

· 专家述评 ·



陈佳艺，上海交通大学医学院附属瑞金医院放射治疗科主任、主任医师，上海交通大学肿瘤学博士研究生导师。长期致力于肿瘤放疗的临床和转化型研究，尤其擅长乳腺癌、胃肠道肿瘤、恶性淋巴瘤等的放疗和综合治疗，是国内最早开展粒子治疗研究的学者之一。长期从事上海市放疗质控中心专家组的工作，对数字化和信息化管理及质控管理有深入的研究。目前担任上海市医学会肿瘤放射治疗专业委员会候任主任委员，中国抗癌协会整合肿瘤心脏病学专业委员会副主任委员，中国临床肿瘤学会神经系统肿瘤专家委员会副主任委员，中国临床肿瘤学会乳腺癌专家委员会常委，中国临床肿瘤学会肿瘤放射治疗专家委员会常委。曾获得2018年度上海市三八红旗手，2019年度上海市最美女医师，2019年度上海市巾帼建功标兵。“中国临床肿瘤学会乳腺癌诊疗指南”放疗部分执笔人，并参与编写国内多个乳腺癌放疗指南。以项目负责人身份先后承担国家自然科学基金面上项目2项，科技部重大项目子课题1项，省部级课题2项，申康“三年行动计划”项目2项，上海市局级课题1项。以第一作者或通信作者在国内权威、核心和SCI收录期刊上发表论文70余篇。

放射治疗在胃癌全程管理中的现状与挑战

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〔摘要〕 胃癌是常见的消化道恶性肿瘤之一。放疗是胃癌综合治疗的重要手段之一。近年来，包括放疗在内的局部进展期胃癌的围手术期治疗的探索不断取得突破，这些疗法对胃癌患者生存的积极影响也越来越明显。近年来在胃癌的新辅助放疗、辅助放疗、进展期肿瘤放疗及免疫联合放疗领域均有新的研究成果。本文深入分析国内外的相关研究进展，系统阐述放疗在胃癌治疗中的应用现状与进展。

〔关键词〕 胃癌；放射治疗；新辅助治疗；辅助治疗

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The current data and challenge of radiotherapy in the case management of gastric cancer CAI Gang, WANG Shubei, CHEN Jiayi (Department of Radiation Oncology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China)

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〔Abstract〕 Gastric cancer is one of the common malignant tumors of digestive tract. Radiotherapy is one of the important comprehensive treatment modalities for patients with gastric cancer. In recent years, there have been breakthroughs in perioperative treatment for locally advanced gastric cancer by radiotherapy and other treatments. The positive impact of such therapies on survival in patients with gastric cancer has become clearer over time. In recent years, new achievements have been made in the fields of neoadjuvant radiotherapy, adjuvant radiotherapy, advanced tumor radiotherapy and combined immunoradiotherapy for gastric cancer.

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This article analyzed the relevant research progress at home and abroad, and systematically expounded the current status and progress of radiotherapy in the treatment of gastric cancer.

[**Key words**] Gastric cancer; Radiotherapy; Neoadjuvant therapy; Adjuvant therapy

胃癌是全世界范围内较常见的恶性肿瘤之一。国家癌症中心最新统计数据显示,胃癌发病率和死亡率均居中国恶性肿瘤的第3位^[1]。胃癌的高死亡率反映出患者就诊时大多数为进展期肿瘤。根治性手术切除仍然是局限期胃癌的首要治疗手段,但早期研究^[2]报道,仅接受单纯手术而未接受围手术期放化疗的局部进展期胃癌患者的5年生存率仅为20%左右。近年来,包括化疗、放疗、靶向治疗、免疫治疗在内的各种治疗手段迅速发展,也给胃癌患者的生存带来更积极的影响。多学科诊疗逐渐成为胃癌治疗的基础,而放疗是其中不可替代的组成部分,并发挥着重要作用。

目前放疗主要应用于局部进展期可切除胃癌患者的术前新辅助放疗、术后辅助放疗,局部进展期潜在可切除肿瘤、不可切除肿瘤的放化疗,术后局部区域复发患者的挽救性治疗,不伴腹膜转移的单一远处转移的治疗,以及晚期肿瘤的姑息性治疗等。

