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Clinical significance and research progress of microsatellite instability in gastric cancer

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Abstract: The occurrence and development of gastric cancer (GC) is determined by many factors, and its morbidity and mortality are at the forefront of global cancer. In recent years, the development of molecular biology has provided new ideas for the diagnosis and treatment of GC. Microsatellite instability (MSI) GC is a special type of GC caused by the body's DNA mismatch repair (MMR) gene defect. After studying and analyzing the clinical characteristics, molecular mechanisms and prognosis of this type of GC, it is found that this type of patients has specific clinicopathological features and better prognosis compared with ordinary types of GC. However, there are still some controversies in the study of MSI gastric cancer at home and abroad. This article aims to review the concept of MSI, the relationship between MSI and clinicopathological features of gastric cancer, and the treatment progress of MSI gastric cancer.

Keywords: Gastric cancer; Microsatellite instability; Mismatched repair; Chemotherapy; Immunotherapy; Fluorouracil; Pembrolizumab; Nivolumab; Ipilimumab

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The incidence of gastric cancer ranks fifth, and its mortality rate ranks fourth globally among all cancers, with the incidence in males being twice of females [1]. Various factors have been found to be associated with the occurrence and progression of gastric cancer, including gender, age, dietary habits, smoking, alcohol consumption, and consumption of red meat, especially infection with *Helicobacter pylori* (Hp) and Epstein-Barr virus (EBV) [2]. Due to the lack of obvious clinical manifestations and specific early diagnostic markers, most gastric cancer patients were diagnosed at the medium and advanced stages, missing the optimal period for surgical treatment. Postoperative patients are prone to recurrence and metastasis, and the treatment effect is often unsatisfactory. Microsatellite instability (MSI) is an easily testable biomarker, often used as an alternative to identify specific molecular subtypes of gastric cancer according to the classifications proposed by The Cancer Genome Atlas (TCGA) network and the Asian Cancer Research Group (ACRG) [3-4]. MSI occurs due to the DNA mismatch repair deficiency (dMMR), leading to the inability to repair DNA mismatches in microsatellites. Previous studies had shown that MSI was associated with the occurrence and progression of colorectal cancer, and were considered a favorable pathological feature for the prognosis of colorectal cancer. However, the relationship between MSI and clinical pathological features and prognosis of gastric cancer remains controversial. This article mainly reviews the relationship between MSI and clinical pathological features, prognosis, and treatment progress.

1 Concept of MSI

A microsatellite is a short tandem repeat sequence in the genome DNA, consisting of 1 to 6 nucleotides. These repeat units are often located in the non-coding regions of genes or near the telomeres of chromosomes, with high mutability that can affect gene replication and expression. The mismatch repair (MMR) system maintains the stability of microsatellites by correcting base pairs, replacing mismatches, insertions or deletions, and ensuring the accuracy of DNA replication [5]. Currently, the MMR system consists of at least seven proteins: hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2. When these proteins bind to specific ligands in the body, they can recognize mismatches in base pairs and some small nucleotide insertions or deletions during DNA replication. When the proofreading ability of exonucleases in DNA polymerases is deficient, the function of MMR gene is lost, and the errors occurring in the DNA replication process cannot be corrected in time by the organism, leading to the accumulation of microsatellite frameshift mutations or insertions/deletions, increasing susceptibility to colorectal cancer, endometrial cancer, ovarian cancer, and gastric cancer in humans and other mammals, thereby generating MSI [6].

2 Detection of MSI

Currently, there is no unified standard for MSI testing and interpretation of gastric cancer. The detection of MSI in gastric cancer often refers to colon cancer, using immunohistochemistry (IHC) or polymerase chain reaction (PCR) methods [7]. In clinical practice, IHC is mainly used to detect the expression of four protein antibodies (hMLH1, hMSH2, hPMS1, and hMSH6) and these antibodies can determine the occurrence of MSI. If

the expression of any of the four protein antibodies is absent or <25%, it is determined as MSI; if the absence of protein expression ≥2, it is determined as high MSI (MSI-H); if only one expression is absent, it is determined as low MSI (MSI-L), and if all four protein antibodies are expressed, it is identified as microsatellite-stable (MSS). Earlier studies indicated that there was about 5% inconsistency in the detection of MSI-H by IHC and PCR. Recent reports showed that a large part of these differences was due to misinterpretation of IHC. The overall sensitivity of IHC was 94%, almost the same as that of PCR [8]. PCR is usually used to detect loci such as BAT25, BAT26, D2S123, D5S346, and D17S250. Due to the advantages of PCR technology in detecting MSI-H classification compared to IHC, it is often used as the standard detection method for MSI [9]. Currently, next-generation DNA-sequencing (NGS) is becoming a research hotspot for MSI detection due to its high accuracy, specificity, and thorough interrogation of microsatellite sites across tumor types. It is expected to be the best method for standardizing MSI classification. These tests overcome the limitations of traditional PCR and IHC methods, allowing genome-wide MSI analysis and evaluation of other biomarkers in a single test, providing the possibility of detecting all gene variations in a single tumor simultaneously and hot gene variations across tumor types [10]. The 2022 National Comprehensive Cancer Network (NCCN) gastric cancer guidelines also recommended that all newly diagnosed gastric cancer patients undergo MMR testing through PCR, NGS, or IHC, and further evaluation should be conducted based on clinical assessment for MSI-H gastric cancer patients [11].

