

术前放化疗与单纯手术治疗可切除食管癌的Meta分析

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■背景资料

中国食管癌粗发
病率和死亡率
均居世界第1位。
CRTS治疗可切除
食管癌得到越来
越多的关注, 已进
行大量的临床研
究, 但研究结果不
一致。

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Preoperative chemoradiotherapy followed by surgery versus surgery alone for resectable oesophageal carcinoma: A meta-analysis

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Abstract

AIM: To assess the efficacy of preoperative chemoradiotherapy followed by surgery (CRTS) in the management of resectable esophageal carcinoma.

METHODS: Randomized controlled trials (RCTs) comparing the efficacy of preoperative chemoradiotherapy versus surgery alone (SA) in the treatment of resectable oesophageal carcinoma were searched in PubMed, China National Knowledge Infrastructure (CNKI) and Wan Fang databases. The RevMan 5.1 software was used for meta-analysis.

RESULTS: This meta-analysis included 21 RCTs.

Compared to the SA group, the 1-, 3-, and 5-year survival rates were significantly higher in the CRTS group (all $P < 0.05$). The 3- and 5-year survival rates for the Eastern patients, Western patients, patients undergoing concurrent chemoradiotherapy, and patients with squamous cell carcinoma were significantly higher in the CRTS group (all $P < 0.05$). There were no statistical significances in the 3- and 5-year survival rates for patients undergoing sequential chemoradiotherapy or patients with adenocarcinoma between the two groups (all $P > 0.05$). Compared to the RCTS group, the surgery rate in the SA group was higher ($P < 0.05$), while the CRTS group had significantly higher radical resection rate, R0 resection rate and lower postoperative local recurrence rate (all $P < 0.05$). The differences in postoperative complication incidence, post-operative distant metastasis and postoperative mortality rate were not statistically significant between the two groups (all $P > 0.05$).

CONCLUSION: CRTS can significantly improve the survival and surgical conditions of patients with resectable esophageal carcinoma.

Key Words: Esophageal carcinoma; Chemoradiotherapy followed by surgery; Surgery alone; Randomized controlled trials; Meta-analysis

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摘要

目的: 探讨术前放化疗(chemoradiotherapy followed by surgery, CRTS)与单纯手术治疗对可切除食管癌患者生存及手术的影响。

方法: 检索PubMed、中国知网和万方数据资源系统中所有CRTS与单纯手术(surgery alone, SA)治疗可切除食管癌的随机对照研究(randomized controlled trial, RCT), 应用RevMan 5.1软件进行Meta分析。

结果: 共21篇文献。CRTS组比SA组提高了1、

■同行评议者

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3、5年生存率, 差异均有统计学意义($P<0.05$); 提高了东方、西方、同步放化疗和鳞癌患者3、5年生存率, 差异均有统计学意义($P<0.05$). 两组序贯放化疗、腺癌患者3、5年生存率相比差异均无统计学意义($P>0.05$). SA组比CRTS组有较高的手术率, 差异有统计学意义($P<0.05$); 而CRTS组比SA组有更显著的根治切除率、R0切除率和较低的术后局部复发率, 差异均有统计学意义($P<0.05$). 两组术后并发症发生率、远处转移率及死亡率比较, 差异均无统计学意义($P>0.05$).

结论: CRTS比SA明显改善了可切除食管癌患者的生存预后及手术情况.

关键词: 食管癌; 术前放化疗; 单纯手术; 随机对照研究; Meta分析

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<http://www.wjgnet.com/1009-3079/20/3140.asp>

0 引言

食管癌是原发于食管黏膜上皮的恶性肿瘤, 全球年新发病例约为482 300例, 每年年死亡约406 800例^[1], 术后5年总生存率2001年和2005年间保持在30.5%^[2]. 目前认为与单一外科手术相比较, 术前放疗对延长总体远期生存作用有限, 化疗增加患者的不良反应, 对提高切除率和完全性切除率不明显^[3]. 因此, 近年来食管癌术前放化疗(chemoradiotherapy followed by surgery, CRTS)得到越来越多的关注, 已进行了大量临床研究, 但其是否能改善可切除食管癌患者生存预后及手术情况的研究结果不一致. 为此我们选择关于CRTS对比单纯手术(surgery alone, SA)治疗可切除食管癌的前瞻性临床随机对照研究(randomized controlled trial, RCT)进行Meta分析, 以期临床决策提供有价值的循证依据.

1 材料和方法

1.1 材料 检索PubMed、中国知网和万方数据资源系统, 检索文献起止时间均为1992-01/2012-04. 所有检索均采用主题词与自由词相结合的方式, 检索词主要包括“neoadjuvant therapy、chemoradiotherapy followed by surgery、chemoradiotherapy、surgery or operation or esophagectomy、esophagus or esophageal cancer or carcinoma”等及对应的中文检索词, 检索语种不限,

同时运用搜索引擎在互联网上查找相关文献, 以期扩大检索范围.

1.2 方法

1.2.1 纳入标准: (1)研究设计: CRTS与SA治疗可切除食管癌的前瞻性RCT, 无论是否采用盲法; (2)研究对象: 经组织或细胞病理学确诊的未治疗过的可切除食管癌, 且对患者的血常规、肝肾心肺等进行评估, 确认患者能否耐受手术. 原始文献中有明确的随访截止日期的存活例数或有清晰的生存曲线, 随访率 $>95\%$.

1.2.2 排除标准: 研究对象为曾接受单独化疗或单独放疗的食管癌患者, 剔除重复报道、信息太少以及数据描述不详的文献.

1.2.3 结局指标: 主要指标为两组1、3和5年生存率, 次要指标为两组手术率、手术根治率、R0切除率、术后局部复发率、术后并发症、术后死亡率和术后远处转移率.

1.2.4 数据提取: 所有数据均由2位评价者提取, 分歧通过协商解决.

统计学处理 采用RevMan 5.1(从Cochrane图书馆下载)软件进行Meta分析. 其结局变量为接受CRTS和SA的患者生存率、术后根治率等发生率之比, 即治疗相对危险度(relative risk, RR). 各纳入研究结果之间的异质性采用 χ^2 检验, 若纳入研究具有足够一致性($P>0.1$)时, 采用固定效应模型计算合并RR及95%可信区间(95%CI); 否则采用随机效应模型. 以 $P<0.05$ 为差异有统计学意义. 对主要结果进一步行亚组、漏斗图和/或敏感性分析.

2 结果

2.1 文献特征 初检314篇相关文献, 阅读文献标题和摘要后初步纳入RCT59篇, 进一步阅读全文后排除文献38篇(不符合纳入标准11篇, 非随机对照15篇, 回顾性研究10篇, 未发表全文2篇). 最终纳入RCT 21篇, 患者2 755例, 其中CRTS组1 366例, SA组1 389例(表1).