1 胃癌新辅助放疗

目前主要有部分针对胃贲门癌和食管胃结合部癌的临床试验采用了新辅助放疗的方式(表1)。术前放疗主要有以下优势:①术前患者的耐受性比术后更好,完成率较术后辅助治疗更高;②根据术前放疗的效果判断患者对放疗的敏

表1 局部进展期胃癌新辅助放化疗相关研究

Tab. 1 Study on neoadjuvant chemoradiotherapy for locally advanced gastric cancer

Study	Publication year	Country/region	Study design	Tumor site	Group	R0 resection rate	pCR rate	OS
CROSS ^[3]	2012	Netherlands	Phase III randomized control	Esophagus/esophagogastric junction	Surgery (n=188); Carboplatin+taxol +radiotherapy+surgery (n=178)	69%; 92%	-; 29%	24.0 months (median OS); 49.4 months (median OS)
POET ^[4]	2009	Germany	Phase III randomized control	Esophagus/gastric cardia	Cisplatin+FU/LV (n=59); Cisplatin+FU/LV+radiotherapy (concurrent chemotherapy: cisplatin+etoposide) (n=60)	70%; 72%	2%; 16%	24.4% (5-year OS rate); 39.5% (5-year OS rate)
NEO-AEGIS	2021 (preliminary result)	International	Phase III randomized control	Esophagus/esophagogastric junction	ECF/ECX/EOF/EOX, FLOT (n=184); Carboplatin+taxol+radiotherapy (n=178)	82%; 95%	5%; 16%	56% (3-year OS rate); 57% (3-year OS rate)
TOPGEAR ^[5]	2017 (midterm result)	Europe, Canada	Phase III randomized control	Esophagogastric junction/gastric	ECF/ECX+surgery+ECF/ECX (n=60); ECF/ECX+radiotherapy+surgery+ECF/ECX (n=60)			
PREACT	Ongoing	China	Phase III randomized control	Esophagogastric junction/gastric	SOX+chemoradiotherapy+SOX+surgery+SOX; SOX+surgery+SOX			
CRITICS II	Ongoing	Netherlands	Phase III randomized control	Gastric	DOC+surgery; DOC+chemoradiotherapy+surgery; Chemoradiotherapy+surgery			
ESOPEC	Ongoing	Germany	Phase III randomized control	Gastric	FLOT+surgery+FOLT; Chemoradiotherapy+surgery			
5010	Ongoing	China	Phase III randomized control	Gastric	Radiotherapy+XELOX+surgery+XELOX; XELOX+surgery+XELOX			

pCR: Pathological complete response; OS: Overall survival.

感性,协助判断预后并指导术后辅助治疗;③术前肿瘤的血供较好,因此对放疗的敏感性较高;④术前患者靶区勾画也更清晰。不过,由于胃癌新辅助放疗还未有足以改变临床实践的充分证据,因此临床上胃癌患者是否接受新辅助放疗,还需要在多学科综合讨论后决定。

2012年发布的CROSS研究^[3]纳入了366例食管或食管胃结合部癌患者,对比了新辅助放化疗后手术与单纯手术的疗效,结果显示,放化疗组的R0切除率显著提高,且中位生存时间延长^[3]。尽管该研究纳入了部分食管癌患者,但是结果提示新辅助放疗可能给患者带来生存获益。德国POET试验^[4]直接比较了新辅助放化疗与单纯诱导化疗的效果,放化疗与单纯化疗相比带来的生存获益存在一定差异,但差异无统计学意义[总生存(overall survival, OS)率: $P=0.055$]。

NEO-AEGIS试验直接比较了CROSS研究的放化疗方案与化疗方案,初步结果显示,放化疗组的R0切除率、病理学完全缓解(pathological complete response, pCR)率、病理学检查淋巴结阴性患者比例均更高,但3年OS率并未因此改善。同样,欧洲和加拿大的TOPGEAR研究^[5]评估了在新辅助化疗的基础上增加放疗是否可改善生存,中期结果提示术前放化疗较单纯化疗并未显著增加不良反应的发生率,目前这项研究的生存结果尚在随访中。

