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述评 EDITORIAL

胃肠道间质瘤的研究进展

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Advances in research of gastrointestinal stromal tumors

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Abstract
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, arising from the interstitial cells of Cajal (ICCs), primarily in the stomach and small intestine. The growth of most GISTs is driven by the mutations of genes encoding oncogenic receptor tyrosine kinase KIT or platelet derived growth factor receptor alpha (PDGFRα). The pathogenesis of GISTs may involve ICCs, microRNAs (miRNAs), signaling pathways, DNA methylation, and KIT or PDGFRα gene mutations. This article systematically describes the advances in research of GISTs in terms of clinical features, imaging characteristics, endoscopic features, histopathological features, diagnosis and therapies.

Key Words: Gastrointestinal stromal tumors; Pathogenesis; Diagnosis; Therapy

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摘要
胃肠道间质瘤(gastrointestinal stromal tumors, GISTs)是胃肠道最常见的间叶源性肿瘤, 起源于Cajal间质细胞(interstitial cells of Cajal, ICCs), 主要发生于胃和小肠. 大多数GISTs的生长由原癌基因受体酪氨酸激酶Kit或血小板衍生生长因子受体α(platelet derived growth factor receptor alpha, PDGFRα)突变所致. GISTs的发病机制可能涉及ICCs、microRNAs(miRNAs)、信号通路、DNA甲基化以及*Kit*或*PDGFRα*基因突变等因素. 此外, 本文还详尽阐述了GISTs的临床特征、影像学特征、内镜特征、组织病理学特征、诊断以及治疗领域的最新研究进展.

关键词: 胃肠道间质瘤; 发病机制; 诊断; 治疗

核心提示: 胃肠道间质瘤(gastrointestinal stromal tumors, GISTs)的发病机制可能涉及细胞起源、miRNAs、信号通路、DNA甲基化以及原癌基因受体酪氨酸激酶Kit或血小板衍生生长因子受体α(platelet derived growth factor receptor alpha)突变等因素. 免疫组织化学仍是GISTs的重要诊断工具, 内镜切除、腹腔镜切除、外科手术以及靶向药物伊马替尼为其主要的治疗方法.

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0 引言
胃肠道间质瘤(gastrointestinal stromal tumors,

■背景资料
胃肠道间质瘤(gastrointestinal stromal tumors, GISTs)是源于胃肠道的间叶源性肿瘤, 是一种独立的临床实体瘤, 曾一度被误认为平滑肌肿瘤或神经源性肿瘤. 1983年, Mazur和Clark等首次提出了GISTs的概念. 1998年, Hirota等证实了*Kit*(*CD117*)原癌基因活化突变对GISTs的致病作用, 随后GISTs被证实具有Cajal间质细胞的特性, 从而确定了GISTs的细胞起源. 2000年,分子靶向药物伊马替尼对进展期GISTs的试用成功, 预示着GISTs靶向治疗新时代的来临.

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伊马替尼作为GISTs新的辅助治疗药物,主要通过阻断GISTs信号传导、抑制GISTs增殖而达到治疗目的,因此一旦停用伊马替尼,GISTs是否会再次生长成为目前的研究热点之一.

GISTs)是胃肠道最常见的间叶源性肿瘤[1-3], 约占全部胃肠道肿瘤的1%-2%[2], 常发生于胃或小肠, 其他部位罕见[3], 而与其特征相似的胃肠道外间质瘤(extragastrointestinal stromal tumors, EGISTs)则十分罕见, 仅占GISTs的6%(9/142例)[4], 偶发生于脾脏[4]、胰腺[5]、前列腺[6]、精囊[7]、膀胱[8]、子宫[9]、直肠阴道隔膜[10]、外阴[11]、胸膜[12]、后腹膜[4]、网膜[13]、肠系膜[14]、阑尾系膜[15]、骨盆[4]及腹壁[16]等. 大约5%-15%的GISTs含有血小板衍生生长因子受体α(platelet derived growth factor receptor alpha, *PDGFRα*)基因活化突变[17,18], 55%-84%的GISTs含有*Kit*基因活化突变[18,19]. 此外, *DOG1*(discovered on GIST1)基因对GISTs的高度敏感性和特异性已使其成为新的诊断标志物[20,21]. 由于GISTs生物学行为的多样性, 依据临床和组织学特征很难区分侵袭性与非侵袭性病变, 故全部GISTs均被视为有恶性倾向[2], 其范围可从良性肿瘤中的微小病灶直至致命性的肉瘤[3]. 随着分子生物学、形态学、生物行为学的飞速发展以及内镜技术和分子靶向治疗的进步, GISTs的研究已取得巨大进展. 本文就此概述如下.

1 发病机制

1.1 GISTs的细胞起源 GISTs的细胞起源尚存争议[22-24]. Terada等[22]研究发现, GISTs起源于胃肠道平滑肌细胞和/或胃肠道干细胞. 但多数学者认为, GISTs起源于Cajal间质细胞(interstitial cells of Cajal, ICCs)或其干细胞前体[23,24], ICCs位于肠肌丛及环行肌黏膜下边缘, 是胃肠自发电慢波的起搏器和传导者, 对调控胃肠道蠕动与肠神经系统的协调一致至关重要, 而c-Kit作为一种跨膜糖蛋白则在ICCs的发育和成熟中起重要作用, ICCs网络的缺失或紊乱常导致胃肠动力疾病[25-27]. 但有些研究结果仍令人困惑. Deshpande等[28]发现, ICCs普遍存在于食管固有肌层的平滑肌瘤(leiomyomas, LMs)中, 偶尔也存在于胃和小肠的LMs中, 因此酷似GISTs而极易被误诊. Gromova等[29]发现, 神经降压素受体1在GISTs表达阳性, 而在ICCs则表达阴性, 其机制尚不清楚.

1.2 GISTs与microRNAs microRNAs(miRNAs)是一类小分子非编码RNA, 通过与靶基因序列的相互作用调控细胞增殖、分化和凋亡过程, miRNAs失调可能在GISTs的发生、发展中起重要作用[30]. Kelly等[31]研究证实, miRNAs的后转录调节异常涉及GISTs的发病机制. Yamamoto等[32]发现, miR-133b在高级别GISTs表达下调, 而肌成束蛋白-1(fascin-1)mRNA则表达上调, 提示fascin-1可能为miR-133b的直接靶点. fascin-1的超表达与GISTs的无病生存期缩短、肿瘤大小、有丝分裂计数、风险等级、血管侵袭以及黏膜溃疡等因素显著相关[32]. 此研究表明, miR-133b下调与fascin-1的超表达在GISTs的进程中可能起重要作用, fascin-1有望成为GISTs侵袭行为的有效生物标志物[32]. Koelz等[33]发现, miR-221、miR-222下调与Kit表达显著相关, 提示miR-221、miR-222可能通过调控Kit表达在GISTs的分子机制中发挥作用. 此外, Niinuma等[34]证实, miR-196a的超表达与GISTs的高风险等级、肿瘤转移以及低生存率密切相关, 提示miR-196a有望成为恶性GISTs的有效生物标志物及治疗靶点.

