Advances in Clinical Medicine 临床医学进展, 2025, 15(8), 735-746
Published Online August 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1582291

Hans汉斯

胃肠间质瘤的诊疗进展与现状

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收稿日期：2025年7月9日；录用日期：2025年8月1日；发布日期：2025年8月13日

摘　要

胃肠间质瘤(GIST)是消化道最常见的间叶源性肿瘤。近年来，随着分子生物学和影像学技术的快速发展，对GIST的诊断方法、外科治疗策略及靶向药物治疗等领域取得了显著进展。本文通过系统回顾国内外相关文献，从流行病学特征、临床诊断技术、外科治疗以及靶向治疗新策略等方面，对GIST的研究现状及进展进行综述。

关键词

胃肠间质瘤，诊断，治疗

Progress and Current Status of Diagnosis and Treatment of Gastrointestinal Stromal Tumor

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Received: Jul. 9th, 2025; accepted: Aug. 1st, 2025; published: Aug. 13th, 2025

Abstract

Gastrointestinal stromal tumor is the most common mesenchymal tumors of the digestive tract. Gastrointestinal stromal tumor is the most common mesenchymal tumors of the digestive tract. In recent years, with the rapid development of molecular biology and imaging technology, remarkable progress has been made in the fields of diagnostic methods, surgical treatment strategies and targeted drug therapy for GIST. This article reviews the relevant literature at home and abroad, and

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文章引用: 李俊昱, 涂利文, 饶仕晗, 李佳聪, 曾祥福. 胃肠间质瘤的诊疗进展与现状[J]. 临床医学进展, 2025, 15(8): 735-746. DOI: 10.12677/acm.2025.1582291

reviews the research status and progress of GIST from the aspects of epidemiological characteristics, clinical diagnostic techniques, surgical treatment, and new strategies of targeted therapy.

Keywords

Gastrointestinal Stromal Tumor, Diagnosis, Therapy

1. 引言

胃肠间质瘤(gastrointestinal stromal tumor, GIST)作为消化道最常见的间叶源性肿瘤，占胃肠道恶性肿瘤的1%~3% [1]，该肿瘤概念由Mazur等[2]于1983年通过电镜观察和免疫组化研究首次提出。其诊疗领域在过去数十年经历了革命性变革，GIST已从缺乏有效治疗手段的难治性肿瘤转变为实体瘤靶向治疗的典范。现就胃肠间质瘤的流行病学、发病机制、诊断及治疗方面进行综述。

2. 流行病学

胃肠间质瘤是消化道最常见的间叶源性肿瘤，可发生在胃肠道的任何部位，绝大多数发生在胃(50%~70%)，其次小肠(25%~35%)、结直肠(5%~10%)，食道(<1%)，另有约5%的病例发生于胃肠道外(如肠系膜、网膜等) [3] [4]。流行病学数据显示，GIST占全部胃肠道恶性肿瘤的1%~3%，年发病率约为(11~14.5)/100万[5]。值得注意的是，近年来随着诊断技术的进步和认识水平的提高，GIST的临床检出率呈现上升趋势，其发病年龄主要集中在50~70岁的中老年人群，性别分布无显著差异[6]。

3. 发病机制

1998年Hirota等学者的里程碑式研究发现GIST可能起源于调控胃肠道蠕动的Cajal间质细胞(ICC)，这一发现为理解GIST的生物学特性奠定了基础[7]。现代分子生物学研究证实，约80%的GIST病例存在c-kit基因功能获得性突变，其中最常见的是外显子11突变，这种突变导致KIT受体酪氨酸激酶持续活化，从而促进肿瘤细胞异常增殖；另有约10%的病例由血小板衍生生长因子受体α(PDGFRA)基因突变驱动，主要集中在外显子18区域[8]-[12]。值得注意的是，约10%的GIST为野生型，既不携带c-kit也不存在PDGFRA基因突变，其中42%与琥珀酸脱氢酶(SDH)复合体功能缺陷相关[13] [14]。近年来，随着分子检测技术的发展，在野生型GIST中还发现了V600E BRA或NF1等罕见突变[15] [16]。这些分子机制的阐明不仅解释了GIST的发病基础，也为靶向治疗提供了关键的理论依据，推动了个体化精准医疗的发展。

