

新辅助放化疗对食管癌手术和预后的影响

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【摘要】 目的 对术前放化疗(新辅助放化疗,CRTS)与单纯手术(S)治疗食管癌的随机对照试验研究(RCTs)进行 Meta 分析,探讨 CRTS 对食管癌手术及预后的影响。**方法** PubMed 及手工检索所有已发表的关于 CRTS 与 S 治疗食管癌的 RCTs。检验异质性,并根据异质性结果选择相应的效应模型。**结果** 14 项 RCTs 纳入本研究,共 1737 例食管癌患者,文献质量评价根据 Cochrane Reviewers' Handbook 4. 2. 2 为 A 或 B。CRTS 组与 S 组比较,1 年生存率差异无统计学意义,但 CRTS 组 2 年、3 年、4 年、5 年生存率明显提高。相对危险度(RR)分别为 1.06 (95% CI 0.99 ~ 1.13; $P=0.1$)、1.18 (95% CI 1.04 ~ 1.33; $P=0.01$)、1.39 (95% CI 1.23 ~ 1.58; $P<0.00001$)、1.27 (95% CI 1.04 ~ 1.55; $P=0.02$)、1.41 (95% CI 1.18 ~ 1.69; $P=0.0001$)。切除率二者差异无统计学意义,RR 1.01 (95% CI 0.97 ~ 1.05; $P=0.67$),但 CRTS 组有较高的完全切除率,RR 1.44 (95% CI 1.23 ~ 2.74; $P=0.008$)。总体死亡率二者比较,差异无统计学意义,RR 1.12 (95% CI 0.89 ~ 2.48; $P=0.503$),但 CRTS 组手术相关死亡率相对较高,RR 1.70 (95% CI 1.12 ~ 2.56; $P=0.01$)。二者并发症发生率差异无统计学意义,RR 1.23 (95% CI 0.93 ~ 1.78; $P=0.13$)。二组远处转移率及总体肿瘤复发率比较,均差异无统计学意义,RR 分别为 1.18 (95% CI 0.75 ~ 1.68; $P=0.71$)、1.07 (95% CI 0.76 ~ 1.56; $P=0.18$),但 CRTS 组局部区域复发率降低,RR 1.18 (95% CI 1.22 ~ 1.61; $P=0.0001$)。CRTS 组病理完全缓解率达 10.0% ~ 45.5%。同步 CRTS 与序贯性 CRTS 比较,前者(RR 1.34, 95% CI 1.06 ~ 1.89, $P=0.013$)比后者(RR 0.86, 95% CI 0.67 ~ 1.38, $P=0.29$)更有益于提高患者 5 年生存率。**结论** 与 S 治疗食管癌相比,CRTS 降低了肿瘤局部区域复发率,提高了患者的 3 年、5 年生存率;手术切除率二者差异无统计学意义,而 CRTS 完全切除率提高,但其手术相关死亡率相对较高。二者并发症发生率比较差异无统计学意义。

