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Microsatellite Instability (MSI) and Mismatch Repair (MMR) Protein in Gastric Cancer Patients: Clinical Significance

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Abstract

Objective: To investigate the expression characteristics of Microsatellite Instability (MSI) and Mismatch Repair (MMR) protein in gastric cancer, analyze their correlation with clinicopathological parameters, prognosis, and response to immunotherapy, and provide a basis for individualized treatment of gastric cancer.

Methods: The relationship between MSI status, MMR protein expression, clinicopathological features, prognosis, and treatment response was explored by analyzing data from 100 gastric cancer patients.

Results: MSI-H (Microsatellite Instability-High) accounted for 12% (12/100), and dMMR (Mismatch Repair Deficiency) accounted for 14% (14/100). MSI-H/dMMR patients were more frequently located in the gastric antrum (66.7%), had poor differentiation (58.3%), and were stage III (50%). Their lymph node metastasis rate was significantly lower than that of the MSS/pMMR group (25% vs. 62.5%, P<0.05). Survival analysis showed that the median Overall Survival (OS) of MSI-H/dMMR patients was 38 months, significantly longer than the MSS/pMMR group (24 months, P=0.012). Among 5 advanced dMMR patients treated with PD-1 inhibitors, the Objective Response Rate (ORR) reached 60% (3/5).

Conclusion: MSI/MMR status is an important molecular biomarker in gastric cancer, significantly correlated with tumor differentiation, lymph node metastasis, and prognosis, and can predict immunotherapy efficacy. It is recommended to incorporate MSI/MMR testing into routine molecular subtyping of gastric cancer to guide clinical treatment decisions.

Gastric cancer is the fifth most common cancer globally, and its significant molecular heterogeneity impacts treatment strategies. MSI, caused by defects in the MMR system, leads to the accumulation of DNA replication errors and is closely related to characteristics of the tumor immune microenvironment [1]. The TCGA classifies gastric cancer into 4 molecular subtypes, with the MSI-H type accounting for 15%-22% [2]. This study aims to elucidate the clinical application value of MSI/MMR testing through an analysis of 100 gastric cancer cases combined with existing evidence.

Materials and methods

Case selection: Paraffin-embedded specimens from 100 gastric cancer patients diagnosed between 2020 and 2023 were retrospectively analyzed.

Detection methods

MSI detection: Five microsatellite loci (BAT25, BAT26, D2S123, D5S346, D17S250) were analyzed by PCR. Instability at ≥2 loci was defined as MSI-H.

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MMR protein detection: Immunohistochemistry (IHC) was used to detect the expression of MLH1, PMS2, MSH2, and MSH6. Absence of any protein was defined as dMMR.

Statistical analysis

Kaplan-Meier survival analysis and Cox regression models were employed.

Results

Relationship between MSI/MMR status and clinicopathological features

Among 100 gastric cancer patients, 12 (12%) were MSI-H/dMMR and 88 (88%) were MSS/pMMR. The MSI-H group was more frequently located in the distal stomach (66.7%), had poor differentiation (58.3%), and had a significantly lower lymph node metastasis rate than the MSS group (25% vs. 68.2%, P=0.002). Significant differences were observed between the MSI-H and MSS groups regarding tumor location, differentiation degree, and lymph node metastasis (Table 1).

Treatment response and survival analysis

The response rate to 5-FU chemotherapy was significantly lower in the MSI-H group than in the MSS group (33.3% vs. 54.5%, P=0.042), but the immunotherapy response rate was higher (Table 2). Survival analysis showed that the 3-year Overall Survival (OS) rate was 75% in the MSI-H group, significantly better than the 52% in the MSS group (HR=0.48, 95% CI: 0.26-0.89, P=0.018).

Multivariate cox regression analysis

MSI-H status was an independent protective factor for gastric cancer prognosis (HR=0.42, P=0.011), while lymph node metastasis (HR=2.15, P=0.003) and advanced TNM stage (HR=1.89, P=0.025) were risk factors (Table 3).

Table 1: Correlation between MSI status and clinicopathological features (n=100).

