# Traditional and cumulative meta-analysis: Chemoradiotherapy followed by surgery versus surgery alone for resectable esophageal carcinoma

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Abstract. The role of neoadjuvant chemoradiotherapy followed by surgery (CRTS) compared with surgery alone (SA) for resectable esophageal carcinoma has been established by several randomized controlled trials (RCTs). The present study aimed to investigate the difference in survival between the two treatments by a review of meta-analyses. Related research indicators were extracted from RCTs investigating CRTS or SA for resectable esophageal carcinoma by searching electronic databases for eligible articles. Outcomes were synthesized by adopting a fixed- or random-effects model with 95% confidence interval (CI). A total of 22 RCTs including 3,419 patients were selected. The odds ratio (OR) (95% CI, P-value), expressed as CRTS vs. SA, was 1.06 (0.94-1.19, P=0.348) for 1-year overall survival rate (OSR1y), 1.38 (1.20-1.58, P<0.001) for 3-year overall survival rate (OSR3y), and 1.42 (1.22-1.66, P<0.001) for 5-year overall survival rate (OSR5y). The R0 resection rate increased in patients treated by CRTS (OR=2.76, 95% CI: 2.15-3.53, P<0.001). CRTS lowered the locoregional cancer recurrence (OR=0.49, 95% CI: 0.36-6.65, P<0.001) and distant metastasis rate (OR=0.76, 95% CI: 0.60-0.97, P=0.02). However, the incidence of postoperative mortality was similar between the two groups (OR=0.97, 95% CI: 0.72-1.32,

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P=0.87). The subgroup analysis revealed that OSR3y and OSR5y for Asian, European and American populations were significantly higher in the CRTS group compared with those in the SA group (P<0.05). When comparing the OSR1y between the two groups for patients in all three continents, there was no significant difference (P>0.05). Histological subgroup analysis indicated that patients with esophageal adenocarcinoma may benefit from CRTS in terms of OSR1y (OR=1.55, 95% CI: 1.09-2.20, P=0.01), OSR3y (OR=1.77, 95% CI: 1.34-2.36, P<0.0001) and OSR5y (OR=1.92, 95% CI: 1.34-2.75, P=0.0004). The pooled OR of squamous cell carcinoma in terms of OSR3y and OSR5y between the two groups was 1.57 (95% CI: 1.21-2.04, P=0.0006) and 1.69 (95% CI: 1.32-2.16, P<0.0001), respectively, but there was no statistical difference in terms of OSR1y (OR=1.13, 95% CI: 0.88-1.45, P=0.35). Thus, neoadjuvant CRT followed by surgery may improve long-term survival and surgical parameters, and reduce locoregional cancer recurrence and distant metastasis.

## Introduction

Esophageal cancer is the eighth most common type of cancer worldwide, with >480,000 new cases diagnosed annually (1). Esophageal cancer has a high mortality rate (sixth worldwide), causing >400,000 deaths annually (2). Squamous cell carcinoma is the most frequently type occurring in Asians, particularly in China, where it accounts for 70% of global morbidity (3). However, the incidence of esophageal adenocarcinoma in Western populations is rapidly increasing, whereas that of squamous cell carcinoma remains unchanged (4). Esophagectomy is considered to be the standard treatment for patients with resectable esophageal carcinoma, despite a detailed assessment of preoperative staging showing that 25% of patients treated with definitive surgery had microscopically positive resection margins (R1). However, the 5-year survival rate scarcely exceeds 40% (5); in addition, due to the morbidity and mortality associated with surgery, this approach is limited to a minority of medically fit patients.

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Since the 1980s, there have been several randomized clinical trials (RCTs) assessing the efficacy of preoperative chemoradiotherapy followed by surgery (CRTS) in the treatment of esophageal cancer. However, the sample-size of these RCTs was small, with a short-term follow-up and adverse outcomes in the surgical monotherapy arm of combination treatment trials when compared with surgery alone (SA) case-series (6). Furthermore, the majority of the trials did not have sufficient statistical power to produce a definitive conclusion. Thus, a comprehensive analysis was conducted to compare the potential objective value of CRTS with SA for resectable esophageal carcinoma.

As regards the differences between traditional and cumulative meta-analysis, cumulative meta-analysis refers to a meta-analysis of the obtained studies in a certain order; those studies are treated as a continuous whole and multiple meta-analyzes are performed by accumulating studies sequentially in a specified sequence (such as publication time). In addition, if a new test result is published, a new meta-analysis may follow. Traditional meta-analysis is performed only once, whereas cumulative meta-analysis is performed several times; the former may obtain summary results, but cannot distinguish the impact of each study result on the summary results, whereas the latter does not only obtain the results of the summary and compare the dynamic results of summary changes, but also compares the effect of the newly added studies on overall outcome. The cumulative meta-analysis is controversial in terms of test level. Some scholars object to performing multiple meta-analyses due to the increasing probability of committing class I error, and claim the test level should be adjusted for each analysis; some scholars believe that the analysis of the Bayesian theory may be used to explain, without the need for adjustment.

Based on this theory, the present study aimed to combine the traditional and cumulative meta-analysis to explore the pooled results of the relevant studies.

#### **Data collection methods**

Search strategy. The relevant articles identified were RCTs retrieved from Embase, PubMed and The Cochrane Library (issue 4, 2016) and the deadline for trial publication and/or presentation was October 1st, 2016. The American Society of Clinical Oncology (ASCO) and the Cochrane Collaboration's Central Register of Controlled Clinical Trials were searched for updates of the trials. The search terms were as follows: Esophageal neoplasms, esophageal cancer, esophageal carcinoma, esophageal tumor, neoadjuvant therapy, chemoradiotherapy, esophagectomy, resection, surgery and operation.

Inclusion and exclusion criteria. In our meta-analysis, the study focus was locoregional resectable esophageal cancer patients who received either CRTS or SA. The eligible studies were required to meet the following inclusion criteria: i) Prospective RCTs comparing CRTS vs. SA in the initial management of resectable esophageal cancer; ii) outcome indices containing survival data; iii) no significant differences in baseline characteristics between the CRTS and SA groups; and iv) definitive follow-up survival number of cases or survival curve, with a follow-up rate of >95% in the original RCTs. Studies focusing on patients with esophageal cancer who had been treated with neoadjuvant chemotherapy alone or radiotherapy alone, other studies without usable data, letters, editorials, case reports and reviews were excluded.

Data extraction and quality assessment. Two investigators independently extracted data to avoid bias in the course of the extraction. Disagreements were resolved by consensus or consultation with third parties. Statistics for each available outcome were extracted from trials in the light of the key information including patient characteristics, first author, year of publication, country/region, the regimen of the CRTS, and tumor histology. The methodological quality assessment of individual studies followed the Cochrane risk of bias method.

Statistical analysis. Overall survival rates at 1, 3 and 5 years (OSR1y, OSR3y and OSR5y, respectively), R0 resection rate, postoperative mortality, postoperative local recurrence rate and postoperative distant metastasis rate were extracted and pooled with 95% confidence intervals (CIs) by adopting the fixed- or random-effects model where heterogeneity was assessed with the inconsistency statistic (I<sup>2</sup><50%, P>0.05; and I<sup>2</sup>≥50%, P≤0.05, respectively). The odds ratio (OR) was estimated with 95% CI and P-values in both the CRTS and SA groups. All calculations were performed using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark), R software version 3.2.2, and STATA version 12.0 (StataCorp LP- College Station, TX, USA). Statistical significance was set at P<0.05.

