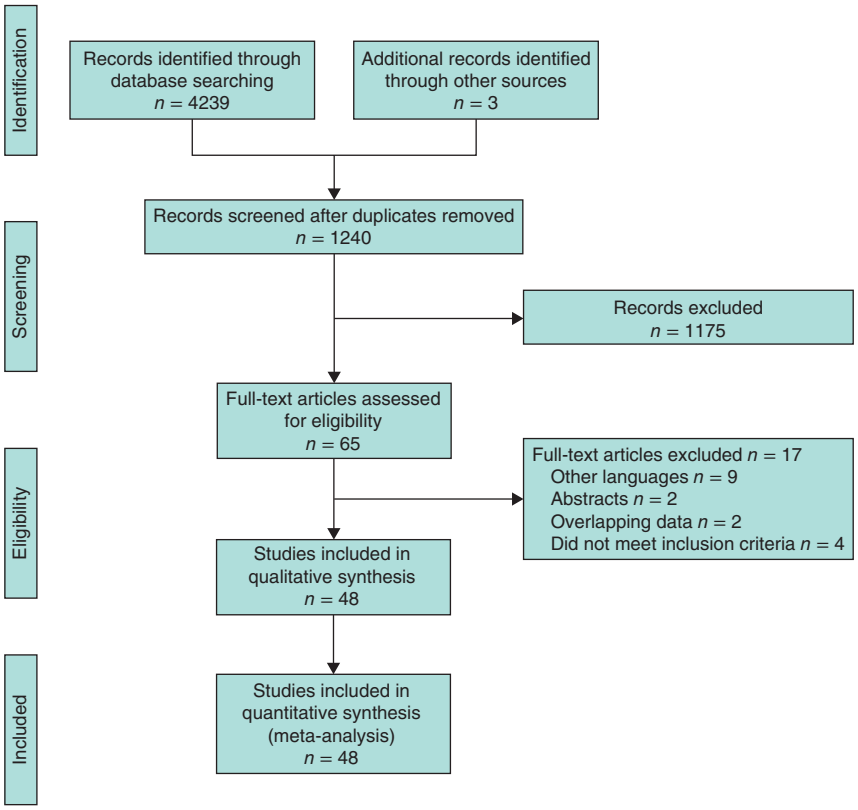

Fig. 1 PRISMA flow chart showing selection of articles for review

by a random-effects model using the DerSimonian and Laird approach[16]; otherwise, a fixed-effect model was used. A χ^2-based Q test was also performed to check between-study heterogeneity, with $P < 0{\cdot}100$ considered statistically significant. Potential sources of heterogeneity were investigated in subgroup analyses. Publication bias was evaluated by visual inspection of the funnel plot for symmetry (an asymmetric plot suggested possible publication bias) and quantified by means of Egger's test; $P < 0{\cdot}050$ was considered indicative of statistically significant publication bias. Where significant heterogeneity existed across studies, sensitivity analysis was performed by omitting each study sequentially to test the influence of each individual study on the pooled result.

Results

Study selection and characteristics

The initial search produced 4239 studies, of which 3002 were excluded because of duplication. After checking the relevant bibliography, three additional articles were included. The titles and abstracts of the remaining 1240 records were screened and 65 studies fulfilled the criteria for eligibility (*Fig. 1*). Of 17 articles that were subsequently excluded, nine were not written in English, two were abstracts only and two contained duplicated data (*Table S1*, supporting information). Two papers[21,22] were excluded because they tested only one MSI marker. One retrospective study[23] was excluded because the authors investigated the relationship between MSI and the expression of *hMSH2* and/or *hMLH1* in patients with cancer of the gastric remnant. Finally, a study[24] investigating clinicopathological and molecular features between *MLH1* methylation-positive and -negative MSI gastric cancers was not included. Forty-eight studies published between 1994 and 2016, with a study interval ranging from 1980 and 2013, were included in the review (*Table S2*, supporting information)[3–5,7–10,12–14,25–62]. The total number of patients included was 18 612, ranging from 24[13] to 2959[25] per study.