4. 诊断

4.1. 临床表现

胃肠间质瘤(GIST)的临床表现具有显著的异质性和渐进性特征，其临床症状主要取决于肿瘤的解剖学特点和生物学行为。根据肿瘤与胃肠道管壁之间的关系，分为壁间型(I型)、内生型(II型)、外生型(III型)及哑铃型(IV型)这四种生长类型，各型呈现特征性临床表现[17]。早期GIST (直径 <2 cm)多无明显症状，常在影像学检查或消化内镜检查中偶然发现。随着肿瘤进展，患者可出现：① 压迫症状：包括腹痛、

腹胀及消化道梗阻等表现；② 出血表现：从隐匿性出血(黑便、贫血)进展到肿瘤破溃时的急性大出血(呕血、便血)；③ 急腹症：主要由肿瘤破裂或扭转引起[18]。GIST 最常见于肝脏和腹膜转移，有器官转移者可出现转移器官的相应临床表现。这些临床表现的演变规律为 GIST 的早期识别和临床评估提供了重要依据。

4.2. 影像学检查

影像学检查在 GIST 的诊断与鉴别诊断、术前定位、周围器官侵犯、危险度分级、播散转移、术前靶向治疗效果监测以及复发等方面起着至关重要的作用。2024CSCO 胃肠间质瘤诊疗指南指出 CT 是 GIST 首选的影像学检查方式，能够对肿瘤边界、内部结构、肿瘤密度、肿瘤大小、生长方式以及对邻近器官侵犯情况等清晰显示[19]。临床上在对可疑 GIST 的患者进行 CT 检查时，通常会选择在 CT 平扫基础上增强扫描，通过造影剂产生血管强化，从而更加清晰的观察肿瘤的形态、生长方式等特征，GIST 的 CT 表现与生物学行为及恶性程度存在一定的相关性，掌握其特征对于 GIST 的诊断、治疗及预后评价具有重要意义[20]，CT 成像还可为术前靶向治疗的疗效评估提供帮助[21]。然而 CT 在应用中也存在一定的局限性，CT 无法区分炎性粘连和邻近器官受累，在胃 GIST 的情况下，很难确定肿瘤原发部位，特别是在肛门直肠间质瘤，其周围生理结构较多，又涉及到肛门功能保留的问题，在无法判断肿瘤与周围组织是否能手术中完整剥离时可行 MRI 检查[22] [23]。2024CSCO 胃肠间质瘤诊疗指南也推荐 MRI 作为 CT 增强扫描禁忌或怀疑肝转移时进一步检查的手段，且作为直肠 GIST 的首选检查方法。因此直肠间质瘤 MRI 检查是非常有必要的，甚至还要在直肠 MRI 平扫的基础上加做增强，以协助判断肿瘤病变在肠壁浸润程度。随着科学技术的发展，PET-CT 在临床上使用越来越广泛，近些年 PET-CT 也越来越多地用于 GIST 的初步诊断、肿瘤分期、疗效评价、复发和转移监测。PET-CT 是通过静脉注射放射性示踪剂来反映细胞对葡萄糖类似物的代谢特征，从而提供有关组织代谢的信息。这些放射性示踪剂能够在组织高代谢的地方浓聚，提供患者可疑的转移灶所在。Ahmed M 表示 PET-CT 不仅是 GIST 分期的理想检查，也是评估治疗反应、评估对治疗的原发性和继发性耐药以及解决临床状态和 CT 结果之间差异结果的理想检查[24]。但是 PET-CT 不仅检查费用昂贵且需要注射放射性示踪剂，受限于卫生经济学因素，因此临床上在评估 GIST 时并不常规使用。