1.3 GISTs与信号通路 GISTs主要归因于Kit及PDGFRα的活化突变驱动, 但其他信号通路可能也参与其发病机制[35]. Gu等[35]发现, 胰岛素生长因子1(insulin-like growth factor 1, IGF1)的过度表达与GISTs的高风险行为显著相关, IGF1受体(IGF1 receptor, IGF1R)的过度表达也与IGF1的过度表达、高有丝分裂以及高风险行为显著相关. 提示IGF1和IGF1R可能是预测GISTs复发以及侵袭行为的有效标志物[35]. 但Lasota等[36]发现, IGF1R的阳性率仅为8%, 且基本局限于琥珀酸脱氢酶(succinate dehydrogenase, SDH)缺陷型的胃GISTs(89% IGF1R阳性). 提示IGF1R可作为SDH缺陷型GISTs的有效标志物[36]. 哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)是一种非典型丝氨酸/苏氨酸蛋白激酶, 可整合细胞外信号, 影响基因转录与蛋白质翻译, 从而参与调控细胞生长、增殖等过程[37]. Li等[37]发现, 不同风险等级的GISTs在其信号转导通路中的mTOR、p-mTOR存在差异性表达. 提示信号转导通路中的mTOR、p-mTOR在GISTs的发生、发展进程中起重要作用. Bravou等[38]证实, Notch信号通路与转化生长因子β(transforming growth factor β, TGF-β)信号通路具有协同作用, TGF-β/Smad信号通路可能参与GISTs的发病机制[38]. Notch信号通路是一种进化十分保守的信号传递机制, 作为启动或抑制因子在肿瘤进展中至关重要[39]. Dumont等[39]首次证实, Notch信号通路可通过Kit的负反馈机制对GISTs产生抑制作用.

1.4 GISTs与DNA甲基化 肿瘤的发生、发展受表观遗传修饰的影响, 负责真核细胞修饰的DNA甲基化是一种重要的表观遗传修饰方式,

DNA甲基化的异常在肿瘤的发生发展中至关重要[40]. 但表观遗传异常是否促进GISTs的侵袭仍不清楚[40]. Okamoto等[40]对GISTs的4种抑癌基因(*RASSF1A*、*p16*、*CDH1*、*MGMT*)的甲基化分析显示, *RASSF1A*基因的甲基化从小GISTs至恶性GISTs间逐渐增加, *p16*基因的甲基化在有恶性倾向的GISTs及恶性GISTs均特别显著, 甲基化CpG岛扩增微阵列(methylated CpG island amplification microarrays, MCAM)分析显示, 进展期GISTs的甲基化基因远多于小GISTs(平均473基因 *vs* 360基因, $P = 0.012$), 恶性GISTs的甲基化属性明显受其位置影响, 经MCAM分析新认定的2个基因*REC8*和*PAX3*的甲基化在小GISTs和恶性GISTs之间呈现差异性表达, 至少REC8、*PAX3*或*p16*甲基化的患者其预后显著变差($P = 0.034$). 此研究表明, DNA的甲基化异常与GISTs的侵袭性显著相关[40]. 此外, Mason等[41]研究发现, 90%(9/10例)的SDH缺陷型GISTs的5-羟甲基胞嘧啶(5-hydroxymethylcytosine, 5-hmC)染色阴性, 换言之, 几乎所有的SDH缺陷型GISTs不存在5-hmC. 此研究表明, SDH缺陷可能通过琥珀酸的积累和双加氧酶的抑制促进GISTs发生, 反过来, TET(ten-eleven translocation, 一个新的DNA修饰酶家族)蛋白的活性抑制可能改变SDH缺陷型GISTs的总DNA甲基化和基因表达[41].

1.5 GISTs与基因突变

1.5.1 Kit蛋白: Kit蛋白(CD117)是一种位于细胞膜上的受体酪氨酸激酶(receptor tyrosine kinase, RTK), 绝大多数GISTs细胞中存在Kit蛋白, 75%的GISTs是由于原癌基因*c-Kit*突变所致[23]. Kit蛋白属于第三型RTK家族, 由含有5个免疫球蛋白样结构域、1个跨膜结构域以及1个含有近膜结构域和酪氨酸激酶(tyrosine kinase, TK)结构域的胞质区构成, Kit复合体中偶极化的配体与受体结合后, 会导致受体的结构改变, 受体间D4-D4与D5-D5会产生相互作用[42], Kit受体酪氨酸激酶的结构受D4近膜结构域抗体的抑制[43]. TK结构域又分为三磷酸腺苷(adenosine triphosphate, ATP)结构域(TK1)和磷酸转移酶(phosphotransferase)结构域(TK2), 配体与胞外结构域结合形成二聚体, 胞质区TK结构域内酪氨酸磷酸化, 引发磷酸化级联反应, 激活Ras/MAPK、Rac/Rho-JNK、PI3K/AKT和SFK/STAT等多条信号网络[44]. Minárik等[45]对278例GISTs研究发现, 83.81%的患者发生基因突变, *c-kit*基因突变主要发生于外显子11(62.95%)、而较少发生于外显子9(8.27%)、外显子13(1.44%)、外显子17(0.00%), 此结果与Calibasi等[46]结论相似. 此外, Huss等[47]对1351例GISTs的*c-kit*基因突变研究显示, 仅有2例发生于外显子8(0.15%).

1.5.2 PDGFRα: 大约5%-15%的GISTs存在*PDGFRα*基因突变[17,18]. Minárik等[45]研究显示, *PDGFRα*基因突变发生于外显子18(7.55%)、外显子12(2.52%)、外显子14(1.08%). Bayraktar等[44]认为, 大多数*PDGFRα*基因突变影响TK2结构域(外显子18), 这些基因突变改变了正常的细胞激活通路, 活化的PDGFRα通过激活与活化的Kit相同的信号通路导致GISTs的发生. 染色体畸变在GISTs的发生中至关重要[18]. Schaefer等[18]对53例*PDGFRα*基因突变的GISTs研究显示, 外显子18突变(91%的病例)与胃GISTs显著相关, 外显子12突变(9%的病例)与肠GISTs显著相关. *PDGFRα*突变的染色体畸变率显著低于Kit突变的染色体畸变率, 仅2例进展期患者存在与中、高风险相关的染色体-9p、-13q、-22q畸变以及与低生存率相关的染色体-1p、+8q畸变[18].