#### Results

*Summary of included studies*. A total of 1279 records were identified according to the search strategy and 22 were finally included in the meta-analysis after removing duplicated, ineligible and unrelated studies (Fig. 1). Ten countries, including China, Australia, Japan, Korea, Thailand, United States of America, France, The Netherlands, Ireland and Norway, were included in the RCTs. Of the 22 studies, 20 (7-26) reported OSR1y, 19 (7-21,24-27) reported OSR3y and 15 (8,11-13,15-17,19-12,24-27) reported information on OSR5y after SA or CRTS for resectable esophageal carcinoma.

As regards pathological type, 5 RCTs (10,15,24,26,27) on adenocarcinoma and 12 studies (7-9,11,13,14,16,21,23,24,26) on squamous cell carcinoma investigated OSR1y, OSR3y and OSR5y after CRTS or SA for resectable esophageal carcinoma.

A total of 9 studies (7,9,11,13-15,23,27,28) reported R0 resection rate, 10 (9,12-15,16,19-21,26) included postoperative local recurrence rate and distant metastasis rate, and 15 (7-12,14-16,20,21,28) provided postoperative mortality information.

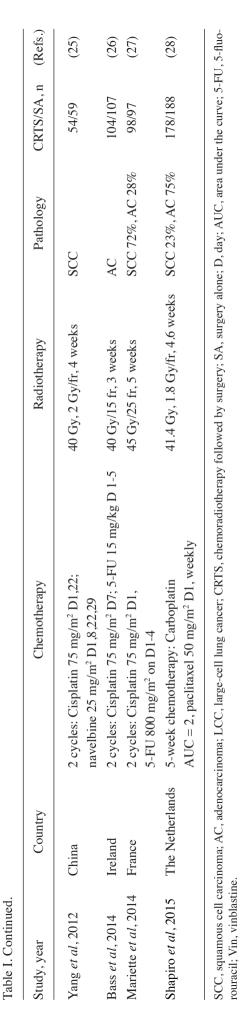
With respect to the treatment efficacy of both methods in different countries or regions, 8 trials (8,13,14,16-19,23) collected data from Asian populations, 7 studies (7-11,24-26) from European populations, and 2 (12,20) from USA populations. The study characteristics are summarized in Table I.

*Survival rate.* The heterogeneity test at all the time points had a  $I^2$  value of <55%; thus, the fixed-effects model was used.

OSR1y, OSR3y and OSR5y outcomes of traditional and cumulative meta-analysis. Traditional meta-analysis provided

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Table I. Outline of the l	iterature search	Table I. Outline of the literature search findings and the general characteristics of the included studies.				
Study, year	Country	Chemotherapy	Radiotherapy	Pathology	CRTS/SA, n	(Refs.)
Nygaard <i>et al</i> , 1992	Norway	2 cycles: Cisplatin 20 mg/m² D1-5; bleomycin 5 mg/m² D1-5	35 Gy, 1.75 Gy/fr, 4 weeks	SCC	47/41	(2)
Apinop et al, 1994	Thailand	2 cycles: Cisplatin 100 mg/m <sup>2</sup> D1; 5-FU 1,000 mg/m <sup>2</sup> D1-4	40 Gy, 2 Gy/fr, 4 weeks	SCC	35/34	(8)
Le Prise et al, 1994	France	2 cycles: Cisplatin 100 mg/m² D1,21; 5-FU 600 mg/m² D2-5, 22-25	40 Gy, 20 Gy/10 fr, 2 weeks	SCC	41/45	(6)
Walsh <i>et al</i> , 1996	Ireland	2 cycles: Cisplatin 75 mg/m² D1; 5-FU 15 mg/kg D1-5	40 Gy/15 fr, 3 weeks	AC	58/55	(10)
Bosset et al, 1997	France	2 cycles: Cisplatin 80 mg/m <sup>2</sup> D1-2	37 Gy, 3.7 Gy/fr, 2 weeks	SCC	143/139	(11)
Urba <i>et al</i> , 2001	NSA	2 cycles: Cisplatin 20 mg/m <sup>2</sup> D1-5; 5-FU 300 mg/m <sup>2</sup> D1-21; Vin 1 mg/m <sup>2</sup> D1-4	45 Gy; 1.5 Gy/fr, 3 weeks	SCC 25%, AC 75%	50/50	(12)
An <i>et al</i> , 2003	China	2 cycles: 5-FU 1 mg/m <sup>2</sup> D1-5, 21-25; cisplatin 25 mg/m <sup>2</sup> D1, 22-25	36 Gy, 1.2 Gy/fr, 3 weeks	SCC	48/49	(13)
Lee et al, 2004	Korea	2 cycles: Cisplatin 60 mg/m <sup>2</sup> D1; 5-FU 1,000 mg/m <sup>2</sup> D3-5	45.6 Gy, 1.2 Gy/fr, 4 weeks	SCC 40%, AC 60%	51/50	(14)
Burmeister et al, 2005	Australia	One cycle: Cisplatin 80 mg/m <sup>2</sup> D1; 5-FU 800 mg/m <sup>2</sup> D1-4	35 Gy/15 fr, 3 weeks	SCC	128/128	(15)
Law <i>et al</i> , 2006	China	5-FU 500 mg/m <sup>2</sup> D1-5, D24-28; cisplatin 100 mg/m <sup>2</sup> D1,24	40 Gy, 2 Gy/fr, 3 weeks	SCC	170/109	(16)
Natsugoe <i>et al</i> , 2006	Japan	Cisplatin 7 mg over 2 h; 5-FU 350 mg over 24 h	40 Gy, 2 Gy/fr, 4 weeks	SCC	22/23	(17)
Cao et al, 2007	China	Cisplatin 20 mg/m <sup>2</sup> D1-5, mitomycin 10 mg/m <sup>2</sup> /day D1, 5-FU 500 mg/m <sup>2</sup> D1-5	40 Gy, 2 Gy/fr, 4 weeks	SCC	118/118	(18)
Jin <i>et al</i> , 2008	China	Cisplatin 20-30 mg/m <sup>2</sup> , D1-5, 22-26; paclitaxel 135 mg/m <sup>2</sup> , D1,22	38-44 Gy, 2 Gy/fraction	SCC 90%, AC 10%	30/30	(19)
Peng et al, 2008	China	2 cycles: 5-FU 500 mg/m <sup>2</sup> over 5 days, cisplatin 75 mg/m <sup>2</sup> D1	40 Gy, 2 Gy/fraction 4 weeks	SCC	40/40	(20)
Tepper <i>et al</i> , 2008 Lv <i>et al</i> , 2010	USA China	2 cycles: 5-FU 1,000 mg/m <sup>2</sup> D1-4; cisplatin 100 mg/m <sup>2</sup> D1 2 cycles: Cisplatin 20 mg/m <sup>2</sup> D1-3, 22-25; paclitaxel 135 mg/m <sup>2</sup> D1-3, 22-25	50.4 Gy, 1.8 Gy/fr, 5.6 weeks 40 Gy, 2 Gy/fr, 4 weeks	SCC 25%, AC 75% SCC	30/26 119/119	(21) (22)
Jin <i>et al</i> , 2011 van Hagen <i>et al</i> , 2012	China The Netherlands	2 cycles: 5-FU 500 mg/m <sup>2</sup> D1-5; cisplatin 75 mg/m <sup>2</sup> D1 5-week chemotherapy: Carboplatin AUC = 2, paclitaxel 50 mg/m <sup>2</sup> D1, weekly	50 Gy, 2 Gy/fr, 5 weeks 41.4 Gy, 1.8 Gy/fr, 4.6 weeks	SCC 90%, AC 10% SCC 23%, AC 75%LCC 2%	30/30 178/188	(23) (24)