【关键词】 食管肿瘤; 放射疗法; 抗肿瘤药; 手术后并发症; 前瞻性研究; 随机对照试验; Meta 分析

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【Abstract】 Objective To evaluate the role of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma by performing a meta-analysis of randomized controlled trials (RCTs) that compared neoadjuvant chemoradiotherapy and surgery with surgery alone for esophageal carcinoma. **Methods** PubMed and manual searches were done to identify all published RCTs that compared neoadjuvant chemoradiotherapy and surgery with surgery alone for esophageal cancer. According to the test of heterogeneity, a fixed-effects model or a random effects model was used and the relative risk (RR) was the principal measure of effect. **Results** Fourteen RCTs that included 1737 patients were selected with quality assessment ranging from A to C (Cochrane Reviewers' Handbook 4. 2. 2). Relative risk (95% confidence interval [CI]; P value), expressed as chemoradiotherapy and surgery versus surgery alone chemoradiotherapy-surgery (CRTS) versus surgery alone (S); value >1 favor CRTS, was 1.06 (95% CI 0.99 ~ 1.13; $P=0.1$) for 1-year survival, 1.18 (95% CI 1.04 ~ 1.33; $P=0.01$) for 2-year survival, 1.39 (95% CI 1.23 ~ 1.58; $P<0.00001$) for 3-year survival, 1.27 (95% CI 1.04 ~ 1.55; $P=0.02$) for 4-year survival, 1.41 (95% CI 1.18 ~ 1.69; $P=0.0001$) for 5-year survival, 1.01 (95% CI 0.97 ~ 1.05; $P=0.67$) for rate of resection, 1.44 (95% CI 1.23 ~ 2.74; $P=0.008$) for rate of complete resection, 1.70 (95% CI 1.12 ~ 2.56; $P=0.01$) for operative mortality, 1.12 (95% CI 0.89-2.48; $P=0.503$) for all treatment mortality, 1.23 (95% CI 0.93 ~ 1.78; $P=0.13$) for the rate of adverse treatment, 1.18 (95% CI 1.22 ~ 1.61; $P=0.0001$) for local-regional cancer recurrence, 1.18 (95% CI 0.75 ~ 1.68; $P=0.71$) for distant cancer recurrence, and 1.07 (95% CI 0.76 ~ 1.56; $P=0.18$) for all cancer recurrence. A complete pathological response to chemoradiotherapy occurred in 10% ~ 45.5% of patients. The 5-year survival benefit was most pronounced when chemotherapy and radiotherapy were given concurrently (RR

1.34, 95% CI 1.06 ~ 1.89, $P=0.013$) instead of sequentially (RR 0.86, 95% CI 0.67 ~ 1.38, $P=0.29$). **Conclusions** Compared with surgery alone, neoadjuvant chemoradiotherapy and surgery improved 3-year, 5-year survival and reduced local-regional cancer recurrence. It was associated with a higher rate of complete (R0) resection and operative mortality although no significance about the rate of esophageal resection, There was a nonsignificant trend toward increased all treatment mortality with neoadjuvant chemoradiotherapy. Concurrent administration of neoadjuvant chemotherapy and radiotherapy was superior.

【Key words】 Esophageal neoplasms; Radiotherapy; Antineoplastic agents; Postoperative complications; Prospective studies; Randomized controlled trials; Meta-analysis

食管癌是常见的恶性肿瘤之一,居世界癌症死因第七位,中国癌症死因第四位^[1],多数患者确诊时已是中晚期,长期生存率较低^[2]。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%^[3-5]。其疗效不佳的主要原因在于肿瘤复发和转移。多数看似可切除的食管癌患者治愈前景黯淡。由于食管邻近纵隔重要组织器官影响了肿瘤的完整切除,同时进行食管癌确诊时微转移灶常已存在,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。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。已有研究提出放化疗联合手术治疗可延长切除性食管癌患者长期生存率^[6-8]。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,尤其对外科医师来说,新辅助放化疗可能会增加手术相关并发症和死亡率。针对这些问题已展开随机对照试验(RCTs)研究,但意见并不一致。由于一些RCTs样本量较小,说服力有限,因此本中心针对术前放化疗(新辅助放化疗,CRTS)与单纯手术(S)治疗可切除性食管癌的RCTs展开了一项Meta分析。

资料与方法

一、一般资料

由两名研究者各自独立地通过PubMed数据库和手工进行检索,检索出所有已发表的关于CRTS和S治疗可切除性食管癌的RCTs。检索结果如不一致,重新检查直至意见一致。入选文献语种不限,肿瘤组织类型不限;未发表的RCTs排除在外。在PubMed数据库上通过检索式“esophageal neoplasms/surgery OR esophagectomy OR oesophagectomy OR esophageal cancer OR oesophageal cancer”检索出37 604篇文献,继以检索式“antineoplastic agents OR chemotherapy OR radiotherapy”检索出文献2 448 725篇,两次检索策略以布尔运算符“AND”再次检索,得到8974篇关于化疗、放疗、手术治疗食管癌的文獻,随后以“randomized controlled trial”对该检索结果加以限制,产生340篇文献。从这些文献中评审出所有关于CRTS和S治疗食管癌的RCTs,最终产生14篇符合纳入标准的文献^[9-22]。

