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文献综述 REVIEW

不可切除胃癌“转化治疗”的临床进展

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背景资料
不可切除胃癌病例初诊时病期已晚、难以根治性切除, 目前国际胃癌诊疗指南推荐以全身化疗为主的姑息治疗方式, 但其中位生存期仅有5-12 mo, 5年生存率约10%, 远低于可行根治性手术的进展期胃癌病例.

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Conversion therapy for unresectable gastric cancer

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Abstract
Unresectable gastric cancer cases are often diagnosed at a far advanced stage, which are hard to resect radically and suffer a poor prognosis. Therefore, palliative chemotherapy is recommended as the main treatment by the current clinical guidelines for gastric cancer. Fortunately, in recent years some clinical studies revealed that after treatment with chemotherapy, radiotherapy, targeted therapy, interventional therapy, hyperthermic intraperitoneal chemotherapy (HIPEC) and so on, and multidisciplinary assessment, many unresectable gastric cancer cases could be converted into resectable cases, which consequently prolongs their survival time and improves their quality of life significantly. In the present review, we summarize the status and progress of treatment for unresectable gastric cancer, as well as the strategy and case selection for conversion therapy.

Key Words: Unresectable gastric cancer; Conversion therapy; Chemotherapy; Surgery; Prognosis

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摘要
不可切除胃癌是指初次确诊时病期较晚、难以根治性切除的病例, 其总体预后不佳, 目前的国际胃癌指南推荐以姑息化疗为其主要治疗方式. 近年来有许多临床研究发现, 通过给予合理的化疗、放疗、靶向、介入、腹腔热灌注治疗等综合治疗, 结合多学科团队(multidisciplinary team, MDT)评价, 许多不可切除胃癌病例能够“转化”为可根治性切除的病例, 从而显著延长患者生存时间并提高其生活质量. 本文就不可切除胃

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癌的治疗现状与进展、“转化治疗”的应用策略以及病例选择等做了全面的综述.

关键词: 不可切除胃癌; 转化治疗; 化疗; 手术; 预后

核心提示: 不可切除胃癌的转化治疗是通过采取化疗、放疗、靶向、介入等综合治疗模式治疗晚期胃癌, 选择其中不可切除因素部分或完全缓解并“转化”为可切除者, 给予胃癌D2/D2+根治术, 从而延长患者生存时间、提高患者生活质量.

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0 引言

胃癌作为全球发病率排名第五、死亡率排名第三的恶性疾病[1], 严重威胁人类健康, 并给患者家庭及社会带来沉重的经济负担. 尽管胃癌的发病率和死亡率在东亚地区呈下降趋势, 但在我国仍然是发病率和死亡率排名第三的癌症[2]. 我国胃癌病例以进展期胃癌为主(超过总数的90%), 其中不可切除胃癌约占10%[3]. 其中位生存期仅为5-12 mo[4-8], 5年生存率约为10%[9,10]. 对于不可切除进展期胃癌的治疗, 美国国家综合癌症网络(National Comprehensive Cancer Network, NCCN)指南、日本胃癌规约均推荐以氟尿嘧啶或紫杉醇为基础的全身化疗为其主要治疗方式, 也可以给予靶向治疗、支持治疗等.

目前外科手术仍然是胃癌获得根治性治疗的主要手段, 因此由不可切除胃癌病例转化为可切除病例是使患者获得“治愈”的最佳选择. 近几年陆续有学者报道[11,12], 许多不可切除进展期胃癌病例在接受全身化疗后其不可切除因素部分或完全缓解, 赢得了根治性胃癌切除的机会, 并最终获得了较长期的术后生存时间和/或无复发生存时间. 由此各国专家提出了不可切除胃癌的综合治疗新策略: “转化治疗”.

1 不可切除胃癌的治疗现状

不可切除胃癌是指在手术学上难以对肿瘤病灶实施根治性切除(R0切除)、术后会有肿瘤残留的进展期胃癌, 包括难以切除的局部进展期胃癌, 如邻近结构(胰头、肝门静脉等)受侵、腹腔动脉旁淋巴结融合或包裹血管等, 和有远处转移的胃癌, 如腹膜转移或腹水胃癌细胞阳性, 肝转移和/或其他远隔脏器转移, 远处淋巴结转移等.