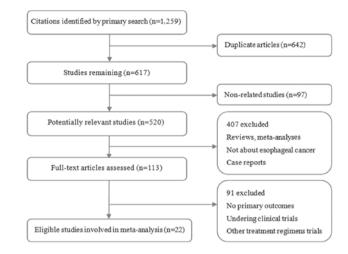


Figure 1. Trial selection process.

evidence that, compared with the SA group, the OSR3y and OSR5y were significantly higher in the CRTS group. The pooled OSR3y was 44% (95% CI: 37-52%) vs. 30% (95% CI: 23-38%), respectively, and the OSR5y was 36% (95% CI: 32-42%) vs. 24% (95% CI: 19-29%), respectively, with an OR of 1.38 (1.20-1.58, P<0.001) and 1.42 (95% CI: 1.22-1.66, P<0.001), respectively. However, there was no statistically significant difference in OSR1y between the CRTS and SA groups; the pooled OSR1y was 71% (95% CI: 65-78%) vs. 68% (95% CI: 60-76%), respectively, and the OR was 1.06 (95% CI: 0.94-1.19, P=0.348) (Figs. 2A, 3A, 4A and 5; Table II).

Cumulative meta-analyses were performed in chronological order. With the increase in the number of cases, OR point estimates and 95% CIs of all survival rates tended to be stable and exhibited an improving trend. When multiple studies with large sample sizes were added, the effect on the outcome was only a reduction in the length of the confidence interval, reflecting an increase in the accuracy of the estimated overall treatment response. Under the  $\alpha$ =0.05 test standard, cumulative meta-analyses demonstrated there was no statistical difference between CRTS and SA in terms of OSR1y (Fig. 2B), and the P-value decreased gradually, stabilizing at P=0.334 (calculated via Microsoft Excel). As regards OSR3y (Fig. 3B), it was observed that the difference was initially confirmed to be statistically significant (OR=2.10, 95% CI: 1.18-3.72, P<0.05) when adding a 113 sample size study by Walsh et al (10) in 1996 under the selection criteria. The P-value was >0.05 when subsequent studies were added successively and the analysis was re-accumulated, and it again became <0.05 when including a 100 sample size study by Urba et al (12) in 2001 (OR=1.45, 95% CI: 1.04-2.02, P<0.05). Subsequently, the cumulative analysis of successively included studies demonstrated that the difference was statistically significant, with P-values stable at <0.05. As regards OSR5y (Fig. 4B), cumulative meta-analyses demonstrated that the difference was initially statistically significant in 2007, when a 102 sample size study was conducted by Cao et al (18) (OR=1.33, 95% CI: 1.06-1.66, P<0.05), after which time the P-values were stable at < 0.05.

*Surgical factors.* The CRTS group had a significantly higher R0 resection rate and a lower local recurrence and distant

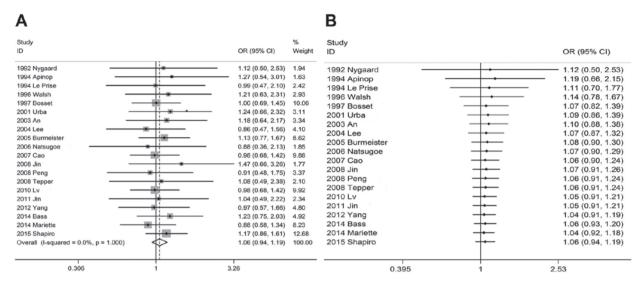


Figure 2. Traditional and cumulative meta-analysis for 1-year overall survival rate. OR, odds ratio; CI, confidence interval.

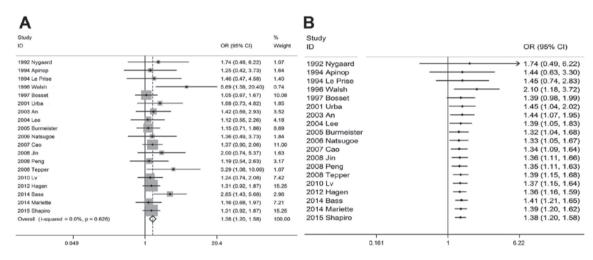


Figure 3. Traditional and cumulative meta-analysis for 3-year overall survival rate. OR, odds ratio; CI, confidence interval.

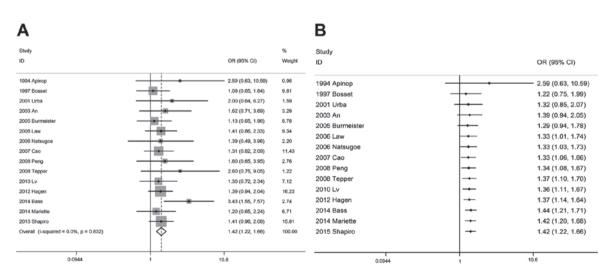


Figure 4. Traditional and cumulative meta-analysis for 5-year overall survival rate. OR, odds ratio; CI, confidence interval.

metastasis rate compared with the SA group, with a pooled OR of 2.76 (95% CI: 2.15-3.53, P<0.001), 0.49 (95% CI: 0.36-6.65,

P<0.001) and 0.76 (95% CI: 0.60-0.97, P=0.02), respectively; the differences were statistically significant. However, the

		No. of	patients		
Variables	No. of studies	CRTS	SA	OR (95% CI)	P-value
Survival rate					
OSR1y	20	1,424	1,429	1.06 (0.94-1.19)	0.348
OSR3y	19	1,479	1,488	1.38 (1.20-1.58)	< 0.0001
OSR5y	15	1,361	1,437	1.42 (1.22-1.66)	< 0.0001
Surgery conditions					
R0 resection rate	9	774	874	2.76 (2.15-3.53)	< 0.0001
Local recurrence rate	10	668	679	0.49 (0.36-0.65)	< 0.0001
Distant metastasis rate	10	668	679	0.76 (0.60-0.97)	0.02
Postoperative mortality	15	1,086	1,205	0.97 (0.72-1.32)	0.87

Table II. Survival rate and surgical parameters of patients with EC by treatment approach.

The fixed-effects model was used. EC, esophageal carcinoma; CRTS, neoadjuvant chemoradiotherapy followed by surgery; SA, surgery alone; OR, odds ratio; CI, confidence interval; OSR, overall survival rate; y, year.

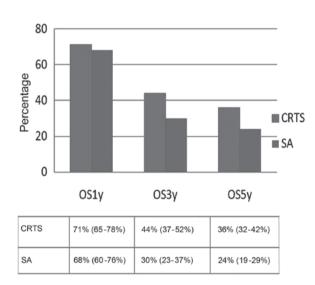


Figure 5. Survival rate and (95% confidence interval) for CRTS and SA. OS1y, 1-year overall survival; OS3y, 3-year overall survival; OS5y, 5-year overall survival; CRTS, neoadjuvant chemoradiotherapy and surgery; SA, surgery alone.

incidence of postoperative mortality in the two groups suggested there was no significantly statistical difference, with an OR of 0.97 (95% CI: 0.72-1.32, P=0.87) (Fig. 6, Table II).

