

Annals of Gastroenterology and Digestive Disorders

Review Article

Open Access

Diagnostic and Prognostic Significance of Microsatellite Instability in Endoscopic Biopsies from Patients with Gastric Adenocarcinoma: A Review

Elena Vargas^{1*}, Daniel Okafor² and Ingrid Larsen³

¹Department of Gastroenterology, University of Barcelona, Barcelona, Spain

²Department of Surgical Oncology, University of Cape Town, Cape Town, South Africa

³Department of Hepatology, Karolinska Institute, Stockholm, Sweden

*Correspondence to: Elena Vargas, Department of Gastroenterology, University of Barcelona, Barcelona, Spain

Received: 17 April 2023; Accepted: 16 July 2023; Published: 15 October 2023

Volume: 6; Issue: 1; ISSN: 2643-2609

Copyright: © 2023 EV, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Microsatellite instability decides treatment in gastric adenocarcinoma well before a stomach is removed. Chemotherapy is chosen, or withheld, on the strength of a few millimetres of tissue taken at endoscopy, which makes the reliability of that small sample a clinical question rather than a laboratory one.

Objectives: To review what published evidence shows about the accuracy of MSI and mismatch repair testing on endoscopic biopsies against the resection specimen, the prevalence of MSI-high disease across clinical settings, and the prognostic and predictive weight the result carries once obtained.

Material and Methods: Narrative review of matched-sample diagnostic studies, randomised trial analyses and prospective cohorts indexed in PubMed and the major oncology journals. Studies were eligible if they reported paired biopsy and surgical MSI or MMR results, MSI-high prevalence in a defined gastric or gastroesophageal population, or outcomes stratified by MSI status. No new patient data were generated. All frequencies, hazard ratios and response rates quoted are those published by the original investigators.

Results: In paired samples, endoscopic biopsy performed well against the resection specimen, with concordance of 96.2 per cent by PCR and 97.8 per cent by immunohistochemistry, and specificity of 98 per cent for both. Sensitivity was lower, at 85 and 86 per cent. Biopsy material was more often uninformative by IHC than by PCR. In a cohort restricted to MSI-high cases, discrepancy between biopsy and resection reached 19.7 per cent, consistent with clonal heterogeneity of mismatch repair loss. Prevalence falls as disease advances, from around 12 per cent in resectable series to 4.0 per cent in third-line trial populations. In the MAGIC trial, MSI-high or dMMR status was associated with better survival after surgery alone (HR 0.42) and worse survival when chemotherapy was added (HR 2.18, 95% CI 1.08-4.42), with median overall survival of 9.6 against 19.5 months in the chemotherapy arm. Response to pembrolizumab in MSI-high advanced disease reached 57.1 per cent in third line and above.

Conclusion: Endoscopic biopsy is an adequate substrate for MSI and MMR testing, and the published concordance figures support testing at diagnosis rather than waiting for a resection specimen. The qualification is that errors are asymmetric: a positive biopsy result is close to definitive, while a negative one carries a real false-negative rate driven by sampling. Because a positive result may argue against chemotherapy and in favour of immunotherapy, that asymmetry has direct consequences for treatment.

Abbreviations: MSI – Microsatellite Instability, MSI-H – Microsatellite Instability-High, MSS – Microsatellite Stable, MMR – Mismatch Repair, dMMR – Deficient Mismatch Repair, pMMR – Proficient Mismatch Repair, IHC – Immunohistochemistry, PCR – Polymerase Chain Reaction, GEJ – Gastroesophageal Junction, ORR – Objective Response Rate, OS – Overall Survival, HR – Hazard Ratio.

Keywords: Microsatellite Instability; Gastric Adenocarcinoma; Endoscopic Biopsy; Mismatch Repair; Immunotherapy

Introduction

For most of the history of gastric cancer surgery, the resection specimen was where the pathology happened. The stomach came out, the pathologist reported it, and the report informed what came next. Perioperative chemotherapy inverted that sequence. Since the MAGIC trial established that chemotherapy before and after surgery

improves survival in resectable gastroesophageal cancer [1], the decisive treatment decision is made before any resection specimen exists.

That places considerable weight on the endoscopic biopsy. If microsatellite instability is to influence whether a patient receives chemotherapy, it has to be measurable on the small, sometimes crushed fragments obtained at diagnosis, and it has to be measurable

reliably.