二、方法

由两名研究者各自独立地对入选文献进行文献质量评价,按照Cochrane Reviewers' Handbook 4.2.2^[23]标准将文献分为A、B、C三个等级。若文献评价等级不一致,检查其中偏差直至意见一致。试验数据的提取也将由两名研究者各自独立完成,比较其中偏差直至取得共识。Meta分析结果包括1年、2年、3年、4年、5年生存率,食管癌切除率(包括根治性切除和姑息性切除,转流术及探查术不包括在内),完全切除率,手术相关死亡率,并发症发生率,总体死亡率,局部区域复发率,远处转移率及总体肿瘤复发率。因大多文献中手术相关死亡率是指术后30 d内死亡率,故提取术后30 d死亡率数据作为手术相关死亡率定量分析。术后并发症包括文献中所有报道过的如吻合口漏、肺炎、呼吸衰竭等。总体死亡率包括术前死亡率(通常由放化疗所致)及术后死亡率。对5年生存数据进行敏感性分析,以评价肿瘤组织学类型(鳞癌或腺癌)及同步或序贯性CRTS对生存分析的影响。

三、统计学分析

统计软件为Revman 4.2。对各研究进行异质性检验。如果相对危险度(RR)齐性,采用固定效应模型作合并效应量估计。如果RR非齐性,采用随机效应模型进行统计。假设齐性检验的 α 值为0.1,若齐性检

验的 $P > 0.1$, 认为 RR 是齐性的, 否则为非齐性。 RR 为判定 CRTS 组与 S 组数据对比的基本指标, $RR > 1$ 支持 CRTS 组(具有较高的期望事件发生率)。绘制漏斗图, 通过观察其对称性, 评估发表偏倚的影响^[24]。由于文献中患者原始数据不够充分, 中位生存数据并未进行 Meta 分析。

结 果

14 个入选 RCTs 共包括 1737 例患者。由于放化疗治疗方法固有盲法的限制, RCTs 研究质量评估只有 4 篇 A 级, 其余 10 篇为 B 级。CRTS 组与 S 组 1 年生存率对比差异无统计学意义, 但 2 年、3 年、4 年、5 年生存率 CRTS 组优于 S 组(图 1, 2)。1 年、2 年、3 年、4 年、5 年生存率 RR 分别如下: 1.06 (95% CI 0.99 ~ 1.13; $P = 0.1$)、1.18 (95% CI 1.04 ~ 1.33; $P = 0.01$)、1.39 (95% CI 1.23 ~ 1.58; $P < 0.00001$)、1.27 (95% CI 1.04 ~ 1.55; $P = 0.02$)、1.41 (95% CI 1.18 ~ 1.69; $P = 0.0001$)。

Review: Impact of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma
 Comparison: 01 CRTS versus S
 Outcome: 03 3yr-survival rate