# Subgroup analysis

Survival rate of squamous cell carcinoma and adenocarcinoma. The pooled OR of squamous cell carcinoma in terms of OSR3y and OSR5y in the CRTS and SA groups was 1.57 (95% CI: 1.21-2.04, P=0.0006) and 1.69 (95% CI: 1.32-2.16, P<0.0001), respectively; the differences were statistically significant. However, there was no statistically significant difference in terms of OSR1y (OR=1.13, 95% CI: 0.88-1.45, P=0.35). Compared with adenocarcinoma patients treated with SA, the OSR1y, OSR3y and OSR5y were significantly higher in CRTS, with an OR of 1.55 (95% CI: 1.09-2.20, P=0.01), 1.77 (95% CI: 1.34-2.36, P<0.0001) and 1.92 (95%

CI: 1.34-2.75, P=0.0004), respectively; the differences were statistically significant (Table III).

Survival rates of different countries or regions. The subgroup analysis of OSR3y, OSR5y for Asian, European and American populations were significantly higher in the CRTS group compared with those in the SA group, and the differences were all statistically significant (P<0.05). However, when comparing the OSR1y between the two groups in patients from the three continents, the difference was not significant (P>0.05; Table III).

*Publication bias*. A funnel plot analysis of all the studies was performed in the meta-analysis of OSR1y, OSR2y and OSR3y between CRTS and SA. This indicated that the publication bias was low in the present meta-analysis (Fig. 7).

## Discussion

CRT is quickly becoming the neoadjuvant treatment of choice for patients with resectable esophageal carcinoma prior to surgery. However, trials and meta-analyses on this subject are limited and varied, with small sample sizes and heterogeneity of population distribution characteristics, tumor pathological types, tumor location, radiation doses, chemotherapy regimens, surgical approach, postoperative care and adequacy of surgical resections, despite all the advantages of trimodality therapy.

In the CROSS trial (26), CRTS improved the long-term overall and progression-free survival in patients with resectable esophageal carcinoma; this improvement was statistically significant and clinically relevant for both the adenocarcinoma and squamous cell carcinoma subtypes. In addition, locoregional control and distant disease control also improved significantly. However, Mariette *et al* (25) reported that, compared with SA, CRTS with cisplatin plus fluorouracil did not improve R0 resection rate or survival, but rather enhanced postoperative mortality in patients with resectable esophageal carcinoma. Burmeister *et al* (15) obtained results