有3项独立的Ⅱ期研究对非贲门胃癌患者的新辅助放化疗进行了探索,结果表明,术前放疗的pCR率为20%~30%,且70%~78%的患者在放化疗之后能够进行R0切除^[6-8]。此外对于非贲门胃癌的新辅助放化疗,目前有包括CRITICS Ⅱ、PREACT、ESOPEC和5010研究等在内的多项国内外研究正在进行中。

因此,中国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)指南^[9]推荐对于Ⅱ~Ⅲ期的食管胃结合部癌,行新辅助放化疗+胃切除术D2+辅助化疗为ⅠB类证据。目前指南仍未对非贲门部胃腺癌患者的新辅助放疗作出推荐,原因可能是术前放化疗更常用于食管、食管

胃结合部癌和胃贲门癌,而不是潜在可切除性非贲门部胃腺癌。

2 胃癌辅助放疗

相比胃癌根治术后单纯化疗,术后放化疗是否有生存获益,目前仍有争议。多项研究反映了这种争议(表2)。美国INT0116研究^[10-11]纳入的556例患者在胃癌根治术后分为两组,分别接受观察或辅助放化疗,结果表明,放化疗组的中位生存期和5年OS率更长,该结果使美国的胃癌根治术后的标准治疗方案由术后单纯观察改为了辅助放化疗。然而,由于研究开展的时代较为久远,该研究中完成D2清扫的患者只有10%,目前D2淋巴结清扫已广泛开展,该研究结果是否能够沿用仍未可知。荷兰D1D2试验^[12]的回顾性数据同样表明,放化疗降低了D1淋巴结清扫后的局部复发率并改善了生存,但D2淋巴结清扫后无此获益,该结论也得到了其他回顾性研究^[13]的证实。不过另一些研究^[14-15]数据显示,即使在D2淋巴结清扫后,放化疗也可能有益。

目前有多项研究直接对比了术后辅助化疗与放化疗的效果(表2)。最具代表性的韩国ARTIST试验^[14]将458例胃癌D2根治术后患者分为两组,分别接受术后化疗与放化疗,结果显示,两组患者的3年无病生存(disease-free survival, DFS)率和OS率的差异均无统计学意义,但亚组分析表明,淋巴结阳性患者接受放化疗后的DFS更高。后续的ARTIST2试验^[16]将淋巴结阳性的D2根治术后胃癌患者随机分入S-1化疗组、SOX化疗组和SOX+放化疗组,发现SOX基础上加用放疗并未显著改善生存。但该研究同样存在一些问题,试验中很少提及放疗的实施情况,无法明确放疗质控,而且期中分析时DFS事件数过少。此外,荷兰的CRITICS试验^[17]纳入了潜在可切除性胃癌患者,在诱导化疗后手术,然后分入术后化疗组和放化疗组,两组的生存率差异无统计学意义。但该研究纳入了很大一部分早期胃癌患者,且每组仅约半数患者完成了术后全部治疗。后续更新了研究结果,中位随访6.7年时,意向性治疗(intention-to-treat, ITT)分析显示,两组的5年生存率无显著差异,遵循研究

表2 局部进展期胃癌辅助放化疗相关研究

Tab. 2 Study on adjuvant chemoradiotherapy for locally advanced gastric cancer

Study	Publication year	Country/region	Study design	Group	Surgical method	DFS	OS
INT-0116 ^[10]	2012	North America	Phase II randomized control	Surgery (<i>n</i> =277); Surgery+radiotherapy+FU/LV (<i>n</i> =282)	D1 or D2	19 months (median DFS); 27 months (median DFS)	27 months (median OS); 35 months (median OS)
ARTIST ^[13]	2012	Korea	Phase III randomized control	Surgery+XP (<i>n</i> =228); Surgery+XP+radiotherapy (<i>n</i> =230)	D2	74.2% (3-year DFS rate); 78.2% (3-year DFS rate)	73% (5-year OS rate); 75% (5-year OS rate)
ARTIST II ^[15]	2021	Korea	Phase III randomized control	Surgery+S-1 (<i>n</i> =182); Surgery+SOX (<i>n</i> =181); Surgery+SOX+radiotherapy (<i>n</i> =183)	D2	64.8% (3-year DFS rate); 74.3% (3-year DFS rate); 72.8% (3-year DFS rate)	
CRITICS ^[17]	2018	Netherlands	Phase III randomized control	Chemotherapy+surgery+chemotherapy (<i>n</i> =393); Chemotherapy+surgery+chemoradiotherapy (<i>n</i> =395)	D1 or above		ITT: no difference; PP: 57.9% and 45.5% (5-year OS rate)