3 Mechanisms of occurrence of MSI gastric cancer

MSI was initially discovered in colorectal cancer and was served as a marker for hereditary nonpolyposis colorectal cancer (HNPCC). Subsequent studies have shown that MSI in approximately 15% of sporadic colorectal cancer, gastric cancer, and endometrial cancer, with lower frequencies in other cancers [12-13]. In colorectal cancer, MSI is primarily caused by mutations of the MMR genes *hMLH1* and *hMSH2*. However, MSI is mostly (over 50%) caused by *hMLH1* silencing because of promoter hyper-methylation in gastric cancer [9]. A recent meta-analysis indicated that gene methylation occurs during the malignant transformation of gastric mucosa and accumulates progressively with disease progression. The levels of high methylation of *hMLH1* and *MGMT* in gastric cancer tissues were significantly higher than those in non-cancerous tissues [14]. Therefore, MSI has significance in premalignant lesions and may serve as a potential molecular indicator for early diagnosis and prevention of gastric cancer.

During the development of MSI-H gastric cancer, there is a series of mutations in target genes involved in various cellular processes such as cell growth regulation (*TGFβRII, IGFIIR, RIZ, TCF4, DP2*), apoptosis (*BAX, BCL10, FAS, CASPASE5, APAF1*), and DNA repair (*hMSH6, hMSH3, MED1, RAD50, BLM, ATR, MRE11*) [15]. *ACVR2A* is the most frequently mutated gene in MSI-H gastric cancer. It encodes a transmembrane type 2 receptor that mediates the function of activin, which is divided into extracellular receptor region, transmembrane region, and intracellular kinase region. Activin is a member of the superfamily of transforming growth factor-β (TGF-β), involved in various biological processes, including epithelial mesenchymal transition [16]. PTEN, a common tumor suppressor gene involved in double-strand break repair and nucleotide excision repair. It controls cell growth and apoptosis by inhibiting the PI3K/AKT pathway, and controls cell adhesion, migration, and tumor invasion by down regulating the activity of adhesion kinases. It also regulates DNA damage response pathways by interacting with Chk1 and p53. Nonsense mutations is one of the mechanisms of PTEN inactivation in gastric cancer. Studies suggest that PTEN mutations may disrupt the process of DNA damage repair, leading to the occurrence of MSI [17].

Furthermore, *Helicobacter pylori* (Hp) infection can lead to decreased expression of MMR genes and related proteins, allowing accumulate continuous mutations in gastric mucosal cells. The duration of Hp infection may affect the methylation levels of the *MLH1* promoter *in vivo* [18]. Moreover, after Hp eradication, the expression of MLH1 and MSH2 in gastric mucosal cells returns to levels similar to those in uninfected individuals, indicating that the inhibition of MMR gene expression is reversible [19].

4 Incidence and pathological characteristics of MSI gastric cancer

According to TCGA data, 21.7% of gastric cancer patients have MSI. However, due to the lack of a standardized testing algorithm, the incidence of MSI gastric cancer varies greatly in some related studies. van Velzen *et al*.[20] reported an MSI-H incidence of 6% to 24% in gastric esophageal adenocarcinomas, which can reach 85% in patients aged 48 years and older. Guan *et al*. [21] reported MSI-H incidence in gastric cancer ranging from 8% to 25%. A meta-analysis of four trials suggested an MSI-H incidence of 7.8% [22]. However, An *et al*. [23] reported lower MSI-H incidence in Eastern studies (8.2% to 9.5%) compared to Western studies (16.0% to 25.2%). In summary, there is considerable variation in the incidence of MSI-H gastric cancer among different countries and ethnicities. Therefore, a standardized diagnostic algorithm for MSI gastric cancer is crucial for better understanding its characteristics in clinical practice.

A Chinese study found that MSI-H gastric cancer patients often exhibit characteristics such as older age, more common in females, located in the distal stomach, early TNM staging, and intestinal type according to Lauren classification, better differentiation, and HER2 negativity [21]. A study in Korea indicated that MSI-H gastric cancer is more common in elderly patients, signet ring cell type, and intestinal type according to Lauren classification,

lower tumor location, and absence of per-neural invasion [24]. However, some studies found no association between MSI status and age, sex, depth of invasion, lymph node metastasis, tumor differentiation, histological type (WHO or Lauren classification), TNM staging, vascular invasion, nerve invasion, and prognosis [25-26]. Despite many studies confirming risk factors associated with MSI-H gastric cancer, there is still significant variation. It has been suggested that MSI-H gastric cancer patients have a better prognosis compared to non-MSI-H gastric cancer patients, possibly due to higher levels of tumor-infiltrating lymphocytes [27]. Additionally, a study on three European cohorts showed that regardless of perioperative treatment, female MSI-H gastric cancer patients have higher survival rates than male patients, suggesting that MSI-H is a prognostic factor for females but not males [28]. Compared to colorectal cancer, the clinical significance and role of MSI in gastric cancer remain controversial, partly due to the relatively small sample sizes in these studies. Further large-scale clinical trials are needed to confirm the specificity of MSI gastric cancer.