1.5.3 *DOG-1*基因: 大约在80%-95%的GISTs中, Kit免疫组织化学染色阳性, 而其余5%-20%阴性, 对于Kit、CD34、S-100及SMA染色均为阴性者, 其诊断仍面临挑战, *DOG1*基因是一种膜通道蛋白, 在GISTs过度表达, 因DOG-1较Kit更具敏感性和特异性, 甚至在Kit阴性的GISTs中也呈阳性染色, 故已成为非常有效的GISTs分子标志物[20,21]. Wada等[20]研究证实, DOG-1是Kit阴性GISTs的有效诊断标志物. Wang等[48]对147例GISTs研究显示, 大约96%GISTs的DOG-1免疫组织化学染色阳性, 其特异性100%. 提示DOG-1是一种高敏感性、高特异性的生物标志物[48].

1.5.4 其他基因: 最近, O'Brien等[49]对279例GISTs研究显示, *CYP1B1*基因的单核苷酸多态性(single nucleotide polymorphisms, SNPs)与*Kit*基因外显子11密码子557-8缺失及野生型GISTs显著相关, 其他的一些潜在的风险基因还包括*GSTM1*、*RAD23B*、*ERCC2*[49]以及SDH[36,41].Wang等[48]发现, 90.5%GISTs的蛋白激酶C-θ(protein kinase C-θ, PKC-θ)染色阳性, 提示PKC-θ可能是一种有效的生物标志物, 尤其是CD117阴性和/或DOG-1阴性GISTs者. 此外, Corless等[23]认为, 大约15%的GISTs无Kit和*PDGFRA*基因突变, 即所谓的野生型GISTs, 其可能

■相关报道
国外研究证实, *DOG1*基因在大多数GISTs中过度表达, 且具有高度的敏感性和特异性, 甚至在KIT阴性的GISTs中也呈阳性染色, 故已成为具有良好应用前景的GISTs标志物.

■创新盘点
本文结合大量国外文献, 详尽阐述了GISTs的发病机制、诊断以及治疗领域的最新研究进展, 内容丰富, 观点新颖.

与多发性神经纤维瘤1型(neurofibromatosis type Ⅰ, *NF-Ⅰ*)基因、*RAS*基因、*BRAF*基因以及*SDH*基因突变有关.

2 流行病学

GISTs的年发病率约为6.5/1000000-14.5/1000000[50]. GISTs几乎可发生于胃肠道的任何部位, 依次为胃(50%-70%)、小肠(25%-35%)、结肠(5%-10%)及食管(<5%)[2]. GISTs患者的中位年龄为59岁(21岁-90岁), 男性占64.3%, 女性占35.7%, 69.9%的GISTs为局部病灶, 30.1%发生转移, 其中, 极低度风险者3.2%, 低度风险者16.1%, 中度风险者22.5%, 高度风险者47%, 不明风险者11.5%[51].

3 临床特征

大约70%的GISTs患者有症状, 20%无症状者是被偶然发现的, 10%则是在尸检中发现的, 症状无特异性, 多与肿瘤部位相关, 大多数有腹部不适(60%-70%)和消化系出血(30%-40%), 一些罕见的症状常与肿瘤的部位有关, 如食管GISTs引起吞咽困难, Vater壶腹周围GISTs致胆道梗阻, 小肠GISTs致肠套叠[52], 肛管GISTs致直肠出血、疼痛、排便习惯改变、梗阻或尿路刺激征等[53]. 淋巴结转移并不常见, 远处转移通常发生于GISTs患者的腹膜、网膜、肠系膜及肝脏等[52].

4 影像学特征

GISTs常被计算机断层扫描(computed tomography, CT)时偶然发现, 增强CT通常用于探查≥2 cm的GISTs, 尤其适用于伴腔外生长、坏死、出血及钙化者[54]. CT对监测GISTs的术后复发或转移有其重要价值[54,55]. Plumb等[55]对81例完整切除的GISTs患者CT随访时发现, 58%于1年内复发, 84%于3年内复发, 19例复发者均为高危人群, 其中12例(63%)为肝转移, 9例(47%)为网膜和肠系膜转移, 3/4者无症状[55], 此结论与Patnaik等[54]研究结果相似. 此外, Wong等[56]证实, 正电子发射断层扫描(positron emission tomography, PET)和CT联合应用对GISTs的罕见部位病灶、转移灶有其特殊诊断价值. Yoshikawa等[57]研究发现, PET/CT可预估GISTs的恶性倾向, 最大标准化摄取值(maximum standardized uptake value, SUVmax)>5的病例可能有恶性潜能.

5 内镜特征

无症状的小黏膜下肿瘤(small submucosal tumors, SMT)通常由内镜检查时偶然发现, 可遍及整个胃肠道, 多数表现为伴有光滑、完整及正常黏膜覆盖的隆起性病灶[58]. SMT包括胃肠道外的器官或病灶挤压、先天性肿瘤、炎症、良性或恶性肿瘤性病变等, 但应用普通内镜很难对GISTs做出确定诊断[58]. 超声内镜(endoscopic ultrasonography, EUS)及EUS引导下的细针抽吸活检(EUS-guided fine-needle aspiration, EUS-FNA)无疑对GISTs的诊断发挥关键作用[58,59]. Ito等[59]对23例GISTs患者研究发现, EUS的术前确诊率为91.7%, EUS-FNA的确诊率为84.6%, EUS-FNA活检病理诊断准确率为100%[59]. 双气囊小肠镜(double-balloon enteroscopy, DBE)和胶囊内镜(capsule endoscopy, CE)有助于诊断小肠疾病导致的胃肠道不明原因出血[60]. Nakatani等[60]研究显示, DBE、CE以及CT对小肠GISTs的检出率分别为 92%、60%和67%, 提示DBE或CE与CT联合应用有助于小肠GISTs的检测[60]. 谐波造影增强超声内镜(contrast-enhanced harmonic EUS, CH-EUS)是通过选择性描述来自超声造影剂的信号, 以评估微血管和器官实质灌注的一项全新技术[61]. CH-EUS可被用于评估GISTs的恶性倾向, 有助于区别良恶性淋巴结肿大[61]. Kannengiesser等[62]研究证实, CH-EUS可准确区分GISTs与其他黏膜下良性病灶. 若采取CH-EUS-FNA可能对GISTs更有诊断价值[62]. 对于内镜无法活检病灶, 可采用腹腔镜活检, 但有导致出血、穿孔及肿瘤腹膜种植风险[50].