CRTS         SA         Oude Ratio         Odds Ratio           Difference         Events         Total         Vents         Total									
Reference in rate           1992 No sand           1992 No sand           1994 Le Prise         35         41         44         48         6.0           1994 Le Prise         35         44         8         10 <th colspan<="" td=""><td>Study or Subgroup</td><td></td><td></td><td></td><td>Total</td><td>Weight</td><td></td><td></td></th>	<td>Study or Subgroup</td> <td></td> <td></td> <td></td> <td>Total</td> <td>Weight</td> <td></td> <td></td>	Study or Subgroup				Total	Weight		
1992 / Vipsard       20       6.3       15       00       9.9%       2.22 [1:0, 6.05]         1997 Boset       112       143       94       139       26.0%       1.73 [1:0; 10.33, 35]         1997 Boset       112       143       94       139       26.0%       1.73 [1:0; 10.33, 25]         2003 An       44       80       6%       10.86 [0.59, 19.48]         2004 Lee       109       109       100       13.0%       25.07 [1:0; 6.86]         2012 Yang       44       66       507       1.76 (6.86)       6.90       2.86, 863         2012 Yang       47       49       69       5.4%       1.08 [0.05, 5.00]       2.76 [2.15, 3.53]         2012 Yang       47       64       507       7.4%       1.08 [0.65, 0.50]       2.06         2012 Yang       64       10.4       49       5.5%       0.276 [0.50, 5.00]       4.9%         2012 Yang       64       10.4       10.0%       2.76 [2.15, 3.53]       2.0%       1.58 [0.50, 5.00]         2012 Yang       6.34       10.4       10.40, 0.57       2.20 [0.05, 10.2]       2.0%       2.0%       2.24 [1.01, 0.51, 1.23]       4.9%       4.9%       4.9%       2.0%       2.276 [0.65, 0.0]			Tota	Lvans	Tota	vvolgin	man, rixed, 35% C		
1984 Lep Fine 35 41 38 45 6.7% 107 [0 33, 3.51]  1997 Bosset 112 143 94 139 2.60% 1.17 [0 13, 3.51]  2003 An 41 48 22 48 6.8% 3.11 [1.5, 8.41]  2004 Lee 35 55 42 48 6.8% 3.11 [1.5, 8.41]  2005 Low data 197 106 120 16 0.0% 2.37 [1.70, 6.68]  2012 Hagen 148 168 111 168 158 (% 50.0) 2.8, 8.68]  2012 Yang 47 48 99 59 3.4% 0.18 [0.01, 3.41]  Total events 944 59 59 7.4% 100.0% 2.76 [2.5, 5.53]  Total events 944 59 7 74 69 [= 0.07], F= 45%  Test for overal effect Z = 0.12 (% 10.0) (% 2.76 [2.5, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.76 [2.6, 5.53]  2005 Lum 16 (% 10.0) (% 2.28] (% 2.71 [0.8, 10.8]  2005 Lum 16 (% 10.0) (% 2.28] (% 2.71 [0.8, 10.8]  2005 Lum 16 (% 10.0) (% 2.28] (% 2.71 [0.8, 10.8]  2005 Lum 16 (% 10.0) (% 2.28] (% 2.71 [0.8, 10.8]  2005 Lum 16 (% 10.0) (% 2.28] (% 2.71 [0.8, 10.8]  2005 Lum 16 (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 2.28] (% 10.0) (% 10.15, 10.6] (% 10.0) (% 2.28] (% 10.0) (% 10.15, 10.6] (% 10.0) (% 10.25, 10.6] (% 10.0) (% 10.25, 10.6] (% 10.0) (% 10.25, 10.6] (% 10.25, 10.6] (% 10.0) (% 10.25, 10.6] (% 10.0) (% 10.25, 10.2] (% 10.0) (% 10.26, 10.2) (			53	15	50	9.9%	2.25 [1.00, 5.05]		
2003 An 41 48 32 49 5.8% 3.11 [17.5 8.41] 2004 Lee 35 56 42 49 0.6% 10.861 55, 19.9.44 2005 Law 97 103 120 76 123 18.7% 2.20 [16.1, 4.94] 2005 Law 97 103 120 77 1 30.0% 3.71 17.0 5.65 2017 Hagen 148 168 111 168 15.6% 5.00 [2.86, 8.06] 2017 Hagen 148 168 597 Hetrogenety: Ch <sup>2</sup> = 14.87, df = 8 $f$ = 0.07, h = 45% Test for overal effect Z = 8.03 $\theta^{2} < 0.0000$ Distant focurrence 19.4 Le Price 6 44 50 77 44 100.0% 2.76 [2.15, 3.53] Total events 644 50 77 45 97 44 100.0% 2.76 [2.15, 3.53] Total events 644 50 77 45 97 44 100.0% 2.76 [2.15, 3.53] Total events 644 50 77 45 97 44 100.0% 2.76 [2.15, 3.53] Total events 644 50 77 45 97 44 100.0% 2.76 [2.15, 3.53] Total events 644 50 97 40 7.4% 100.0% 2.76 [2.15, 3.53] Total events 20 97 40 97 40 00.0% 0.77 [10.80, 10.9] 2003 Lep 6 5 41 12 40 42 144 1.144 40 124 [1.14] 2005 Burreister 46 128 42 128 16.8% 1.15 [0.69, 1.02] 2006 Tapper 5 30 9 22 42 31 16% 2.77 [10.8] 10.88 10.13 2007 Total events 20 92 242 Hetrogenety: Ch <sup>2</sup> = 14.82, df = 9 = 0.10, h = 39% Test for overal effect Z = 2.25 $\theta^{2} = 0.02$ Cocal-regional recurrence 1934 Le Prise 7 41 9 45 11.5% 0.82 [0.28, 2.46] 2005 Hages 9 = 0.02 Hages 9 = 0.10, h = 39% Test for overal effect Z = 2.25 $\theta^{2} = 0.02$ Cocal-regional recurrence 19 50 31% 0.15 [0.67, 17.89 2006 Nature 9 5 40 9 40 5.7% 0.44 [0.15, 16.8] 2007 Hages 9 5 40 9 40 5.7% 0.42 [0.15, 17.8] 2008 Hages 9 5 5 34 4.2% 0.77 [0.33, 17.8] 2008 Hages 9 5 5 34 4.2% 1.39 [0.35, 5.39] 2008 Hages 9 5 5 34 4.2% 2.27 [10.38, 10.05] 2009 Tapper 1 10.28 (df = 9 = 0.00); h = 39% Total events 9 3 168 148 10.06 0.49 [0.36, 0.05] 1997 Hagen 9 34 5 5 34 4.2% 1.29 [0.33, 5.79] 2008 Hages 117 138 5 137 52% 3.71 [1.33 [0.38] 2009 Hages 117 138 5 137 52% 3.71 [1.33 [0.38] 2000 Hages 117 138 5 137 52% 2.27 [10.38, 10.39] 2010 Unb 1 1 47 2 20 22% 0.25 [0.05, 5.99] 2030 Law 0 1038 4170 4179 40 0.070 [0.77, 410] 2010 Unb 1 1 47 2 20 12% 10.85 [0.38, 0.03] 2014 Hagen 10 108 13 188 138% 0.035 [0.32, 0.03] 2014 Hagen 10 108 13 188 138% 0.358 [0		35	41	38	45	6.7%			