GIST 绝大多数来源于胃肠道，起源于胃肠道外的 GIST 较为罕见占比约 5%，因此消化内镜的检查对 GIST 的早期诊断及治疗有非常重要的意义。目前临床上常用的消化内镜技术包括电子胃镜、电子结肠镜、胶囊内镜及超声内镜(endoscopic ultrasound, EUS)等。普通的胃肠镜仅可用于检查胃肠道黏膜下肿物且肿物需向腔内生长，对黏膜下肿瘤和腔外压迫难以明确区分，而 EUS 检查很好的解决这样问题。超声内镜能够不被肠道积气的影响，通过超声探明肿瘤的肿瘤位置、大小、起源层次、肿瘤的回声特性、肿瘤边界等情况并可对肿瘤的恶性程度进行初步判断[25] [26]。就来源于胃壁黏膜下层及固有肌层的肿瘤而言，尤其是直径 ＜2 cm 的胃间质瘤，EUS 诊断的特异性和准确性受到一定限制。尽管 EUS 在诊断 GIST 上有一定的局限，但不可否认的是，EUS 作为一种无创检查方法，在协助治疗策略的制定和辅助进行有创检查等领域具有重要意义，特别是需行术前靶向治疗的 GIST，需病理明确肿瘤性质时。因此超声内镜被推荐作为 GIST 的首选检查方式[27] [28]。

4.3. 病理诊断

病理活组织检查及免疫组化是诊断 GIST 的金标准，免疫组化检测的指标有 CD117、CD34、DOG-1、S-100、Ki-67、Desminl 等，其中最重要的是前三项指标[29] [30]。GIST 的组织学类型包括梭形细胞型、上皮样型、上皮样－梭形细胞混合型、去分化型。其细胞形态是中高危险度 GIST 患者术后预后的影

响因素[31]。免疫组织化学检测是确诊的关键环节，CD117 (c-kit 蛋白)阳性率可达 70%~100%，KIT 突变的分子遗传学检测可以诊断 95%的 GIST，DOG1 表达率 80.5%~96%，两者联合检测可将诊断准确率提高[32]-[44]。目前，一代测序(Sanger 法)对 KIT、PDGFRA 突变型 GIST 诊断、分子分型、靶向治疗等的临床价值已基本足够，二代测序(NGS 法)主要用于野生型 GIST 的精准分类和临床研究。最新指南建议对中高危、不能手术、拟行靶向治疗、复发及转移性 GIST 进行分子检测，这对指导肿瘤的治疗及预后至关重要。这些病理诊断技术的进步显著提高了 GIST 的诊断精确性和治疗针对性。原发可切除 GIST 术后复发风险评估是指导患者术后靶向治疗的重要依据。目前我国所使用的 GIST 复发危险度分级标准以美国国立卫生研究院(National Institutes of Health, NIH) (2008 改良版)分级为主(见表 1)，该标准根据肿瘤大小、核分裂计数、肿瘤原发部位、肿瘤是否破裂，依次分为极低危、低危、中危、高危四个危险度等级；肿瘤直径越小、原发部位在胃、核分裂计数越少、无肿瘤破裂的 GIST 危险度越低[45] [46]。危险度评估具有中高危复发风险的患者作为术后辅助治疗的适应人群。

Table 1. Risk stratification for primary GIST following surgical resection (modified NIH 2008 criteria)
表 1. 原发 GIST 切除术后危险度分级(NIH 2008 改良版)

危险度分级	肿瘤大小(cm)	核分裂象计数(/50HPF)	肿瘤原发部位
极低	≤2	≤5	任何部位
低	2.1~5	≤5	任何部位
中等	2.1~5	6~10	胃
	<2	6~10	任何部位
	5.1~10	≤5	胃
高	任何	任何	肿瘤破裂
	>10	任何	任何部位
	任何	>10	任何部位
	>5	>5	任何部位
	>2 且≤5	>5	非胃原发
	>5 且≤10	≤5	非胃原发