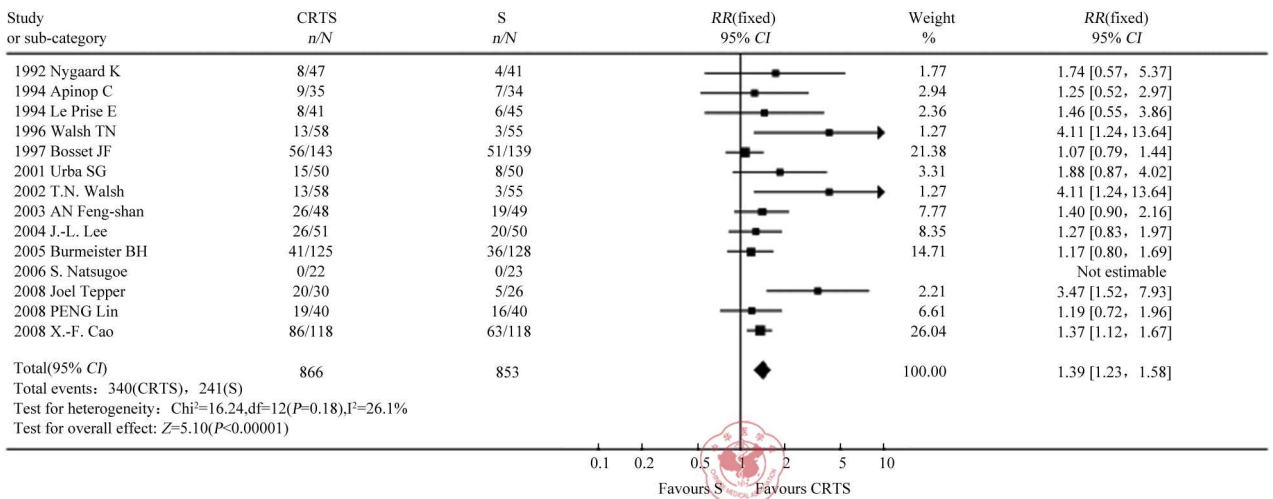


图1 两组3年生存率

Review: Impact of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma
 Comparison: 01 CRTS versus S
 Outcome: 05 5yr-survival rate

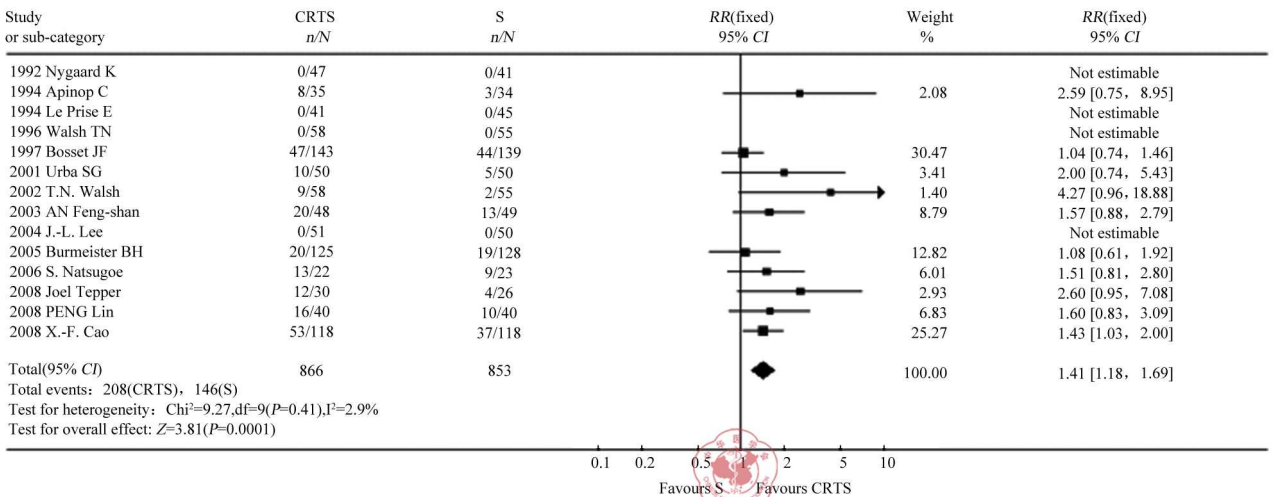


图2 两组5年生存率

对 5 年生存率进行敏感性分析后发现, 若只入选食管鳞癌 RCTs, 二组 5 年生存率比较结果类似 (RR 1.32, 95% CI 1.07 ~ 1.62; $P = 0.09$)。由于只有 2 组 RCTs 单独研究食管腺癌^[12, 15], 且只有 1 篇给出 5 年生存率, 故剔除鳞癌文献进行 Meta 分析不可行。如只入选同步放化疗 RCTs, CRTS 组 5 年生存率显著优于 S