对于不可切除胃癌, 美国NCCN指南、日本胃癌规约[13]和欧洲ESMO指南[14]均推荐以全身化疗为主的姑息治疗. 目前主要以DCF[多西他赛、顺铂、5-氟尿嘧啶(5-fluorouracil, 5-Fu)]或ECF(表柔比星、顺铂、5-Fu)及其改良方案[5,15]作为一线用药, 能够有效地缓解症状并延长生存时间. 最近一项法国的III期临床试验[16], 发现伊立替康也可以作为一线用药, 有效地治疗不可切除胃癌. 研究[17]证实对于HER2-neu阳性的晚期胃癌患者, 应用曲妥珠单抗联合化疗能够显著改善其中位生存期. Shi等[18]发现采用免疫细胞过继转移疗法: 细胞因子诱导杀伤细胞(cytokine-induced killer cells, CIK)治疗局部晚期胃癌也是安全有效的. 这些姑息性治疗方法, 虽然延长了不可切除胃癌患者中位生存时间(9.2-13.8 mo), 但是其中位生存时间仍低于接受根治性手术的患者(17 mo)[19]. 值得庆幸的是, 近年来许多研究[11,19,20]发现部分晚期胃癌患者的不可切除因素在接受全身化疗后可以显著缓解并能够接受根治性切除手术, 结果其生存时间显著延长, 因此提出了不可切除胃癌的“转化治疗”策略.

不可切除胃癌的“转化治疗”, 是指通过全身化疗、放疗、靶向、介入治疗及其他个体化治疗的综合治疗模式, 使晚期胃癌患者的不可切除因素出现部分或完全缓解, 并筛选出能够获得胃癌根治性切除的病例实施手术治疗, 从而实现胃癌的手术学治愈和达到延长总体生存时间和/或无复发生存时间以及提高生活质量的目的.

2 “转化治疗”的全身治疗方案

“转化治疗”在对不可切除的转移性结直肠癌尤其是肝转移患者的治疗上已经比较成熟, 通过转化治疗能够使32%-60%的患者获得根治性手术[21], 并显著提高患者术后生存, 而且“转化治疗”已成为目前转移性结直肠癌主要治疗方法. 尽管不可切除胃癌“转化治疗”理念的提出已经有20余年的历史[19,20], 但是由

研发前沿
全身化疗结合放疗、靶向、介入、腹腔热灌注化疗及转移灶切除等治疗方式, 能够有针对性的使部分不可切除因素出现部分或完全缓解. 但是目前的治疗方法、病例选择等尚缺乏权威的循证依据.

相关报道
Kodera全面总结了PAN16a2-b1淋巴结清扫对于不切除胃癌患者获得胃癌D2+根治术的可行性、生存获益以及相关临床试验的优劣, 并且提出JCOG9501研究关于腹主动脉旁淋巴结清扫无生存获益的结论尚需进一步研究论证.

于化疗反应率较低及手术理念存在争议等限制, 转化治疗的研究长期停留在小样本研究甚至个案报道的水平上.

意大利的一项观察性研究[19]应用三药联合(表柔比星、顺铂、氟尿嘧啶)治疗不可切除胃癌, 发现化疗反应率为49%, 手术转化率45%, 4年总体中位生存时间为17 mo, 总体生存率为31%. 尽管该研究缺乏单纯化疗对照病例、术后数据收集不完整, 但是该研究说明不可切除胃癌的“转化治疗”模式具有可行性. 日本学者Yoshikawa等[22]则采用二线化疗方案(伊立替康+顺铂)联合根治性胃癌切除术(D2+腹主动脉旁淋巴结清扫)开展研究, 结果其化疗反应率为55%, R0切除率为65%, 总体中位生存期为14.6 mo, 3年生存率为27%. 可惜的是, 中期结果提示该方案毒性大、死亡率较高(>5%, 骨髓抑制2例, 术后并发症1例), 该临床试验被迫终止.

随着DCF及其改良方案作为晚期胃癌一线用药地位的确立, 许多学者开始研究此方案作为不可切除胃癌“转化治疗”用药的有效性. Sym等[23]发现DXP(多西他赛、卡培他滨、顺铂)方案具有较高的安全性和有效性, 其临床反应率为65%, R0切除率为63%, R0术后病例中位无复发生存时间为54.3 mo, 总体中位无复发生存时间和总体生存时间分别为12.1 mo和22.9 mo, 而未行R0切除术者总体生存时间仅11.5 mo. Kinoshita等[24]报道多西他赛、顺铂、S-1(DCS)化疗方案联合胃癌根治术(D2/D2+), 化疗反应率为73.7%, 手术率转化为59.6%, 手术率转化为59.6%, R0切除率79.4%, 术后总体3年生存率和中位生存时间优于单纯化疗者(50.1% *vs* 0%, 29.9 mo *vs* 9.6 mo). 此外还有学者尝试用两药方案(S-1+顺铂)治疗不可切除胃癌, 结果发现尽管其R0切除率均不高(48.1%或22.0%), 但是根治术后中位生存时间都较长(50.1 mo或53.0 mo), 这可能与其纳入的患者病情相对较轻有关[11,25]. 总之, 全身化疗是不可切除胃癌的“转化治疗”的主要治疗方法.