Origin of studies

Five[3,26–29] of 48 studies (637 patients, 3·4 per cent) were multicentre studies from the USA, Canada, Germany, Korea, Poland, Russia, Ukraine, Vietnam, the UK,

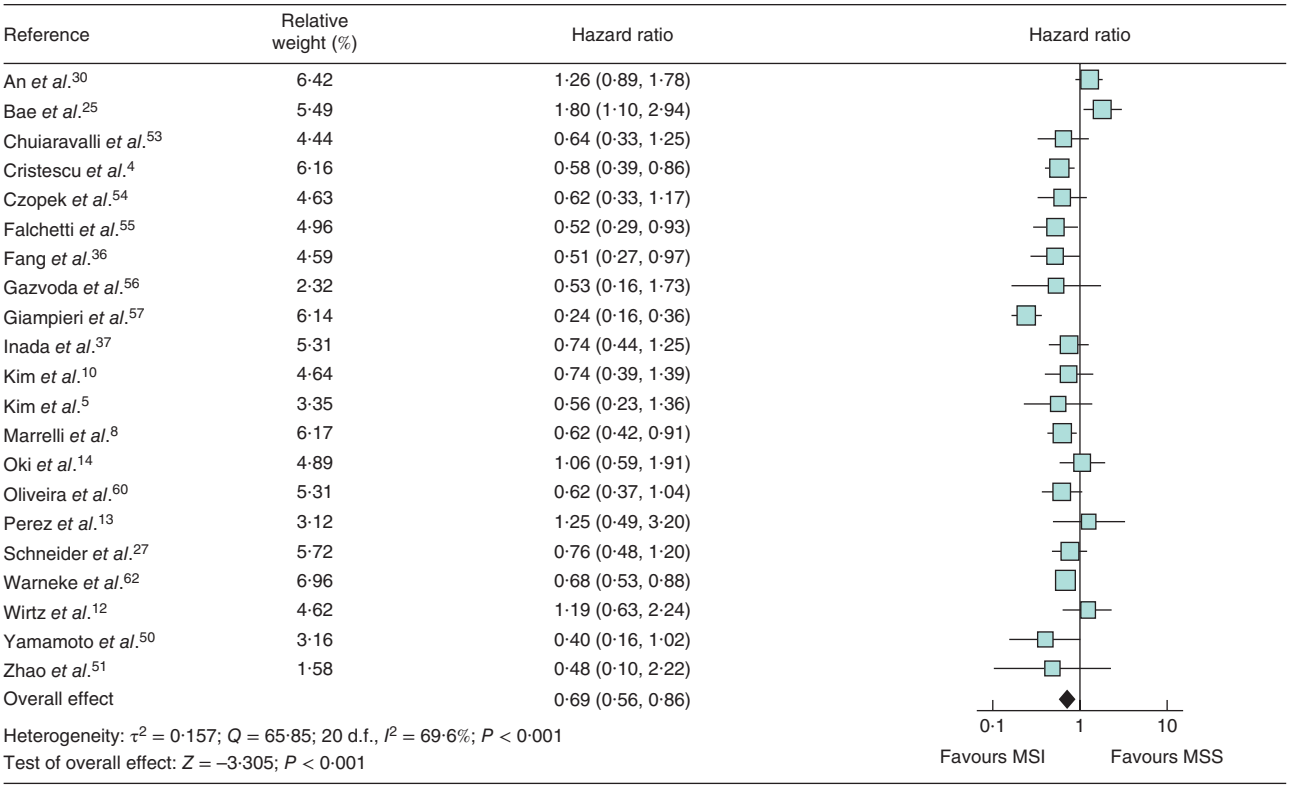

Fig. 2 Forest plot for the effect of microsatellite instability (MSI) status on overall survival. A random-effects model was used for meta-analysis. Hazard ratios are shown with 95 per cent confidence intervals. MSS, microsatellite stable

South Africa, Chile, Colombia and Japan. The other 43 studies were performed in single centres in Eastern populations (15 529 patients, 83·4 per cent) from Japan, China, Korea and Taiwan[4,5,7,10,14,25,30–51], or in Western populations (2446 patients, 13·1 per cent) from Italy, Poland, Slovenia, the UK, Portugal, Brazil and Germany[8,9,12,13,52–62].

Tests used for microsatellite instability

Overall, 33 studies[3–5,7,8,10,12–14,26,28–36,38–40,42,44,46,48,49,51,54,56,59–61] used MSI PCR testing alone, five employed[37,41,50,57,58] immunohistochemistry testing, and ten[9,25,27,43,45,47,52,53,55,62] used both MSI PCR and immunohistochemistry testing to determine MSI status. The overall proportion of patients with MSI was 9·2 per cent (1718 of 18 612), ranging from 5·6 per cent[5] to 33·3 per cent[42]. As not all studies reported all variables examined in the meta-analysis, only studies reporting the variable of interest were included, in turn, for quantitative synthesis to investigate the association between MSI status and that variable.