组(RR 1.34, 95% CI 1.06 ~ 1.89; $P=0.013$);若只入选序贯性放化疗 RCTs, CRTS 组 5 年生存率未显示优势(RR 0.86, 95% CI 0.67 ~ 1.38; $P=0.29$)。

虽然 S 组比 CRTS 组似乎有较高的食管癌手术切除率,但二者合并 RR 显示差异无统计学意义(RR 1.01, 95% CI 0.97 ~ 1.05; $P=0.67$)。然而, CRTS 组完全手术切除率明显比 S 组高(RR 1.44, 95% CI 1.23 ~ 2.74; $P=0.008$)。同时 CRTS 组有 10.0% ~ 45.5% 的病理完全缓解率。对于手术切除及淋巴结清扫的范围和质量,很难从入选文献中作出评估。

二组并发症发生率显示差异无统计学意义(RR 1.23, 95% CI 0.93 ~ 1.78; $P=0.13$)。虽然二组总体死亡率差异无统计学意义(RR 1.12, 95% CI 0.89 ~ 2.48; $P=0.503$),但数据分析显示 CRTS 组的手术相关死亡率相对较高(RR 1.70, 95% CI 1.12 ~ 2.56; $P=0.01$),见图 3。

Review: Impact of neoadjuvant chemoradiotherapy on prognosis and surgery for esophageal carcinoma
Comparison: 01 CRTS versus S
Outcome: 06 OPERATIVE MOTALITY

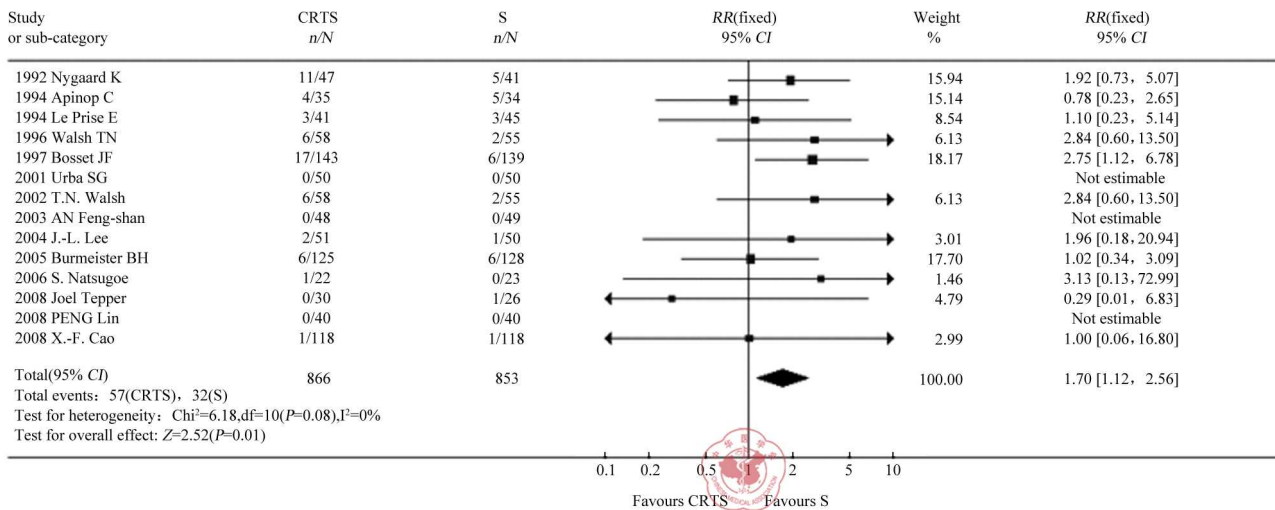


图3 两组手术相关死亡率

至于肿瘤的复发转移率, CRTS 组局部区域复发率较低(RR 1.18, 95% CI 1.21 ~ 1.61; $P=0.0001$),但二组远处转移率(RR 1.18, 95% CI 0.75 ~ 1.68; $P=0.71$)和总体肿瘤复发率(RR 1.07, 95% CI 0.76 ~ 1.56; $P=0.18$)比较差异无统计学意义。漏斗图呈倒置的基本对称的图形,提示无发表偏倚(图 4)。