许多研究将靶向药物如曲妥珠单抗[26]、拉帕替尼[27]、索拉非尼[28]等, 与化疗药联用治疗晚期胃癌, 发现癌灶可以出现部分缓解, 甚至延长生存期. 尽管拉帕替尼是否能够显著延长患者的总体生存期尚存在争议[29], 但是曲妥珠单抗已经成为美国NCCN胃癌指南推荐的不可切除胃癌的姑息性治疗的靶向药物. 最近Mitsui等[30]发现应用DCS方案化疗联合曲妥珠单抗治疗HER2-neu阳性的不可切除胃癌患者, 可获得56.3%的手术转化率, 术后病例的总体生存时间超过18.3 mo. 因此, 以曲妥珠单抗为代表的靶向药物可用于转化治疗, 但是还需要更多的临床研究来提供高级别循证依据.

此外, 有学者发现联合放化疗是否可以作为不可切除胃癌“转化治疗”的方案尚存在争议. Rivera等[31]开展了同步放化疗IC/RT(伊立替康+顺铂+放疗) II 期临床试验, 结果发现其安全性差(死亡3/17)、R0切除率低(5/17), 难以实现不可切除胃癌的转化治疗. 而Ratosa等[32]采用5-Fu+顺铂联合同步放疗的方案, 发现总体手术转化率为64.3%, 手术病例R0切除率86.1%, 2年无病生存率82.9%, 2年总体生存率(57.1%)大于单纯化疗患者(<20%), 因此该方案是一个安全有效的选择. 总之, 放化疗联合方案用于不可切除胃癌的“转化治疗”的有效性和安全性尚需更多循证医学研究的论证.

3 “转化治疗”的个体化治疗方案

3.1 介入治疗 介入治疗如射频消融、动脉化疗栓塞、门静脉栓塞等, 对于消除血供丰富的转移灶具有较高的应用价值. 大约2%-9%的胃癌患者伴有同时性肝转移[33,34], 而仅有10%-20%的肝转移患者能够接受根治性切除[35], 其中位生存期不足6 mo. Cheon等[36]发现同期行胃癌D2根治术加射频消融或肝转移灶切除相对于单纯化疗能够显著提高患者的中位生存期(17.0 mo *vs* 8.1 mo)和3年生存率(31.7% *vs* 0%). Liu等[37]对同时性胃癌肝转移病例给予肝动脉化疗栓塞联合全身化疗后行胃癌D2根治术或单纯化疗, 结果其中位生存时间相对于单纯化疗明显延长(14 mo *vs* 8 mo). 因此, 介入治疗可以作为胃癌肝转移患者的“转化治疗”方案.

3.2 腹腔热灌注化疗 腹腔热灌注化疗针对伴有腹腔转移或隐匿性腹膜转移(腹腔探查发现转移结节或腹水癌细胞阳性者)的胃癌患者, 是通过温度为43 ℃±0.5 ℃含有化疗药物的生理盐水灌洗腹腔, 达到降低或消除腹腔转移风险的效果. Wu等[38]对隐匿性腹腔转移患者实施胃癌减瘤术, 并给予术中腹腔热灌注化疗(hyperthermic intraperitoneal chemotherapy, HIPEC)加全身化疗, 发现可以使其获得长达25 mo的中位生存期. 因此, 腹腔热灌注化疗可以作为隐

匿性腹腔转移患者的“转化治疗”方案. 尽管Xia等[39]发现对胃癌腹膜转移患者行腹腔镜胃癌并腹膜切除联合HIPEC可延缓肿瘤进展, 但是明确伴有腹腔转移如Krukenberg瘤或广泛腹腔结节者[40], 腹腔热灌注化疗仍然只能作为姑息性治疗而非“转化治疗”.

3.3 远隔脏器或淋巴结切除 对于可手术切除的远隔脏器转移如胃癌肝转移的切除尚无明确共识, 但是通常全身治疗后, 肝转移灶局限于肝外侧叶、个数较少、直径较小者可行肝外叶或半肝切除. Liu等[41]发现对于同时性肝转移患者, 同期行胃癌D2根治术联合肝转移灶切除相对于单纯性胃癌根治术, 其术后中位生存时间更长(24 mo *vs* 12 mo), 但是仅获得D1淋巴结清扫者的预后则没有改善. 值得注意的是, 尽管不可切除胃癌肝转移灶应该选择同期切除还是分期切除, 尚缺乏循证依据, 但是根据结直肠癌肝转移的研究来看, 两者的安全性和5年生存率并无差异, 而同期切除的费用更低、生活质量获益更高[42,43].