2.2 生存分析 21篇RCT提供1年生存率、20篇提供3年生存率、13篇提供5年生存率, 异质性分析 P 值分别为0.11、0.38和0.80, 采用固定效应模型分析, 结果两组1、3、5年生存率相比RR(95%CI, P 值)分别为1.08(1.03-1.12, $P=0.001$)、1.38(1.26-1.50, $P<0.00001$)、1.41(1.25-1.60, $P<0.00001$), 差异均有统计学意义(图1).

2.3 亚组分析 对两组种族、放化疗顺序及病理

■研究前沿

CRTS与SA相比, 能否明显改善可切除食管癌患者的生存预后及手术情况? 迫切需要允许个体化的多学科综合治疗局部晚期食管癌的预测指标, 及更为有效、安全的CRTS方案.

■创新盘点

本文提示与SA治疗可切除食管癌相比, CRTS降低了肿瘤术后局部复发率, 提高了患者的生存率、肿瘤根治率、R0切除率; 提高了东西方、同步放化疗、鳞癌患者3、5年生存率, 且不增加术后并发症发生率、死亡率和远处转移率。

表 1 文献检索结果概述和纳入研究的一般特征

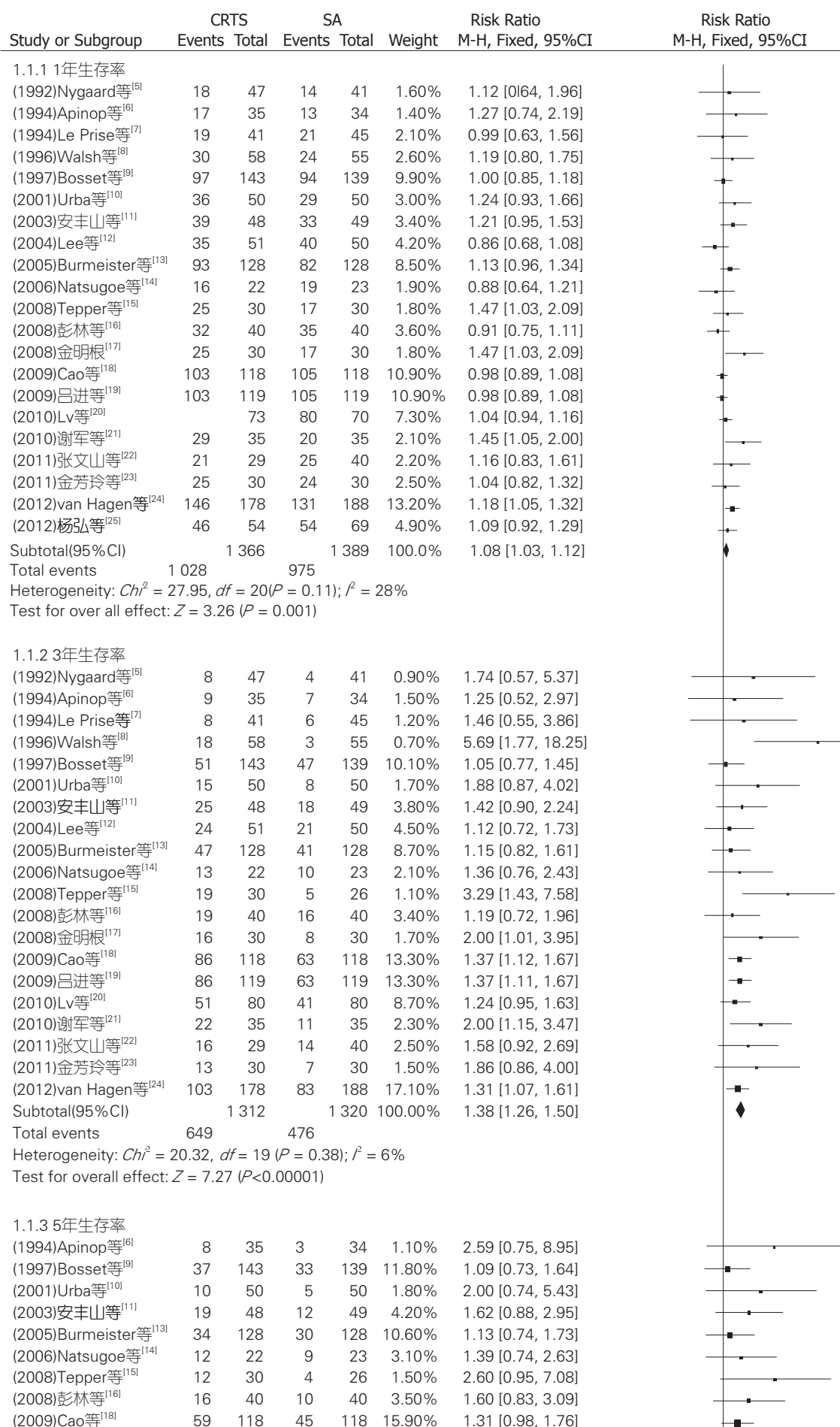
作者	年份	国家	放疗方案	化疗方案	放化疗顺序	病例类型	手术前分期	分组	人数(n)	男/女 (n)	中位 年龄	中位生 存期(mo)	中位随 访期(mo)	Jadad 评分 ^[4]
Nygaard等 ^[5]	1992	Norway	35 Gy, 1.75 Gy per fraction over 4 wk	Two cycles: cisplatin 20 mg/ m ² d1-5; bleomycin 5 mg/m ² 1-5 d	Sequential	SCC	T1 or T2, Nx, M0	CRTS	47	33/14	60.1	7	18	2
Apinop等 ^[6]	1994	Thailand	40 Gy, 2 Gy per fraction over 4 wk	Two cycles: cisplatin 100 mg/m ² 1 d; fluorouracil 1000 mg/m ² 1-4 d	Concurrent	SCC	IIb(11); III(57)	SA CRTS	41 35	31/10 28/7	61.4 59.6	7 9.7	12	1
Le Prise等 ^[7]	1994	France	40 Gy, 20 Gy in 10 fractions over 12 d	Two cycles: cisplatin 100 mg/m ² d1, 21; fluorouracil 600 mg/m ² 2-5 d, 22-25 d	Sequential	SCC	I(23); II(63)	SA CRTS	34 41	26/8 80/6	59.8 56	7.4 10.2	16	2
Walsh等 ^[8]	1996	Ireland	40 Gy in 15 fractions over 3 wk	Two cycles: cisplatin 75 mg/ m ² 1 d; fluorouracil 15 mg/kg 1-5 d	Concurrent	AC	not distant metastases	SA CRTS	45 58	39/19	59 65	11 16	10	2
Bosset等 ^[9]	1997	France	37 Gy, 3.7 Gy per fraction over 2 wk	Two cycles: cisplatin 80 mg/ m ² 0-2 d	Sequential	SCC	T1N0(49); T2N0(92); T3N0(76); T1N1 or T2N1(65)	SA CRTS	55 143	44/11 129/14	65 56.7	11 18.6	55.2	3
Urba等 ^[10]	2001	USA	45 Gy; 1.5 Gy per fraction over 3 wk	Two cycles: cisplatin 20 mg/m ² 1-5 d; fluorouracil 300 mg/m ² 1-21 d; vinblastine 1 mg/m ² 1-4 d	Concurrent	SCC(25%); AC(75%)	not distant metastases	SA CRTS	139 50	134/5 42/8	56.6 62	18.6 16.9	98.4	2
安丰山等 ^[11]	2003	China	36 Gy, 1.2 Gy per fraction over 17 d	First cycle: 5-fluorouracil 1 mg/m ² , 5-6 h, 1-5 d; cisplatin 25 mg/m ² .	Sequential	SCC	II, III	SA CRTS	50 48	43/7 31/17	64 58.4	17.6 42	34.12	3
								SA	50	47/3	63	27.3		