方案 (Per-protocol, PP) 分析显示, 化疗组的5年OS率为57.9%, 优于放化疗组 (45.5%)^[18]。

同时, 中国的一项研究^[19]将胃癌根治术后的患者分入放化疗组和化疗组, 放化疗组方案参照了INT0116研究, 但采用了调强放疗, 结果表明, 放化疗组的3年DFS率更高, OS率也显著更高。一篇meta分析^[20]纳入了6项直接比较辅助放化疗与化疗的试验, 分析结果表明, 虽然放化疗组的5年DFS率更高, 局部区域复发更少, 但生存获益差异无统计学意义。武汉大学中南医院的回顾性研究^[21]数据表明, D2术后的胃癌患者, 化疗和放化疗后的OS及DFS差异均无统计学意义, 但在亚组分析中可以观察到, IIIc期患者放化疗后的DFS及OS均更高。同期, 复旦大学附属肿瘤医院针对淋巴结阳性的胃癌患者开展了一项回顾性研究^[22], 发现淋巴结阳性的患者中术后放化疗对比化疗有一定的获益, 尤其对于胃癌N₁₋₂期患者而言, 放化疗的生存获益明显。而在此基础上开展的另一项针对pN₃期患者的回顾性研究^[23], 发现了D2术后放化疗对比化疗的优势。

鉴于以上几项研究存在较大差异, 得出的

结果也不尽相同, 究竟哪些患者最能够从辅助放疗中获益, 目前仍是一个等待回答的问题。目前欧洲肿瘤内科学会 (European Society for Medical Oncology, ESMO) 指南^[24]建议, 对于未行新辅助化疗的≥ I B期胃癌术后患者, 可给予辅助放化疗或辅助化疗。美国国家综合癌症网络 (National Comprehensive Cancer Network, NCCN) 指南^[25]则推荐, 对于淋巴结清扫未达到D2的T_{3/4}期或淋巴结阳性的胃癌患者, 应行辅助放化疗。而CSCO指南^[9]推荐, 对于R0切除未达到D2者, 术后放化疗为1A类证据; 对于R1/2切除者, 术后放化疗为2A类证据; 而对于D2根治术后患者, 辅助放化疗为3类证据。

针对胃癌D2术后患者复发模式的回顾性分析^[26]亦发现, 放疗可以显著降低D2术后患者的局部区域复发风险, 具有年龄≥65岁、血清癌胚抗原 (carcinoembryonic antigen, 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。可以据此建立列线图模型, 作为D2

根治术后胃癌局部区域复发的简便个体化预测工具,从而更精确地选择能够从放疗中获益的人群。但这些结果同样需要通过进一步的前瞻性多中心随机对照研究进行验证。

3 复发模式对靶区的指导

靶区定义不够准确导致照射范围相应较大,最终使患者放疗耐受性降低,是目前接受放疗患者比例仍然偏低的原因之一。明确胃癌术后的局部复发高危部位,优化靶区定义,从而缩小照射体积,就可以减轻放疗相关的不良反应。在术后未行放疗的胃癌患者,以及手术清扫时阴性淋巴结数目较少的患者中,局部区域复发十分常见^[27]。局部区域复发的主要部位包括切缘、瘤床和引流淋巴结区^[28]。同时既往研究^[29]表明,胃癌术后残胃放疗并未改善患者生存,而照射残胃会导致呕吐和腹泻的发生率明显升高。因此,目前推荐胃癌D2根治术后的辅助放疗需包含切缘、瘤床(T_{3,4}期患者中)和高危淋巴引流区,同时可不包含残胃。