The reason it matters is that MSI does not behave as a simple prognostic marker in this disease. An exploratory analysis of MAGIC found that mismatch repair deficiency was associated with better survival in patients treated by surgery alone and with worse survival in patients who also received chemotherapy [2]. If that holds, a positive result is not merely informative but potentially a reason to change treatment, and a false-negative biopsy is not a neutral error.

Immunotherapy has raised the stakes further. MSI-high status predicts response to PD-1 blockade across tumour types, and in advanced gastric cancer the response rates reported in MSI-high subgroups are far above those seen in unselected populations [6]. The aim of this review is to examine how well the endoscopic biopsy answers the question, how common MSI-high disease is in the populations where the question is asked, and what follows clinically from the answer.

Material and Methods

Search strategy: PubMed and the archives of the major oncology, pathology and gastroenterology journals were searched for studies addressing microsatellite instability or mismatch repair status in gastric and gastroesophageal adenocarcinoma. Search terms combined microsatellite instability, mismatch repair and dMMR with gastric adenocarcinoma, endoscopic biopsy, concordance, immunohistochemistry, perioperative chemotherapy and immune checkpoint inhibition. Reference lists of retrieved articles were screened by hand.

Eligibility: Studies were included if they reported paired analysis of endoscopic biopsy and surgical specimen for MSI or MMR status; the prevalence of MSI-high or dMMR disease in a defined gastric or gastroesophageal population; or clinical outcomes stratified by MSI or MMR status. Randomised trial analyses were included where MSI status was determined centrally. Studies confined to non-gastric primaries were cited only where they inform methodology.

Data extraction and handling: Design, sample size, assay platform, reported diagnostic performance and reported effect estimates with their confidence intervals were extracted as published. No pooling or re-analysis was performed and no patient-level data were obtained. Prevalence figures from different populations are reported separately rather than combined, since MSI-high frequency varies with stage, geography and assay. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How well the biopsy performs: The most direct evidence comes from a retrospective series of matched pre-therapeutic biopsies and surgical specimens from patients with oesogastric adenocarcinoma collected between 2009 and 2019, with the surgical specimen taken as the reference standard. Concordance between biopsy and resection was 96.2 per cent for PCR and 97.8 per cent for immunohistochemistry. Sensitivity and specificity of the biopsy were 85 and 98 per cent for PCR and 86 and 98 per cent for IHC (Figure 1) [4].

The shape of that result matters more than the headline number. Specificity is near-perfect and sensitivity is not, which means the errors run in one direction: a biopsy that reports MSI-high is almost always right, while a biopsy that reports microsatellite stability is wrong in roughly one case in seven [4].

ENDOSCOPIC BIOPSY AGAINST SURGICAL SPECIMEN FOR dMMR/MSI

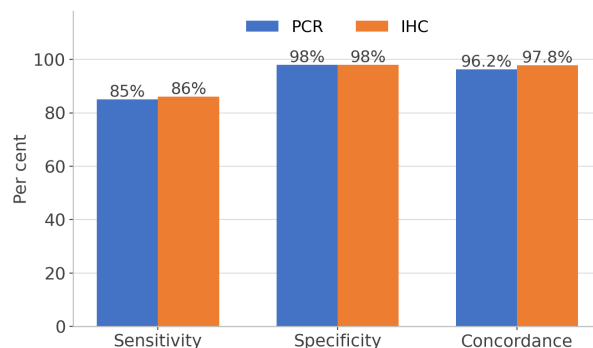


Figure 1: Diagnostic performance of endoscopic biopsy against the matched surgical specimen for dMMR/MSI status, by assay [4]

Uninformative results and heterogeneity: A second practical finding from the same series is that assays fail at different rates on small samples. PCR was conclusive on 53 of 55 biopsies (96.4 per cent), while IHC was conclusive on 47 (85.5 per cent) [4]. The authors recommend increasing the number of biopsy fragments taken at diagnosis to reduce inconclusive results.

A larger concern emerges from a multi-institutional series restricted to cases classified as MSI-high or dMMR, in which discordance between endoscopic biopsy and surgical specimen reached 19.7 per cent [5]. That figure is not incompatible with the 96 to 98 per cent overall concordance above, because the two are computed on different denominators, but it identifies where the residual error sits. Loss of mismatch repair protein expression can be clonal and unevenly distributed within a tumour, so a single fragment may miss it. Sampling from several areas of the tumour is the practical mitigation [5].

