·述评·

胃癌综合治疗策略与思考

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【摘要】 胃癌是一种致死率很高的恶性肿瘤，早期诊断困难且治疗效果受多因素影响。近年来，综合治疗模式（包括手术、化疗、放疗、靶向和免疫治疗）成为提升疗效的关键策略。综合治疗的优势主要体现在局部进展期和晚期胃癌患者中，其中局部进展期患者主要以手术为核心，围手术期应用多种治疗手段增加手术疗效；晚期患者则是以药物治疗为主，局部治疗手段为辅，争取最大程度获益。随着对胃癌发生发展分子机制的不断了解，应用分子标志物进行预后分层以及作为靶向或免疫药物的使用指导，成为综合治疗中非常重要的一环。笔者结合最新研究进展，探讨不同阶段胃癌的综合治疗策略，为提高疗效和改善预后提供思路。

【关键词】 胃肿瘤；　靶向治疗；　精准治疗；　联合治疗；　综合治疗

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Strategies and thoughts on comprehensive treatment of gastric cancer

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【Abstract】 Gastric cancer is a highly lethal malignant tumor, with early diagnosis being difficult and treatment outcomes influenced by multiple factors. In recent years, comprehensive treatment approach, incorporating surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, has significantly improved efficacy. The advantages of comprehensive treatment are most important in patients with locally advanced and metastatic gastric cancer. For locally advanced cases, surgery serves as the core treatment, with various therapeutic modalities applied during the perioperative period to enhance surgical outcomes. For metastatic patients, drug therapy is the primary method, supplemented by local treatments to achieve the best benefit. With the understanding of the molecular mechanisms underlying gastric cancer development, the use of molecular biomarkers for prognostic stratification and guidance for targeted therapy or immuno-therapy has become a crucial aspect of comprehensive treatment. Based on the latest research advancements, the authors discuss comprehensive treatment strategies for gastric cancer at different stages, offering insights into improving efficacy and prognosis.

【Key words】 Stomach neoplasms;　Targeted therapy　Precision treatment;　Combined therapy;　Comprehensive treatment

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胃癌是全世界第5大常见恶性肿瘤和第4大恶性肿瘤相关死亡原因，其临床治疗面临诸多挑战[1]。传统的治疗手段包括手术、放疗和化疗。由于胃癌的高度异质性、分子生物学特征的复杂性以及晚期诊断的高发率，单一疗法常无法满足临床需求。因此，综合治疗方案正成为胃癌治疗的新趋势[2]。新的治疗手段为胃癌患者提供了更多治疗选择。然而，如何合理制订个体化治疗方案、优化治疗流程，依然是胃癌治疗领域亟待解决的关键问题。因此，笔者探讨胃癌治疗领域中多种治疗方式的结合与协同作用，分析当前综合治疗在临床中的应用现状与挑战，并展望未来胃癌综合治疗的研究方向和潜力。

一、胃癌的分子生物学特征及精准检测

随着对胃癌分子生物学特征的不断深入研究，精准检测为个体化治疗提供了理论和实践依据。胃癌的分子分型，特别是基于癌症基因组图谱（the cancer genome atlas program，TCGA）的研究，揭示了胃癌的异质性。TCGA将胃癌划分为微卫星不稳定性（microsatellite instability，MSI）、染色体不稳定性、EB病毒阳性和基因组稳定性4种亚型。每种亚型具有不同的分子特征和临床表现以及对治疗的不同敏感性。

常见的基因变异如TP53、HER2、PIK3CA和MET等是胃癌发生和发展的关键。如人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）基因扩增对胃癌治疗至关重要，曲妥珠单克隆抗体等靶向治疗已成为标准治疗方案。MET基因扩增与转移及耐药性相关，靶向MET的治疗在临床试验中显示潜力。