5. 治疗

5.1. 手术治疗

目前 R0 切除是早期可切除 GIST 公认的最有效的根治性治疗方法。手术方式有内镜切除、开腹手术以及腹腔镜手术等。GIST 手术治疗基本原则包括：(1) 通过外科手术完整切除肿瘤并保证切缘阴性；(2) GIST 很少发生淋巴结转移，故不推荐常规淋巴结清扫。而对于年轻胃 GIST 病人，如术中发现淋巴结病理性肿大的情况，须考虑有 SDH 缺陷型野生型 GIST 的可能，应切除病变淋巴结[47]；(3) 术中注意保护肿瘤假性包膜完整，避免肿瘤破裂[48]。目前对于病理诊断的直径 <2 cm 的 GIST 治疗策略仍存在争议，CSCO 指南与 NCCN 指南针对直径 <2 cm 且无临床表现和超声胃镜不良征象的胃 GIST 建议通过超声内镜或 CT 定期随访观察；有临床表现及超声胃镜不良征象的胃 GIST 则建议手术切除[49]。然而 ESMO 指出 GIST 是具有可变临床行为的恶性间充质肿瘤，即使是直径 <2 cm 的肿瘤也建议手术切除。日本临床肿瘤学会也指出虽然没有报告显示手术对这些小 GIST 的有效性，但专家共识推荐对<2 cm 的胃小 GIST

进行手术切除[50]。生长于小肠、结直肠等部位的非胃小 GIST 其临床与预后特征明显有别于来源于胃的小 GIST，目前国内外相关指南均推荐予以手术切除。

GIST 的内镜下治疗包括内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)、内镜下全层切除术(endoscopic full-thickness resection, EFTR)、经黏膜下隧道内镜肿瘤切除术(submucosal tunneling endoscopic resection, STER)及腹腔镜和内镜联合术(laparoscopic and endoscopic cooperative surgery, LECS)等。ESD 主要适用于直径 ≥2 cm、并<5 cm，术前 EUS 或 CT 评估向腔内生长的 GIST；EFTR 主要适用于术前 EUS 和 CT 评估起源于固有肌层，并向浆膜外生长及 ESD 术中发现瘤体与浆膜层紧密粘连而无法分离的 GIST；STER 主要适用于食管(距咽部 3~5 cm 外)、贲门、胃大弯等易建立隧道部位的 GIST；LECS 通过实时腹腔镜监测显著提升较大 GIST 内镜切除的安全性且实现微小病灶的精准定位及靶向切除，腹腔镜和内镜两者协同显著优化了微创治疗效果[51]。大量研究显示，内镜下治疗 GIST 对比腹腔镜切除术具有手术时间短、术中失血少、胃肠道功能恢复快、住院时间短及费用低的优势，并且具有与腹腔镜相当的完全切除率、术后并发症发生率、复发率及无病生存率[52]-[55]。目前针对肿瘤直径 ＜2 cm 的 GIST，内镜手术已经逐渐成为多数医师及患者的首先选择。近年来国内外进行了多项关于胃间质瘤腹腔镜手术与开放手术的对比研究，相比于开腹手术，腹腔镜胃间质瘤切除术具有术中失血量少、胃肠道功能恢复快、住院时间短、术后并发症发生率低等优点[56]-[58]。现有临床证据表明大于 5 cm GIST 的腹腔镜手术与开放手术的结局，腹腔镜手术在短期结局如术中失血量、手术时间、住院时间和围手术期并发症等方面及长期结局如 5 年无病生存率和总生存期优于或等同于开放手术[59]-[61]。近年来，随着手术机器人技术的快速发展与成熟，多项临床研究证实其在 GIST 切除术中具有与腹腔镜手术相当的肿瘤学安全性，可以被认为是腹腔镜手术的肿瘤学安全替代方案[62] [63]。然而，对大于 8 cm 的 GIST，不一定推荐进行腹腔镜手术，因为没有足够的证据表明对于如此大的 GIST，腹腔镜手术结局会优于开放手术。对于>10 cm 的 GIST 以及怀疑不完全切除或术中肿瘤破裂的 GIST，建议进行术前新辅助伊马替尼治疗，一项在日本和韩国进行的前瞻性单臂 II 期研究，53 名 GIST ≥ 10 cm 的患者接受了为期 6~9 个月的伊马替尼新辅助治疗，没有行新辅助伊马替尼治疗的 R0 切除率预计为 70%，但在这项研究中，R0 切除率显著提高为 91% [64]。