Microsatellite instability status and survival of patients with gastric cancer

Median follow-up was 12 to 183·6 months; 30 studies[4,7,9,10,13,26–29,31,32,35,37–42,44–46,49,52,53,56–60,62] did not clearly specify the duration of follow-up for survival. Overall survival was reported in 21 studies: 12[5,10,25,30,36,37,50,51,53,55,57,62] reported HRs and 95 per cent confidence intervals for the influence of MSI status in gastric cancer on overall survival, for one study[8] these values were obtained directly from the author, and in one instance[4] the author calculated values from the raw data available from the study author. The HR was estimated from a Kaplan–Meier curve in seven studies[12–14,27,54,56,60]. Eight studies[5,10,12–14,30,37,53] did not find a statistically significant prognostic difference, in terms of overall survival, between MSI and MSS groups. However, the other 13 studies reported that the prognosis of the MSI group was better than that of patients with MSS gastric cancer.

The pooled HR for overall survival, based on 21 studies, showed a significant benefit for patients with MSI gastric cancer compared with those who had MSS gastric cancer (HR 0·69, 95 per cent c.i. 0·56 to 0·86; $P < 0·001$) (*Fig. 2*).

Table 1 Summary of meta-analyses investigating relationship between microsatellite instability status and demographic and clinicopathological characteristics

	No. of studies	Pooled odds ratio	*P*	Heterogeneity		Effect model
				I^2 (%)	*P*	
Sex (F *versus* M)	35	1·57 (1·31, 1·89)	< 0·001	54·1	< 0·001	Random
Age (≥ 65 *versus* < 65 years)	48	1·58 (2·20, 1·13)	< 0·001	0	< 0·001	Fixed
Laurén classification (intestinal *versus* diffuse/mixed)	34	2·23 (1·94, 2·57)	< 0·001	29·9	0·05	Fixed
Tumour location (upper *versus* middle/lower)	36	0·38 (0·32, 0·44)	< 0·001	43·9	< 0·05	Fixed
Lymph node metastasis (yes *versus* no)	35	0·70 (0·57, 0·86)	< 0·001	61·0	< 0·001	Random
TNM stage (I–II *versus* III/IV)	8	1·77 (1·47, 2·13)	< 0·001	0	< 0·001	Fixed

Values in parentheses are 95 per cent confidence intervals.

Significant heterogeneity was found among the included studies ($I^2 = 69·6$ per cent, $P < 0·001$), and a random-effects model was used for meta-analysis. Sensitivity analysis was repeated by omitting each study sequentially, with no change in the primary outcome on omission of all but three of the studies[25,30,57]. A further sensitivity analysis omitting these three studies did not improve the HR of MSI for overall survival (HR 0·67, 0·59 to 0·76; $P < 0·001$).

To explore the heterogeneity, subgroup analysis was carried out according to quality of studies (high–moderate *versus* low), median year of publication (before 2012 *versus* 2012 onwards), origin of participants (Eastern *versus* Western countries), median sample size (less than 214 *versus* 214 or more), and median number of molecular markers used to detect MSI. Subgroup analysis did not substantially alter the findings regarding the prognostic role of MSI in overall survival (*Table S3*, supporting information), except in the stratified analysis by median number of molecular markers used to detect MSI, which might partly explain the heterogeneity ($P = 0·014$).

Microsatellite instability status and clinicopathological characteristics in gastric cancer

To further elucidate the role of MSI in tumour progression, the association between MSI status and demographic and clinicopathological features of gastric cancer was investigated (*Table 1*).

Sex

Thirty-five studies including 14 404 patients reported available data regarding MSI status and sex. The proportion of women was 46·2 per cent in the MSI group and 33·7 per cent in the MSS group. The pooled analysis indicated that women had a significantly increased risk of MSI compared with men (OR 1·57, 95 per cent c.i. 1·31 to 1·89; $P < 0·001$). Significant heterogeneity was found among the included studies ($I^2 = 54·1$ per cent, $P < 0·001$), and a random-effect analysis model was used. Sensitivity analysis was repeated by omitting each study sequentially, with no change in the outcome.

Age

All selected studies reported data on MSI status and age. The weighted mean age of patients with MSI was 65·9 years and that of patients with MSS disease was 60·4 years. Seven studies, including 1605 patients, reported available data regarding MSI status and age expressed in subgroups (65 years or more and less than 65 years). The pooled analysis showed a significant association between MSI status and age 65 years or older (OR 1·58, 95 per cent c.i. 2·20 to 1·13; $P < 0·001$).