目前，临床治疗中对一些分子特征的检测已成为决定治疗方案的重要依据。MSI和PD-L1表达水平的检测，对于筛选免疫治疗的获益患者至关重要：微卫星高度不稳定（microsatellite instability-high，MSI-H）患者对免疫治疗反应较好[3-4]；PD-L1高表达者可能受益于免疫治疗。HER2扩增患者可通过靶向HER2治疗获益[5-7]。Claudin18.2和FGFR2b等新靶点研究为胃癌靶向治疗提供新方向。高肿瘤突变负荷的胃癌患者可能对免疫治疗有较好反应。此外，还有更多的靶点正在研究中。常见胃癌分子分型与对应治疗方案详见表1。

随着分子生物学研究的进展，胃癌精准检测和精准治疗都取得显著进展。笔者预测：未来，随着新靶点和治疗手段的不断创新，胃癌患者的综合治疗前景将更加广阔。

二、胃癌的现代综合治疗模式

（一）综合治疗的概念与原则

胃癌综合治疗是根据患者的具体情况、肿瘤分期和分型，结合手术、化疗、放疗、靶向治疗、免疫治

表1 胃癌分子分型与对应治疗方案[8]

Table 1 Molecular typing of gastric cancer and corresponding treatment strategies[8]

分子分型	一线治疗	二线/进展后治疗
人表皮生长因子受体2阳性	曲妥珠单克隆抗体+化疗	维迪西妥单克隆抗体（抗体药物偶联物类药物） 曲妥珠单克隆抗体+化疗
微卫星高度不稳定/错配修复缺陷	帕博利珠单克隆抗体±化疗 纳武利尤单克隆抗体+伊匹木单克隆抗体	恩沃利单克隆抗体 替雷利珠单克隆抗体 斯鲁利单克隆抗体
Claudin18.2阳性	佐妥昔单克隆抗体+化疗	佐贝妥昔单克隆抗体+化疗 免疫治疗+化疗 Claudin18.2-CAR-T（临床试验）
程序性死亡受体配体1阳性	程序性死亡受体1单克隆抗体（帕博利珠单克隆抗体、纳武利尤单克隆抗体等）+化疗	卡度尼利单克隆抗体 程序性死亡受体1单克隆抗体+化疗
成纤维细胞生长因子受体2b扩增	未明确推荐	成纤维细胞生长因子受体2抑制剂（贝玛妥珠单克隆抗体/佩米替尼/英菲格拉替尼） 程序性死亡受体1单克隆抗体+化疗
MET基因扩增	未明确推荐	MET抑制剂（如克唑替尼、卡博替尼等） 临床试验

疗等多种手段，制订个体化治疗方案，以达到最佳治疗效果。其主要目标是提高生存率、延缓疾病进展、改善生命质量，并减少治疗副作用。

（二）局部进展期胃癌的综合治疗

局部进展期胃癌，按 AJCC/UICC 第 8 版胃癌 cTNM 分期法，结合解剖学定义，临床分期为 cT1~2 N+M0 期或 cT3~4bNanyM0 期。其综合治疗以手术为核心，结合新辅助化疗、放疗和靶向或免疫治疗，旨在提高手术切除率并改善术后长期生存。

新辅助放化疗有助于降低肿瘤分期、提高 R_0 切除率、控制微转移、减少复发风险，从而改善预后。MAGIC、FLOT4 和 RESOLVE 研究为西方国家和中国胃癌新辅助化疗标准奠定基础，病理学完全缓解率约为 5%[9-10]。CROSS 研究和 POET 研究证实术前放疗对于胃癌局部控制和预后的显著优势[11-12]。TOPGEAR 研究中期分析结果也显示：围手术期化疗联合术前放疗具有良好安全性，但术前行放化疗未带来额外的无进展生存或总生存获益[13]。近年来亚洲多个围手术期放化疗的研究均未能获得成功，而目前联合免疫治疗的研究广泛开展，在此基础上联合放疗是否还有可能进一步改善患者结局，值得探究。