Study	n	Design	Principal reported finding
Cunningham et al. 2006 [1]	503	RCT	Perioperative chemotherapy improves survival in resectable disease
Smyth et al. 2017 [2]	503	Trial analysis	MSI-H/dMMR favourable with surgery alone, unfavourable with chemotherapy
Asesio et al. 2023 [4]	55	Paired samples	Biopsy concordance 96.2% by PCR, 97.8% by IHC
Fornaro et al. 2023 [5]	dMMR	Paired samples	19.7% discordance between biopsy and resection
Chao et al. 2021 [6]	1,370	Pooled trials	Pembrolizumab response 46.7-64.7% in MSI-H disease

Table 1: Principal studies reviewed, with design and the finding as reported by the original investigators

How often the question returns a positive answer: MSI-high prevalence in gastric adenocarcinoma is not a single number, and the variation is systematic rather than random. In the matched biopsy series above, 12.5 per cent of surgical specimens were MSI-high [4]. In the MAGIC trial population of resectable disease, 6.6 per cent were MSI-high [2]. In the advanced-disease trial populations, prevalence fell as the line of therapy advanced: 7.3 per cent of 682 patients in a first-line trial, 5.3 per cent of 514 in second line, and 4.0 per cent of 174 in third line and beyond (Figure 2) [6].

The gradient is consistent with MSI-high tumours being over-represented in early-stage, resectable disease and under-represented in the heavily pretreated metastatic population, which is what a favourable natural history would predict.

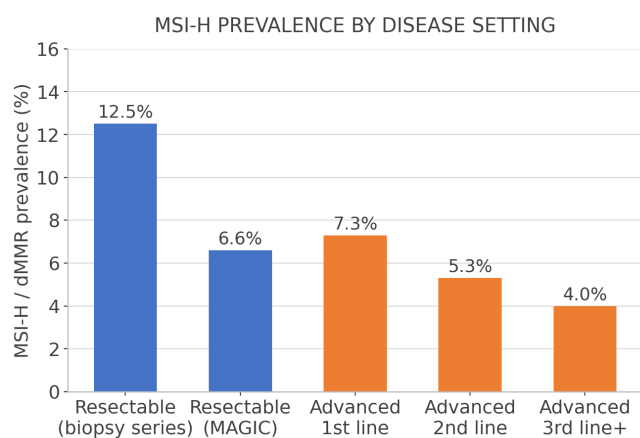


Figure 2: Reported MSI-H prevalence across resectable and advanced gastric or GEJ cancer populations [2,4,6]

Prognostic and predictive weight: The exploratory MAGIC analysis is the most consequential single result in this literature. Among patients treated with surgery alone, those with MSI-high or dMMR tumours had a median overall survival that was not reached, against 20.5 months for patients with neither feature (HR 0.42, 95% CI 0.15-1.15, $p = 0.09$). Among patients who received perioperative chemotherapy, the direction reversed: median overall survival was 9.6 months for MSI-high or dMMR against 19.5 months (HR 2.18, 95% CI 1.08-4.42) (Figure 3) [2]. A post hoc analysis of a separate adjuvant trial reached a compatible conclusion [3].

Two cautions apply. The MAGIC subgroup was small, the surgery-alone comparison did not reach conventional significance, and the analysis was exploratory rather than prespecified [2]. The finding is best read as hypothesis-generating, and it has not stopped chemotherapy being given to MSI-high patients in practice.

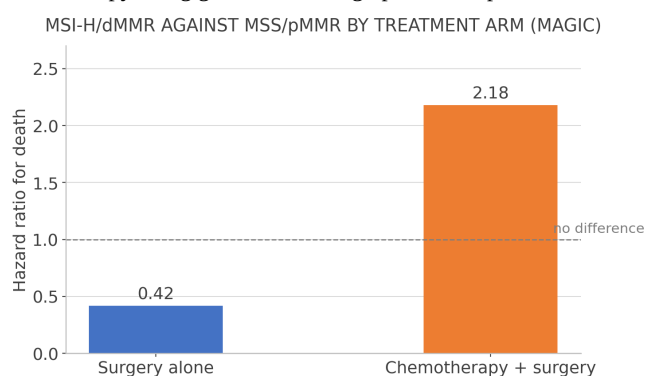


Figure 3: Hazard ratio for death in MSI-H/dMMR against MSS/pMMR tumours, by treatment arm, in the MAGIC trial [2]