■同行评价

本文选题较好, 文章内容能从多方面进行比较, 相对全面, 具有一定的临床参考价值.

吕进等 ^[19]	2009	China	40 Gy, 2 Gy/d, 1-5 d, 8-12, 15-19, 22-26	Two cycles: Paclitaxel 125 mg/m ² , 1 d; cisplatin 20 mg/m ² , 1-3 d	Concurrent SCC	IIb(15); III(213); IV(10)	CRTS	119	61/58	-	30.5	-	2
Lv等 ^[20]	2010	China	40 Gy, 2 Gy per fraction over 4 wk	Two cycles: cisplatin 20 mg/(m ² · d), 1-3 d, 22-25; paclitaxel 135 mg/m ² starting on 1 d, 22 of radiotherapy	Concurrent SCC	II(71); III(89)	SA CRTS	119 80	68/51 52/28	-	18.3 53	-	2
谢军等 ^[21]	2010	China	45-51 Gy, 2 Gy per fraction, 1-5 d/wk, total 21-25 fractions	5-fluorouracil 2.4 g/m ² 1-3 d, Concurrent 22-24; cisplatin 75 mg/m ² , 1 d, 22	Concurrent SCC	II(22); III(47); IVa(1)	SA CRTS	80 35	50/30 27/8	-	36 -	-	3
张文山等 ^[22]	2011	China	40 Gy, 1.8-2.0 Gy per fraction over 4 wk	Two cycles 5-fluorouracil 500 mg/m ² , 1-5 d; cisplatin 30 mg/(m ² · d)	Concurrent -	III	SA CRTS	35 29	25/10 18/11	-	- 40	-	3
金芳玲等 ^[23]	2011	China	50 Gy, 2 Gy per fraction over 5 wk	Two cycles: cisplatin 75 mg/(m ² · d), d1; 5-fluorouracil 500 mg/(m ² · d), 1-5 d	Concurrent SCC(92%); AC(8%)	IIa(10); IIb(9); III(41)	SA CRTS	40 30	26/14 18/12	52.2 54	29 34	-	2
van Hagen等 ^[24]	2012	Netherlands	41.4 Gy, 1.8 Gy per fraction over 4.6 wk	5 wk chemotherapy; carboplatin area under curve = 2 and paclitaxel 50 mg/m ² on 1 d weekly	Concurrent SCC(23%); AC(75%)	T1N1 or T2-3N0-1M0	SA CRTS	30 178	21/9 134/44	22 60	22 49.4	45.4	2
杨弘等 ^[25]	2012	China	40 Gy, 2 Gy per fraction over 4 wk	Two cycles: navelbine 25 mg/m ² 1,8,22,29 d; cisplatin 75 mg/m ² 1,22 d	Concurrent SCC	IIB(20) III(113)	SA CRTS	188 54	152/26 46/8	60 54	24 -	-	3

SCC: 鳞癌; AC: 腺癌; CRTS: 术前放疗; SA: 单纯手术; -: 文中未提及.



(2009)吕进等 ^[19]	60	119	36	119	12.70%	1.67 [1.20, 2.31]
(2010)Lv等 ^[20]	35	80	27	80	9.60%	1.30 [0.87, 1.92]
(2011)张文山等 ^[22]	10	29	7	40	2.10%	1.97 [0.85, 4.56]
(2012)van Hagen等 ^[24]	84	178	64	188	22.00%	1.39 [1.08, 1.78]
Subtotal(95%CI)	1 020		1 034		100.00%	1.41 [1.25, 1.60]
Total events	396		285			
Heterogeneity: $Chi^2 = 7.77, df = 12 (P = 0.80); I^2 = 0\%$						
Test for overall effect: $Z = 5.48 (P < 0.00001)$						

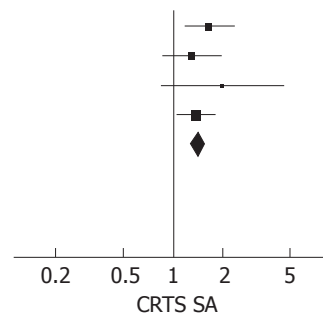


图1 CRTS组与SA组的1年、3年、5年生存率的比较(固定效应模型). CRTS: 术前放化疗; SA: 单纯手术.