6 组织病理学特征

Fülöp等[63]对79例GISTs的形态学研究显示, 67%为梭形细胞型肿瘤, 13%为上皮细胞型肿瘤, 9%为梭形细胞和上皮细胞混合型肿瘤, 39%的GISTs有细胞核的多形性, 而巨型多核细胞仅占9例, 54%的GISTs有炎性细胞浸润, 7例GISTs有转移灶, 其中3例为肝转移, 4例为淋巴结转移, 32%的GISTs有丝分裂活性升高(非典型有丝分裂指数>10个/50 HPF). 依据肿瘤大小、有丝分裂指数及肿瘤部位对GISTs恶性风险等级的分类标准[50], 7例(9%)GISTs为极低度恶性, 17例(21%)为低度恶性, 18例(23%)为中度恶性, 37例(47%)为高度恶性[63]. 免疫组织化学研究显示, 79例GISTs中77例CD117染色阳性, 仅2例阴性, 阳性率97%, 提示CD117对GISTs具有高度特异性, 50例CD34染色阳性, 29例阴性, 阳性率为63%, 19例SMA染色阳性, 余60例均阴性, 阳性率24%,

10例(13%)S100阳性, 87%阴性[63]. 此研究表明, 免疫组织化学仍是GISTs病理诊断的重要工具, 有助于与其他黏膜下肿瘤的鉴别诊断[63]. 对于c-Kit(CD117)染色阴性的GISTs, DOG-1染色具有高度敏感性和特异性, 可作为GISTs的诊断标志物[20,21]. 此外, Choi等[64]首次报道了1例直径30 cm的未分化小肠GISTs病例, 其细胞呈多形性, CD117和DOG-1染色均阴性, 此病例极为罕见, 诊断仍面临挑战.

7 治疗

7.1 内镜手术治疗 内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)常用于治疗2.0-5.0 cm的GISTs[65]. He等[65]对31例GISTs研究显示, ESD切除的肿瘤平均2.70 cm ± 0.72 cm(2.0-5.0 cm), 6例(19.35%)并发2-10 mm穿孔, 内镜下金属夹或尼龙绳修复, 3例(9.68%)术中出血, 采用亚离子凝固术或电凝止血, 24例(77.42%)为极低度风险, 7例(22.58%)为低度风险, CD117、DOG-1、CD34染色阳性率分别为 83.87%、12.90%、100%[65]. 此研究表明, ESD对GISTs的治疗安全、有效[65]. 根据肿瘤大小, 对源于胃固有肌层的GISTs通常采用内镜套扎切除术(endoscopic ligation and resection, ELR)、内镜黏膜下挖除术(endoscopic submucosal excavation, ESE)以及内镜全层切除术(endoscopic full-thickness resection, EFR)等3种治疗方式[66]. Huang等[66]研究显示, 38例<1.2 cm的GISTs采用ELR治疗, 3例并发穿孔, 金属夹修复, 18例>1.5 cm的GISTs采用ESE治疗, 未并发穿孔, 13例>2.0 cm的GISTs采用EFR治疗, 均并发穿孔, 采用金属夹修复, 提示对源于胃固有肌层的GISTs可采用内镜技术成功处理[66].

7.2 腹腔镜手术治疗 大多数的腹腔镜切除术仅限于治疗胃GISTs, 而对其他部位GISTs的切除效果仍不确切[50]. 但Chen等[67]研究发现, 腹腔镜切除<5.0 cm的胃及小肠GISTs均安全有效. Jeong等[68]证实, 腹腔镜切除>5.0 cm的胃GISTs也安全可行. 直肠GISTs在临床上罕见, 对于较大的直肠GISTs通常采取腹会阴联合切除治疗, 伊马替尼(imatinib)作为GISTs一种新的辅助治疗药物, 可以使瘤体明显缩小, 故有望避免扩大手术治疗[69]. Fujimoto等[69]对5例直肠GISTs患者于术前采用伊马替尼治疗, 致使瘤体由平均31 mm缩至24 mm, 然后再成功实施腹腔镜保肛手术. Fujimoto等[69]认为, 腹腔镜直肠GISTs保肛手术安全可行.

7.3 腹腔镜和内镜联合手术治疗(laparoscopic and endoscopic cooperative surgery, LECS) 因单独采用腹腔镜定位GISTs较为困难, 而内镜切除的缝合技术至今尚不成熟, 故LECS不失为一种处理GISTs的重要手段, LECS不仅可准确定位、及时处理穿孔, 还可以观察肿瘤是否切除完整、是否并发腔内出血、闭合是否严密以及闭合后是否导致胃腔狭窄等[70]. Qiu等[71]研究证实, LECS治疗胃GISTs具有微创、安全及可行性, 且预后良好. Dong等[70]对LECS进行改良后发现, 新型LECS对于GISTs是一种快速、优化、恢复迅速、安全有效的治疗方法.

7.4 外科手术治疗 对于>2.0 cm的原发局限性胃GISTs, 外科手术仍为首选, 且是目前取得临床治愈的最佳治疗方法, 一般采用局部切除或楔形切除, 对于<2.0 cm的胃GISTs, 若EUS示肿瘤不规则、囊性变、回声不均等高风险征象时, 应考虑手术治疗, 否则应EUS随访观察, 对于其他部位的可切除性GISTs, 手术也应为首选[23,72]. Schwameis等[72]研究发现, GISTs的外科手术完整切除率为85.2%, 而44.4%的未完整切除者以及6.6%的完整切除者最终死于GISTs, 其术后的复发率低于腹腔镜治疗(7.5% *vs* 23%). 此外, 对于有局部浸润或远端转移的GISTs, 应在可根治的前提下行联合脏器切除术[73]. Bauer等[74]发现, 转移灶完整切除的GISTs患者其长期生存率延长, 而未完整切除者(包括大块切除术患者)其生存率缩短.

7.5 分子靶向治疗 大多数GISTs的发生与Kit(75%)或PDGFRα(10%)的基因突变密切相关[23], 基因突变可引起受体酪氨酸激酶(Kit和PDGFRα)的自身磷酸化, 进而激活Ras/MAPK、Rac/Rho-JNK、PI3K/AKT和SFK/STAT等多条信号网络, 最终导致细胞增殖失控及凋亡受抑[23,44], 酪氨酸激酶抑制剂可以靶向作用于Kit和PDGFRα, 从而有效控制转移性或复发性GISTs[23]. 然而, *Kit*或*PDGFRα*基因二次突变导致的耐药几乎见于90%的GISTs患者[23]. 伊马替尼作为一种选择性Kit酪氨酸激酶抑制剂, 被认为是转移性GISTs的标准一线治疗药物, 而其他激酶抑制剂如舒尼替尼、瑞戈非尼则分别为二线、三线治疗药物[75]. 最近, 索拉非尼也被作为进展期GISTs的标准治疗药物[75]. 伊马替尼辅助治疗通常被用于降低初次手术后GISTs的复发可能性, 因此, 评估切除肿瘤的预后对病理学家

■应用要点

本文详尽阐述细胞起源、microRNAs、信号通路、DNA甲基化以及*KIT*和*PDGFRα*基因突变等因素对GISTs的致病作用, 重点阐述了GISTs在诊断和治疗领域的最新研究进展, 对于基础研究和临床工作有重要的指导意义.