5 MSI gastric cancer and chemotherapy

5-Fluorouracil (5-FU) is the main adjuvant chemotherapy for colorectal cancer. Current guidelines suggest that all stage II MSI phenotype colorectal cancer patients should not receive adjuvant therapy based on 5-FU. However, the benefits of adjuvant chemotherapy for stage III MSI-H colorectal cancer patients are still controversial [29]. The updated NCCN guidelines in 2013 recommend MSI testing for all stage II colorectal cancer patients because some studies suggest that patients with MSI colon cancer often have relatively better prognosis but do not benefit from adjuvant chemotherapy with 5-FU [30]. 5-FU is also an important adjuvant chemotherapy for gastric cancer, however, the efficacy of 5-FU-based chemotherapy for MSI gastric cancer patients is currently controversial [31]. A recent meta-analysis suggested that adjuvant chemotherapy did not benefit MSI-H gastric cancer patients undergoing surgery, while for MSS/MSI-L gastric cancer patients, chemotherapy had significant benefits for disease-free survival (DFS) and overall survival (OS) [22]. A retrospective study by Tsai *et al*. [23] suggested that MSI gastric cancer patients only showed a better prognosis in stage III regardless of whether adjuvant chemotherapy was used. However, some studies have also shown that there is no significant OS difference between MSI-H and MSS/MSS-L comparisons, and adjuvant chemotherapy does not affect the DFS or OS of MSI-H/dMMR patients [21, 25]. A recent meta-analysis showed that dMMR/MSI-H gastric cancer patients can still benefit from adjuvant chemotherapy [33]. The predictive role of adjuvant chemotherapy efficacy for MSI gastric cancer patients is still controversial in the current reported results of relevant studies. In gastric cancer, two phase III trials, KEYNOTE-585 (NCT 03221426) and MATTERHORN (NCT 04592913), are currently underway to evaluate the addition of anti-PD-1/PD-L1 in perioperative chemotherapy. In addition, in adjuvant therapy, the ongoing phase III trial ATTRACTION-5 (NCT 03006705) is studying the standard adjuvant chemotherapy regimen using tegafur or capecitabine plus oxaliplatin combined with nivolumab for patients with pathologically confirmed stage III gastric cancer (including gastroesophageal junction cancer) after D2 or more extensive lymph node dissection.

6 Immunotherapy progress in msi gastric cancer

In recent years, immunotherapy has become a hot topic in cancer research. MSI has been shown to be a biomarker for predicting the prognosis and response of immune checkpoint inhibitors (ICI), possibly because MSI-H tumors preferentially express some new antigens that are easily recognized by the immune system [35]. Tumors with MSI-H status also attract more immune cell infiltration, thereby enhancing the efficacy of ICI [36]. MSI gastric cancer patients can also benefit from the immunotherapy. PD-L1 or PD-1 expression, tumor mutational burden (TMB), and MSI-H are often used as predictive biomarkers for guiding the clinical application of ICI therapy, among which MSI-H has unique advantages, and tumors with MSI-H are particularly sensitive to PD-1 and PD-L1 inhibitors. Many approved immunotherapies inhibit the PD-1/PD-L1 interaction to stimulate immune responses against cancer cells [37]. According to previous studies, the response rate to immunotherapy varies among tumor types in MSI-H tumors, with response rates of 15% for head-and-neck cancer and 57%-86% for gastric cancer [35]. In addition, most gastric cancers are not sensitive to single-agent ICI therapy, so gastric cancer patients may need combination therapy to improve their responses to anti-PD-1 treatment or other ICIs [38]. A retrospective study also showed that in advanced MSI gastric cancer patients, immune therapy combined with chemotherapy achieved a higher objective response rate (ORR) than single-agent immune therapy (61.5% *vs.* 25%) [21]. Relevant studies indicate that tumor patients can induce early formation of immune memory and enhance T cell immune responses to tumor antigens better after receiving new adjuvant immunotherapy. These mechanisms enhance the body's anti-tumor ability and help eradicate postoperative micro-residual or micro-metastatic disease [39]. When ICI is used as neoadjuvant therapy for MSI/dMMR tumors, it can achieve a higher pathological response rate for potentially resectable tumors and ultimately provide the opportunity to cure tumors, regardless of whether surgery is performed. There are currently several phase II studies exploring the application of ICI in the neoadjuvant/adjuvant setting for MSI tumors, especially gastric cancer (NCT04006262, NCT04817826, and NCT04152889) [40].

Pembrolizumab is a humanized monoclonal antibody sourced from mice that targets PD-1. It promotes tumor cell apoptosis by binding to the PD-1 receptor on T cells and disrupting the interaction between PD-L1 molecules on tumor cells [37]. Recently, the FDA approved pembrolizumab for the treatment of patients with

unresectable or metastatic dMMR/MSI-H tumors, regardless of tumor types [41]. Pembrolizumab has also shown significant efficacy in patients with MSI-H tumors who have progressed after previous chemotherapy [6]. Studies suggest that pembrolizumab may serve as a second-line or subsequent therapy for MSI-H or high tumor mutation burden (TMB-H) patients [42]. However, some reports on MSI-H tumor patients suggest no significant association between MSI-H and TMB-H. Results from the KEYNOTE-061 and KEYNOTE-062 trials indicate that MSI-H tumor patients treated with pembrolizumab achieved ORRs of 47% and 57%, respectively, leading to improved clinical outcomes [34].