5.2. 药物治疗

5.2.1. 术前新辅助治疗

虽然目前手术切除是原发性 GIST 的首选根治性治疗，但大量临床研究证实，术前评估预期肿瘤难以达到 R0 切除、特殊部位(如十二指肠、低位直肠、食管或食管－胃交界处等)和需联合脏器切除的 GIST，应考虑通过术前新辅助治疗有效缩小肿瘤体积，不仅可以降低了术中肿瘤破裂风险，而且能够最大限度保留重要脏器结构和功能，从而显著改善患者术后生活质量[65]-[72]。在直肠 GIST 的亚组分析中，新辅助伊马替尼组观察到较高的 R0 切除率趋势，范围为 85.3%~98.8%，而无新辅助治疗组的切除率范围为 74.4%~92.0%，直肠 GIST 受益于新辅助伊马替尼在肿瘤缩小和 R0 切除方面的成就。尽管新辅助伊马替尼在无病生存期方面没有显著优势，但接受新辅助伊马替尼联合手术的直肠 GIST 患者总生存期优于接受前期手术的患者[73]。目前 NCCN、CSCO 等各大指南推荐进行甲磺酸伊马替尼术前新辅助治疗的初始剂量为 400 mg/d，每 2~3 月进行影像学检查，对于术前辅助治疗时间目前尚没有统一标准，一般认为术前给予伊马替尼治疗 6 个月左右比较适宜。基因检测指导下的精准新辅助治疗策略对特定基因亚型的胃肠间质瘤至关重要。现有证据表明，SDH 缺陷型、KRAS 突变型、BRAF 突变型、NF1 突变型以及 TRK 融合型 GIST 可能无法从伊马替尼治疗中获益[74]-[79]。因此，在新辅助治疗开始前，须行病理活检明确诊断，并推荐行基因检测，检测结果将直接影响治疗方案选择，如 SDH 缺陷型 GIST 可选择舒尼替尼，

而 TRK 融合型 GIST 则可考虑拉罗替尼等靶向药物。

5.2.2. 术后辅助治疗

R0 切除是 GIST 公认的最有效的根治性治疗方法，然而，在靶向治疗药物问世之前，即使接受了 R0 手术切除其预后仍不理想，术后多数患者会出现复发、转移，尤其是中高危患者。目前伊马替尼用于 GIST 术后辅助治疗的疗效已经得到公认，但是临床上对于术后伊马替尼辅助治疗的时限尚存在争议。研究发现，相比于术后应用伊马替尼辅助治疗 12 个月的高危患者，术后辅助治疗 36 个月的高危患者能够获得更高的无复发生存期和总生存期[80] [81]。中国 CSCO 指南推荐伊替尼术后辅助治疗的剂量为 400 mg/d，对于中度危险的 GIST 患者，术后伊马替尼辅助治疗时间不少于 1 年，高度危险的 GIST 患者，术后辅助治疗不少于 3 年，如果术中发生了肿瘤破裂，应延长伊马替尼辅助治疗时间。目前有一项前瞻性研究表明高危患者术后辅助治疗 5 年可以获得更高的无进展生存期，建议高危 GIST 患者接受伊马替尼治疗至少 5 年[82]。目前正在进行中的 PERSIST-5 和 SSGXVIII/AIO 这两项关键临床研究旨在评估延长伊马替尼辅助治疗时限对高危 GIST 患者的疗效差异，其研究结果将为临床实践中辅助治疗最佳持续时间的确定提供高级别循证医学证据[80] [83]。