免疫检查点抑制剂在晚期胃癌中的疗效促进了新辅助免疫治疗的研究不断发展[14-16]。对于 HER2 阴性患者，KEYNOTE 585、MATTERHORN、DROGAN Ⅳ、Wuhan UHGI001、PANDA 等多项Ⅱ期或Ⅲ期临床研究结果显示：化疗联合免疫治疗作为新辅助治疗可提升病理学完全缓解率和主要病理学缓解率，病理学完全缓解率为 12.9%~45%[17-21]。在化疗和免疫治疗的基础上，Neo-PLANET、SHARED、PROCEED 3 项Ⅱ期研究联合新辅助放疗，可能有更高的病理学完全缓解率（33.3%~38.2%）[22-24]。对于 HER2 阳性患者，新辅助化疗联合免疫及抗 HER2 靶向治疗也获得较高的病理学完全缓解率，其中 PANTHERA 研究为 31.3%，NCT04819971 研究中病理学完全缓解率高达 58.3%[25-26]。尽管这些研究都有较高的病理学完全缓解率，但目前尚无确凿证据表明新辅助免疫治疗能带来生存获益。其原因可能在于获得病理学完全缓解的患者仍较少，且对整体生存贡献有限；另外，术后患者无事件生存期较长，相比病理学完全缓解率的提高，无事件生存期获益的影响因素更多、更复杂，需更大样本量研究进一步研究验证。正在进行的 HLX10 研究通过对入组人群的进一步精准筛选，有可能实现无事件生存期和总生存期获益。

对于 MSI-H 的局部进展期胃癌患者，GERCOR NEONIPIGA 研究和 INFINITY 研究证实双免疫治疗的病理学完全缓解率分别为 58.6% 和 60%[3-4]。笔者认为：如果在大样本量的研究中能重复确认这样的疗效，甚至未来的药物联合治疗还能进一步提高病理学完全缓解率以及获得持续缓解，对这部分人群的治疗策略可能发生改变。手术患者选择、切除范围、手术时机甚至是否进行手术治疗，都可能发生改变。

目前手术根治性切除仍为局部进展期胃癌的主要治疗手段，根治性胃切除术联合 D_2 淋巴结清扫是全世界公认的标准手术方式[27]。胃癌腹腔镜手术取得显著发展，已有多项大型前瞻性研究支持腹腔镜手术在局部进展期胃癌治疗中的应用。如 CLASS-01、JLSSG0901、KLASS-02 等研究均显示：经过合格外科医师执行的腹腔镜远端胃切除术联合 D_2 淋巴结清扫，安全性和有效性均与传统开放手术相当[28-30]。腹腔镜手术成为一种可行的治疗选择，为患者带来更好的预后和更低的术后并发症发生率。近年来，机器人手术系统的进步迅速，机器人胃癌根治术在手术安全性以及淋巴结清扫方面逐渐展现出优势，将成为未来胃癌手术治疗的研究热点[31-32]。此外，随着胃癌淋巴结转移研究的深入，部分保功能胃切除术（近端胃切除术、保留幽门的胃切除术）也已成为特定部位胃癌的手术方式选择[33-35]。

中晚期胃癌的复发率>50%，规范的术后辅助治疗显得尤为重要。CLASSIC 和 ARTIST 等Ⅲ期临床研究证实，术后辅助化疗可改善患者无复发生存期和总生存期[36]。ATTRACTION-5 研究探讨术后免疫联合化疗在Ⅲ期胃癌中的疗效，虽然未达到主要终点，但亚组分析结果显示：PD-L1≥1%、病理学分期为ⅢC 期的患者无复发生存期显著延长[37]。这提示未来可能需要进一步探索不同的免疫治疗方案、患者选择标准或联合用药策略。

晚期胃癌中，PD-1 单克隆抗体的获益主要集中在 PD-L1 阳性患者，且其无进展生存期延长仅 0.6~2.5 个月，总生存期延长 2~5 个月[14-16]。对于术后辅助治疗患者，首先需通过分子标志物筛选可能从免疫治疗中获益的群体；其次，术后标准化疗的 3 年无病生存率可达 60%，在此基础上进一步提高生存率的难度高于晚期患者；此外，手术过程中淋巴结的广泛清扫可能破坏免疫反应的关键环节。因此，术后辅助免疫治疗是否优于标准化疗仍需更多精