Laurén classification

According to the Laurén classification, intestinal-type gastric cancer accounted for 59·5 per cent of tumours, mixed type 6·3 per cent and diffuse type 34·1 per cent. Furthermore, 10·7 per cent of intestinal-type, 0·9 per cent of mixed-type and 2·9 per cent of diffuse-type gastric cancers overall showed MSI. Thirty-four studies were analysed for the association between MSI status and histological classification according to Laurén. The pooled analysis showed that the risk of MSI was greater for intestinal than for diffuse/mixed-type gastric cancers (OR 2·23, 95 per cent c.i. 1·94 to 2·57; $P < 0·001$).

Tumour location

Some 15·5 per cent of tumours were located in the upper part of the stomach, 23·4 per cent in the middle and 61·2 per cent in the lower part. Of these tumours, 9·5, 8·8 and 22·0 per cent respectively showed MSI. Quantitative synthesis of 36 studies including 11 101 patients showed a significant association between MSI and middle/lower gastric cancer location (OR 0·38, 95 per cent c.i. 0·32 to 0·44; $P < 0·001$).

Lymph node metastases

Lymph node metastases were identified in 12·9 per cent of patients with MSI among all studies reporting this

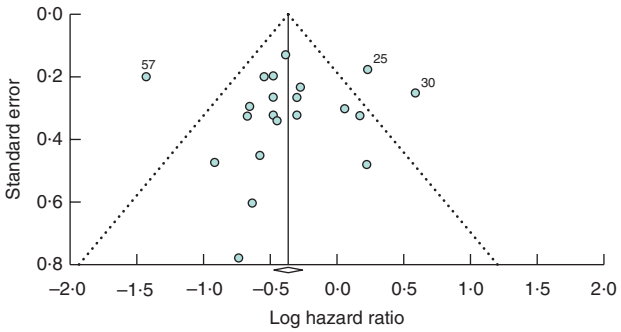

Fig. 3 Funnel plot of overall survival for estimation of publication bias. Reference numbers are shown for studies that fall outside the funnel

information. Thirty-five studies reported available data regarding MSI status and lymph node metastases (N0 *versus* N+). The pooled analysis showed a significant association between MSI and absence of lymph node metastases (OR 0·70, 95 per cent c.i. 0·57 to 0·86; $P < 0·001$). Significant heterogeneity was found among the included studies ($I^2 = 61·0$ per cent, $P < 0·001$), and a random-effect analysis model was used. Sensitivity analysis with sequential omission each study did not alter the outcome.

TNM stage

Only eight studies[3,8,31,32,34,36,51,62] determined the stage of gastric cancer according to seventh edition of the AJCC classification[63]. The distribution of gastric cancers by stage was: stage I, 35·2 per cent; stage II, 21·8 per cent; stage III, 33·7 per cent; and stage IV, 9·2 per cent. Some 11·2 per cent of stage I, 21·2 per cent of stage II, 10·8 per cent of stage III and 7·9 per cent of stage IV gastric cancers showed MSI. The pooled analysis showed a significant association between MSI status and TNM stage I and/or II at diagnosis (OR 1·77, 95 per cent c.i. 1·47 to 2·13; $P < 0·001$).

Quality assessment

Twenty-six studies were considered to be of high, 19 of moderate and three of low methodological quality according to the QUIPS tool[18] (*Table S4*, supporting information). All studies were included in the analysis, irrespective of methodological quality, to avoid the potential risk of excluding valuable insights from the synthesis. A sensitivity analysis was conducted that evaluated the impact of removal of low- or high-quality studies on the effect sizes; the results showed that the low-quality studies did not bias the overall results.

Publication bias and sensitivity analysis

A Begg's funnel plot was used to assess the presence of potential publication bias by plotting the effect sizes calculated from individual studies examining the association between MSI status and overall survival. The funnel plot was symmetrical, suggesting the absence of significant biases ($P = 0·482$, Egger's test), even though three studies[25,30,57] were outside the funnel (*Fig. 3*). Although found to be heterogeneous in a sensitivity analysis, these studies did not influence the pooled HRs and confidence intervals significantly, suggesting that the estimates were robust.

Discussion

In this meta-analysis, gastric cancer with MSI was associated with better overall survival than MSS disease. Overall, MSI was found in a subgroup of gastric cancers, accounting for 9·2 per cent of the total. MSI was associated with female sex, intestinal histological type, increasing age, N0 status, tumours located in the mid or distal stomach, TNM stage I–II disease, and with better prognosis determined by overall survival. The results are similar to those reported in previous meta-analyses[64–66] for gastric cancer based on much smaller numbers of patients.