2004 Lee 35 35 42 44 0 0.06% 10.86 (15, 199, 49 2005 Burreniter 103 126 76 1120 1170 13.06% 3.27 (17.0, 6.68 2012 Magen 148 111 186 111 181 15.6% 500 [2.88, 6.68 2012 Yang 47 48 0 59 99 3.4% 0.16 [0.01, 3.41] 2012 Magen 148 111 186 111 181 15.6% 500 [2.88, 6.68] 2012 Yang 47 48 0 59 99 3.4% 0.16 [0.01, 3.41] 2014 Magen 47 48 0 59 99 3.4% 0.16 [0.01, 3.41] 2015 Uran 50 (2.16) 147 49 0 59 7 146%. Test for overal effect $Z = 0.30$ $e^{+} < 0.00001$ . Distant recurrence 1994 Le Prise 8 41 6 45 2.9% 1.58 [0.50, 5.00] 2003 Vina 28 50 27 50 7.4% 1.58 [0.50, 5.00] 2003 Vina 28 50 27 50 7.4% 1.58 [0.50, 5.00] 2003 Vina 28 50 27 50 7.4% 1.58 [0.50, 5.00] 2003 Vina 28 50 27 50 7.4% 1.58 [0.50, 5.00] 2003 Vina 28 50 27 50 7.4% 1.58 [0.50, 5.00] 2003 Pang 4 40 11 40 5.2% 0.44 [0.14, 1.43] 2004 Lee 16 13 12 29 16.7% 0.29 [0.8, 1.04] 2005 Pang 4 40 11 40 5.2% 0.29 [0.8, 1.04] 2005 Pang 4 40 11 40 5.2% 0.29 [0.8, 1.04] 2005 Pang 4 40 11 40 5.2% 0.29 [0.8, 1.04] 2005 Pang 4 40 11 40 5.2% 0.29 [0.8, 1.04] 2005 Pang 4 40 11 40 5.2% 0.29 [0.8, 1.04] 2005 Pang 4 40 11 40 5.2% 0.27 [0.28, 2.48] 2005 Pang 6 14 0.9% 0.10 [0.60, 1.78] 2005 Pang 6 14 0.9 0 11.5% 0.22 [0.28, 2.49] 2003 Vina 8 0.01 9 0 9 0.31 [0.12, 0.06] 2003 Vina 4 4 48 8 49 5.2% 0.47 [0.13, 1.68] 2004 Lee 8 51 5 50 3.1% 1.50 [0.06, 1.78] 2005 Nature 11 128 114 128 9.2% 0.77 [0.33, 1.78] 2005 Nature 11 128 1164 128 9.2% 0.77 [0.33, 1.78] 2005 Nature 11 128 1164 128 9.2% 0.77 [0.33, 1.78] 2005 Nature 11 128 118 44 128 9.2% 0.20 [0.16, 0.57] 1001 Urb 8 0 28 80 17.9% 0.20 [0.28, 0.48] 2004 Lee 8 51 5 50 3.1% 1.50 [0.06, 1.78] 2005 Nature 11 128 1.18% 1.28 [0.38, 0.38] 2005 Nature 11 128 1.18% 0.45 [0.28, 0.47] 2005 Nature 11 128 1.18% 0.45 [0.28, 0.47] 2005 Nature 11 128 1.18% 0.45 [0.28, 0.47] 2005 Nature 11 128 1.18% 0.45 [0.28, 0.47] 2016 Urb 8 3 35 3 4.22 2.9% 1.22 [0.23, 0.48] 2016 Lee 1 35 1 4.48 [0.46% 0.28 [0.78, 0.28] 2016 Lee 1 35 1 4.48 [0.46% 0.28 [0.78, 0.28] 2016 Lee 1 35 1 4.48 [0.46% 0.28 [0.77, 1.40] 2017 Nature									
2005 Euroreister 103 128 76 128 18.7% 2.12 [15], 4.94 2005 Euroreister 103 128 76 128 18.7% 2.12 [15], 4.94 2012 Hagen 148 168 111 168 15.8% 5.00 [2.8, 8.68 2012 Hagen 148 168 111 168 15.8% 5.00 [2.8, 8.68 2012 Hagen 148 168 111 168 15.8% 5.00 [2.8, 8.68 2012 Hagen 148 168 111 168 15.8% 5.00 [2.8, 8.68 2016 Euroreister 5.04 9 ( $0.000$ ); $D = 45\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 45\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 45\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 25\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 25\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 15\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 15\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 15\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 15\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 15\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 15\%$ Test for overal seffect 2.2 e.0.27 ( $0.000$ ); $D = 15\%$ Test for overal seffect 2.2 e.0.29 ( $0.000$ ); $D = 120$									
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2012 Yang 47 49 59 49 33 40 11 106 15 8% 5.00 [286,8.66] Stubtotal (95); Ch 774 974 90 59 3.4% 2.76 [2.15,3.53] Total events 64 587 Heterogenety: Ch# 14.87, df = 8 0 = 0.07, if = 45% Heterogenety: Ch# 14.87, df = 8 0 = 0.07, if = 45% Heterogenety: Ch# 14.87, df = 8 0 = 0.07, if = 45% Heterogenety: Ch# 14.87, df = 8 0 = 0.07, if = 45% 1094 Le Pise 6 51 12 50 6.7% 0.42 [0.14, 1.44] 2003 An 5 48 10 49 5.6% 0.45 [0.14, 1.44] 2004 Lee 6 51 12 50 6.7% 0.42 [0.14, 1.44] 2004 Lee 6 51 12 200 6.7% 0.42 [0.14, 1.44] 2005 Burmeister 46 128 42 21 428 18.8% 2009 Peng 4 40 11 40 6.2% 2007 Peng 4 40 11 40 6.2% 2008 Dengenety: Ch# 14.83, df = 9 0 = 0.10; if = 38% Exet for overal effect Z = 8.0.29 [0.06, 1.02] 2001 Log 1 40 50 11 5% 2005 Dengenety: Ch# 14.83, df = 9 0 = 0.10; if = 38% Exet for overal effect Z = 2.25 0 = 0.02) Local-teglinal recurrence 1994 Le Pise 7 41 9 45 5.1% 0.32 [0.28, 2.49] 2005 Marsugoe 1 122 1 23 0.7% 1.05 [0.60, 0.97] 2005 Marsugoe 1 122 1 23 0.7% 1.05 [0.60, 0.97] 2005 Marsugoe 1 122 1 123 0.7% 1.05 [0.06, 1.78] 2005 Marsugoe 1 122 1 123 0.7% 1.05 [0.05, 1.78] 2005 Burnetizer 1 138 14 128 3.2% 0.24 [0.10, 0.54] 2005 Burnetizer 1 138 14 128 3.2% 0.24 [0.10, 0.54] 2005 Burnetizer 1 30 3 26 2.2% 0.28 [0.03, 2.71] 2005 Burnetizer 1 30 3 26 2.2% 0.28 [0.03, 2.71] 2005 Burnetizer 1 30 3 26 2.2% 0.24 [0.10, 0.54] 2005 Burnetizer 1 3 3 1 44 1.0% 1.38 [0.36, 6.59] 1994 Le Pise 3 35 3 44 2.29% 1.22 [0.38, 6.5] 905 Burnetizer 1 3 3 1 44 5 2.2 12 33 [1.28, 0.44] 1992 Myapard 8 34 5 38 4.3% 2.03 [0.05, 2.49] 1993 Marsugoe 1 29 0 23 0.178 5.2% 3.71 [1.33, 1.03] 2004 Deng 5 3 5 3 4 42 2.9% 2.32 [0.38, 2.5] 905 Low 10 100 4 13 45 2.28 (2.71 10.38, 1.03 (2.38, 0.54) 1994 Le Pise 3 35 1 44 0 10% 1.38 [0.36, 6.5] 905 Burnetizer 1 35 1 44 0 10% 0.13 [0.06, 0.52 [0.32, 0.71] 1994 Aphrop 5 20 5 20 5 21 5 228 3.71 [1.33, 1.03 (2.38, 0.54) 1994 Aphrop 5 20 5 20 5 21 5 2.28 3.71 [1.33, 1.03 (2.38, 0.54) 1994 Aphrop 5 20 5 20 5 20 5 20 5 20 5 20 5 20 5 2									
2012 Yang 47 49 59 50 47 100.0% 2012 Yang 54 10 59 50 27 20 7.4% Test for overall effect Z = 0.3 P = 0.0001) Distant for the form tercurence 1994 Le Prise 5 10 27 50 7.4% 109 104 2.38 2003 Pang 5 48 10 49 56% 0.42 1014 1.44 2005 Burnelster 46 128 42 128 18.8% 1.15 105 65, 102 2005 Pang 4 40 11 40 6.2% 0.28 10.84 2006 Pang 4 40 11 40 6.2% 0.29 10.0% 2015 Yang 70 718 90 18 33.3% 2016 Yang 70 718 90 198 33.3% 2016 Yang 70 718 90 198 33.3% 2017 Urba 7 41 9 46 5.1% 0.38 10.11, 1.33 2010 Urba 7 41 9 9 0 = 0.10; P = 30% Test for overall effect Z = 2.25 P = 0.02 Local-regional recurrence 1994 Le Prise 7 41 9 46 5.1% 0.38 10.11, 1.68 2003 Pang 5 40 9 40 5.7% 0.31 10.12, 0.89 2003 An 4 48 8 49 5.2% 0.28 10.03, 1.78 2004 Lee 8 51 5 50 3.1% 1.67 10.51, 5.52 2005 Subtod (29% C) 2005 Subtod (29% C) 2005 Subtod (29% C) 2005 Subtod (29% C) 2005 Burnelster 11 128 144 28 0.2% 0.29 10.06, 1.78 2004 Lee 8 51 5 50 3.1% 1.67 10.65, 1.52 2005 Burnelster 11 128 144 28 0.2% 0.49 10.32, 2.71 2005 Burnelster 11 22 1 23 0.7% 1.05 10.06, 0.57] 2005 Burnelster 11 33 3 20 2.2% 0.49 10.03, 2.71 40 57% 0.49 10.13, 1.76 2005 Burnelster 1 3.33 2010 Lee 8 51 5 50 3.1% 1.67 10.06, 1.7.89 2005 Burnelster 1 3 33 44 5 38 4.3% 2003 Lee 8 51 5 50 3.1% 1.67 10.06, 0.45 10.20 2005 Burnelster 1 3.33 201 2.2% 0.49 10.32, 2.71 2005 Burnelster 1 3.33 201 2.2% 0.49 10.32, 2.71 2005 Burnelster 1 3.33 201 2.2% 2015 Subtod (29% C) 2016 Subtod (29% C) 2016 Subtod (29% C) 2027 Pang 5 100.0% 0.49 10.23, 0.45 10.20 2037 Pang 5 100 6.0% 0.49 10.23, 0.45 10.20 204 Lee 1 3 35 1.48 10.0% 0.49 10.23, 0.48 10.32 0.49 10.32, 0.48 10.32 0.49 10.32, 0.48 10.32 0.40 10.40 10.34 10.38 0.08 0.08 10.41, 0.38 0.08 0.05 10.00, 0.49 10.23, 0.49 10.00 100 100 100 100 100 100 100 100 1									