准筛选和大样本量研究。目前进行中的JUPITER 15研究比较PD-L1阳性Ⅲ期胃癌患者接受化疗联合免疫治疗与单纯化疗效果，期望为该问题提供答案。

对于放疗在围手术期治疗中的尝试，美国INT0116研究证明在<D_2淋巴结清扫术的条件下，行术后放疗可显著获益，确立了放疗在胃癌术后辅助治疗中的地位[38]。但随着D_2手术的进展以及韩国ARTIST和ARTIST-2两项研究的阴性结果，胃癌术后放疗的价值尚存争议[39-40]。胃癌术后放疗的效果在不同患者群体中存在差异。1项研究结果显示：D_2手术后胃癌患者行化疗和放化疗的总生存期、无病生存期比较，差异均无统计学意义；但亚组分析发现，Ⅲc期胃癌患者接受放化疗后，无病生存期和总生存期均有所改善[41]。另有研究指出：淋巴结阳性胃癌患者术后放化疗相比单纯化疗能带来生存获益，特别是在N1~2期患者中，放化疗的生存优势更为明显[42]。此外，针对pN3期患者的研究进一步证实D_2术后放化疗相较于单纯化疗的生存优势[43]。针对胃癌D_2术后患者复发模式的回顾性分析结果也显示：放疗可以显著降低D_2术后患者的局部区域复发风险，具有年龄≥65岁、血清CEA升高、pT4期、淋巴结转移和淋巴管血管侵犯等危险因素的患者，发生局部区域复发的风险较高，尤其是同时具有多个危险因素的患者，可能更能从放疗中获益[44]。

在根治性切除手术后，早期应用腹腔热灌注化疗（hyperthermic intraperitoneal chemotherapy，HIPEC）可有效清除微小癌细胞和亚临床病灶，减少术后腹膜转移复发率。有研究结果显示：HIPEC结合热化疗和机械冲刷作用，对于预防胃癌术后腹膜转移具有显著疗效。如朱正纲教授团队的研究结果显示：与传统术后静脉化疗比较，HIPEC能显著提高进展期胃癌患者的4年和6年生存率，分别达到18%和30%，并将术后腹膜复发率降低24%[45]。梁寒教授团队的研究结果也显示：HIPEC治疗显著提高Ⅲb期胃癌患者的5年生存率，达13.6%[46]。目前，多个国内外前瞻性RCT正在探索HIPEC联合根治性切除术治疗胃癌的安全性与有效性，初步结果令人鼓舞。

在实体肿瘤中，微小残留病变与术后复发和预后分层的相关性证据不断积累[47-50]。多项小样本量研究结果显示：微小残留病变检测可预测根治性手术后胃癌患者的复发风险，并且术后或辅助治疗后的纵向监测可提前6个月预测复发，且优于影像学检查[51-53]。因此，笔者建议：进展期胃癌患者在根治性手术后或首次随访时进行微小残留病变检测，以辅助预后判断并制订后续治疗策略。在结直肠癌中，基于微小残留病变分层的干预治疗已显示出良好的临床价值，但在胃癌中，是否可以通过微小残留病变筛选辅助治疗人群并制订个体化治疗方案，仍缺乏相关研究，值得进一步探索。

（三）胃癌寡转移的综合治疗

寡转移胃癌指虽已发生远处转移，但转移灶数量和范围相对有限，侵袭性和危害性较低。对于此类患者，转化治疗（包括多种治疗手段的综合应用）旨在争取R_0切除，提升治愈可能性[54-57]。

近10年的回顾性研究结果显示：越来越多的转移性胃癌患者从药物治疗中获益，并能接受根治性手术[57-58]。AIO-FLOT3研究提出：局限性远处转移的晚期胃癌应优先进行转化治疗，术前化疗及R_0切除可显著改善预后[56]。尽管随后开展的AIO-FLOT5前瞻性Ⅲ期临床试验未达到研究终点，但亚组分析结果显示：腹膜后淋巴结转移患者可能从转化治疗及手术中获益[54,59]。