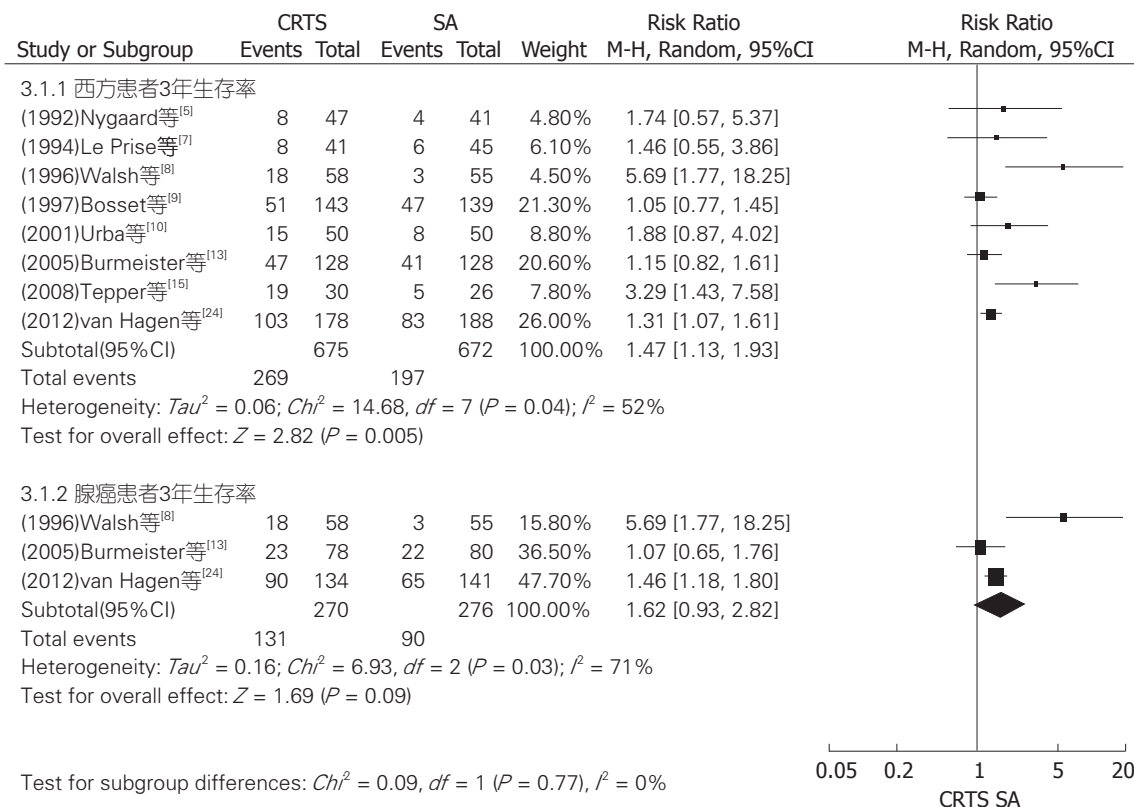
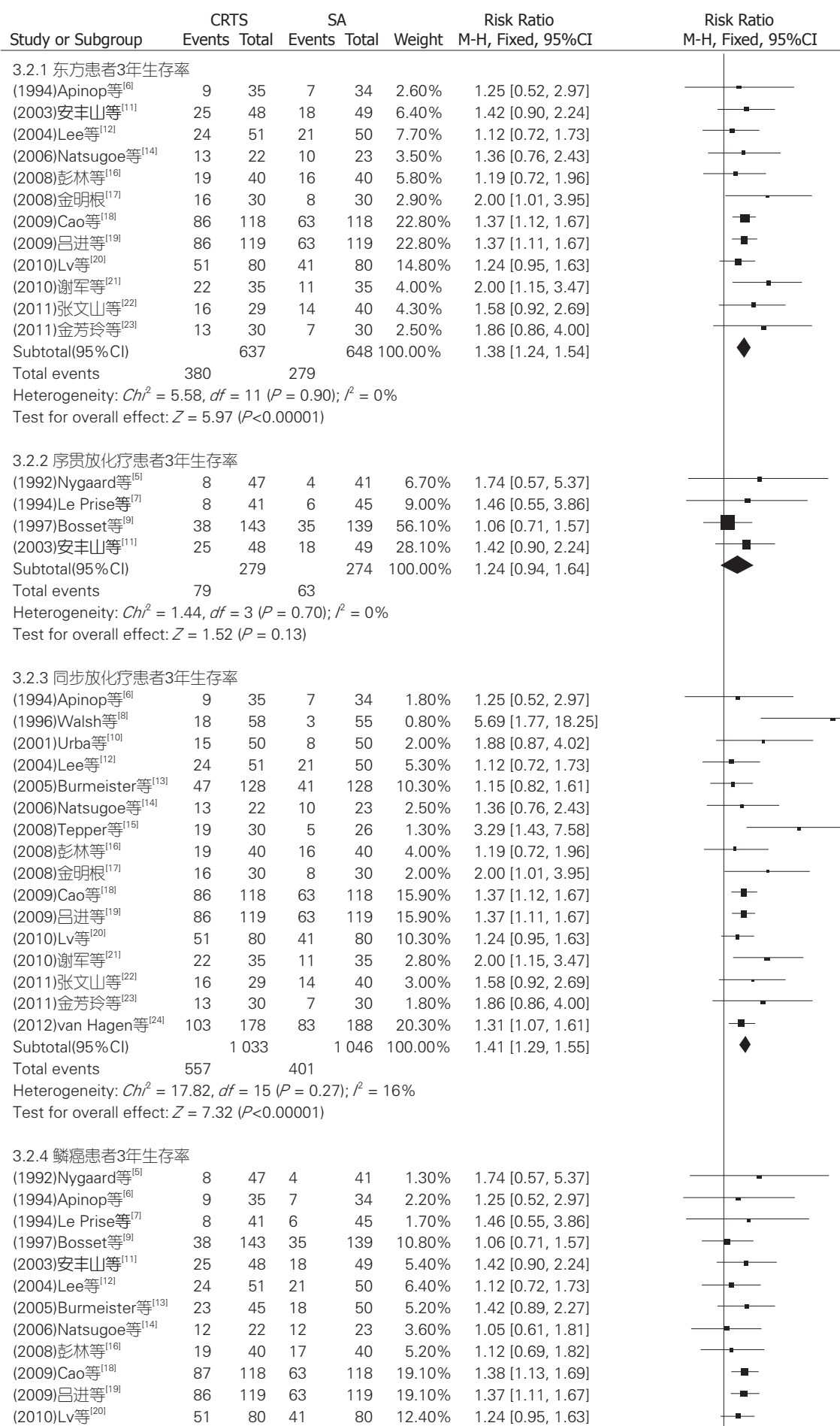


图2 CRTS组与SA组中西方、腺癌亚组3年生存率的比较(随机效应模型). CRTS: 术前放化疗; SA: 单纯手术.

类型不同的患者3、5年生存率行亚组分析(图2-4). CRTS组比SA组提高了东方、西方、同步放化疗和鳞癌患者3、5年生存率, 其3年生存率相比RR(95%CI, P 值)分别为1.38(1.24-1.54, $P < 0.00001$)、1.47(1.13-1.93, $P = 0.005$)、1.41(1.29-1.55, $P < 0.00001$)、1.34(1.21-1.48, $P < 0.00001$); 其5年生存率相比RR(95%CI, P 值)分别为1.50(1.27-1.78, $P < 0.00001$)、1.32(1.11-1.58, $P = 0.002$)、1.45(1.27-1.65, $P < 0.00001$)、1.37(1.17-1.59, $P < 0.0001$), 差异均有统计学意义. 两组序贯放化疗、腺癌患者3年生存率相比RR(95%CI, P 值)分别为1.24(0.94-1.64, $P = 0.13$)、1.62(0.93-2.82, $P = 0.09$); 5年生存率相比RR(95%CI, P 值)分别为

1.23(0.88-1.72, $P = 0.23$)、1.17(0.90-1.52, $P = 0.24$), 差异均无统计学意义.

