· 综述 ·

食管鳞癌新辅助化疗的研究进展

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【摘要】 我国是全世界食管癌高发国家，95%为食管鳞癌。外科手术是治疗食管鳞癌的主要手段，但单纯手术对局部晚期食管鳞癌患者疗效较差。与术后辅助治疗比较，新辅助治疗可使食管鳞癌患者肿瘤体积缩小，提高手术切除率，消灭亚临床远处转移灶，可能延长患者生存时间、改善预后。笔者结合近年循证医学证据，对食管鳞癌新辅助化疗的研究进展进行综述。

【关键词】 食管肿瘤；　食管鳞癌；　新辅助化疗；　外科手术
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Research progress of neoadjuvant chemotherapy for esophageal squamous cell carcinoma

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【**Abstract**】 China is a high risk region of esophageal cancer in the world, and 95% of the esophageal cancer is the squamous cell carcinoma. Surgery is the main therapy for esophageal squamous cell carcinoma, however, the efficacy of single surgery for locally advanced esophageal squamous cell carcinoma is unsatisfactory. Compared with postoperative adjuvant treatment, neoadjuvant chemotherapy may reduce tumor volume, increase surgical resectability, eliminate subclinical metastases, prolong survival time and improve prognosis of patients with esophageal squamous cell carcinoma. Through combining recent evidence-based medicine, the authors review research progress of new adjuvant chemotherapy for esophageal squamous cell carcinoma.

【**Key words**】 Esophageal neoplasms; Squamous cell carcinoma; Neoadjuvant chemotherapy; Surgical procedures, operative
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我国是全世界食管癌高发国家，每年新发病例数>28.7 万例、死亡病例数为 21.1 万例。其发病率居我国各类恶性肿瘤第 5 位，病死率居第 4 位[1]。我国食管癌患者中 95%为食管鳞癌[2]。外科手术是治疗食管鳞癌的主要手段，但单纯手术对局部晚期食管鳞癌患者疗效较差。病理学分期为 T3~T4 期或区域淋巴结分期晚于 N1 期的食管鳞癌患者，单纯行外科手术治疗后 3 年生存率为 10%~25%[3]。单一手术治疗效果欠佳，促使食管鳞癌治疗理念和模式逐步转变为以手术为主，联合放疗和（或）化疗的综合治疗。但现有研究结果显示：与单纯手术治疗比较，联合术后辅助治疗并不能显著延长食管鳞癌患者生存时间，却可能增加术后并发症发生率[4-5]。

1　新辅助化疗的优势

与术后辅助治疗比较，新辅助治疗可使食管鳞癌患者肿瘤体积缩小、一定程度缓解吞咽困难症状，提高手术切除率，消灭亚临床远处转移灶，从而延长患者生存时间、改善预后[6]。

目前尚缺乏研究结果证实食管鳞癌患者行新辅助放疗有效。一项 Meta 分析结果显示：食管鳞癌患者行新辅助放疗后，5 年生存率绝对获益仅为 4%[7]。2017 年美国国立综合癌症网络（NCCN）指南和日本最新指南均未推荐新辅助放疗为食管鳞癌最佳治疗方式[8-9]。2009 年英国医学研究委员会（MRC）的大样本研究结果显示：新辅助化疗可有效提高食管鳞癌患者术后 5 年生存率[10]。也有较多研究结果显示：新辅助放化疗可为食管鳞癌患者带来生存获益[11-12]。2012 年《新英格兰杂志》的一项研究结果显示：新辅助放化疗尽管可能导致患者 WBC 计数减少、厌食、乏力，但可有效提高患者术后生存率[13]。关于食管鳞癌新辅助化疗与新辅助放化疗效果比较的研究较少[14-15]。新辅助放化疗过程中，放疗和化疗毒性相互叠加，更易引起患者心、肺功能损害[16]。新辅助化疗应是目前进展期食管鳞癌较好的治疗方案。

2　新辅助化疗效果评价

客观的食管鳞癌新辅助化疗效果评价标准十分重要。WHO 相关标准及实体瘤疗效评价标准是目前较为常用的标准。已有前瞻性研究结果证实：与 WHO 标准比较，实体瘤疗效评价标准更为准确[17]。新辅助化疗后获得病理学完全缓解的食管鳞癌患者预后显著更好[18]。Mandard 等[19]将行新辅助治疗后食管鳞癌患者残留肿瘤细胞数量分为 1~5 级，用以评价新辅助化疗效果和患者预后，其研究结果证实：该分级与患者预后具有较好相关性。Schneider 等[20]对该标准进行改良，提出 Cologne Regression Scale：1 级为食管鳞癌残留肿瘤细胞数量百分比>50%，2 级为 10%~50%，3 级为<10%，4 级为无肿瘤细胞残留。上述两项评价标准在国外均被广泛