随着免疫与靶向治疗的出现，转化治疗面临新机遇[60-61]。免疫治疗不仅提高了肿瘤退缩的比例和深度，还可能使患者获得长期缓解。梁寒教授团队开展的CO-STAR研究证实了免疫治疗转化后手术的患者获得较好生存[61]。Liang等[62]的回顾性研究亦证明免疫治疗转化手术能显著延长生存期。笔者团队的回顾性倾向评分匹配分析也证实了相同结论。但是，对于胃癌寡转移的患者在经过免疫治疗获得疾病稳定或客观缓解后，能否从手术等局部治疗中获益，仍需通过前瞻性RCT验证。

腹膜转移曾被视为手术禁忌证。但近年研究结果显示：细胞减灭术联合HIPEC可改善部分患者预后。CYTO-CHIP研究结果显示：与单独细胞减灭术比较，细胞减灭术联合HIPEC显著提高患者的中位生存时间（18.8个月比12.1个月，P=0.005）[63]。该研究认为：对于经过严格筛选的局限性胃癌腹膜转移患者，尤其是能够实现满意细胞减灭的患者，细胞减灭术联合HIPEC具有重要的治疗价值，且不会增加手术并发症或死亡风险。GASTRIPEC-I研究结果则显示：行细胞减灭术联合HIPEC与单独细胞减灭术患者总生存期比较，差异无统计学意义，但前者在无进展生存期和远处无转移生存期方面均表现出明显优势，且未增加不良事件风险，值得进一步研究[64]。

在研究设计中，除了药物治疗方案、术前治疗

疗程、手术时机、手术清扫范围及局部治疗方式等问题，还需关注两个关键因素：(1)转移部位。目前寡转移的定义涵盖多种转移可能，包括腹膜后淋巴结、肝、腹膜、卵巢、肾上腺、腹腔外淋巴结及局灶性骨转移等。尽管以上皆属寡转移，但这些患者的预后差异较大，未来研究应进一步区分。(2)除了根治性手术切除外，还应考虑联合局部消融或局部放疗，尽可能灭活肿瘤细胞，达到无瘤状态，从而提高患者获益[65-68]。

(四)晚期胃癌的综合治疗

晚期不可手术胃癌的治疗策略目前以化疗联合免疫治疗为基础，并以生物标志物为指导，联合其他靶向药物作为未来研究的方向。多个Ⅲ期临床研究结果已确立免疫联合化疗在HER2阴性晚期胃癌一线治疗中的基础地位[14-16]。但总体疗效仍非常有限。因此，越来越多的临床研究聚焦于探索化疗联合免疫治疗的多种组合模式，如联合抗血管生成、抗HER2、抗FGFR2b单克隆抗体、抗Claudin18.2单克隆抗体、MET抑制剂等，以及其他免疫检查点抑制剂。

抗血管生成药物在结直肠癌中已广泛应用，但在胃癌中的疗效仍在探索中。RAINBOW-Asia研究结果显示：雷莫西尤单克隆抗体已成为晚期转移性胃癌的二线治疗新标准[69]。FRUTIGA研究证实了抗血管生成药物在晚期胃癌中的临床价值，为未来的联合治疗提供了基础[70]。近年来，越来越多研究在化疗联合免疫治疗药物基础上，联合抗血管酪氨酸激酶抑制剂药物或贝伐珠单克隆抗体，获得了>70%的客观缓解率，展示了这一治疗方案的巨大潜力[71]。

ToGA研究为胃癌的抗HER2靶向治疗奠定了重要基础[72]。KEYNOTE 811结果显示：化疗联合曲妥珠单克隆抗体基础上联合免疫治疗比不联合免疫治疗显著延长无进展生存期和总生存期，且获益群体主要为PD-L1≥1的患者，再次证实了PD-L1表达对免疫治疗效果的重要性。针对HER2的抗体药物偶联物已成为研究热点，除了德曲妥珠单克隆抗体和维迪西妥单克隆抗体，还有数十种药物正在研发中[5-7]。

FGFR2b阳性患者在晚期胃癌中的比例(20%~30%)较高。Ⅱ期FIGHT研究初步证明FGFR靶向治疗在FGFR2b阳性胃癌患者中的良好抗肿瘤效果[73-74]。随着Ⅲ期临床试验的进一步验证，靶向FGFR2b的药物有望造福更多晚期胃癌患者。