2.4 术后分析 均以实际手术人数进行分析. 12篇RCT报道了手术率、11篇报道了手术根治率、4篇报道了R0切除率(图5), 18篇RCT报道了术后并发症发生率、9篇报道了术后远处转移率、17篇报道了术后死亡率(图6), 各RCT间均有异质性, 均采用随机效应模型进行Meta分析; 9篇RCT报道了术后局部复发率(图7), 各RCT间无异质性, 采用固定效应模型分析. 结果显示: SA组比CRTS组有较高的手术率, 差异有统计学意义, RR(95%CI, P 值)为0.89(0.84-0.94, $P < 0.0001$); 而CRTS组比SA组有更显著的治切除率、R0切除率和较低的术后局部复发率, 差



(2010)谢军等 ^[21]	22	35	11	35	3.30%	2.00 [1.15, 3.47]
(2012)van Hagen等 ^[24]	28	41	15	43	4.40%	1.96 [1.24, 3.10]
Subtotal(95%CI)		865		866	100.00%	1.34 [1.21, 1.48]
Total events	440		331			
Heterogeneity: $Chi^2 = 8.82$, $df = 13$ ($P = 0.79$); $I^2 = 0\%$						
Test for overall effect: $Z = 5.62$ ($P < 0.00001$)						

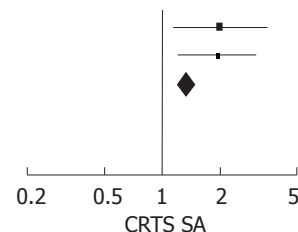


图3 CRTS组与SA组中东方、序贯放化疗、同步放化疗、鳞癌亚组3年生存率的比较(固定效应模型)。CRTS: 术前放化疗; SA: 单纯手术。

Study or Subgroup	CRTS Events	CRTS Total	RS Events	RS Total	Weight	Risk Ratio M-H, Fixed, 95%CI	Risk Ratio M-H, Fixed, 95%CI
5.2.1 东方患者5年生存率							
(1994)Apinop等 ^[6]	8	35	3	34	2.20%	2.59 [0.75, 8.95]	
(2003)安丰山等 ^[11]	19	48	12	49	8.60%	1.62 [0.88, 2.95]	
(2008)彭林等 ^[16]	16	40	10	40	7.20%	1.60 [0.83, 3.09]	
(2009)Cao等 ^[18]	59	118	45	118	32.40%	1.31 [0.98, 1.76]	
(2009)吕进等 ^[19]	60	119	36	119	25.90%	1.67 [1.20, 2.31]	
(2010)Lv等 ^[20]	35	80	27	80	19.50%	1.30 [0.87, 1.92]	
(2011)张文山等 ^[22]	10	29	7	40	4.20%	1.97 [0.85, 4.56]	
Subtotal(95%CI)		469		480	100.00%	1.50 [1.27, 1.78]	
Total events	207		140				
Heterogeneity: $Chi^2 = 3.00$, $df = 6$ ($P = 0.81$); $I^2 = 0\%$							
Test for overall effect: $Z = 4.69$ ($P < 0.00001$)							
5.2.2 西方患者5年生存率							
(1997)Bosset等 ^[9]	37	143	33	139	23.30%	1.09 [0.73, 1.64]	
(2001)Urba等 ^[10]	10	50	5	50	3.50%	2.00 [0.74, 5.43]	
(2005)Burmeister等 ^[13]	34	128	30	128	20.90%	1.13 [0.74, 1.73]	
(2006)Natsugoe等 ^[14]	12	22	9	23	6.10%	1.39 [0.74, 2.63]	
(2008)Tepper等 ^[15]	12	30	4	26	3.00%	2.60 [0.95, 7.08]	
(2012)van Hagen等 ^[24]	84	178	64	188	43.30%	1.39 [1.08, 1.78]	
Subtotal(95%CI)		551		554	100.00%	1.32 [1.11, 1.58]	
Total events	189		145				
Heterogeneity: $Chi^2 = 3.94$, $df = 5$ ($P = 0.56$); $I^2 = 0\%$							
Test for overall effect: $Z = 3.07$ ($P = 0.002$)							
5.2.3 同步放化疗患者5年生存率							
(1994)Apinop等 ^[6]	8	35	3	34	1.30%	2.59 [0.75, 8.95]	
(2001)Urba等 ^[10]	10	50	5	50	2.10%	2.00 [0.74, 5.43]	
(2005)Burmeister等 ^[13]	34	128	30	128	12.60%	1.13 [0.74, 1.73]	
(2006)Natsugoe等 ^[14]	12	22	9	23	3.70%	1.39 [0.74, 2.63]	
(2008)Tepper等 ^[15]	12	30	4	26	1.80%	2.60 [0.95, 7.08]	
(2008)彭林等 ^[16]	16	40	10	40	4.20%	1.60 [0.83, 3.09]	
(2009)Cao等 ^[18]	59	118	45	118	19.00%	1.31 [0.98, 1.76]	
(2009)吕进等 ^[19]	60	119	36	119	15.20%	1.67 [1.20, 2.31]	
(2010)Lv等 ^[20]	35	80	27	80	11.40%	1.30 [0.87, 1.92]	
(2011)张文山等 ^[22]	10	29	7	40	2.50%	1.97 [0.85, 4.56]	
(2012)van Hagen等 ^[24]	84	178	64	188	26.20%	1.39 [1.08, 1.78]	
Subtotal(95%CI)		829		846	100.00%	1.45 [1.27, 1.65]	
Total events	340		240				
Heterogeneity: $Chi^2 = 6.02$, $df = 10$ ($P = 0.81$); $I^2 = 0\%$							
Test for overall effect: $Z = 5.47$ ($P < 0.00001$)							
5.2.4 序贯放化疗患者5年生存率							
(1997)Bosset等 ^[9]	37	143	33	139	73.80%	1.09 [0.73, 1.64]	
(2003)安丰山等 ^[11]	19	48	12	49	26.20%	1.62 [0.88, 2.95]	
Subtotal(95%CI)		191		188	100.00%	1.23 [0.88, 1.72]	
Total events	56		45				
Heterogeneity: $Chi^2 = 1.13$, $df = 1$ ($P = 0.29$); $I^2 = 11\%$							
Test for overall effect: $Z = 1.20$ ($P = 0.23$)							
5.2.5 鳞癌患者5年生存率							
(1994)Apinop等 ^[6]	8	35	3	34	1.60%	2.59 [0.75, 8.95]	

(1997)Bosset等 ^[9]	10	143	12	139	6.50%	0.81 [0.36, 1.81]
(2003)安丰山等 ^[11]	19	48	12	49	6.30%	1.62 [0.88, 2.95]
(2005)Burmeister等 ^[13]	15	50	19	45	10.70%	0.71 [0.41, 1.22]
(2006)Natsugoe等 ^[14]	12	22	10	23	5.20%	1.25 [0.69, 2.29]
(2008)彭林等 ^[16]	16	40	10	40	5.30%	1.60 [0.83, 3.09]
(2009)Cao等 ^[18]	58	118	43	118	22.90%	1.35 [1.00, 1.82]
(2009)吕进等 ^[19]	60	119	36	119	19.20%	1.67 [1.20, 2.31]
(2010)Lv等 ^[20]	35	80	27	80	14.40%	1.30 [0.87, 1.92]
(2012)van Hagen等 ^[24]	23	41	15	43	7.80%	1.61 [0.99, 2.62]
Subtotal(95%CI)		696		690	100.00%	1.37 [1.17, 1.59]
Total events	256		187			
Heterogeneity: $Chi^2 = 10.71, df = 9 (P = 0.30); I^2 = 16\%$						
Test for overall effect: $Z = 4.07 (P < 0.0001)$						