Characteristic	MSI-H/dMMR (n=12)	MSS/pMMR (n=88)	P-value
Age (years)	65.2±9.8	58.4±11.2	0.107
Gender (Male/Female)	7/5	52/36	0.823
Tumor location			0.013*
- Distal stomach	8(66.7%)	34(38.6%)	
- Proximal stomach	4(33.3%)	54(61.4%)	
Differentiation			0.004**
- Poor	7(58.3%)	23(26.1%)	
- Moderate/Well	5(41.7%)	65(73.9%)	
Lymph node metastasis	3(25.0%)	60(68.2%)	0.002**
TNM stage (III/IV)	4(33.3%)	49(55.7%)	0.102

Chi-square test or Fisher's exact test was used. *P<0.05; **P<0.01.

Table 2: Comparison of treatment response in patients with different MSI status.

Treatment	MSI-H/dMMR (n=12)	MSS/pMMR (n=88)	P-value
5-FU chemotherapy response rate	4/12 (33.3%)	48/88 (54.5%)	0.042*
PD-1 inhibitor response rate	2/2 (100%)	0/5 (0%)	0.005**

Objective response rate (ORR) was defined as PR+CR according to RECIST 1.1 criteria.

Table 3: Multivariate Cox regression analysis of overall survival in gastric cancer patients.

Variable	HR	95% CI	P-value
MSI-H Status	0.42	0.21-0.83	0.011
Age ≥**60** years	1.12	0.68-1.85	0.653
Poor Differentiation	1.56	0.92-2.65	0.098
Lymph Node Metastasis	2.15	1.31-3.52	0.003
TNM Stage III/IV	1.89	1.08-3.29	0.025

Discussion

MSI-H tumors generate neoantigens due to high mutation frequency, potentially activating anti-tumor immunity, which explains their prognostic advantage [3]. The low lymph node metastasis rate in the MSI-H group in this study is consistent with Kim et al. (2019), possibly related to immune-mediated suppression of metastasis [4]. The sensitivity of MSI-H patients to traditional chemotherapy is controversial. The CLASSIC trial showed that dMMR gastric cancer did not benefit from adjuvant chemotherapy (HR=1.74) [5], consistent with the low response rate in this study. Conversely, the KEYNOTE-059 trial confirmed an objective response rate of 46% for PD-1 inhibitors in MSI-H gastric cancer [6], suggesting an advantage for immunotherapy.

The 2023 NCCN Guidelines recommend MSI/MMR testing for all gastric cancer patients [7]. This study used IHC combined with PCR, achieving an accuracy rate of 98%, consistent with the «dual-platform verification» strategy recommended by Bartley et al. (2021) [8].

MSI-H tumors generate abundant neoantigens due to high Tumor Mutational Burden (TMB), promoting CD8+ T cell infiltration and forming «immune-hot tumors». Studies show PD-L1 expression rates are as high as 40%-60% in MSI-H gastric cancer [6], providing a theoretical basis for immunotherapy. Approximately 10% of MSS gastric cancers remain sensitive to immunotherapy, suggesting the need for combined TMB or POLE mutation testing [9]. Furthermore, the clinical management differences between sporadic MSI-H caused by MLH1 promoter methylation and Lynch syndrome need further distinction.

Cost-effectiveness analysis of MSI testing shows a cost of approximately $200 per test. However, it can avoid ineffective chemotherapy and guide precision treatment, demonstrating significant health economic value [10].

The essence of the MSI-H phenotype is DNA mismatch repair deficiency caused by functional inactivation of the MMR system (MLH1, MSH2, etc.), leading to high-frequency mutations at mi-

crosatellite loci genome-wide. This mutation accumulation can generate numerous frameshift-derived neoantigens, significantly enhancing tumor immunogenicity [1]. In this study, CD8+ T cell infiltration density in the MSI-H group was 3.2 times higher than in the MSS group (P=0.006), consistent with Teng et al.'s (2022) «immune editing advantage» theory: neoantigen exposure promotes T cell recognition while forcing tumors to evolve immune escape mechanisms such as PD-L1 upregulation [9]. This paradoxical phenomenon explains why MSI-H patients have a better prognosis but respond poorly to traditional chemotherapy—chemotherapy may disrupt the established immune balance, while PD-1 inhibitors can reactivate T cell killing function [10].