In the recent CheckMate-649 trial, advanced gastric cancer patients treated with nivolumab in combination with chemotherapy showed better median OS (14.4 months vs. 11.1 months, *HR*=0.70, *P*<0.01) and median PFS (7.7 months vs. 6.0 months, *HR*=0.68, *P*<0.01) compared to chemotherapy alone [43], and the survival benefit of MSI-H tumor patients is greater. Based on the results of CheckMate-649, the FDA approved the addition of nivolumab to standard chemotherapy as first-line treatment for advanced gastric cancer patients, regardless of PD-L1 combined positive score (CPS), although NCCN guidelines recommend it as the preferred option for patients with PD-L1 and CPS≥5 [11]. CTLA-4 inhibitors can potentially activate T cells and kill tumor cells. When used in combination with chemotherapy, ipilimumab, as a CTLA-4 antibody, achieved an ORR of 57% (95% *CI*: 18%-90%) in dMMR gastric cancer, while its combination with nivolumab showed high efficacy (ORR of 70%, 95% *CI*: 35%-93%) [44]. Additionally, the GERCOR NEONIPIGA phase II study demonstrated that the pathological complete response rate in MSI gastric cancer patients was 58.6% (17/29) when treated with neoadjuvant therapy combining nivolumab and ipilimumab [45].

Enfortumab vedotin is a humanized single-domain anti-PD-L1 antibody derived from camels. It is more soluble and stable compared to full monoclonal antibodies, allowing for faster tissue penetration and enabling subcutaneous administration in less than 30 seconds, potentially avoiding infusion reactions [46]. Despite overall positive outcomes with anti-PD-1 therapy, the ORRs in the dMMR/MSI-H subgroup remain within the range of 40% to 60%, indicating inherent mechanisms of resistance in a considerable portion of individuals [47].

However, with the development of immunotherapy, many patients receiving ICIs exhibit resistance. Revealing molecular determinants of ICI response may aid in developing new biomarkers or combination therapies to overcome resistance in MSI-H/dMMR tumors. Studies suggest that a higher number of mutations in the PI3K-AKT-mTOR pathway may be one of the mechanisms of immune evasion and primary resistance to immunotherapy in MSI-H/dMMR gastric adenocarcinoma [48]. Mutations in the β-2 microglobulin gene caused by MSI-H/dMMR can also lead to loss of class I major histocompatibility complex-mediated antigen presentation, impairing cytotoxic $CD8^+$ T cell recognition of tumor cells, thus resulting in acquired resistance to ICIs [49]. ICI resistance in MSI-H/dMMR gastrointestinal tumors can be overcome by targeting the Wnt/β-catenin pathway [50]. In a phase II clinical trial of pembrolizumab in advanced MSI-H gastric cancer, non-responders showed frequent mutations in the Wnt/β-catenin pathway and abundant cancer-associated fibroblasts. These findings may contribute to further development of combination ICI therapy for advanced MSI-H/dMMR gastric cancer [51].

After ICI therapy, MSI-H gastric cancer cases exhibit relatively improved long-term survival rates compared to MSS/MSI-L cases, possibly because alterations in MMR genes lead to the production of abnormal tumor-specific peptides, which recruit lymphocytes to the tumor and induce an immune response. However, due to the relatively low overall frequency of MSI phenotypes in gastric cancer and the small number of patients included, the role of ICI therapy in MSI gastric cancer treatment remains less successful than the results obtained in colorectal cancer trials.

7 Conclusion

MSI gastric cancer, has its unique aspects in clinical pathological characteristics and treatment. Similar to patients with colorectal cancer, MSI-H gastric cancer patients have a better prognosis compared to MSS/MSI-L gastric cancer patients, but they often do not benefit from neoadjuvant chemotherapy. However, MSI-H gastric cancer patients seem to achieve better results after receiving immunotherapy. Therefore, evaluating the MSI status in gastric cancer patients helps in assessing prognosis and guiding treatment. It is hoped that future research on this special type of gastric cancer will be conducted with larger sample sizes to better validate its biological characteristics and establish systematic diagnostic and treatment standards, thereby providing individualized treatment guidelines for MSI patients.

Conflict of Interest None

Reference

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· 研究进展 ·

微卫星不稳定型胃癌的临床意义和研究进展

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摘要：胃癌的发生发展过程是由多种因素决定的。近年来，分子生物学的发展给胃癌的诊断、治疗提供了新的思路。微卫星不稳定（MSI）胃癌是由于机体 DNA 错配修复（MMR）基因缺陷导致的一种特殊的胃癌类型。对 MSI 胃癌的临床特征、分子机制以及预后进行研究发现，这类患者相较于普通类型的胃癌具有特定的临床病理特征和较好的预后。但目前国内外对 MSI 胃癌的研究仍然存在一些争议，本文意在从 MSI 的概念、MSI 与胃癌的临床病理特征的关系及 MSI 胃癌的治疗进展等方面进行综述。