■同行评价
本文结合大量新近文献, 对胃肠道间质瘤的发病机制、临床表现及治疗方法等方面进行了详细的综述. 尤其着重阐述了胃肠道间质瘤的分子生物学机制, 以及新近靶向治疗方面的内容, 对于临床工作具有重要指导意义.

极为重要[23]. Fujimoto等[69]研究发现, 采用伊马替尼的术前靶向治疗, 可显著缩小直肠GISTs的瘤体, 以增加腹腔镜保肛手术的成功率. Bamboat等[73]认为, 伊马替尼作为GISTs新的辅助治疗药物, 具有良好的安全性、耐受性和可行性. Bauer等[74]证实, 对于转移灶切除术的GISTs患者, 伊马替尼的辅助治疗, 有助于延长患者的长期生存率. 最近, Singeltary等[75]报道1例罕见的Kit外显子17突变的Ⅳ期直肠GISTs病例, 分别单独采用伊马替尼、舒尼替尼、瑞戈非尼及索拉非尼治疗, 病情持续进展, 后采用索拉非尼和伊马替尼联合治疗, 患者病情稳定接近2年, 提示靶向治疗药物的联合应用有助于减少耐药.

8 结论

*Kit*或*PDGFRα*基因突变在GISTs中的作用不仅有助于GISTs与其他黏膜下肿瘤的鉴别诊断, 也为其靶向治疗奠定了坚实的基础, 以伊马替尼为代表的靶向治疗显著提高了原发、转移或复发GISTs患者的生存率. 各种内镜及腹腔镜技术的日臻成熟, 即减轻了患者的手术创伤, 也缩短了住院时间, 值得推广. 外科手术仍是GISTs的一线治疗, 也是唯一可完全缓解原发GISTs的方法. 如何解决靶向治疗的耐药以及GISTs的复发或转移问题将是未来努力的方向, 前景值得期待.

9 参考文献

1 Miettinen M, Lasota J. Gastrointestinal stromal tumors. *Gastroenterol Clin North Am* 2013; 42: 399-415 [PMID: 23639648 DOI: 10.1016/j.gtc.2013.01.001]
2 Chandrasekhara V, Ginsberg GG. Endoscopic management of gastrointestinal stromal tumors. *Curr Gastroenterol Rep* 2011; 13: 532-539 [PMID: 21931997 DOI: 10.1007/s11894-011-0224-6]
3 Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumour. *Lancet* 2013; 382: 973-983 [PMID: 23623056 DOI: 10.1016/S0140-6736(13)60106-3]
4 Barros A, Linhares E, Valadão M, Gonçalves R, Vilhena B, Gil C, Ramos C. Extragastrointestinal stromal tumors (EGIST): a series of case reports. *Hepatogastroenterology* 2011; 58: 865-868 [PMID: 21830406]
5 Kim HH, Koh YS, Park EK, Seoung JS, Hur YH, Kim JC, Cho CK, Kim HJ. Primary extragastrointestinal stromal tumor arising in the pancreas: report of a case. *Surg Today* 2012; 42: 386-390 [PMID: 22258729 DOI: 10.1007/s00595-011-0080-x]
6 Ou Z, Cao Z, He Y, Tang D. Diagnosis and multimodal therapy for extragastrointestinal stromal tumor of the prostate: A case report. *Exp Ther Med* 2013; 6: 378-380 [PMID: 24137192 DOI: 10.3892/etm.2013.1156]
7 Song W, Yang JR, Wang YH, Liang QC. Primary extragastrointestinal stromal tumor of the seminal vesicles. *Urology* 2012; 79: e36-e37 [PMID: 22386441 DOI: 10.1016/j.urology.2011.11.026]
8 Shin HS, Cho CH, Kum YS. Extragastrointestinal stromal tumor of the urinary bladder: a case report. *Urol J* 2011; 8: 165-167 [PMID: 21656481]
9 Peitsidis P, Zarganis P, Trichia H, Vorgias G, Smith JR, Akrivos T. Extragastrointestinal stromal tumor mimicking a uterine tumor. A rare clinical entity. *Int J Gynecol Cancer* 2008; 18: 1115-1118 [PMID: 17986244 DOI: 10.1111/j.1525-1438.2007.01121.x]
10 Muñoz M, Echeverri C, Ramirez PT, Echeverri L, Pareja LR. Extragastrointestinal stromal tumor in the rectovaginal septum in an adolescent. *Gynecol Oncol Case Rep* 2013; 5: 67-69 [PMID: 24371702 DOI: 10.1016/j.gynor.2013.05.004]
11 Fukuda T, Sumi T, Nakano Y, Morishita M, Nobeyama H, Yoshida H, Matsumoto Y, Yasui T, Honda KI, Ishiko O. Extragastrointestinal stromal tumor originating from the vulva. *Oncol Lett* 2011; 2: 797-799 [PMID: 22866129 DOI: 10.3892/ol.2011.343]
12 Yi JH, Sim J, Park BB, Lee YY, Jung WS, Jang HJ, Ha TK, Paik SS. The primary extra-gastrointestinal stromal tumor of pleura: a case report and a literature review. *Jpn J Clin Oncol* 2013; 43: 1269-1272 [PMID: 24168806 DOI: 10.1093/jjco/hyt158]
13 Divakaran J, Chander B. Primary extra-gastrointestinal stromal tumor of the omentum. *J Cancer Res Ther* 2012; 8: 433-435 [PMID: 23174729 DOI: 10.4103/0973-1482.103527]
14 Li H, Li J, Li X, Kang Y, Wei Q. An unexpected but interesting response to a novel therapy for malignant extragastrointestinal stromal tumor of the mesoileum: a case report and review of the literature. *World J Surg Oncol* 2013; 11: 174 [PMID: 23915013 DOI: 10.1186/1477-7819-11-174]
15 Li W, Cui Y, Ren G, Wang J, Wu X. Extragastrointestinal stromal tumor of the mesoappendix: CT findings and a review of the literature. *World J Surg Oncol* 2012; 10: 211 [PMID: 23039908 DOI: 10.1186/1477-7819-10-211]
16 Alkhatib L, Albtoush O, Bataineh N, Gharaibeh K, Matalka I, Tokuda Y. Extragastrointestinal Stromal Tumor (EGIST) in the abdominal wall: Case report and literature review. *Int J Surg Case Rep* 2011; 2: 253-255 [PMID: 22096744 DOI: 10.1016/j.ijscr.2011.07.009]
17 Palmirotta R, De Marchis ML, Ludovici G, Leone B, Covello R, Conti S, Costarelli L, Della-Morte D, Ferroni P, Roselli M, Guadagni F. Mutational analysis of gastrointestinal stromal tumors (GISTs): procedural approach for diagnostic purposes. *Cancer Genomics Proteomics* 2013; 10: 115-123 [PMID: 23741027]
18 Schaefer IM, Delfs C, Cameron S, Gunawan B, Agaimy A, Ghadimi BM, Haller F. Chromosomal aberrations in primary PDGFRA-mutated gastrointestinal stromal tumors. *Hum Pathol* 2014; 45: 85-97 [PMID: 24157063 DOI: 10.1016/j.humpath.2013.05.027]
19 Fisher SB, Kim SC, Kooby DA, Cardona K, Russell MC, Delman KA, Staley CA, Maithel SK. Gastrointestinal stromal tumors: a single institution experience of 176 surgical patients. *Am Surg* 2013; 79: 657-665 [PMID: 23815996]
20 Wada T, Tanabe S, Ishido K, Higuchi K, Sasaki T, Katada C, Azuma M, Naruke A, Kim M, Koizumi W, Mikami T. DOG1 is useful for diagnosis of KIT-negative gastrointestinal stromal tumor of stomach. *World J Gastroenterol* 2013; 19: 9133-9136 [PMID:

