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述评 EDITORIAL

食管癌新辅助放化疗对手术及生存率的影响

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Impact of neoadjuvant chemoradiotherapy on surgery and survival in patients with esophageal carcinoma

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Abstract
Neoadjuvant chemotherapy is often used to treat solid tumors before surgery or during the perioperative period. It is often combined with radiotherapy to improve survival and cure rate and to protect normal organs. Surgery is still the most effective therapy for esophageal cancer. Preoperative (neoadjuvant) chemotherapy and radiotherapy as a treatment modality has been in existence for nearly 20 years. However, it remains controversial over whether neoadjuvant chemoradiotherapy can be used as the standard treatment for esophageal cancer. This paper sums up the impact of neoadjuvant chemotherapy on surgery and survival in patients with esophageal cancer. Moreover, we discuss the limitations and future directions of neoadjuvant chemotherapy for esophageal carcinoma.

Key Words: Esophageal neoplasm; Surgery; Radiotherapy; Antineoplastic agent; Postoperative complication; Prospective study; Randomized controlled trial; Meta-analysis

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摘要
新辅助化疗常应用于实体肿瘤的手术前或围手术期, 常联合应用放疗以提高生存率和治愈率, 并对器官加以保护. 手术仍是最有效的食管癌单一治疗手段. 术前的(新辅助)化疗加放疗虽已经作为治疗食管癌的3种方法中的综合治疗模式存在近20余年, 但他是否可作为食管癌的标准治疗模式仍存在争议. 本文阐述了新辅助放化疗对食管癌手术及生存率的影响, 提出了新辅助放化疗在食管癌治疗中的不足和发展方向.

关键词: 食管肿瘤; 外科治疗; 放射治疗; 抗肿瘤药; 术后并发症; 前瞻性研究; 随机对照试验; Meta分析

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0 引言
食管癌是常见的恶性肿瘤之一, 居世界癌症死因第7位[1], 中国癌症死因第4位. 大多数患者确诊时已是中晚期, 长期生存率较低[2]. 多数看似可切除的食管癌患者治愈前景黯淡. 放疗可控制食管癌的局部复发, 同时化疗也具有抗肿瘤复发转移的作用, 这为食管癌的治疗带来了希望. 已有研究提出化放疗联合手术治疗可切除性食管癌可延长患者长期生存率[3-5]. 同时, 术前放化疗食管癌患者看似比术后放化疗患者更能耐受放化疗所致毒性反应. 基于此, 一些关于新辅助放化疗治疗食管癌的III期临床试验已开展起来. 虽产生了令人鼓舞的结果, 但也带来了不容忽视的问题, 尤其对外科医生来说, 那就是新辅助放化疗可能会增加手术相关并发症和死亡率. 虽然近20年来, 针对这些问题随机对照试验(randomized controlled trials, RCTs)已展开研究,

■背景资料
一些关于新辅助放化疗治疗食管癌的III期临床试验已开展起来. 虽产生了令人鼓舞的结果, 但也带来了不容忽视的问题, 尤其对外科医生来说, 那就是新辅助放化疗可能会增加手术相关并发症和死亡率.

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■研发前沿
毫无疑问, 术前放化疗后, 外科医生将面临手术难度和术后并发症增加的可能, 例如放疗可能会增加吻合口漏和术后急性肺损伤的风险. 总之, 如何权衡新辅助放化疗获得的益处和该治疗手段带来的弊端, 已引起众多学者的重视.

但意见并不一致.

1 新辅助放化疗对食管癌病理完全缓解率的影响

既往一些RCTs进行了术前化疗与单纯手术治疗食管癌的研究[6,7], 但新辅助化疗病理完全缓解率的结果令人失望. 新辅助放化疗出现后在食管癌随机性研究中取得了令人瞩目的临床及病理缓解率[8,9]. 化疗联合放疗可提高杀伤不同周期肿瘤细胞的敏感性, 当放疗在空间上发挥抗肿瘤作用时, 化疗还可发挥抗肿瘤微转移灶的效用, 疗效互补并增益. 在最近的一篇Meta分析中, Lv等[10]对14个入选的RCTs[11-24](共包括1 737例患者)进行了分析, 发现新辅助放化疗后病理完全缓解率10.0%-45.5%. 虽然存在肿瘤的异质性和个体化的不同, 但统计结果还是令人满意的, 说明新辅助放化疗有可能使一些食管癌患者病理完全缓解, 从而达到延长生存期的目的.

2 新辅助放化疗对食管癌复发转移率的影响

对于可切除的食管癌患者来说, 外科手术仍是首选治疗手段, 但单纯手术治疗中晚期食管癌患者的5年生存率只有10%-20%[25-27]. 疗效不佳的主要原因是肿瘤复发和转移. 文献研究显示新辅助放化疗降低了食管癌的局部区域复发率(*OR* = 1.38, 95%CI: 1.23-1.63; *P* = 0.0002), 但并未显著降低食管癌的远处转移率(*OR* = 1.28, 95%CI: 0.85-1.58; *P* = 0.60)和总体肿瘤复发率(*OR* = 1.27, 95%CI: 0.86-1.65; *P* = 0.19), 同时也显示同步放化疗的显著优越性, 与序贯性放化疗相比, 该治疗手段能最大限度地发挥化疗和放疗的抗肿瘤协同效用[10]. 可见新辅助放化疗有可能通过降低食管癌局部区域复发率来提高患者的生存率, 同时也提示该治疗手段并未解决食管癌远处转移的问题. 将来是否可以通过改进术前放疗或化疗方案, 抑或联合应用分子靶向来抑制食管癌的远处转移, 这个问题尚需深入研究.