5.2.3. 复发、转移 GIST 的药物治疗

在靶向药物问世前，手术是复发转移性 GIST 的主要治疗手段，但随着研究的深入，以伊马替尼为代表的靶向治疗已成为当前标准治疗方案，我国推荐初始剂量 400 mg/d。对于胃肠道间质瘤(GIST)的靶向治疗选择，需根据分子分型进行个体化治疗。KIT 外显子 9 突变对标准剂量伊马替尼治疗不敏感，中国患者推荐使用高剂量伊马替尼 600 mg/d，EORTC-ISG-AGITGy 和 S0033 研究表示对于耐受性好的患者特别是西方国家患者可考虑增加至 800 mg/d，交叉使用高剂量伊马替尼是可行且安全的[84]-[87]，而 PDGFRA D842V 突变患者则首选阿伐替尼，一项临床研究显示阿伐替尼治疗 PDGFRA D842V 突变转移性 GIST 的客观缓解率达到 91% [88]；对于 NTRK 融合患者，可选择拉罗替尼或恩曲替尼治疗，两项研究分别评估拉罗替尼与恩曲替尼治疗 NTRK 融合 GIST 患者的疗效，入组的大部分患者显示持续肿瘤退缩[89] [90]。在伊马替尼治疗后确诊进展或罕见不耐受的情况下，治疗策略需相应调整，可换用舒尼替尼，NCT00075218 研究证明对于伊马替尼治疗失败患者舒尼替尼在延长无进展生存期方面有效[91]。该药物遵循服药“4 周/停药 2 周方案”，剂量为 50 mg/d，但基于中国患者的耐受性，优先推荐 37.5 mg/d 的持续给药模式[92]。但 INTRIGUE 研究发现在 KIT 外显子 11 突变人群中，瑞派替尼的客观缓解率高于舒尼替尼，所以 KIT 外显子 11 突变则换用瑞派替尼[93]；在确认舒尼替尼治疗进展后，一项多中心、随机试、安慰剂对照试验证明，瑞戈非尼剂量为每 160 mg/d，每 4 周为 1 个周期，服药 3 周停药 1 周，可延长无进展生存期。因此，对于伊马替尼和舒尼替尼治疗期间未能从中受益的患者，瑞戈非尼是标准的三线治疗药物[94]；INVICTUS 研究表明在接受伊马替尼、舒尼替尼和瑞戈非尼治疗仍出现疾病进展患者使用瑞派替尼后可获益，瑞派替尼可作为四线治疗药物治疗复发转移性 GIST [95]。SDH 缺陷型 GIST 可合并淋巴结转移，完整手术切除仍是其主要治疗手段，同时建议术中行区域淋巴结清扫，CSCO 指南不推荐术后伊马替尼辅助治疗，有研究已经报道了舒尼替尼和瑞戈非尼的活性[96] [97]。目前尚缺乏针对复发转移性 SDH 缺陷型 GIST 的精准靶向药物，但临床研究表明抗血管生成物可能在一定程度上控制或延缓肿瘤进展[75]。

6. 当前挑战与未来展望

近年来，GIST 的诊疗虽已取得显著进展，但耐药性问题始终是临床治疗中的主要挑战。针对这一难题，深入研究耐药机制并加速新型药物研发势在必行。在生物免疫治疗领域，多项具有潜在临床应用价

值的研究正在同步推进，包括细胞因子治疗、免疫检查点抑制剂、抗 KIT 单克隆抗体、双特异性单克隆抗体以及细胞治疗等。值得注意的是，尽管免疫治疗研究热度持续攀升，但现有临床试验结果尚未取得突破性进展。展望未来，GIST 研究应重点聚焦以下几个方向：一是加快新型靶向药物的研发进程；二是构建人工智能辅助诊断系统并完善多学科协作诊疗模式；三是深入探索免疫联合治疗的临床应用潜力；四是制定机器人手术在复杂病例中的规范化应用标准。随着对 GIST 研究的不断深化，特别是耐药机制研究和基因检测技术的突破，我们有理由相信，GIST 治疗中面临的继发性耐药、手术时机选择等关键难题终将得到有效解决。

7. 结论

胃肠间质瘤(GIST)诊疗领域已建立起从分子诊断到精准治疗的完整体系，酪氨酸激酶抑制剂等靶向药物的临床应用显著改善了患者的无进展生存期和总生存期。目前，以根治性手术为核心、联合靶向药物的综合治疗模式已成为临床标准方案，基于基因检测的个体化用药策略进一步优化了治疗疗效。然而，GIST 的诊疗路径优化、继发耐药机制突破及免疫治疗应用等关键问题仍有待解决。随着现代精准医学的发展，GIST 诊疗已全面进入“全程化管理、个体化治疗”的新阶段，将为患者带来更长的生存获益和更好的生活质量。

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