5.2.6 腺癌患者5年生存率

(2005)Burmeister等 ^[13]	16	78	14	80	20.80%	1.17 [0.61, 2.24]
(2012)van Hagen等 ^[24]	60	134	54	141	79.20%	1.17 [0.88, 1.55]
Subtotal(95%CI)		212		221	100.00%	1.17 [0.90, 1.52]
Total events	76		68			
Heterogeneity: $Chi^2 = 0.00, df = 1 (P = 0.99); I^2 = 0\%$						
Test for overall effect: $Z = 1.18 (P = 0.24)$						
Test for subgroup differences: $Chi^2 = 3.70, df = 5 (P = 0.59), I^2 = 0\%$						

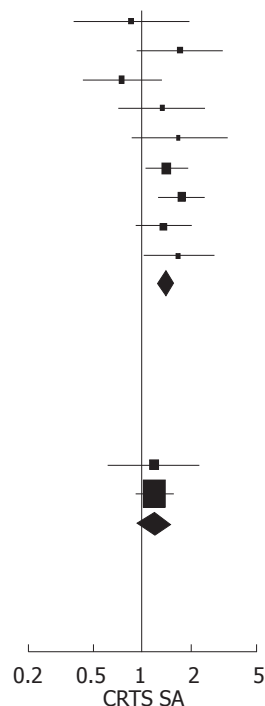



























图 4 CRTS组与SA组中种族、放化疗顺序、病理类型不同亚组5年生存率的比较(固定效应模型). CRTS: 术前放化疗; SA: 单纯手术.

Study or Subgroup	CRTS		SA		Weight	Risk Ratio M-H, Random, 95%CI	Risk Ratio M-H, Random, 95%CI
	Events	Total	Events	Total			
4.1.1 手术率							
(1992)Nygaard等 ^[5]	34	47	38	41	5.20%	0.78 [0.64, 0.95]	
(1994)Apinop等 ^[6]	26	35	34	34	5.10%	0.75 [0.61, 0.91]	
(1994)Le Prise等 ^[7]	35	41	42	45	7.20%	0.91 [0.79, 1.06]	
(1997)Bosset等 ^[9]	138	143	137	139	13.70%	0.98 [0.94, 1.02]	
(2001)Urba等 ^[10]	47	50	50	50	11.30%	0.94 [0.87, 1.02]	
(2004)Lee等 ^[12]	35	51	48	50	5.30%	0.71 [0.59, 0.87]	
(2005)Burmeister等 ^[13]	105	128	110	128	9.50%	0.95 [0.86, 1.06]	
(2006)Natsugoe等 ^[14]	20	22	23	23	6.90%	0.91 [0.78, 1.06]	
(2008)Tepper等 ^[15]	26	30	26	26	6.90%	0.87 [0.75, 1.02]	
(2010)谢军等 ^[21]	25	35	35	35	4.70%	0.72 [0.58, 0.89]	
(2012)van Hagen等 ^[24]	168	178	186	188	13.60%	0.95 [0.92, 0.99]	
(2012)杨弘等 ^[25]	49	54	69	69	10.60%	0.91 [0.83, 0.99]	
Subtotal(95%CI)	814		828		100.00%	0.89 [0.84, 0.94]	
Total events	708		798				
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 42.78$, $df = 11$ ($P < 0.0001$); $I^2 = 74\%$							
Test for overall effect: $Z = 4.01$ ($P < 0.0001$)							
4.1.2 手术根治率							
(1992)Nygaard等 ^[5]	26	34	15	38	2.40%	1.94 [1.25, 2.99]	
(1994)Le Prise等 ^[7]	35	35	38	42	11.90%	1.10 [0.99, 1.23]	
(1997)Bosset等 ^[9]	112	138	94	137	10.20%	1.18 [1.03, 1.36]	
(2001)Urba等 ^[10]	45	47	45	50	11.80%	1.06 [0.95, 1.19]	
(2003)安丰山等 ^[11]	41	48	32	49	6.00%	1.31 [1.03, 1.65]	
(2008)彭林等 ^[16]	39	40	36	40	11.60%	1.08 [0.97, 1.21]	
(2008)金明根 ^[17]	28	30	21	30	5.50%	1.33 [1.04, 1.72]	
(2009)Cao等 ^[18]	116	118	87	118	11.80%	1.33 [1.19, 1.49]	
(2009)吕进等 ^[19]	117	119	88	119	11.90%	1.33 [1.19, 1.48]	
(2010)Lv等 ^[20]	76	80	64	80	11.20%	1.19 [1.05, 1.34]	
(2010)谢军等 ^[21]	22	25	26	35	5.80%	1.18 [0.93, 1.51]	
Subtotal(95%CI)	714		738		100.00%	1.21 [1.12, 1.30]	
Total events	657		546				
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 26.62$, $df = 10$ ($P = 0.003$); $I^2 = 62\%$							
Test for overall effect: $Z = 5.12$ ($P < 0.00001$)							

4.1.3 R0 切除率

(2004)Lee等 ^[12]	35	35	42	48	25.30%	1.14 [1.01, 1.28]
(2005)Burmeister等 ^[13]	103	105	76	110	24.70%	1.42 [1.25, 1.61]
(2012)van Hagen等 ^[24]	148	168	111	186	24.50%	1.48 [1.30, 1.68]
(2012)杨弘等 ^[25]	47	49	59	69	25.50%	1.12 [1.00, 1.26]
Subtotal(95%CI)		357		413	100.00%	1.28 [1.09, 1.50]

Total events 333 288

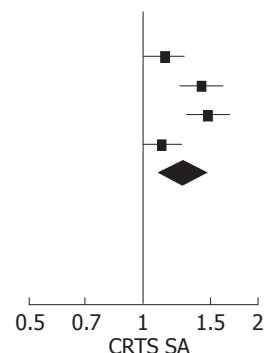
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 20.96$, $df = 3$ ($P = 0.0001$); $I^2 = 86\%$ Test for overall effect: $Z = 2.97$ ($P = 0.003$)

图 5 CRTS组与SA组手术率、手术根治率、R0切除率的比较(随机效应模型). CRTS: 术前放化疗; SA: 单纯手术.