对于远隔淋巴结转移者, 尤其是腹主动脉旁淋巴结[No. 16a2-b1(PAN16a2-b1)]转移, 是否应该给予切除尚存在争议. 尽管Sasako等[44]开展的JCOG9501研究发现腹主动脉旁淋巴结的清扫并不能延长患者总体生存时间, 但是近年来的研究[45]发现行PAN16a2-b1淋巴结的清扫的患者有显著的生存获益. Wang等[46]应用XELOX化疗方案合并联合胃癌根治术治疗PAN16a2-b1转移, 结果化疗合并手术患者相对于单纯化疗者的无进展生存时间(18.1 mo *vs* 5.6 mo)及总体生存时间(超过58.7 mo *vs* 12.5 mo)均显著延长.

Tsuburaya等[47]通过CS化疗方案治疗腹腔动脉旁淋巴结融合或腹主动脉旁淋巴结转移, 并在转移淋巴结出现影像学缓解后给予胃癌根治术, 结果R0切除率达到82%, 病理反应率为51%, 3年及5年生存率达到59%和53%. 因此, 远隔脏器转移或淋巴结转移患者, 可以通过全身化疗联合手术切除达到“转化治疗”的目的.

3.4 免疫治疗 目前NCCN胃癌指南等尚未推荐免疫治疗作为不可切除胃癌的治疗方法, 而且免疫细胞过继转移疗法如CIK等, 尚缺乏用于不可切除胃癌转化治疗的研究. 但是日本的一项I期临床试验[48]发现LY6K-177肽疫苗可以使不可切除胃癌病灶显著缩小. 另外有研究[49]采用免疫调节剂云芝多糖联合CS化疗方案治疗1例胃癌肝转移患者, 结果使其肝转移灶完全缓解并获得胃癌D2根治术. 因此, 免疫治疗将来有可能成为不可切除胃癌“转化治疗”的方法, 但是目前尚缺乏循证医学证据.

创新盘点

本文归纳了不可切除胃癌转化治疗策略的概念, 全面总结了不可切除胃癌转化治疗的主要治疗方法以及病例选择的原则, 提出了不可切除胃癌转化治疗面临的挑战.

4 “转化治疗”的方案选择

有研究[50]发现, 单一不可切除因素、较高的化疗反应率和获得R0切除是使不可切除胃癌患者术后生存时间显著延长的重要因素, 而仅获得R1或R2切除者的预后则无明显改善[24]. 腹主动脉旁淋巴结转移和少于3个结节的肝外周叶转移的病例预后较好, 而腹膜转移、无法切除的远隔脏器转移则复发率高、预后较差[23,50], 因此, ECOG体力评分≤2分, 重要脏器功能可耐受, 仅有单一不可切除因素或有多个不可切除因素但有缓解可能者, 可给予“转化治疗”.

因此, 对于转化治疗有效, 不可切除因素部分或完全缓解者, 可行胃癌D2根治术, 并给予术后随访; 治疗后不可切除因素部分缓解, 但术后有肿瘤残余(R1或R2)者, 术后给予姑息治疗; 治疗后不可切除因素未缓解, 疾病稳定或进展者, 则无法给予手术, 继续给予姑息治疗.

值得注意的是, 不可切除胃癌的病情评价和方案选择尚缺乏权威的循证医学证据, 目前主要依赖MDT协作讨论来做出决策. 因此, 建设多学科诊疗模式和开展大样本、多中心的队列研究对于不可切除胃癌“转化治疗”的病例筛选、方案选择具有重要的意义.

5 结论

不可切除胃癌“转化治疗”的临床研究表明, 部分晚期患者经过有效的“转化治疗”可以赢得接受根治性胃癌切除术的机会, 能够显著提高其术后生存时间并改善其生存质量. 单一不可切除因素、较高的化疗反应率和获得R0切除及D2/D2+淋巴结清扫是不可切除胃癌患者获得长期术后生存时间的重要保证. 目前“转化治疗”在病情评估、病例筛选、方案选择等方面还缺乏权威的循证医学依据, 因此亟待开展大样本、多中心的队列研究甚至随机对照临床试验研究.

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应用要点

本文总结了不可切除胃癌转化治疗策略的概念与应用方法, 启示医生同行可以为该类患者选择更积极的“转化治疗”模式, 并且揭示了开展不可切除胃癌转化治疗的多中心、大样本研究的必要性与紧迫性.

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名词解释

转化治疗：即通过化疗、放疗、靶向、介入等综合治疗模式治疗不可切除胃癌，使其不可切除因素出现缓解，对其中有获得R0切除可能者实施胃癌D2/D2+根治术，最终使患者获得较长生存时间的治疗策略.

同行评价

本文选择了一个正在备受争议并且是临床关注的话题, 很精彩、值得探讨; 同时很好地提出了转化治疗的概念, 并对“不可切除”的概念也给予明确表述.

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