The formal meta-analysis of the available literature estimated the overall prevalence of MSI gastric cancer at 9·2 per cent. Recent genomic analysis studies[3,4] have reported a substantially higher rate of MSI gastric cancer (21·7 and 22·7 per cent respectively). In the TCGA study, it is possible that the MSI rate is linked to the country of origin, and probably also with high- and low-risk areas of gastric cancer incidence[67,68]. Further analysis of factors that cause MSI gastric cancer and its association with gastric cancer incidence is needed.

Patients presenting with MSI gastric cancer are older than those with MSS tumours[69]. This has to be taken into account clinically in the future, as the majority of these older patients may present with other co-morbidities and could therefore be offered less aggressive treatment. Such patients may also be under-represented in clinical trials.

Heterogeneity was substantial across the studies analysed here. One of the most important factors was laboratory methodology. A wide variety of different markers was used to investigate MSI status. Furthermore, according to the results of subgroup analysis, the number of molecular markers used to detect MSI may partly explain the statistical heterogeneity. A challenge for the future is to standardize the detection process for MSI in gastric cancer.

The present meta-analysis has some limitations. The methodology for MSI detection was not standardized

among the studies. In addition, the selection of patients varied across studies according to different clinical and pathological criteria. It must also be noted that no neoadjuvant studies were included. This is especially important in the light of modern treatment where the neoadjuvant approach plays an important role. Future analyses based on neoadjuvant treatment and the effects of different types of chemotherapy in patients with MSI gastric cancer will be of interest.

Acknowledgements

This research received funding from the European Union Seventh Framework Programme (FP7) GastricGlycoExplorer under grant agreement number 316929 (K.P., F.R.).
Disclosure: The authors declare no conflict of interest.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics 2012. *CA Cancer J Clin* 2015; **65**: 87–108.
2 Marrelli D, Polom K, de Manzoni G, Morgagni P, Baiocchi GL, Roviello F. Multimodal treatment of gastric cancer in the west: where are we going? *World J Gastroenterol* 2015; **21**: 7954–7969.
3 Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202–209.
4 Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS *et al.* Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 2015; **21**: 449–456.
5 Kim JY, Shin NR, Kim A, Lee HJ, Park WY, Kim JY *et al.* Microsatellite instability status in gastric cancer: a reappraisal of its clinical significance and relationship with mucin phenotypes. *Korean J Pathol* 2013; **47**: 28–35.
6 Lin JT, Wu MS, Shun CT, Lee WJ, Wang JT, Wang TH *et al.* Microsatellite instability in gastric carcinoma with special references to histopathology and cancer stages. *Eur J Cancer* 1995; **31A**:1879–1882.
7 Kim SY, Choi YY, An JY, Shin HB, Jo A, Choi H *et al.* The benefit of microsatellite instability is attenuated by chemotherapy in stage II and stage III gastric cancer: results from a large cohort with subgroup analyses. *Int J Cancer* 2015; **137**: 819–825.
8 Marrelli D, Polom K, Pascale V, Vindigni C, Piagnerelli R, De Franco L *et al.* Strong prognostic value of microsatellite instability in intestinal type non-cardia gastric cancer. *Ann Surg Oncol* 2016; **23**: 943–950.
9 Beghelli S, de Manzoni G, Barbi S, Tomezzoli A, Roviello F, Di Gregorio C *et al.* Microsatellite instability in gastric cancer is associated with better prognosis in only stage II cancers. *Surgery* 2006; **139**: 347–356.
10 Kim H, An JY, Noh SH, Shin SK, Lee YC, Kim H. High microsatellite instability predicts good prognosis in intestinal-type gastric cancers. *J Gastroenterol Hepatol* 2011; **26**: 585–592.
11 An C, Choi IS, Yao JC, Worah S, Xie K, Mansfield PF *et al.* Prognostic significance of CpG island methylator phenotype and microsatellite instability in gastric carcinoma. *Clin Cancer Res* 2005; **11**: 656–663.
12 Wirtz HC, Müller W, Noguchi T, Scheven M, Rüschoff J, Hommel G *et al.* Prognostic value and clinicopathological profile of microsatellite instability in gastric cancer. *Clin Cancer Res* 1998; **4**: 1749–1754.
13 Perez RO, Jacob CE, D'Ottaviano FL, Alvarenga C, Ribeiro AS, Ribeiro U *et al.* Microsatellite instability in solitary and sporadic gastric cancer. *Rev Hosp Clin Fac Med Sao Paulo* 2004; **59**: 279–285.
14 Oki E, Kakeji Y, Zhao Y, Yoshida R, Ando K, Masuda T *et al.* Chemosensitivity and survival in gastric cancer patients with microsatellite instability. *Ann Surg Oncol* 2009; **16**: 2510–2515.
15 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M *et al.*; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**: 1.
16 Higgins J, Green S; Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley-Blackwell: Hoboken, 2008.
17 Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995; **123**: A12–A13.
18 Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006; **144**: 427–437.
19 Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; **8**: 16.
20 Higgins J, Green S (eds); The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1.0) [updated March 2011]. http://handbook-5-1.cochrane.org/ [accessed 1 August 2017].
21 Chang MS, Lee HS, Kim HS, Kim SH, Choi SI, Lee BL *et al.* Epstein–Barr virus and microsatellite instability in gastric carcinogenesis. *J Pathol* 2003; **199**: 447–452.
22 Iacopetta BJ, Soong R, House AK, Hamelin R. Gastric carcinomas with microsatellite instability: clinical features and mutations to the TGF-beta type II receptor, IGFII receptor, and BAX genes. *J Pathol* 1999; **187**: 428–432.
23 Aya M, Yashiro M, Nishioka N, Onoda N, Hirakawa K. Carcinogenesis in the remnant stomach following distal gastrectomy with billroth II reconstruction is associated with high-level microsatellite instability. *Anticancer Res* 2006; **26**: 1403–1411.
24 Kim KJ, Lee TH, Cho NY, Yang HK, Kim WH, Kang GH. Differential clinicopathologic features in microsatellite-unstable gastric cancers with and without *MLH1* methylation. *Hum Pathol* 2013; **44**: 1055–1064.