但由于目前对淋巴引流区重要性的理解不同,胃癌放疗的靶区勾画尚无统一论。Zhu等^[30]通过回顾性研究胃癌淋巴结转移的规律来指导胃癌围手术期靶区的勾画。复发模式相关研究^[31-32]发现,区域淋巴结转移第2、3站淋巴结,第16、12、14和13组淋巴结转移较为常见。韩国的淋巴结复发模式相关回顾性研究^[33]则发现,D2术后高复发率的主要为第9~16组淋巴结。另一项回顾性研究^[34]则表明,90.4%的区域复发发生于D2清扫区域及16b1组淋巴结。复旦大学附属肿瘤医院的回顾性研究^[35]则发现,胃癌根治术后局部或区域复发部位主要包括吻合口、十二指肠残端、肿瘤床、残胃和区域淋巴结,其中淋巴结转移主要发生在Ⅰ、Ⅲ和Ⅵ区。而上海交通大学医学院附属瑞金医院的回顾性研究^[36]则发现,无论原发肿瘤部位,D2术后患者中以腹主动脉旁淋巴结(第16组淋巴结)转移最为常见,其中又以16a2和16b1两个亚组的淋巴结转移尤为常见,进一步对放疗后患者的复发模式分析则表明,放疗后16a2和16b1两个亚组淋巴结

的复发风险明显减少。目前推荐胃癌辅助放疗临床靶区中的高危淋巴引流区应包括腹主动脉旁淋巴结的16a2和16b1区域。同样有学者认为,手术时不同阳性淋巴结区域患者,发生16组淋巴结转移的风险亦不同,这些观点可以通过后续的回溯性及前瞻性研究结果进行进一步探索。

《中国胃癌放疗指南(2020版)》^[37]推荐的照射范围中,术前放疗为肿瘤区(gross tumor volume, GTV)、肿大淋巴结, GTV邻近的亚临床病灶区、肿大淋巴结外扩和高危淋巴结区域,对于术后放疗而言,CTV包括切缘不足的吻合口、切缘不足的十二指肠残端或残胃,瘤床原则上不常规包括。同时,依据不同原发肿瘤部位对照射淋巴结区域进行了推荐,腹主动脉旁淋巴结区(主要为16a2和16b1区)也可纳入照射,在临床靶区勾画中可参考。

4 潜在可切除/不可切除的局部进展期肿瘤

对于潜在可切除的局部进展期肿瘤,指南推荐在新辅助放化疗后行胃切除术,再行术后辅助治疗。对于体能状态良好的不可切除的局部进展期胃癌患者, NCCN指南^[25]及CSCO指南^[9]均推荐可以先尝试应用化疗、放化疗或两者联合进行降期,随后进行再分期及手术探查。初步研究^[38-39]数据表明,术前放化疗后,最初不可切除的局部进展期胃癌患者中约有70%可行根治性切除, pCR率可达13%~30%。然而,这些早期数据的样本量都较小,最终还需进行随机试验来证实这些结果。对于未接受过放疗的局部复发患者,回顾性研究^[40-41]显示,同步放化疗的反应率高达61.9%,中位生存期为35个月,且对疼痛、出血及梗阻症状的控制明显。

5 展望

纵观局部进展期胃癌的放疗进展,对潜在可切除、不可切除、孤立远处转移患者均能带来获益。围手术期放疗方面,在D2根治术+术后辅助化疗基础上再行放疗目前仍有争议,而新辅助放疗的效果仍在验证中,未来将进一步明确放疗在局部进展期胃癌中的作用。免疫治疗与放疗的联合也有可能带来新突破,南京鼓楼医院开展的一项研究^[42]评估了信迪利单抗联合新辅助同步

放化疗对局部晚期胃癌/食管胃结合部腺癌的疗效, 初步报道的pCR率高达42.1%, 提示免疫联合放疗具有较大潜力。

放疗在现代胃癌多学科治疗中的效果仍然在进一步的验证中, 随着临床试验的广泛开展和放疗技术的不断进步, 相信局部进展期胃癌患者的生存未来有望得到进一步改善。

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