3 新辅助放化疗对食管癌手术切除率及并发症、相关死亡率的影响

食管癌患者如无远处转移证据($cT_{1-3}N_{0-1}M_0$), 则认为是可切除性的, 外科手术切除仍为首选手段, 但由于食管邻近纵隔重要组织器官影响了肿瘤的完整切除, 同时食管癌确诊时往往存在微转移灶, 这为肿瘤的复发转移创造了条件, 从而限制了手术治疗食管癌的疗效. 研究结果显示, 虽然单纯手术比新辅助放化疗似乎有较高的食管癌手术切除率, 但二者合并优势比显示无意义(*OR* = 0.82, 95%CI: 0.39-1.73; *P*<0.34). 然而, 新辅助放化疗完全手术切除率明显比单纯手术高(*OR* = 1.53, 95%CI: 1.33-2.84; *P* = 0.007)[10]. 虽然手术切除, 淋巴结清扫的范围和效果与主刀外科医生的手术技能有很大关系, 但有理由相信新辅助放化疗可通过肿瘤降期从而有利于肿瘤完全切除[28,29], 这也解释了为何新辅助放化疗后食管癌患者的局部区域复发率较低.

另外, 研究表明新辅助放化疗的并发症发生率与单纯手术比较并未显示差异(*OR* = 1.33, 95%CI: 0.94-1.88; *P* = 0.04). 虽然二组总体死亡率无差异(*OR* = 1.12, 95%CI: 0.89-2.48; *P* = 0.503), 但数据分析显示新辅助放化疗组的手术相关死亡率相对较高(*OR* = 1.78, 95%CI: 1.14-2.78; *P* = 0.79)[10]. 毫无疑问, 术前放化疗后, 外科医生将面临手术难度和术后并发症增加的可能, 例如放疗可能会增加吻合口漏和术后急性肺损伤的风险. 总之, 如何权衡新辅助放化疗获得的益处和该治疗手段带来的弊端, 已引起众多学者的重视.

4 新辅助放化疗对食管癌患者生存率的影响

单纯手术治疗食管癌疗效并不满意. 迄今为止, 各式各样的综合治疗手段层出不穷[30-32]. 无论是术前放疗还是术后放疗, 都缺乏有力证据显示有益于延长生存期[33,34]. 术后化疗常用以研究预防、延缓或治疗食管癌的复发转移, 然而只有很少的RCTs能提供术后化疗有益于患者提高生存率的证据[35,36]. 此外, 也有一些RCTs进行了新辅助化疗治疗食管癌的研究, 但结果令人失望, 当前新辅助化疗手段仍不足以提高食管癌患者的总体生存率[37,38]. 而新辅助放化疗是否能延长食管癌患者生存期意见仍未统一. 但最新Meta分析显示新辅助放化疗与单纯手术比较, 1年生存率对比无差异, 但2、3、4、5年生存率新辅助放化疗显著提高. 同时显示同步放化疗5年生存率显著优于单纯手术(*OR* = 1.45, 95%CI: 1.26-1.79; *P* = 0.015), 但序贯性放化疗5年生存率未显示优势(*OR* = 0.85, 95%CI: 0.64-1.35; *P* = 0.26)[10]. 虽然放化疗治疗方法固有盲法在一定程度上限制了RCTs和Meta分析的研究质量[39,40], 但Meta分析结果相对更具说服力, 说明新辅助放化疗有益于可切除性食管癌患者的长期生存, 其原因与降低了肿瘤的局部区域复发率有关.

5 结论

在总体上, 大多数试验均发现新辅助放化疗的食管癌患者预后更好, 并且Meta分析结果显示新辅助放化疗与单纯手术治疗食管癌相比, 能提高患者长期生存率, 降低肿瘤局部区域复发率. 二者切除率合并优势比显示虽无意义, 但新辅助放化疗与单纯手术治疗食管癌相比完全切除率显著提高. 不容忽视的是, 新辅助放化疗治疗食管癌伴随着术后死亡率增加的风险. 由于文献的研究对象来自不同种族、人群, 受到多种因素的影响, 故此结论尚需大样本多中心随机对照临床研究进一步论证, 欲证实该结论还需要大约2 000例患者甚至更多. 另外, 该研究对单纯手术患者涉及到科学性和伦理道德问题, 因此, 在实践中临床医生对于该研究的可行性问题应慎重对待并妥善处理.

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■相关报道

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■同行评价
本文选题实用, 观点鲜明, 论据充分, 具有较好的参考价值.

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• 消息 •

WJC, *WJGE*, *WJGO*, *WJGS*, *WJH*, *WJR* 6本期刊被PMC收录

本刊讯 我们于2010-08-17收到PubMed Central(PMC)的通知, 经过美国国立医学图书馆机构咨询委员会The Literature Selection Technical Review Committee评定, 决定*WJC*, *WJGE*, *WJGO*, *WJGS*, *WJH*, *WJR* 6本期刊被PMC收录. PMC是一个提供生命科学期刊文献的全文数据库, 他是由隶属美国国立医学图书馆(National Library of Medicine)的国家生物技术信息中心(National Center for Biotechnology Information)所创建与管理的. (常务副总编辑: 张海宁 2010-08-17)