25 Bae YS, Kim H, Noh SH, Kim H. Usefulness of immunohistochemistry for microsatellite instability screening in gastric cancer. *Gut Liver* 2015; **9**: 629–635.
26 Buffart TE, Louw M, van Grieken NC, Tijssen M, Carvalho B, Ylstra B *et al.* Gastric cancers of Western European and African patients show different patterns of genomic instability. *BMC Med Genomics* 2011; **4**: 7.
27 Schneider BG, Bravo JC, Roa JC, Roa I, Kim MC, Lee KM *et al.* Microsatellite instability, prognosis and metastasis in gastric cancers from a low-risk population. *Int J Cancer* 2000; **89**: 444–452.
28 Sepulveda AR, Santos AC, Yamaoka Y, Wu L, Gutierrez O, Kim JG *et al.* Marked differences in the frequency of microsatellite instability in gastric cancer from different countries. *Am J Gastroenterol* 1999; **94**: 3034–3038.
29 Theuer CP, Campbell BS, Peel DJ, Lin F, Carpenter P, Ziogas A *et al.* Microsatellite instability in Japanese *vs* European American patients with gastric cancer. *Arch Surg* 2002; **137**: 960–965.
30 An JY, Kim H, Cheong JH, Hyung WJ, Kim H, Noh SH. Microsatellite instability in sporadic gastric cancer: its prognostic role and guidance for 5-FU based chemotherapy after R0 resection. *Int J Cancer* 2012; **131**: 505–511.
31 Arai T, Sakurai U, Sawabe M, Honma N, Aida J, Ushio Y *et al.* Frequent microsatellite instability in papillary and solid-type, poorly differentiated adenocarcinomas of the stomach. *Gastric Cancer* 2013; **16**: 505–512.
32 Choi HS, Lee SY, Kim JH, Sung IK, Park HS, Shim CS *et al.* Low prevalence of microsatellite instability in interval gastric cancers. *Dig Dis Sci* 2014; **59**: 322–327.
33 Choi SW, Choi JR, Chung YJ, Kim KM, Rhyu MG. Prognostic implications of microsatellite genotypes in gastric carcinoma. *Int J Cancer* 2000; **89**: 378–383.
34 Choi J, Nam SK, Park DJ, Kim HW, Kim HH, Kim WH *et al.* Correlation between microsatellite instability-high phenotype and occult lymph node metastasis in gastric carcinoma. *APMIS* 2015; **123**: 215–222.
35 Chung HW, Lee SY, Han HS, Park HS, Yang JH, Lee HH *et al.* Gastric cancers with microsatellite instability exhibit high fluorodeoxyglucose uptake on positron emission tomography. *Gastric Cancer* 2013; **16**: 185–192.
36 Fang WL, Chang SC, Lan YT, Huang KH, Chen JH, Lo SS *et al.* Microsatellite instability is associated with a better prognosis for gastric cancer patients after curative surgery. *World J Surg* 2012; **36**: 2131–2138.
37 Inada R, Sekine S, Taniguchi H, Tsuda H, Katai H, Fujiwara T *et al.* ARID1A expression in gastric adenocarcinoma: clinicopathological significance and correlation with DNA mismatch repair status. *World J Gastroenterol* 2015; **21**: 2159–2168.
38 Jahng J, Youn YH, Kim KH, Yu J, Lee YC, Hyung WJ *et al.* Endoscopic and clinicopathologic characteristics of early gastric cancer with high microsatellite instability. *World J Gastroenterol* 2012; **18**: 3571–3577.