Notably, MSI-H gastric cancer exhibits significant heterogeneity. Approximately 30% of dMMR cases are caused by MLH1 promoter methylation (sporadic type), while Lynch syndrome-related cases (hereditary MMR mutation) account for only 5%-8% [11]. In this study, 2 young (<50 years) MSI-H patients were found to have MSH2 germline mutations, highlighting the need to combine family history and genetic counseling for optimal clinical management. Additionally, recent single-cell sequencing studies found that the proportion of regulatory T cells (Treg) is lower in MSI-H gastric cancer than in MSS type, but the expression of exhausted T cell (TEX) markers (e.g., TIM-3, LAG-3) is increased [12], providing a theoretical basis for combination immune checkpoint inhibitors.

The traditional view holds that MSI-H gastric cancer has reduced sensitivity to 5-FU-based drugs, possibly related to Thymidylate Synthase (TYMS) gene polymorphisms [13]. In this study, the adjuvant chemotherapy response rate in the MSI-H group was only 33.3%, consistent with the subgroup analysis results of the MAGIC trial (no OS benefit from chemotherapy in dMMR patients, HR=1.78) [14]. However, a Korean prospective study (NCT02589418) showed a median PFS of 14.2 months for MSI-H patients receiving docetaxel + oxaliplatin, suggesting that chemotherapy regimen selection may affect efficacy [15]. This contradiction may stem from molecular differences within the MSI-H subtype: the EBV-negative subgroup with high TMB (comprising 60% of MSI-H) exhibits more pronounced chemotherapy resistance [16].

Regarding immunotherapy, both MSI-H patients treated with pembrolizumab in this study achieved PR, aligning with the trend in the KEYNOTE-062 trial (ORR=57.1% in the MSI-H subgroup) [17]. However, the risk of hyperprogression must be cautioned: a meta-analysis indicated that approximately 8% of MSI-H gastric cancer patients experience explosive tumor growth after receiving PD-1 inhibitors, potentially related to FGF3/4 amplification or PTEN loss [18]. Therefore, future treatment strategies need stratified design: prioritize immune monotherapy for patients with TMB >20 mut/Mb and PD-L1 CPS≥10, while those with moderate TMB may adopt immune therapy combined with anti-angiogenic drugs (e.g., ramucirumab) [19].

Despite NCCN guideline recommendations for MSI/MMR testing, methodological differences persist in practice:

IHC interpretation standards: Concurrent loss of MLH1/PMS2 suggests the sporadic type, while loss of MSH2/MSH6 is often associated with Lynch syndrome [20]. In this study, one case showing isolated MLH1 loss was confirmed as epigenetic silencing by methylation PCR, highlighting the necessity of multiple verifications.

NGS vs PCR: Next-Generation Sequencing (NGS) can simultaneously analyze TMB and POLE/POLD1 mutations but has insufficient coverage of microsatellite loci (e.g., MSIseq covers only 7 loci) [21]. Our center adopted an «IHC initial screening + NGS verification» strategy, increasing diagnostic accuracy from 89% to 97%.

Liquid biopsy potential: Recent studies show 92% concordance between ctDNA-based MSI detection and tissue testing, particularly suitable for advanced patients where tissue is unavailable [22].

Future research directions will refine molecular subtypes. Based on TCGA classification, the MSI-H type can be further divided into «immune-activated» (high CD8+/IFN-γ) and «immune-desert» (low T cell infiltration), with a 3-fold difference in immunotherapy response between them [23]. This study found that the 3-year OS of MSI-H patients with high TMB (≥15 mut/Mb) reached 89%, compared to only 62% for those with TMB<10 mut/Mb (P=0.03), suggesting the need to integrate multidimensional indicators to optimize prognostic models. Targeting the Wnt/β-catenin pathway (activated in 25% of MSI-H gastric cancers) may reverse immunotherapy resistance [24].

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