Subtoral (95): Ch = 14.87, df = 6 = 0.07); P = 45% Heterogeneity: Ch <sup>2</sup> = 14.87, df = 8 $(P = 0.07);$ P = 45% Test for overall effect Z = 8.03 $(P = 0.007);$ P = 45% Test for overall effect Z = 8.03 $(P = 0.007);$ P = 45% Test for overall effect Z = 8.03 $(P = 0.007);$ P = 45% Test for overall effect Z = 10.37 $(P = 0.07);$ P = 45% Test for overall effect Z = 10.37 $(P = 0.07);$ P = 45% Test for overall effect Z = 10.37 $(P = 0.07);$ P = 45% Test for overall effect Z = 10.37 $(P = 0.07);$ P = 45% Test for overall effect Z = 10.37 $(P = 0.07);$ P = 45% Test for overall effect Z = 10.37 $(P = 0.07);$ P = 35% Test for overall effect Z = 0.37 $(P = 0.07);$ P = 35% Test for overall effect Z = 0.30; P = 0.002; P = 15% Total events 10.93 $(P = 0.002);$ P = 5% Total events 10.93 $(P = 0.002);$ P = 5% Total events 10.93 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5% Test for overall effect Z = 0.17 $(P = 0.002);$ P = 5%									
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2005 Burneleter       46       128       42       128       16.8%       1.15 [0.68, 10.2]         2006 Natsuppe       8       22       4       23       1.6%       2.71 [0.68, 10.2]         2008 Tepper       5       30       9       26       50%       0.38 [0.11, 1.3]         2010 Lv       20       80       31       80       14.6%       0.53 [0.27, 1.04]         2015 Shapino       70       178       90       188       33%       0.71 [0.47, 1.07]         Subtotal (95% C1)       668       6.79       100.0%       0.76 [0.60, 0.97]         Total events       200       242         Heterogeneity: Ch <sup>2</sup> = 14.63, df= 9 (P = 0.10); P= 38%         Test for overall effect Z = 2.25 (P = 0.02)         Local-tegional recurrence         1994 Le Prise       7       19       45       5.1%       0.82 [0.12, 0.80]         2001 Urba       8       50       19       0.01 [0.51, 6.52]									
2006 Natsugce 8 22 4 23 1.6% 2.71 [0.68, 10.84] 2008 Penper 5 30 9 26 5.0% 0.38 [0.11, 1.33] 2008 Penper 5 30 9 26 5.0% 0.38 [0.11, 1.33] 2016 Lv 20 80 31 80 14.6% 0.55 [0.27, 1.04] 2015 Shapino 70 178 90 188 33.3% 0.71 [0.47, 1.07] Subtotal (95% C) 668 679 100.0% 0.76 [0.60, 0.97] Total avents 200 242 Heterogeneity: Ch <sup>2</sup> = 14.53 (1 = 9 0 = 0.10; P = 39% Test for overall effect: Z = 2.25 (P = 0.02) Local-regional recurrence 1994 Le Prise 7 41 9 45 5.1% 0.82 [0.28, 2.46] 2005 Burneiter 11 128 14 128 9.2% 0.77 [0.33, 17.6] 2005 Burneiter 11 128 14 128 9.2% 0.77 [0.33, 17.6] 2006 Natsugce 1 22 14 128 9.2% 0.77 [0.33, 17.6] 2008 Penper 1 30 2 86 17.9% 0.24 [0.10, 0.54] 2008 Penper 1 320 28 80 17.9% 0.24 [0.10, 0.54] 2010 Lv 9 8 80 28 80 17.9% 0.24 [0.10, 0.54] 2015 Shapting effect: Z = 8.9 (P = 0.30); P = 15% Test for overall effect: Z = 0.50, df = 9 (P = 0.30); P = 15% Test for overall effect: Z = 0.17 (P = 0.87) 1996 Le Prise 3 35 3 42 2.9% 1.32 [0.03, 2.7] 906 Natsugce 1 71 138 5 137 5.2% 3.71 [1.33, 10.36] 2006 Natsugce 1 71 138 5 137 5.2% 3.71 [1.33, 10.36] 2006 Natsugce 1 72 18 3.84 0.44 [0.20, 0.52] 1997 Boeset 17 138 5 137 5.2% 3.71 [1.33, 10.36] 2006 Lew 0 10.98 (4 170 4.1% 0.17 [0.01, 3.17] 2006 Natsugce 1 29 0 23 0.6% 2.47 (0.10, 6.36.6] 2005 Burneister 5 105 6 110 6.6% 0.8% 1.27 [0.23, 1.204] 1997 Boeset 17 138 5 137 5.2% 3.71 [1.33, 10.36] 2006 Evalue 1 35 1 4.81 0.9% 1.33 [0.08; 2.2.98] 2006 Evalue 1 35 1 4.81 0.9% 0.32 [0.01, 8.2.4] 2006 Evalue 1 3 188 13.8% 0.85 [0.36, 0.45] 2004 Lee 1 3 35 1 4.81 0.9% 0.32 [0.01, 8.2.4] 2005 Burneister 5 105 6 110 6.6% 0.8% 0.87 [0.24, 2.33] 2006 Evalue 1 31 108 13.188 13.6% 0.85 [0.36, 0.45] 2004 Lee 1 35 1 144 9 107 8.9% 0.32 [0.01, 8.2.4] 2005 Burneister 5 104 19 07 1.9% 0.38 [0.24, 2.30] 2006 Evalue 1 30 00 0.002; P = 59% Test for overall effect Z = 0.17 (P = 0.87) Evalue 28 Executed PETE									
$ \begin{array}{c} 2008 \ {\rm regn} & 4 & 40 & 11 & 40 & 6.2\% & 0.28 \ {\rm [0.05]} $									
2008 Tepper       5       30       9       26       5.0%       0.38 [0.11, 1.3]         2010 Lv       20       80       31       80       14.6%       0.55       10.27, 1.04         2015 Shapino       70       178       90       188       33.3%       0.71 [0.47, 1.07]         2015 Lv events       200       242       243       244       245       246         Total events       200       242       244       245       246       246         1001 Urba       8       50       19       50       11.5%       0.31 [0.12, 0.80]       44         2003 Lee       8       51       5       50       31%       1.67 [0.51, 5.52]       44         2005 Rolzygoe       1       22       123       179%       0.05 [0.56, 17.89]       45         2008 Tepper       1       30       32       22%       0.28 [0.03, 271]       46         2010 Lv       9       80       28       80       17.9%       0.56 [0.03, 271]       46         2008 Tepper       1       30       22       22.2%       0.28 [0.03, 271]       46         4betrogeneity: Chi*= 10.59, df = 9 (P = 0.30); P = 15%       Testo roveral effect Z = 4.98									