Claudin18.2靶向治疗的兴起为晚期胃癌一线治疗带来新机遇。SPOTLIGHT[75]和GLOW研究[76-77]证实靶向Claudin18.2的单克隆抗体佐妥昔单克隆抗体在晚期胃癌患者中的疗效与安全性，确立了Claudin18.2作为重要靶点药物在胃癌一线治疗中的地位。目前，多种针对Claudin18.2的靶向治疗正在研发，包括增强型单克隆抗体、抗体药物偶联物、双特异性抗体以及CAR-T等，预示着抗Claudin18.2治疗在胃癌中的广阔前景，期待能够取得新的突破[78-79]。

MET基因是胃癌治疗的重要靶点，其过度激活可增加肿瘤细胞侵袭性、促进血管生成并提高耐药性[80]。VIKTORY研究结果显示：赛沃替尼对MET扩增胃癌患者的无进展生存期和总生存期优于对照组[81]。国内研究也表明赛沃替尼可达到近50%的客观缓解率[82]。目前，多项针对MET的小分子酪氨酸激酶抑制剂、抗MET单克隆抗体及其与化疗、免疫治疗联合的临床试验正在进行中。

多种免疫检查点抑制剂联合在晚期胃癌治疗中的应用正受到关注。尽管PD-1抗体纳武利尤单克隆抗体与CTLA-4抗体(伊匹木单克隆抗体)的双免联合在HER2阴性微卫星稳定胃癌患者治疗中未能获得更好的疗效[15,83]。然而，在MSI-H患者中，该联合治疗显著提高了客观缓解率。COMPASSION-15研究结果显示：PD-1/细胞毒性T淋巴细胞相关抗原4双特异性抗体卡度尼利单克隆抗体联合化疗显著延长了胃癌患者总生存期，且对PD-L1联合阳性分数<5的患者死亡风险降低30%，打破了低表达群体不能从免疫治疗中获益的传统观念，成为胃癌一线免疫治疗的里程碑[84]。创新型PD-L1/TGF-β双抗药物SHR-1701联合化疗在Ⅲ期临床研究中表现出良好的疗效和安全性，该研究也是第一个PD-L1/TGF-β双抗药物获得阳性结果的研究[85]。

胃癌具有高度异质性，因此，没有单一靶点能够占据绝对主导地位。新靶点的发现及临床研究的成功，使治疗方案更加多样且具有针对性。由于不同患者的肿瘤在基因、分子和免疫等方面的差异，治疗应根据患者具体情况进行个体化调整。笔者建议：未来治疗将更加注重精准医疗和联合治疗，以优化疗效并减少不良反应。

三、结语

胃癌的综合治疗结合了手术、化疗、放疗、介入治疗、靶向治疗和免疫治疗等多种手段，根据患者个体情况制订个性化方案，推动各学科协作、技术

整合，以提升治疗效果，尤其在新辅助治疗和转化治疗中表现突出。早中期患者以根治性手术为核心，整合治疗手段以确保手术切除效果。晚期患者则以药物治疗为基础，依据分子特征进行个体化治疗，必要时辅以手术或放疗等局部治疗。

然而，胃癌综合治疗仍面临诸多挑战：胃癌的恶性程度高，异质性显著，现有靶向免疫治疗对于胃癌的整体获益有限；术后复发风险高，尤其是腹膜转移比例高；对腹膜转移的患者，无论是药物治疗还是灌注治疗，手术治疗都难以给患者带来长期生存获益；另外，各种治疗方法之间的有机整合及优化，各学科成员之间对彼此领域的了解还需要不断加深。

笔者预测：未来胃癌综合治疗将朝着更加个体化和精准化方向发展。随着分子生物学和基因组学的进步，肿瘤的分子特征和免疫表型将为治疗方案的选择提供重要依据。新型靶向治疗和免疫治疗的结合可能成为晚期胃癌长期生存的新希望。同时，液体活检技术的发展，特别是 ctDNA 和循环肿瘤细胞的检测，为早期诊断、治疗监测和复发预警提供了新机遇。

利益冲突 所有作者声明不存在利益冲突

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