24379641 DOI: 10.3748/wjg.v19.i47.9133]
21 Kara T, Serinsoz E, Arpaci RB, Gubur O, Orekici G, Ata A, Colak T, Arican A. Contribution of DOG1 expression to the diagnosis of gastrointestinal stromal tumors. *Pathol Res Pract* 2013; 209: 413-417 [PMID: 23722018 DOI: 10.1016/j.prp.2013.04.005]
22 Terada T. Smooth muscles and stem cells of embryonic guts express KIT, PDGFRRA, CD34 and many other stem cell antigens: suggestion that GIST arise from smooth muscles and gut stem cells. *Int J Clin Exp Pathol* 2013; 6: 1038-1045 [PMID: 23696920]
23 Corless CL. Gastrointestinal stromal tumors: what do we know now? *Mod Pathol* 2014; 27 Suppl 1: S1-16 [PMID: 24384849 DOI: 10.1038/modpathol.2013.173]
24 Beadling C, Patterson J, Justusson E, Nelson D, Pantaleo MA, Hornick JL, Chacón M, Corless CL, Heinrich MC. Gene expression of the IGF pathway family distinguishes subsets of gastrointestinal stromal tumors wild type for KIT and PDGFRA. *Cancer Med* 2013; 2: 21-31 [PMID: 24133624 DOI: 10.1002/cam4.57]
25 Huizinga JD, Chen JH. Interstitial cells of Cajal: update on basic and clinical science. *Curr Gastroenterol Rep* 2014; 16: 363 [PMID: 24408748 DOI: 10.1007/s11894-013-0363-z]
26 Abramovic M, Radenkovic G, Velickov A. Appearance of interstitial cells of Cajal in the human midgut. *Cell Tissue Res* 2014 Jan 11. *[Epub ahead of print]* [PMID: 24414177 DOI: 10.1007/s00441-013-1772-x]
27 Al-Sajee D, Huizinga JD. Interstitial Cells of Cajal: Pathology, injury and repair. *Sultan Qaboos Univ Med J* 2012; 12: 411-421 [PMID: 23275836]
28 Deshpande A, Nelson D, Corless CL, Deshpande V, O'Brien MJ. Leiomyoma of the gastrointestinal tract with interstitial cells of Cajal: a mimic of gastrointestinal stromal tumor. *Am J Surg Pathol* 2014; 38: 72-77 [PMID: 24145645 DOI: 10.1097/PAS.0b013e3182a0d134]
29 Gromova P, Rubin BP, Thys A, Erneux C, Vanderwinden JM. Neurotensin receptor 1 is expressed in gastrointestinal stromal tumors but not in interstitial cells of Cajal. *PLoS One* 2011; 6: e14710 [PMID: 21364741 DOI: 10.1371/journal.pone.0014710]
30 Kim WK, Yang HK, Kim H. MicroRNA involvement in gastrointestinal stromal tumor tumorigenesis. *Curr Pharm Des* 2013; 19: 1227-1235 [PMID: 23092343]
31 Kelly L, Bryan K, Kim SY, Janeway KA, Killian JK, Schildhaus HU, Miettinen M, Helman L, Meltzer PS, van de Rijn M, Debiec-Rychter M, O'Sullivan M. Post-transcriptional dysregulation by miRNAs is implicated in the pathogenesis of gastrointestinal stromal tumor [GIST]. *PLoS One* 2013; 8: e64102 [PMID: 23717541 DOI: 10.1371/journal.pone.0064102]
32 Yamamoto H, Kohashi K, Fujita A, Oda Y. Fascin-1 overexpression and miR-133b downregulation in the progression of gastrointestinal stromal tumor. *Mod Pathol* 2013; 26: 563-571 [PMID: 23196799 DOI: 10.1038/modpathol.2012.198]
33 Koelz M, Lense J, Wrba F, Scheffler M, Dienes HP, Odenthal M. Down-regulation of miR-221 and miR-222 correlates with pronounced Kit expression in gastrointestinal stromal tumors. *Int J Oncol* 2011; 38: 503-511 [PMID: 21132270 DOI: 10.3892/ijo.2010.857]
34 Niinuma T, Suzuki H, Nojima M, Nosho K, Yamamoto H, Takamaru H, Yamamoto E, Maruyama R, Nobuoka T, Miyazaki Y, Nishida T, Bamba T, Kanda T, Ajioka Y, Taguchi T, Okahara S, Takahashi H, Nishida Y, Hosokawa M, Hasegawa T, Tokino T, Hirata K, Imai K, Toyota M, Shinomura Y. Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors. *Cancer Res* 2012; 72: 1126-1136 [PMID: 22258453 DOI: 10.1158/0008-5472.CAN-11-1803]
35 Gu MJ, Bae YK, Choi JH. Clinical significance of insulin-growth factor 1 and insulin-growth factor 1 receptor expression in gastrointestinal stromal tumors. *Hepatogastroenterology* 2013; 60: 1383-1386 [PMID: 24298573]
36 Lasota J, Wang Z, Kim SY, Helman L, Miettinen M. Expression of the receptor for type i insulin-like growth factor (IGF1R) in gastrointestinal stromal tumors: an immunohistochemical study of 1078 cases with diagnostic and therapeutic implications. *Am J Surg Pathol* 2013; 37: 114-119 [PMID: 22892600 DOI: 10.1097/PAS.0b013e3182613c86]
37 Li JC, Zhu HY, Chen TX, Zou LY, Wang XY, Zhao HC, Xu J. Roles of mTOR and p-mTOR in gastrointestinal stromal tumors. *Asian Pac J Cancer Prev* 2013; 14: 5925-5928 [PMID: 24289602]
38 Bravou V, Papanastasopoulos P, Verras D, Kotsikogianni I, Damaskou V, Repanti M. Transforming growth factor β repressor, SnoN, is overexpressed in human gastrointestinal stromal tumors. *J BUON* 2012; 17: 684-690 [PMID: 23335525]
39 Dumont AG, Yang Y, Reynoso D, Katz D, Trent JC, Hughes DP. Anti-tumor effects of the Notch pathway in gastrointestinal stromal tumors. *Carcinogenesis* 2012; 33: 1674-1683 [PMID: 22764137 DOI: 10.1093/carcin/bgs221]
40 Okamoto Y, Sawaki A, Ito S, Nishida T, Takahashi T, Toyota M, Suzuki H, Shinomura Y, Takeuchi I, Shinjo K, An B, Ito H, Yamao K, Fujii M, Murakami H, Osada H, Kataoka H, Joh T, Sekido Y, Kondo Y. Aberrant DNA methylation associated with aggressiveness of gastrointestinal stromal tumour. *Gut* 2012; 61: 392-401 [PMID: 21708825 DOI: 10.1136/gut.2011.241034]
41 Mason EF, Hornick JL. Succinate dehydrogenase deficiency is associated with decreased 5-hydroxymethylcytosine production in gastrointestinal stromal tumors: implications for mechanisms of tumorigenesis. *Mod Pathol* 2013; 26: 1492-1497 [PMID: 23743927 DOI: 10.1038/modpathol.2013.86]
42 Opatowsky Y, Lax I, Tomé F, Bleichert F, Unger VM, Schlessinger J. Structure, domain organization, and different conformational states of stem cell factor-induced intact KIT dimers. *Proc Natl Acad Sci U S A* 2014; 111: 1772-1777 [PMID: 24449920 DOI: 10.1073/pnas.1323254111]
43 Reshetnyak AV, Nelson B, Shi X, Boggon TJ, Pavlenco A, Mandel-Bausch EM, Tome F, Suzuki Y, Sidhu SS, Lax I, Schlessinger J. Structural basis for KIT receptor tyrosine kinase inhibition by antibodies targeting the D4 membrane-proximal region. *Proc Natl Acad Sci U S A* 2013; 110: 17832-17837 [PMID: 24127596 DOI: 10.1073/pnas.1317118110]
44 Bayraktar UD, Bayraktar S, Rocha-Lima CM. Molecular basis and management of gastrointestinal stromal tumors. *World J Gastroenterol* 2010; 16: 2726-2734 [PMID: 20533592 DOI: 10.3748/wjg.v16.i22.2726]