Study or Subgroup	CRST		SA		Weight	Risk Ratio		Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95%CI	M-H, Random, 95%CI		
4.2.1 术后并发症发生率									
(1992)Nygaard等 ^[5]	16	34	13	38	4.80%	1.38 [0.78, 2.43]			
(1994)Apinop等 ^[6]	8	26	5	34	1.90%	2.09 [0.77, 5.65]			
(1994)Le Prise等 ^[7]	14	35	18	42	5.20%	0.93 [0.55, 1.59]			
(1996)Walsh等 ^[8]	47	58	50	55	15.70%	0.89 [0.77, 1.04]			
(1997)Bosset等 ^[9]	45	138	36	137	8.40%	1.24 [0.86, 1.79]			
(2001)Urba等 ^[10]	8	47	7	50	2.10%	1.22 [0.48, 3.09]			
(2003)安丰山等 ^[11]	16	48	16	49	4.80%	1.02 [0.58, 1.80]			
(2004)Lee等 ^[12]	13	35	19	48	4.90%	0.94 [0.54, 1.63]			
(2005)Burmeister等 ^[13]	63	105	70	110	13.40%	0.94 [0.76, 1.16]			
(2006)Natsugoe等 ^[14]	7	20	7	23	2.40%	1.15 [0.49, 2.72]			
(2008)Tepper等 ^[15]	24	26	24	26	15.40%	1.00 [0.85, 1.17]			
(2008)彭林等 ^[16]	20	40	15	40	5.60%	1.33 [0.80, 2.21]			
(2008)金明根 ^[17]	11	30	6	30	2.40%	1.83 [0.78, 4.32]			
(2009)Cao等 ^[18]	6	118	4	118	1.30%	1.50 [0.43, 5.18]			
(2009)吕进等 ^[19]	6	119	4	119	1.30%	1.50 [0.43, 5.18]			
(2010)Lv等 ^[20]	27	80	18	80	5.60%	1.50 [0.90, 2.50]			
(2010)谢军等 ^[21]	10	35	8	35	2.70%	1.25 [0.56, 2.79]			
(2011)金芳玲等 ^[23]	16	30	4	30	2.00%	4.00 [1.51, 10.57]			
Subtotal(95%CI)		1 024		1 064	100.00%	1.13 [0.98, 1.30]			
Total events	357		324						
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 29.54$, $df = 17$ ($P = 0.03$); $I^2 = 42\%$									
Test for overall effect: $Z = 1.64$ ($P = 0.10$)									
4.2.2 术后远处转移率									
(1994)Le Prise等 ^[7]	8	41	6	45	6.80%	1.46 [0.55, 3.86]			
(2001)Urba等 ^[10]	28	43	27	45	21.60%	1.09 [0.79, 1.50]			
(2003)安丰山等 ^[11]	5	46	10	46	6.50%	0.50 [0.19, 1.35]			
(2004)Lee等 ^[12]	6	35	12	48	7.90%	0.69 [0.29, 1.65]			
(2005)Burmeister等 ^[13]	46	105	42	110	21.70%	1.15 [0.83, 1.58]			
(2006)Natsugoe等 ^[14]	8	22	4	23	6.00%	2.09 [0.73, 5.96]			
(2008)Tepper等 ^[15]	5	26	9	26	7.00%	0.56 [0.22, 1.43]			
(2008)彭林等 ^[16]	4	40	11	40	5.90%	0.36 [0.13, 1.05]			
(2010)Lv等 ^[20]	20	80	31	80	16.60%	0.65 [0.40, 1.03]			
Subtotal(95%CI)		438		463	100.00%	0.88 [0.66, 1.17]			
Total events	130		152						
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 14.40$, $df = 8$ ($P = 0.07$); $I^2 = 44\%$									
Test for overall effect: $Z = 0.90$ ($P = 0.37$)									
4.2.3 术后死亡率									
(1992)Nygaard等 ^[5]	8	34	5	38	9.40%	1.79 [0.65, 4.94]			
(1994)Apinop等 ^[6]	5	26	5	34	8.20%	1.31 [0.42, 4.05]			
(1994)Le Prise等 ^[7]	26	41	27	45	19.50%	1.06 [0.76, 1.47]			
(1996)Walsh等 ^[8]	5	58	2	55	5.00%	2.37 [0.48, 11.72]			
(1997)Bosset等 ^[9]	17	138	5	137	9.90%	3.38 [1.28, 8.89]			
(2001)Urba等 ^[10]	1	47	2	50	2.60%	0.53 [0.05, 5.67]			