应用。R_0 切除率也被用于评价新辅助治疗效果[21]。日本 Hamai 等[22]的研究结果显示：PET-CT 检查中，食管癌最大标准摄取值下降率与患者预后相关，且其>70%时，提示患者新辅助化疗效果良好。Van Olphen 等[23]的研究结果显示：食管腺癌患者肿瘤组织中 P53 和性别决定相关基因簇 2 蛋白的异常表达可有效预测新辅助治疗效果。

3　新辅助化疗方案

新辅助化疗概念最早由美国 Feri[24] 于 1982 年提出。2009 年 MRC 的研究结果显示：新辅助化疗组食管癌患者（400 例，顺铂+5-氟尿嘧啶）术后 2、5 年生存率分别为 43%、23%，直接手术组患者（402 例）分别为 34%、17%，两组患者生存情况比较，差异有统计学意义（风险比为 0.84，95%可信区间为 0.72～0.98，P=0.03）[10]。日本肿瘤协作组研究结果显示：新辅助化疗组食管鳞癌患者（164 例）术后 5 年生存率显著优于术后辅助化疗组患者（166 例，55%比 43%，风险比为 0.73，95%可信区间为 0.54～0.99，P=0.04）[25]。顺铂+5-氟尿嘧啶逐渐成为食管癌新辅助化疗标准方案。Boonstra 等[26]的随机对照研究结果显示：新辅助化疗组食管鳞癌患者（85 例，顺铂+依托泊苷）术后中位总体生存时间和 2、5 年生存率分别为 16 个月和 42%、26%，直接手术组患者（84 例）分别为 12 个月和 30%、17%，两组患者术后生存情况比较，差异有统计学意义（风险比为 0.71，95%可信区间为 0.51～0.98，P=0.03）。Yamasaki 等[27]对 162 例行新辅助化疗食管鳞癌患者的随机对照研究结果显示：顺铂+5-氟尿嘧啶+多西他赛组患者 R_0 切除率、2 年无复发生存率、2 年总体生存率分别为 96.2%、64.1%、78.6%，顺铂+5-氟尿嘧啶+阿霉素组患者上述指标分别为 95.9%、42.9%、65.4%，两组比较，R_0 切除率差异无统计学意义（P=0.93），顺铂+5-氟尿嘧啶+多西他赛组患者 2 年无复发生存率、2 年总体生存率均优于顺铂+5-氟尿嘧啶+阿霉素组患者（P<0.05）。日本 Yamashita 等[28]的研究结果显示：顺铂+5-氟尿嘧啶+多西他赛组新辅助化疗食管鳞癌患者术后总体生存时间、无进展生存率（58.3%比 30.5%）均显著优于顺铂+5-氟尿嘧啶组患者。食管鳞癌患者新辅助化疗不同方案的疗效尚待更多前瞻性研究结果进一步证实。

4　新辅助化疗周期及手术时机

吴昊等[29]的研究结果显示：食管鳞癌患者新辅助化疗 2 个周期与 3～4 个周期近期疗效比较，差异无统计学意义；短周期新辅助化疗患者依从性更好。Motoori 等[30]提出：对行 2 个周期新辅助化疗的食管鳞癌患者，完成第 1 个周期后，行 CT 检查判断化疗效果（原发肿瘤体积缩小幅度≥20%为有效、反之为无效），无效者无需再行第 2 个周期化疗。

Kathiravetpillai 等[31]指出：食管癌患者完成新辅助化疗 8 周后手术与 8 周内手术预后比较，差异无统计学意义。Müller 等[32]和 Shapiro 等[33]均认为：食管鳞癌患者完成新辅助治疗后延期手术虽不能改善患者远期总体生存情况，但病理学完全缓解率更高；前者认为新辅助治疗完成时间与手术间隔时间可>40 d，后者认为间隔时间可延长至 12 周，但后者也指出延期手术患者术后并发症发生率更高（肺部并发症最常见）。Haisley 等[34]的研究结果显示：新辅助化疗完成时间与手术间隔时间为 85～98 d 的食管鳞癌患者病理学完全缓解率更高。

综上，笔者认为：临床上对新辅助化疗不良反应较重的食管鳞癌患者可适当延迟手术，但须注意术后并发症的发生。

5　小结

自 20 世纪 90 年代末以来，食管癌新辅助化疗的作用逐渐被认可和接受，并被日本、英国等国家列为标准治疗方案[9,35]。随着影像学检查技术日臻成熟，以及胸腔镜和纵隔镜的联合应用，食管癌临床分期准确性得以提高，临床研究应在第 8 版食管癌 TNM 分期指南指导下，设立更高的标准，以期得出更可靠的结论[36]。

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