45 Minárik G, Plank L, Lasabová Z, Szemes T, Burjanivová T, Szépe P, Buzalková V, Porubský D, Sufliarsky J. Spectrum of mutations in gastrointestinal stromal tumor patients - a population-based study from Slovakia. *APMIS* 2013; 121: 539-548 [PMID: 23106360 DOI: 10.1111/apm.12019]

46 Calibasi G, Baskin Y, Alyuruk H, Cavas L, Oztop I, Sagol O, Atila K, Ellidokuz H, Yilmaz U. Molecular analysis of the KIT gene in gastrointestinal stromal tumors with novel mutations. *Appl Immunohistochem Mol Morphol* 2014; 22: 37-45 [PMID: 23455185 DOI: 10.1097/PAI.0b013e318284a074]

47 Huss S, Künstlinger H, Wardelmann E, Kleine MA, Binot E, Merkelbach-Bruse S, Rüdiger T, Mittler J, Hartmann W, Büttner R, Schildhaus HU. A subset of gastrointestinal stromal tumors previously regarded as wild-type tumors carries somatic activating mutations in KIT exon 8 (p.D419del). *Mod Pathol* 2013; 26: 1004-1012 [PMID: 23599150 DOI: 10.1038/modpathol.2013.47]

48 Wang C, Jin MS, Zou YB, Gao JN, Li XB, Peng F, Wang HY, Wu ZD, Wang YP, Duan XM. Diagnostic significance of DOG-1 and PKC-θ expression and c-Kit/PDGFRA mutations in gastrointestinal stromal tumours. *Scand J Gastroenterol* 2013; 48: 1055-1065 [PMID: 23862765 DOI: 10.3109/00365521.2013.816770]

49 O'Brien KM, Orlow I, Antonescu CR, Ballman K, McCall L, DeMatteo R, Engel LS. Gastrointestinal stromal tumors, somatic mutations and candidate genetic risk variants. *PLoS One* 2013; 8: e62119 [PMID: 23637977 DOI: 10.1371/journal.pone.0062119]

50 Grover S, Ashley SW, Raut CP. Small intestine gastrointestinal stromal tumors. *Curr Opin Gastroenterol* 2012; 28: 113-123 [PMID: 22157511 DOI: 10.1097/MOG.0b013e32834ec154]

51 Selcukbiricik F, Yalçın S, Tural D, Erdamar S, Demir G, Doğusoy G, Mandel NM. Gastrointestinal stromal tumors in Turkey: experiences from 3 centers. *Onkologie* 2013; 36: 18-24 [PMID: 23429327 DOI: 10.1159/000346673]

52 Rammohan A, Sathyanesan J, Rajendran K, Pitchaimuthu A, Perumal SK, Srinivasan U, Ramasamy R, Palaniappan R, Govindan M. A gist of gastrointestinal stromal tumors: A review. *World J Gastrointest Oncol* 2013; 5: 102-112 [PMID: 23847717 DOI: 10.4251/wjgo.v5.i6.102]

53 Carvalho N, Albergaria D, Lebre R, Giria J, Fernandes V, Vidal H, Brito MJ. Anal canal gastrointestinal stromal tumors: case report and literature review. *World J Gastroenterol* 2014; 20: 319-322 [PMID: 24415888 DOI: 10.3748/wjg.v20.i1.319]

54 Patnaik S, Jyotsnarani Y, Rammurti S. Radiological features of metastatic gastrointestinal stromal tumors. *J Clin Imaging Sci* 2012; 2: 43 [PMID: 22919557 DOI: 10.4103/2156-7514.99177]

55 Plumb AA, Kochhar R, Leahy M, Taylor MB. Patterns of recurrence of gastrointestinal stromal tumour (GIST) following complete resection: implications for follow-up. *Clin Radiol* 2013; 68: 770-775 [PMID: 23663875 DOI: 10.1016/j.crad.2013.03.002]

56 Wong CS, Chu YC, Khong PL. Unusual features of gastrointestinal stromal tumor on PET/CT and CT imaging. *Clin Nucl Med* 2011; 36: e1-e7 [PMID: 21285671 DOI: 10.1097/RLU.0b013e31820aa233]