Immunotherapy in MSI-high disease: In a pooled analysis of MSI-high patients from three prospective trials, objective response to pembrolizumab was 57.1 per cent in third line and beyond, 46.7 per cent against 16.7 per cent for chemotherapy in second line, and 57.1 per cent for pembrolizumab, 64.7 per cent for pembrolizumab with chemotherapy and 36.8 per cent for chemotherapy alone in first line (Figure 4) [6]. Median overall survival was not reached for pembrolizumab in any of the three MSI-high cohorts [6].

In the resectable setting, a neoadjuvant trial of dual checkpoint blockade in MSI-high gastric and GEJ adenocarcinoma reported a pathological complete response rate of 60 per cent among 15 patients, with a two-year overall survival of 92 per cent [8]. Numbers of this size cannot settle practice, but they indicate why identifying MSI-high status before treatment has become a priority rather than an academic exercise.

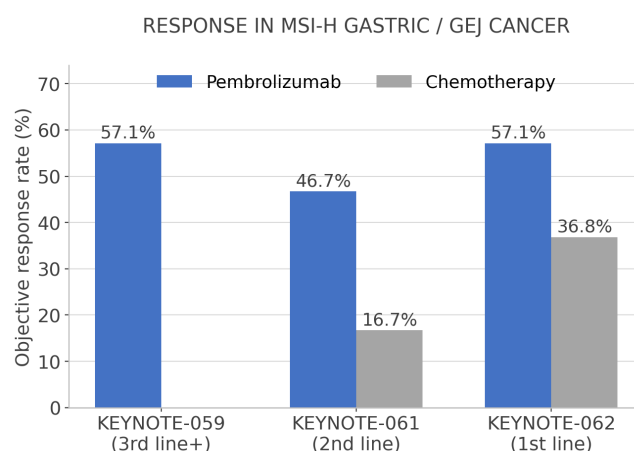


Figure 4: Objective response rate in MSI-H gastric or GEJ cancer by line of therapy; no chemotherapy comparator in the third-line cohort [6]

Measure	PCR	IHC	Comment
Concordance with resection	96.2%	97.8%	Surgical specimen as reference [4]
Sensitivity	85%	86%	False negatives driven by sampling [4]
Specificity	98%	98%	Positive result close to definitive [4]
Conclusive on biopsy	96.4%	85.5%	More fragments reduce failures [4]
Discordance, MSI-H cases only	19.7%	19.7%	Clonal heterogeneity of MMR loss [5]

Table 2: Reported performance of MSI and MMR testing on endoscopic biopsy material

Discussion

The published evidence supports a fairly clear practical position. Endoscopic biopsy is an adequate substrate for MSI and MMR testing in gastric adenocarcinoma, and concordance with the resection specimen in the high nineties is good enough to justify testing at diagnosis rather than after surgery [4]. Given that the treatment decision the result might influence is made before surgery, testing later would be testing too late.

The important qualification concerns the direction of error. Because specificity is near-perfect and sensitivity is not, a negative biopsy result is weaker evidence than a positive one. Where clinical suspicion is high, whether from histology, tumour location or family history, a negative biopsy should not be treated as closing the question, and repeating the assessment on the resection specimen remains reasonable [4,5].

Choice of assay

The two methods performed almost identically on accuracy, which means the practical grounds for choosing between them lie elsewhere. PCR was conclusive more often on small biopsy samples than IHC in the matched series reviewed here [4], while IHC has the advantage of identifying which protein is lost, which is relevant for Lynch syndrome referral. Using both where tissue permits is defensible, and where it does not, the number of fragments taken at endoscopy is a more useful thing to increase than the number of assays run on too few of them.

Study limitations

The limitations are those of the evidence base. The matched-sample diagnostic studies are retrospective, single-country and modest in

size, and the reference standard, the resection specimen, is itself subject to the same heterogeneity that produces the discordance being measured [4,5]. The chemotherapy interaction rests on an exploratory subgroup analysis of one trial, with wide confidence intervals and a small number of MSI-high patients [2]. The immunotherapy response rates come from MSI-high subgroups within trials designed for unselected populations, so they are post hoc by construction [6]. The neoadjuvant results, though striking, rest on very small numbers [8].