关键词：胃癌；微卫星不稳定；错配修复；化疗；免疫治疗；氟尿嘧啶；帕博利珠单抗；纳武利尤单抗；伊匹木单抗
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Clinical significance and research progress of microsatellite instability in gastric cancer

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Abstract: The occurrence and development of gastric cancer (GC) is determined by many factors. In recent years, the development of molecular biology has provided new ideas for the diagnosis and treatment of GC. Microsatellite instability (MSI) GC is a special type of GC caused by the body's DNA mismatch repair (MMR) gene defect. Studies of the clinical characteristics, molecular mechanisms and prognosis of MSI GC found specific clinicopathological features and better prognosis in MSI GC compared with ordinary types of GC. However, there are still some controversies in the study of MSI gastric cancer at home and abroad. This article aims to review the concept of MSI, the relationship between MSI and clinicopathological features of gastric cancer, and the treatment progress of MSI gastric cancer.

Keywords: Gastric cancer; Microsatellite instability; Mismatched repair; Chemotherapy; Immunotherapy; Fluorouracil; Pabolizumab; Navulizumab; Ipilimumab
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胃癌的发病率位居全球癌症第五，死亡率位居全球第四，其中男性的发病率是女性的两倍[1]。已经发现多种因素与胃癌的发生和进展有关，包括性别、年龄、饮食习惯、吸烟、饮酒和红肉，特别是幽门螺杆菌（*Helicobacter pylori*, Hp）和 EB 病毒（Epstein-Barr virus, EBV）的感染[2]。由于早期胃癌的临床表现不明显且没有特异的早期诊断标志物，大多数胃癌患者在发现时就已经处于中晚期阶段，因此错过了手术治疗的最佳时期，且术后患者易出现复发、转移，治疗效果总是不尽如人意。微卫星不稳定性（MSI）是一种易于测试的生物标志物，常作为癌症基因组图谱（TCGA）和亚洲癌症研究小组（ACRG）分型鉴定特定胃癌分子亚群的替代物[3-4]。MSI 的发生是由于 DNA 错配修复系统缺陷（dMMR）导致不能修复微卫星中的 DNA 错配。既往研究显示其与结直肠癌发生发展密切相关，被认为是结直肠癌预后良好的病理特征。然而，MSI 与胃癌临床病理特征及预后等方面的关系仍存在争议，本文主要对 MSI 和胃癌临床病理特征的关系、预后及治疗的进展等方面进行综述。

1　MSI 的概念

微卫星是基因组 DNA 中的一个短串联重复序列，这些重

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复单元由 1~6 个核苷酸组成，常位于基因的非编码区或染色体的端粒区附近，具有高突变性，可影响基因的复制与表达。错配修复（mismatch repair，MMR）系统通过校正碱基，取代错配、插入或缺失来维持微卫星的稳定性，确保 DNA 复制的准确[5]。目前发现 MMR 系统至少由 hMLH1、hMLH3、hMSH2、hMSH3、hMSH6、hPMS1 和 hPMS2 七个蛋白组成，当这些蛋白与机体特定的配体相结合后可在 DNA 复制过程中识别碱基对的错配和一些小核苷酸的插入或缺失。当 DNA 核酸外切酶校对能力存在缺陷时，机体的 MMR 基因功能丧失，DNA 复制过程出现的错误则不能被机体及时矫正，导致微卫星移码突变插入或缺失发生累积，增加人类对结肠癌、子宫内膜癌、卵巢癌和胃癌的易感性，从而产生 MSI[6]。

2　MSI 的检测

目前暂无统一的 MSI 胃癌检测及判读标准，关于 MSI 胃癌的检测往往以结直肠癌为例，常使用免疫组化法（IHC）或聚合酶链反应法（PCR）[7]。临床上目前主要应用 IHC 检测 hMLH1、hMSH2、hPMS1 和 hMSH6 这四个蛋白抗体的表达来判断 MSI 现象。以上四种蛋白抗体只要有一个表达缺失或表达<25%，则判定为 MSI，当表达缺失≥2 个，则判定为高度 MSI（MSI-high，MSI-H）；只有 1 个表达，则判定为低度 MSI（MSI-low，MSI-L）；若上述四种蛋白抗体均表达，则鉴定为微卫星稳定（MSS）。较早的文献表明 IHC 和 PCR 对 MSI-H 的检测约在 5%的病例中不一致。而最近的报告显示，这些差异中有很大一部分原因是由于 IHC 的解释错误。IHC 的总体灵敏度为 94%，与 PCR 几乎相同[8]。通常使用 PCR 检测 BAT25、BAT26、D2S123、D5S346 和 D17S250 等位点，由于 PCR 技术在检测 MSI-H 分型时较 IHC 具有优势，因此常作为 MSI 的标准检测方法[9]。目前，二代测序技术（NGS）凭借较高的精确度和特异性以及更彻底地询问跨肿瘤类型的 MS 位点正成为 MSI 检测的研究热点，有望成为标准化 MSI 分类的最佳方法。这些检测克服了传统 PCR 和 IHC 的局限性，允许在单次测试中进行基因组 MSI 分析以及评估其他生物标志物，为同时检测单瘤种的所有基因变异及泛瘤种的热点基因变异提供了可能[10]。在 2022 年国家综合癌症网络（NCCN）胃癌指南中也建议所有新诊断的胃癌患者都应通过 PCR、NGS 或 IHC 进行 MMR 通用检测，而对于 MSI-H 胃癌患者应根据临床进一步评估[11]。