讨论

食管癌如无远处转移证据($cT1 \sim cT3, N0 \sim N1, M0$)则认为可切除性的,外科手术切除仍为首选手段。然而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^[25-27]。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^[28-29]。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^[30-31]。此外,也有一些 RCTs 进行了术前化疗与 S 治疗食管癌的研究^[32-33],但新辅助化疗病理完全缓解率的结果令人失望,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^[34-35]。

CRTS 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^[36-37]。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。CRTS 通过肿瘤降期有利于肿瘤切除^[38-39],然而是否能延长食管癌患者生存期意见仍未统一。同时, CRTS 似乎增加了食管癌切除术并发症和死亡率的风险,因此 S 治疗食管癌仍是大多数临床 III 期随机研究的对照组。

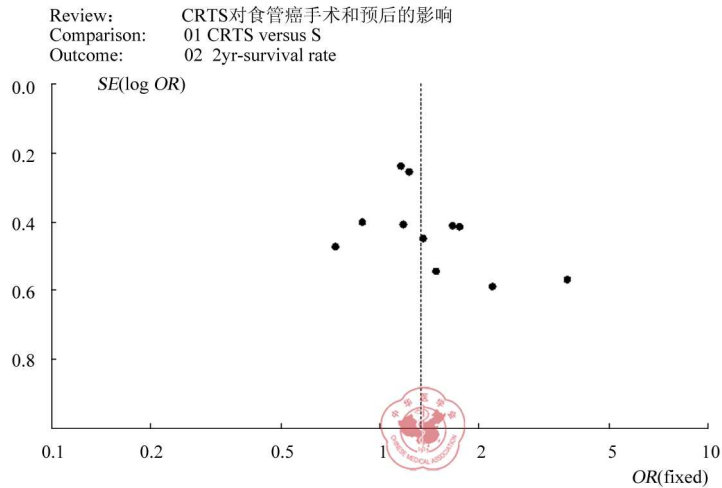


图4 文献发表偏倚度

目前为止,仍少有检验 CRTS 治疗食管癌疗效的 Meta 分析发表,且以前研究均着重于 3 年生存率的综合分析。与此相比,本分析收集的 RCTs 更全(达 14 篇),获取的生存数据更长(达 5 年生存率),同时漏斗图显示无发表偏倚,因此本 Meta 分析结果更具说服力。结果显示 CRTS 有益于可切除性食管癌患者的长期生存,原因与降低了肿瘤的局部区域复发率有关。然而,CRTS 并未显著降低食管癌的远处转移率。同时敏感性分析显示同步放化疗的显著优越性,与序贯性放化疗相比,该治疗手段能最大程度地发挥化疗和放疗的抗肿瘤协同效用。

在手术切除率上,虽 S 组倾向于更多的手术切除,但二者合并 *RR* 显示差异无统计学意义。而 CRTS 组完全切除率显著提高,这也提示 CRTS 能使肿瘤降期并有利于肿瘤完全切除,同时也解释了为何在 CRTS 组局部区域复发率较低。二组总体死亡率(*RR* 1.12, 95% *CI* 0.89 ~ 2.48; *P* = 0.503) 和并发症发生率(*RR* 1.23, 95% *CI* 0.93 ~ 1.78; *P* = 0.13) 比较虽差异无统计学意义,但合并 *RR*(*RR* 1.70, 95% *CI* 1.12 ~ 2.56; *P* = 0.01) 提示 CRTS 组手术相关死亡率相对较高。毫无疑问,CRTS 后,外科医师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 CRTS 提高食管癌患者生存率的益处和该治疗手段增加术后死亡风险的弊端,已引起众多学者的重视。

综上所述,本 Meta 分析显示 CRTS 与 S 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 *RR* 显示虽无统计学意义,但 CRTS 与 S 治疗食管癌相比完全切除率显著提高。不容忽视的是,CRTS 治疗食管癌伴随着术后死亡率增加的风险。由于本组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。

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