57 Yoshikawa K, Shimada M, Kurita N, Sato H, Iwata T, Morimoto S, Miyatani T, Kashihara H, Takasu C, Matsumoto N. The efficacy of PET-CT for predicting the malignant potential of gastrointestinal stromal tumors. *Surg Today* 2013; 43: 1162-1167 [PMID: 23143169 DOI: 10.1007/s00595-012-0411-6]

58 Nishida T, Kawai N, Yamaguchi S, Nishida Y. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. *Dig Endosc* 2013; 25: 479-489 [PMID: 23902569 DOI: 10.1111/den.12149]

59 Ito H, Inoue H, Ryozawa S, Ikeda H, Odaka N, Eleftheriadis N, Maselli R, Sando N, Kimura S, Kudo SE. Fine-needle aspiration biopsy and endoscopic ultrasound for pretreatment pathological diagnosis of gastric gastrointestinal stromal tumors. *Gastroenterol Res Pract* 2012; 2012: 139083 [PMID: 23056038 DOI: 10.1155/2012/139083]

60 Nakatani M, Fujiwara Y, Nagami Y, Sugimori S, Kameda N, Machida H, Okazaki H, Yamagami H, Tanigawa T, Watanabe K, Watanabe T, Tominaga K, Noda E, Maeda K, Ohsawa M, Wakasa K, Hirakawa K, Arakawa T. The usefulness of double-balloon enteroscopy in gastrointestinal stromal tumors of the small bowel with obscure gastrointestinal bleeding. *Intern Med* 2012; 51: 2675-2682 [PMID: 23037455]

61 Kitano M, Sakamoto H, Kudo M. Contrast-enhanced endoscopic ultrasound. *Dig Endosc* 2014; 26 Suppl 1: 79-85 [PMID: 24118242 DOI: 10.1111/den.12179]

62 Kannengiesser K, Mahlke R, Petersen F, Peters A, Ross M, Kucharzik T, Maaser C. Contrast-enhanced harmonic endoscopic ultrasound is able to discriminate benign submucosal lesions from gastrointestinal stromal tumors. *Scand J Gastroenterol* 2012; 47: 1515-1520 [PMID: 23148660 DOI: 10.3109/00365521.2012.729082]

63 Fülöp E, Marcu S, Borda A, Moldovan C, Fülöp EF, Loghin A, Pávai Z. Histopathological and immunohistochemical features of gastrointestinal stromal tumors. *Rom J Morphol Embryol* 2011; 52: 555-562 [PMID: 21655642]

64 Choi JJ, Sinada-Bottros L, Maker AV, Weisenberg E. Dedifferentiated gastrointestinal stromal tumor arising de novo from the small intestine. *Pathol Res Pract* 2014; 210: 264-266 [PMID: 24484970 DOI: 10.1016/j.prp.2013.12.008]

65 He Z, Sun C, Zheng Z, Yu Q, Wang T, Chen X, Cao H, Liu W, Wang B. Endoscopic submucosal dissection of large gastrointestinal stromal tumors in the esophagus and stomach. *J Gastroenterol Hepatol* 2013; 28: 262-267 [PMID: 23190047 DOI: 10.1111/jgh.12056]

66 Huang LY, Cui J, Liu YX, Wu CR, Yi DL. Endoscopic therapy for gastric stromal tumors originating from the muscularis propria. *World J Gastroenterol* 2012; 18: 3465-3471 [PMID: 22807618 DOI: 10.3748/wjg.v18.i26.3465]

67 Chen YH, Liu KH, Yeh CN, Hsu JT, Liu YY, Tsai CY, Chiu CT, Jan YY, Yeh TS. Laparoscopic resection of gastrointestinal stromal tumors: safe, efficient, and comparable oncologic outcomes. *J Laparoendosc Adv Surg Tech A* 2012; 22: 758-763 [PMID: 22957924 DOI: 10.1089/lap.2012.0115]

68 Jeong IH, Kim JH, Lee SR, Kim JH, Hwang JC, Shin SJ, Lee KM, Hur H, Han SU. Minimally invasive treatment of gastric gastrointestinal stromal tumors: laparoscopic and endoscopic approach. *Surg Laparosc Endosc Percutan Tech* 2012; 22: 244-250 [PMID:

22678321 DOI: 10.1097/SLE.0b013e31825078f2]
69 Fujimoto Y, Akiyoshi T, Konishi T, Nagayama S, Fukunaga Y, Ueno M. Laparoscopic sphincter-preserving surgery (intersphincteric resection) after neoadjuvant imatinib treatment for gastrointestinal stromal tumor (GIST) of the rectum. *Int J Colorectal Dis* 2014; 29: 111-116 [PMID: 24018650 DOI: 10.1007/s00384-013-1769-7]
70 Dong HY, Wang YL, Li J, Pang QP, Li GD, Jia XY. New-style laparoscopic and endoscopic cooperative surgery for gastric stromal tumors. *World J Gastroenterol* 2013; 19: 2550-2554 [PMID: 23674858 DOI: 10.3748/wjg.v19.i16.2550]
71 Qiu WQ, Zhuang J, Wang M, Liu H, Shen ZY, Xue HB, Shen L, Ge ZZ, Cao H. Minimally invasive treatment of laparoscopic and endoscopic cooperative surgery for patients with gastric gastrointestinal stromal tumors. *J Dig Dis* 2013; 14: 469-473 [PMID: 23701957 DOI: 10.1111/1751-2980.12076]
72 Schwameis K, Fochtmann A, Schwameis M, Asari R, Schur S, Köstler W, Birner P, Ba-Ssalamah A, Zacherl J, Wrba F, Brodowicz T, Schoppmann SF. Surgical treatment of GIST--an institutional experience of a high-volume center. *Int J Surg* 2013; 11: 801-806 [PMID: 23999064 DOI: 10.1016/j.ijsu.2013.08.016]
73 Bamboat ZM, DeMatteo RP. Metastasectomy for gastrointestinal stromal tumors. *J Surg Oncol* 2014; 109: 23-27 [PMID: 24155153 DOI: 10.1002/jso.23451]
74 Bauer S, Rutkowski P, Hohenberger P, Miceli R, Fumagalli E, Siedlecki JA, Nguyen BP, Kerst M, Fiore M, Nyckowski P, Hoiczyk M, Cats A, Casali PG, Treckmann J, van Coevorden F, Gronchi A. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib - Analysis of prognostic factors (EORTC-STBSG collaborative study). *Eur J Surg Oncol* 2014; 40: 412-419 [PMID: 24491288 DOI: 10.1016/j.ejso.2013.12.020]
75 Singeltary B, Ghose A, Sussman J, Choe K, Olowokure O. Durable response with a combination of imatinib and sorafenib in KIT exon 17 mutant gastrointestinal stromal tumor. *J Gastrointest Oncol* 2014; 5: E27-E29 [PMID:24490049 DOI: 10.3978/j.issn.2078-6891.2013.058]

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