3　MSI 胃癌的发生机制

MSI 最早被发现在结直肠癌中，它是遗传性非息肉病性结直肠癌的标志。之后相关研究表明在约 15%的散发性结直肠癌、胃癌和子宫内膜癌中也观察到 MSI，在其他癌症中频率较低[12-13]。在结肠癌中，MSI 主要由 MMR 基因 *hMLH1* 和 *hMSH2* 的突变引起。然而，在胃癌中由于启动子的高甲基化，MSI 大多数（超过 50%）是由于 *hMLH1* 沉默引起[9]。最近一项荟萃分析表明，基因甲基化发生在胃黏膜恶性转化阶段，并随着疾病的进展而逐渐累积。且胃癌组织中 *hMLH1*、*MGMT* 的高甲基化水平显著高于非癌性组织[14]。因此，MSI 在癌前病变中具有重要意义，可能是胃癌早期诊断和预防的潜在分子指标。

MSI-H 胃癌的发展过程中有一系列靶基因的突变，这些靶基因包括参与细胞生长调节的（*TGFBR2*、*IGF2R*、*RIZ*、*TCF4*、*DP2*），参与细胞凋亡的（*BAX*、*BCL10*、*FAS*、*CASPASE5*、*APAF1*）及参与 DNA 修复的（*hMSH6*、*hMSH3*、*MED1*、*RAD50*、*BLM*、*ATR*、*MRE11*）[15]。*ACVR2A* 是 MSI-H 胃癌中最常突变的基因，*ACVR2A* 编码介导激活素功能的跨膜 2 型受体，分为细胞外受体区、跨膜区和细胞内激酶区，激活素是转化生长因子-β（transforming growth factor-β，TGF-β）超家族的成员，参与多种生物过程，包括上皮—间质转化[16]。*PTEN* 是一种常见的肿瘤抑制基因，参与双链断裂修复和核苷酸切除修复，通过抑制 PI3K/AKT 途径控制细胞生长进而使细胞凋亡，以及通过下调黏附激酶的活性来控制细胞黏附、迁移和肿瘤侵袭，并通过与 Chk1 和 p53 相互作用来调节 DNA 损伤反应途径。无义突变，是胃癌中 PTEN 失活的机制之一。有研究指出 PTEN 突变可能会破坏 DNA 损伤修复的过程，从而导致 MSI 的发生[17]。

此外，Hp 感染会导致 MMR 基因及相关蛋白的表达下降，使胃黏膜细胞中突变不断积累。而 Hp 感染的时间长短可能会影响体内 MLH1 启动子的甲基化水平[18]。Hp 根除后，胃黏膜细胞中 MLH1 和 MSH2 的表达恢复到与未感染者相似，表明 MMR 基因表达受到的抑制是可逆的[19]。

4　MSI 胃癌的发生率和病理学特征

根据 TCGA 资料，21.7%的胃癌患者为 MSI。但由于缺少一个标准化的测试算法，在相关的一些研究中 MSI 胃癌的发病率表现出较大的差异。van Velzen 等[20]的研究显示，在可切除胃食管腺癌中 MSI-H 的患病率为 6%~24%，在 48 岁及以上的患者中 MSI-H 患病率可高达 85%。Guan 等[21]的研究统计胃癌中 MSI-H 的患病率为 8%~25%。一项汇集了四项试验的荟萃分析表明，MSI-H 的患病率为7.8%[22]。An 等[23]研究显示 MSI-H 在东方国家研究的结果（8.2%~9.5%）低于西方国家研究结果（16.0%~25.2%）。总之，MSI-H 胃癌的发病率在不同的国家和种族之间存在较大的差别。可能是因为 MSI-H 的诊断因样本组成、采取的标记和研究方法的不同。因此，为了更好的研究 MSI 胃癌的特征，一个标准化的 MSI 胃癌诊断算法在临床中具有重要意义。

一项中国的研究表明，MSI-H 胃癌患者的病理特征为年龄较大、女性多见、胃远端、TNM 分期较早、Lauren 肠型、分化更好和 HER2 阴性等[21]。一项韩国的研究表明，MSI-H 胃癌更常见于老年患者、印戒细胞类型、Lauren 肠型、肿瘤位置较低且无周围神经浸润[24]。然而，一些研究发现 MSI 状态与年龄、性别、侵袭深度、淋巴结转移、肿瘤分化、组织学类型（WHO 或 Lauren 分型）、TNM 分期、脉管侵犯、神经侵犯和预后之间没有关联[25-26]。目前 MSI-H 胃癌的相关危险因素差异较大。研究表明，MSI-H 胃癌患者比非 MSI-H 胃癌患者预后更好，可能与肿瘤浸润淋巴细胞的水平更高有关[27]。此外，一项关于欧洲三个队列的研究表明，无论是否进行围手术期治疗，MSI-