39 Jee MS, Koo C, Kim MH, Choi C, Lee KM, Choi SK *et al.* Microsatellite instability in Korean patients with gastric adenocarcinoma. *Korean J Intern Med* 1997; **12**: 144–154.
40 Kang JU, Koo SH. Assessment of the beneficial loci and prognostic implications of microsatellite instability in gastric carcinoma. *Mol Med Rep* 2011; **4**: 1175–1181.
41 Lee HJ, Jang YJ, Lee EJ, Kim JH, Park SS, Park SH *et al.* The significance of mismatch repair genes in gastric cancer. *J Cancer Res Ther* 2013; **9**: 80–83.
42 Lin JT, Wu MS, Shun CT, Lee WJ, Sheu JC, Wang TH. Occurrence of microsatellite instability in gastric carcinoma is associated with enhanced expression of erbB-2 oncoprotein. *Cancer Res* 1995; **55**: 1428–1430.
43 Gu M, Kim D, Bae Y, Choi J, Kim S, Song S. Analysis of microsatellite instability, protein expression and methylation status of *bMLH1* and *bMSH2* genes in gastric carcinomas. *Hepatogastroenterology* 2009; **56**: 899–904.
44 Nakashima H, Honda M, Inoue H, Shibuta K, Arinaga S, Era S *et al.* Microsatellite instability in multiple gastric cancers. *Int J Cancer* 1995; **64**: 239–242.
45 Park JH, Kim EK, Kim YH, Kim JH, Bae YS, Lee YC *et al.* Epstein–Barr virus positivity, not mismatch repair-deficiency, is a favorable risk factor for lymph node metastasis in submucosa-invasive early gastric cancer. *Gastric Cancer* 2016; **19**: 1041–1051.
46 Rhyu MG, Park WS, Meltzer SJ. Microsatellite instability occurs frequently in human gastric carcinoma. *Oncogene* 1994; **9**: 29–32.
47 Seo HM, Chang YS, Joo SH, Kim YW, Park YK, Hong SW *et al.* Clinicopathologic characteristics and outcomes of gastric cancers with the MSI-H phenotype. *J Surg Oncol* 2009; **99**: 143–147.
48 Shigeyasu K, Nagasaka T, Mori Y, Yokomichi N, Kawai T, Fuji T *et al.* Clinical significance of MLH1 methylation and CpG island methylator phenotype as prognostic markers in patients with gastric cancer. *PLoS One* 2015; **10**: e0130409.
49 Xiao YP, Wu DY, Xu L, Xin Y. Loss of heterozygosity and microsatellite instabilities of fragile histidine triad gene in gastric carcinoma. *World J Gastroenterol* 2006; **12**: 3766–3769.
50 Yamamoto M, Taguchi K, Yamanaka T, Matsuyama A, Yoshinaga K, Tsutsui S *et al.* Outcome and status of microsatellite stability in Japanese atomic bomb survivors with early gastric carcinoma. *Ann Surg Oncol* 2013; **20**: 798–803.
51 Zhao Y, Zheng ZC, Luo YH, Piao HZ, Zheng GL, Shi JY *et al.* Low-frequency microsatellite instability in genomic di-nucleotide sequences correlates with lymphatic invasion and poor prognosis in gastric cancer. *Cell Biochem Biophys* 2015; **71**: 235–241.
52 Bacani J, Zwingerman R, Di Nicola N, Spencer S, Wegrynowski T, Mitchell K *et al.* Tumor microsatellite instability in early onset gastric cancer. *J Mol Diagn* 2005; **7**: 465–477.
53 Chiaravalli AM, Cornaggia M, Furlan D, Capella C, Fiocca R, Tagliabue G *et al.* The role of histological investigation in prognostic evaluation of advanced gastric cancer. Analysis of