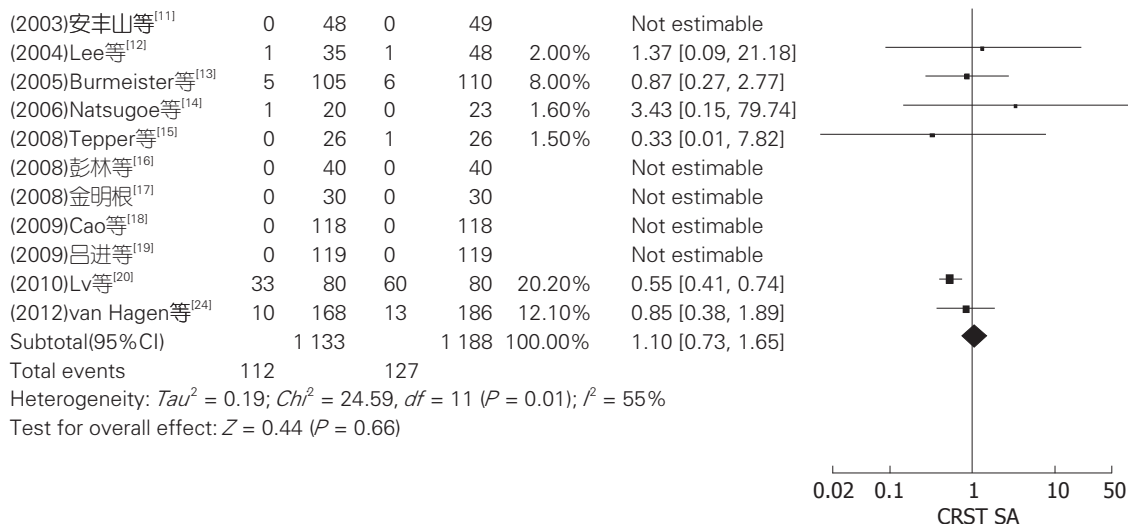


图6 CRST组与SA组术后并发症发生率、远处转移率、死亡率的比较(随机效应模型)。CRST: 术前放化疗; SA: 单纯手术。

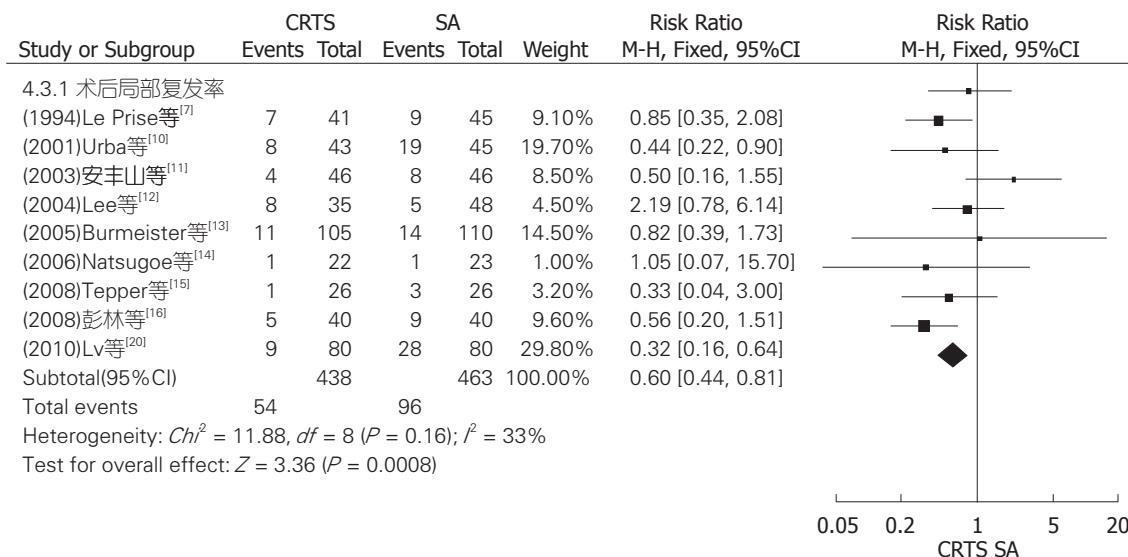


图7 CRST组与SA组术后局部复发率的比较(固定效应模型)。CRST: 术前放化疗; SA: 单纯手术。

异均有统计学意义, $RR(95\%CI, P值)$ 分别为1.21(1.12-1.30, $P < 0.00001$)、1.28(1.09-1.50, $P = 0.003$)和0.60(0.44-0.81, $P = 0.0008$)。两组术后并发症发生率、远处转移率及死亡率比较, $RR(95\%CI, P值)$ 分别为1.13(0.98-1.30, $P = 0.10$)、0.88(0.66-1.17, $P = 0.37$)及1.10(0.73-1.65, $P = 0.66$)。差异均无统计学意义。

2.5 敏感性分析及发表偏倚 剔除任意一篇文献前后, 两组3年生存率、5年生存率、手术率、手术根治率、R0切除率、术后死亡率、术后局部复发率及术后远处转移率Meta分析均未发生明显变化, 结论的性质没有改变。剔除Jadad质量记分为1和2的研究后, 两组1年生存率Meta分析未发生明显变化; 剔除Burmeister等^[13]研究后, 两组术后并发症发生率差异有统计学意义($RR =$

1.19, $95\%CI = 1.001.41$; $P = 0.05$)。结论的性质改变, 但处在统计学意义的边缘, 稳健性较低, 尚待更进一步验证。以RR值为横坐标, $SE[\log(RR)]$ 为纵坐标绘制漏斗图均基本对称, 纳入本研究的文献没有发表偏倚。

3 讨论

食管癌早期诊断较困难, 远处转移是食管癌远期生存的重要影响因素。目前, 任何单一治疗方式都难以大幅度提高食管癌患者的生存率, 而研究显示多学科综合治疗能显著提高食管癌治疗效果^[26]。与传统术后辅助放化疗相比, 理论上术前放化疗具有一定优势^[23]。本文对21篇RCT行Meta分析, 收集文献较齐全, 行生存率和手术情况发生率详细分类比较, 并对远期生存率给予

亚组、敏感性和漏斗图分析,综合评估了CRTS与SA治疗可切除食管癌的优缺点.本Meta分析结果显示:与SA治疗可切除食管癌相比,CRTS降低了肿瘤术后局部复发率,提高了患者生存率、肿瘤根治率、R0切除率,提高了东西方、同步放化疗、鳞癌患者远期生存率,且未增加术后并发症发生率、死亡率和远处转移率,但术后并发症发生率稳健性较低.有报道证明CRTS治疗食管癌可降低远处转移率,部分不良反应增加,但患者能够耐受,可提高局部晚期食管癌的有效率、总生存率^[27].一项更新的荟萃分析^[28]显示:CRTS较SA改善了可切除食管癌患者的生存,可能成为标准治疗措施;这种治疗方案应用之所以在增加,是因为其没有表现重大的不良并发症导致死亡率的增加,可在患者中安全应用^[29];且适当的营养支持可增加患者获得充分放化疗剂量和根治手术的可能性^[30].本Meta分析显示CRTS对序贯放化疗及腺癌患者远期生存率未改善($P>0.05$),间接提示食管同步放化疗及鳞癌患者是CRTS的真正受益者,也许术后放化疗能够使序贯放化疗及腺癌获益,结果尚未明确.同时本文还显示SA较CRTS有更高的手术率($P<0.05$),这可能跟有些术前放化疗的不良反应导致患者体质耐受较差有关.目前CRTS的最佳方案与最佳用药剂量均未明确,新药应用相对较少,每项研究的化疗剂量也各不相同,本项Meta所纳入研究中多采用“5-fluorouracil+cisplatin”方案,因此下一步应研究术后放化疗及不同化疗方案、剂量联合术前放疗治疗可切除食管癌的差异,期待进一步提高临床疗效.

食管癌综合治疗新辅助策略的管理是复杂的,并和现有证据冲突,试验设计已经取得初步建议并试图解决,但这仍是开放的讨论和审议^[31].CRTS较术前化疗间尚未建立明显优势.迫切需要允许个体化的多学科综合治疗局部晚期食管癌的预测指标^[32].到目前为止,治疗食管癌尚无公认的标准治疗方案,但多数临床研究显示,局部晚期食管癌CRTS并手术是一个可提高临床有效率和长期生存率较为现实可行的、有发展前景的、值得进一步研究的三联综合治疗模式,可能会成为标准治疗方案.

总之,与SA治疗可切除食管癌相比,CRTS降低了肿瘤术后局部复发率,提高了患者生存率、肿瘤根治率、R0切除率,提高了东西方、同步放化疗、鳞癌患者远期生存率,且未增加

患者术后并发症发生率、死亡率和远处转移率,但其手术率较低.然而,序贯放化疗及腺癌患者的远期生存率未能从CRTS中受益.本Meta分析来自不同种族人群,病理类型不同;各研究在放化疗剂量、方法及手术方式有差异,时间跨度大等方面存在一定的局限性,尚需更多更高质量的大型临床研究来进一步明确RCTS的作用,并探索更为有效、安全的RCTS治疗方案.

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