H 胃癌女性患者的生存率高于男性患者,MSI-H 只是女性的预后因素,而不是男性的预后因素[28]。与结直肠癌相比,MSI 在胃癌中的临床意义和作用仍存在争议,考虑相关研究中纳入 MSI 胃癌的样本量均较少,部分结果可能存在偏差,期待未来进行大样本的相关临床随机试验进行验证。

5　MSI 胃癌与化疗

5-氟尿嘧啶(5-fluorouracil,5-FU)是结直肠癌的主要辅助化疗手段,目前的指南建议,所有Ⅱ期 MSI 表型结直肠癌患者都不应接受基于 5-FU 的辅助治疗。但辅助化疗对Ⅲ期 MSI-H 结直肠癌患者的益处仍有争议[29]。NCCN 在 2013 年更新的指南建议所有Ⅱ期结直肠癌患者都应该进行 MSI 检测,研究表明 MSI 结肠癌的患者往往有着相对好的预后,但在接受 5-FU 的辅助化疗后并不能从中获益[30]。5-FU 也是胃癌重要的辅助化疗手段,然而,基于 5-FU 的化疗对 MSI 胃癌患者的疗效目前存在争议[31]。最近一篇汇集了四项试验的荟萃分析表明 MSI 对行手术治疗的胃癌患者具有良好的预后作用,并表明辅助化疗对接受手术的 MSI-H 胃癌患者可能缺乏益处,而对于 MSS/MSI-L 胃癌患者,化疗对无病生存期(DFS)和总生存期(OS)有很大益处[22]。Tsai 等[32]进行的回顾性研究表明无论是否使用辅助化疗,MSI 胃癌患者仅在Ⅲ期表现出较好的预后。然而,也有一些研究表明,MSI-H 和 MSS/MSS-L 的比较没有显示出明显的 OS 差异,辅助化疗也不影响 MSI-H/dMMR 患者的 DFS 或 OS[21,25]。一项荟萃分析显示,dMMR/MSI-H 的胃癌患者仍然可以从辅助化疗中受益[33]。对于接受辅助化疗的 MSI 胃癌患者其疗效的预测作用,目前相关研究的结果仍有争议。在胃癌中,正在进行两项Ⅲ期 KEYNOTE-585(NCT03221426)和 MATTERHORN(NCT04592913)试验,以评估在围手术期化疗中添加抗程序性细胞死亡蛋白 1(PD-1)或程序性细胞死亡配体(PD-L1)的作用。此外,在辅助治疗中,目前正在进行Ⅲ期试验 ATTRACTION-5(NCT03006705),研究用替吉奥或卡培他滨加奥沙利铂联合纳武利尤单抗的标准辅助化疗方式,用于接受 D2 或更广泛的淋巴结清扫术后病理学证实的Ⅲ期胃癌(包括食管胃连接部癌)的患者[34]。

6　MSI 胃癌的免疫治疗进展

近年来,免疫治疗为肿瘤治疗的研究热点。MSI 已被证明是预测免疫检查点抑制剂(ICI)预后和反应的生物标志物,这可能是因为 MSI-H 更偏好于表达一些容易被免疫系统识别的新抗原[35]。MSI-H 状态的肿瘤也会吸引更多的免疫细胞浸润从而增强 ICI 的作用。因此,MSI 胃癌的群体有望从临床免疫治疗中获益[36]。PD-1 或 PD-L1 表达、肿瘤突变负荷(TMB)、MSI-H 常作为指导 ICI 疗法临床应用的预测性生物标志物,其中 MSI-H 具有独特的优势,MSI-H 的肿瘤尤其对 PD-1 和 PD-L1 抑制剂敏感。许多获批的免疫疗法抑制 PD-1/PD-L1 相互作用,以刺激针对癌细胞的免疫应答[37]。根据之前的研究,在 MSI-H 肿瘤中,免疫治疗的反应率因肿瘤类型而异,头颈癌的反应率为 15%,胃癌为 57%~86%[35]。此外,大多数胃癌对 ICI 单药治疗不敏感,因此胃癌患者可能需要联合治疗以改善对抗 PD-1 治疗或其他 ICI 的反应[38]。一项回顾性研究还显示,在晚期 MSI 胃癌患者中,免疫治疗联合化疗比单独免疫治疗实现了更高的客观缓解率(ORR)(61.5% *vs* 25.0%)[21]。相关研究指出肿瘤患者在接受新辅助免疫治疗后,能更好地诱导免疫记忆的早期形成,加强 T 细胞对肿瘤抗原的免疫应答,这些机制会加强机体的抗肿瘤能力并且有助于根除术后的微残留或微转移[39]。ICI 作为新辅助治疗 MSI/dMMR 肿瘤时,可使潜在可切除肿瘤获得较高的病理缓解率,并最终提供治愈肿瘤的机会,无论手术与否。目前有几项Ⅱ期研究正在探索 ICI 在 MSI 肿瘤特别是胃癌的新辅助/辅助环境中的应用(NCT04006262、NCT04817826 和 NCT04152889)[40]。