histological structure and molecular changes compared with invasive pattern and stage. *Virchows Arch* 2001; **439**: 158–169.
54 Czopek J, Bialas M, Rudzki Z, Zazula M, Pituch-Noworolska A, Zembala M *et al.* The relationship between gastric cancer cells circulating in the blood and microsatellite instability positive gastric carcinomas. *Aliment Pharmacol Ther* 2002; **16**(Suppl 2): 128–136.
55 Falchetti M, Saieva C, Lupi R, Masala G, Rizzolo P, Zanna I *et al.* Gastric cancer with high-level microsatellite instability: target gene mutations, clinicopathologic features, and long-term survival. *Hum Pathol* 2008; **39**: 925–932.
56 Gazvoda B, Juvan R, Zupanic-Pajnic I, Repse S, Ferlan-Marolt K, Balazic J *et al.* Genetic changes in Slovenian patients with gastric adenocarcinoma evaluated in terms of microsatellite DNA. *Eur J Gastroenterol Hepatol* 2007; **19**: 1082–1089.
57 Giampieri R, Maccaroni E, Mandolesi A, Del Prete M, Andrikou K, Faloppi L *et al.* Mismatch repair deficiency may affect clinical outcome through immune response activation in metastatic gastric cancer patients receiving first-line chemotherapy. *Gastric Cancer* 2017; **20**: 156–163.
58 Grogg KL, Lohse CM, Pankratz VS, Halling KC, Smyrk TC. Lymphocyte-rich gastric cancer: associations with Epstein–Barr virus, microsatellite instability, histology, and survival. *Mod Pathol* 2003; **16**: 641–651.
59 Hayden JD, Cawkwell L, Quirke P, Dixon MF, Goldstone AR, Sue-Ling H *et al.* Prognostic significance of microsatellite instability in patients with gastric carcinoma. *Eur J Cancer* 1997; **33**: 2342–2346.
60 Oliveira C, Seruca R, Seixas M, Sobrinho-Simões M. The clinicopathological features of gastric carcinomas with microsatellite instability may be mediated by mutations of different 'target genes': a study of the TGFbeta RII, IGFII R, and BAX genes. *Am J Pathol* 1998; **153**: 1211–1219.
61 Seruca R, Santos NR, David L, Constância M, Barroca H, Carneiro F *et al.* Sporadic gastric carcinomas with microsatellite instability display a particular clinicopathologic profile. *Int J Cancer* 1995; **64**: 32–36.
62 Warneke VS, Behrens HM, Haag J, Balschun K, Böger C, Becker T *et al.* Prognostic and putative predictive biomarkers of gastric cancer for personalized medicine. *Diagn Mol Pathol* 2013; **22**: 127–137.
63 Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds). *AJCC Cancer Staging Manual* (7th edn). Springer: New York, 2010.
64 Webber EM, Kauffman TL, O'Connor E, Goddard KA. Systematic review of the predictive effect of MSI status in colorectal cancer patients undergoing 5FU-based chemotherapy. *BMC Cancer* 2015; **15**: 156.
65 Choi YY, Bae JM, An JY, Kwon IG, Cho I, Shin HB *et al.* Is microsatellite instability a prognostic marker in gastric cancer? A systematic review with meta-analysis. *J Surg Oncol* 2014; **110**: 129–135.
66 Zhu L, Li Z, Wang Y, Zhang C, Liu Y, Qu X. Microsatellite instability and survival in gastric cancer: a systematic review and meta-analysis. *Mol Clin Oncol* 2015; **3**: 699–705.
67 Polom K, Marrelli D, Pascale V, Roviello G, Voglino C, Rho H *et al.* High-risk and low-risk gastric cancer areas in Italy and its association with microsatellite instability. *J Cancer Res Clin Oncol* 2016; **142**: 1817–1824.
68 Marrelli D, Pedrazzani C, Morgagni P, de Manzoni G, Pacelli F, Coniglio A *et al.*; Italian Research Group for Gastric Cancer. Changing clinical and pathological features of gastric cancer over time. *Br J Surg* 2011; **98**: 1273–1283.
69 Polom K, Marrelli D, Roviello G, Pascale V, Voglino C, Rho H *et al.* Molecular key to understand the gastric cancer biology in elderly patients – the role of microsatellite instability. *J Surg Oncol* 2017; **115**: 344–350.

Supporting information

Additional supporting information can be found online in the supporting information tab for this article.

European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM
ETHICON

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM
Medtronic
Further,Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM
INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM
BD

15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM
Takeda

17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration **www.colorectalsurgery.eu**