Two gaps deserve naming. No study reviewed here reports outcomes for patients managed on the basis of a biopsy result that later proved discordant with the resection specimen, which is the clinically relevant endpoint for a diagnostic test used to select treatment. And prevalence estimates vary widely by geography and assay, so figures drawn from one population should not be applied to another without checking how MSI was defined.

Conclusion

Endoscopic biopsy performs well enough for MSI and mismatch repair testing in gastric adenocarcinoma that testing at diagnosis is justified, and given the timing of the treatment decisions involved, it is the only point at which testing is useful. Concordance with the resection specimen is high, but the errors are asymmetric: positive results are close to definitive, negative results carry a real false-negative rate, and in tumours already suspected of mismatch repair deficiency the discordance rate is substantially higher than the overall figures suggest. Because a positive result may argue against perioperative chemotherapy and in favour of checkpoint inhibition, the practical recommendation that follows is unglamorous: take more fragments, and do not read a negative result as more informative than it is.

Acknowledgements

We are indebted to the researchers who produced and published the primary cohorts drawn together here. Their reported findings are the sole evidence on which this review stands.

Funding

This review was carried out without dedicated funding from public agencies, industry or non-profit organisations.

Conflict of Interest

None of the authors reports a competing interest.

Ethics Statement

This review works entirely from material that is already published. No fresh patient data were gathered and no participants were recruited, so ethical approval did not apply.

References

1. Cunningham D, Allum WH, Stenning SP, et al. "Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer". *N Engl J Med* 355(2006):11-20.
2. Smyth EC, Wotherspoon A, Peckitt C, et al. "Mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial". *JAMA Oncol* 3(2017):1197-1203.
3. Choi YY, Kim H, Shin SJ, et al. "Microsatellite instability and programmed cell death-ligand 1 expression in stage II/III gastric cancer: post hoc analysis of the CLASSIC randomized controlled

study". *Ann Surg* 270(2019):309-316.

4. Asesio N, Mhamdi Aloui N, Bonnereau J, Lehmann-Che J, Bouhidel F, et al. "Assessment of the reliability of MSI status and dMMR proteins deficiency screening on endoscopic biopsy material in esophagus and gastric adenocarcinoma". *Dig Liver Dis* 55(2023):1105-1113.
5. Fornaro L, Lonardi S, Catanese S, Nappo F, Pietrantonio F, et al. "Concordance of microsatellite instability and mismatch repair status in paired biopsies and surgical specimens of resectable gastroesophageal adenocarcinoma: time for a call to action". *Gastric Cancer* 26(2023):958-968.
6. Chao J, Fuchs CS, Shitara K, et al. "Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials". *JAMA Oncol* 7(2021):895-902.
7. Shitara K, Van Cutsem E, Bang YJ, et al. "Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial". *JAMA Oncol* 6(2020):1571-1580.
8. Raimondi A, Lonardi S, Murgioni S, et al. "Tremelimumab and durvalumab as neoadjuvant or non-operative management strategy of patients with microsatellite instability-high resectable gastric or gastroesophageal junction adenocarcinoma: the INFINITY study by GONO". *Ann Oncol* 36(2025):285-296.
9. Fuchs CS, Doi T, Jang RW, et al. "KEYNOTE-059 cohort 1: efficacy and safety of pembrolizumab monotherapy in patients with previously treated advanced gastric cancer". *J Clin Oncol* 35(2017): abstract 4003.
10. Choi YY, Kim H, Yang HK, et al. "Clinical impact of microsatellite instability in patients with stage II and III gastric cancer: results from the CLASSIC trial". *J Clin Oncol* 35(2017): abstract 4022.
11. Smyth EC, Wotherspoon A, Peckitt C, Nankivell MG, Eltahir Z, et al. "Correlation between mismatch repair deficiency (MMRd), microsatellite instability (MSI) and survival in MAGIC". *J Clin Oncol* 34(2016): abstract 4064.

Citation: Vargas E, Okafor D, Larsen I. "Diagnostic and Prognostic Significance of Microsatellite Instability in Endoscopic Biopsies from Patients with Gastric Adenocarcinoma: A Review." *Ann Gastroenterol Dig Disord* (2023) Volume 6, Issue 1 doi: 10.5281/zenodo.22163660