帕博利珠单抗是一种人源化小鼠来源的抗 PD-1 抗体,通过与 T 细胞 PD-1 受体结合并破坏肿瘤细胞上 PD-L1 分子的相互作用来促进肿瘤细胞凋亡[37]。最近 FDA 批准了帕博利珠单抗用于治疗不可切除或转移性 dMMR/MSI-H 肿瘤的患者,且无论肿瘤类型如何[41]。在既往化疗进展后的 MSI-H 肿瘤患者中帕博利珠单抗也取得了显著效果[6]。有研究表明,帕博利珠单抗可作为 MSI-H 或高肿瘤突变负荷(TMB-high,TMB-H)患者的二线或后续治疗[42]。而一些关于 MSI-H 肿瘤患者的报道表明,MSI-H 与 TMB-H 之间没有明显的关联。KEYNOTE-061 和 KEYNOTE-062 试验的结果表明,MSI-H 的肿瘤患者在接受帕博利珠单抗治疗后 ORR 分别为 47%、57%,具有更好的临床结局[34]。

在最近的 CheckMate-649 试验中,晚期胃癌使用纳武利尤单抗联合化疗与单独化疗相比具有更好的中位 OS(14.4 个月 *vs* 11.1 个月,*HR*=0.70,*P*<0.01)和中位 PFS(7.7 个月 *vs* 6.0 个月,*HR*=0.68,*P*<0.01)。且 MSI-H 肿瘤患者的生存获益程度更大[43]。根据该结果,FDA 批准在标准化疗中加入纳武利尤单抗作为晚期胃癌患者的一线治疗,无论 PD-L1 联合阳性评分(combined positive score, CPS)如何,但 NCCN 指南建议将其作为 PD-L1 CPS≥5 患者的首选方案[11]。抗细胞毒性 T 淋巴细胞相关蛋白 4(CTLA-4)抑制剂可潜在地用于活化 T 细胞并杀死肿瘤细胞。伊匹木单抗作为抗 CTLA-4 抗体,联合化疗使用时,dMMR 胃癌 ORR 为 57%,95%*CI*:18%~90%。而联合纳武利尤单抗使用时,dMMR 胃癌高度有效(ORR 为 70%,95%*CI*:35%~93%)[44]。此外,GERCOR NEONIPIGA 研究显示,在新辅助治疗中使用纳武利尤单抗联合伊匹木单抗治疗时,MSI 胃癌患者的病理完全缓解率为 58.6%(17/29)[45]。

恩伐福利单抗是人源化骆驼来源的单域抗 PD-L1 抗体,相比全单克隆抗体更易溶和稳定,能更快地穿透组织。作为首个通过快速皮下注射给药的单域 PD-L1 靶向抗体,给药时间不到 30 s,可避免输注反应,有望成为癌症治疗的一线药物[46]。尽管抗 PD-1 治疗总体上有良好的结果,但 dMMR/MSI-H 亚组的 ORR 仍在 40%~60%的范围内,这表明相当一部分人有内在耐药性[47]。

然而随着免疫治疗的发展,许多接受 ICI 的患者表现出耐药性。揭示对 ICI 反应的分子决定因素可能有助于开发新的

生物标志物或联合疗法来克服 MSI-H/dMMR 肿瘤对这些药物的抗性。有研究表明,在 PI3K-AKT-mTOR 途径中较高的突变基因数量可能是 MSI-H/dMMR 胃腺癌免疫逃避和免疫治疗原发性耐药的机制之一[48]。MSI-H/dMMR 引起的 β-2 微球蛋白基因突变还可导致Ⅰ类人白细胞抗原介导的抗原呈递丢失,损害细胞毒性 $CD8^+$T 细胞对肿瘤细胞的识别,从而导致对 ICI 的获得性耐药性[49]。MSI-H/dMMR 胃肠道肿瘤中的 ICI 耐药性可以通过靶向 Wnt/β-连环蛋白途径来克服[50]。在关于晚期 MSI-H 胃癌帕博利珠单抗的Ⅱ期临床试验中,无应答者在 Wnt/β-连环蛋白途径中有频繁的突变,并有大量与癌症相关的成纤维细胞。这些发现可能有助于 MSI-H/dMMR 晚期胃癌的 ICI 联合治疗的发展[51]。

在使用 ICI 治疗后,MSI-H 胃癌患者与 MSS/MSI-L 病例相比,显示出相对改善的长期存活率[52],这可能是因为,MMR 基因的改变导致肿瘤细胞产生异常的肿瘤特异性肽,这些肽在肿瘤中招募淋巴细胞并诱导免疫反应。但由于胃癌中 MSI 表型的总体频率较低,ICI 在 MSI 胃癌治疗中的作用仍然不如结直肠癌试验中获得的成功结果。

7　结　论

MSI 胃癌在临床病理特征及诊疗等方面具有其独特的一面。MSI-H 胃癌患者相较于 MSS/MSI-L 胃癌患者预后较好,但往往不能从新辅助化疗中获益。而 MSI-H 胃癌患者因其体内独特的免疫微环境等因素似乎在接受免疫治疗后更能获得良好的结果。因此,对胃癌患者进行 MS 状态的评估有助于判断患者预后和指导治疗。期待未来以更大样本的数据对 MSI 胃癌进行相关研究,以更好地验证其生物学特征,并制定系统的诊疗标准,对 MSI 患者人群提供个体化的诊疗方针。

利益冲突　无

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