2010 Lv 20 80 31 80 14.6% 0.53 [0.27, 1.04] Subtotal (95% C) 668 679 100.0% 0.76 [0.60, 0.97] Total events 200 242 Heterogeneity: Ch <sup>2</sup> = 14.63, df = 9 0 = 0.10; P = 38% Test for overal effect: Z = 2.25 (P = 0.02) Local-tegional recurrece 1984 Le Prise 7 41 9 45 51% 0.82 [0.28, 2.49] 2001 Urba 8 50 19 50 11.5% 0.31 [0.12, 0.80] 2004 Lee 8 51 5 50 3.1% 1.67 [0.51, 5.52] 2005 Burmeister 11 128 14 128 0.2% 0.77 [0.33, 176] 2008 Peng 5 40 9 40 5.7% 0.49 [0.15, 1.63] 2008 Tepper 1 30 3 26 2.2% 0.26 [0.03, 2.71] 2008 Tepper 1 30 3 26 2.2% 0.26 [0.03, 2.71] 2010 Lv 9 80 28 80 17.9% 0.24 [0.10, 5.4] 2015 Shapino 39 178 72 188 39.4% 0.45 [0.28, 0.72] 2016 Shapino 39 178 72 188 39.4% 0.45 [0.28, 0.72] 2016 Lv P = 01.59, df = 9 (P = 0.000)! Postoperative montality 1992 Lv Parad 8 3 45 53 44 13% 1.28 [0.35, 5.39] 2004 Lee 1 35 1 44 128 2.2% 0.57 [1.03, 1.03] 2005 Urba 1 47 2 50 2.2% 0.52 [1.03, 5.52] 2010 Lv 9 80 28 80 17.9% 0.24 [0.10, 5.4] 2015 Shapino 39 178 72 188 39.4% 0.45 [0.28, 0.72] 2010 Lv 9 10 668 6 63 44 11% 1.38 [0.35, 5.39] 2010 Lv 9 10 668 6 100 6.6% 0.87 [0.26, 0.52] 4 4 1992 Lv Prise 3 35 1 48 1.0% 1.38 [0.35, 5.39] 2001 Urba 1 47 2 50 2.2% 0.52 [0.05, 5.99] 2004 Lee 1 35 1 48 1.0% 0.13 [0.08, 2.28] 2005 Burmeister 5 105 6 110 6.6% 0.87 [0.26, 2.33] 2006 Law 0 109 4 170 4.1% 0.517 [1.03, 1.03] 2007 Urba 1 29 0.28 1.28 1.7% 0.32 [0.01, 8.24] 2008 Events 5 105 6 110 6.6% 0.87 [0.26, 2.33] 2008 Law 0 109 4 170 4.1% 0.37 [1.03, 1.03] 2009 Lee 1 35 1 48 13.6% 0.85 [0.36, 2.00] 2008 Tepper 0 2.8 1.28 1.7% 0.32 [0.01, 8.24] 2008 Law 0 109 4 170 4.1% 0.37 [1.01, 6.3.60] 2008 Tepper 0 2.8 1.26 1.7% 0.32 [0.01, 8.24] 2014 Base 15 104 9 107 8.9% 1.84 0.77, 4.30] 2014 Base 15 104 9 107 8.9% 1.84 0.77, 4.30] 2014 Lee 6 98 1 97 1.1% 6.26 [0.74, 5.3.01] 2014 Haset 109 117 Heterogeneity: Ch <sup>2</sup> = 3.76 (f = 4 (P = 0.002); P = 59% Test for overal effect: Z = 0.17 (P = 0.87) 2008 Lee 7 = 200 (Z = 20, 20, 20, 20, 20, 20, 20, 20, 20, 20,	2008 Tepper								
Subtotal (95% CI) 668 679 100.0% 0.76 [0.60, 0.97] total events 200 242 Heterogeneity: ChP= 14.63, df= 9 ( $P = 0.10$ ); P= 38% Test for overal effect: Z = 2.25 ( $P = 0.02$ ) Local-regional recurrence 194 Le Prise 7 41 9 45 5.1% 0.82 [0.28, 2.48] 2001 Urba 8 50 19 50 11.5% 0.31 [0.12, 0.80] 2003 An 4 48 8 49 5.2% 0.47 [0.13, 1.68] 2004 Lee 8 51 5 50 3.1% 1.67 [0.51, 5.52] 2005 Burmeister 11 128 14 128 0.2% 0.77 [0.33, 1.76] 2008 Penper 1 30 3 26 2.2% 0.26 [0.03, 2.71] 2010 Lv 9 80 28 80 17.9% 0.24 [0.10, 1.63] 2015 Shapino 39 178 72 188 39.4% 0.24 [0.10, 0.64] Heterogeneity: ChP = 10.59, df = 9 ( $P = 0.30$ ); F= 15% Test for overal effect: Z = 4.98 ( $P = 0.30$ ); F= 15% Test for overal effect: Z = 4.98 ( $P = 0.30$ ); F= 15% 1934 Le Prise 3 35 3 42 2.9% 1.22 [0.39, 1.260] 1937 Boset 17 138 5 137 5.2% 3.71 [1.33, 10.38] 2001 Lub 1 47 2 50 2.2% 0.52 [0.05, 5.39] 1936 Walch 4 562 2 65 2.1% 2.21 [0.39, 1.260] 1937 Boset 17 138 5 137 5.2% 3.71 [1.33, 10.38] 2001 Lub 1 47 2 50 2.2% 0.52 [0.05, 5.39] 1936 Walch 4 562 2 65 1.1% 2.21 [0.39, 1.260] 2004 Lee 1 35 1 48 1.0% 1.38 [0.08, 2.28] 2005 Burmeister 5 105 6 110 6.8% 0.87 [0.28, 2.33] 2006 Law 0 109 4 170 41% 0.17 [1.01, 1.37] 2006 Natsugoe 1 29 0 23 0.8% 2.47 (10.10, 63.60] 2001 Lub 3 0 109 4 170 41% 0.17 [1.01, 1.37] 2006 Natsugoe 1 29 0 23 0.8% 2.47 (10.10, 63.60] 2014 Laes 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2010 Lv 33 80 60 80 41.5% 0.23 [0.12, 0.48] 2014 Mariete 6 98 1 97 1.1% 6.28 [0.74, 5.30] 2014 Hass 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2014 Mariete 6 98 1 97 1.1% 6.28 [0.74, 5.30] 2014 Hass 15 104 9 107 1.9% Total events 15 109 117 Heterogeneity: ChP = 33.76 [f = 14 ( $P = 0.002$ ; $P = 59\%$ Test for overal effect: Z = 0.17 ( $P = 0.87$ )		20	80	31	80	14.6%			
Total events 200 242 Heterogeneity: ChP = 14.63, df = 9 (P = 0.10); P = 38% Test for overall effect: Z = 2.25 (P = 0.02) Local-regional recurrence 1994 Le Prise 7 41 9 45 5.1% 0.82 [0.28, 2.46] 2003 An 4 48 8 49 5.2% 0.47 [0.13, 1.66] 2003 An 4 48 8 49 5.2% 0.47 [0.13, 1.66] 2003 An 4 48 8 49 5.2% 0.47 [0.13, 1.66] 2005 Nateugoe 1 22 1 23 0.7% 1.05 [0.06, 17.86] 2008 Peng 5 40 9 40 5.7% 0.48 [0.15, 1.63] 2008 Tepper 1 3 30 3 26 2.2% 0.26 [0.03, 2.71] 2010 Lv 9 80 28 80 17.9% 0.24 [0.10, 0.54] Total events 93 168 Heterogeneity: ChP = 0.56, df = 9 (P = 0.0001) postop erative montality 1992 Kygsand 8 34 5 38 4.3% 2.03 [0.56, 0.65] 1993 Roset 17 138 5 137 5.2% 0.71 [0.33, 1.76] 2004 Lee 1 35 1 48 1.0% 1.38 [0.35, 5.39] 2005 Lorder for Verall effect: Z = 4.98 (P < 0.00001) postop erative montality 1992 Kygsand 8 34 5 38 4.3% 2.03 [0.56, 0.65] 1997 Booset 17 138 5 137 5.2% 0.71 [1.33, 10.38] 2005 Burmeister 5 105 6 110 6.6% 0.87 [0.28, 0.72] 2004 Lee 1 35 1 48 1.0% 1.38 [0.08, 2.289] 2005 Burmeister 5 105 6 110 6.6% 0.87 [0.28, 0.28] 2005 Burmeister 5 105 6 110 6.6% 0.87 [0.28, 2.93] 2005 Burmeister 5 105 6 1 106 6.6% 0.87 [0.28, 2.93] 2005 Burmeister 5 105 6 1 106 6.6% 0.87 [0.28, 2.93] 2005 Burmeister 5 105 6 1 106 6.6% 0.87 [0.28, 2.93] 2005 Burmeister 5 105 6 1 106 6.6% 0.87 [0.28, 2.93] 2005 Burmeister 5 105 6 1 106 6.6% 0.87 [0.28, 2.93] 2004 Lee na 1 38 1 88 1.8% 0.23 [0.12, 0.46] 2014 Marietle 6 98 1 97 1.1% 6.28 [0.74, 5.30] 2014 Base 15 104 9 107 8.9% 1.34 [0.77, 4.40] 2010 Lv 33 0 60 080 41.5% 0.23 [0.12, 0.46] 2014 Base 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2014 Base 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2014 Base 15 104 (P = 0.002); P = 59% Test for overail effect: Z = 0.17 (P = 0.87) Encource 62 E Encource CETS		70		90				-	
Heterogeneity: $Ch^{\mu} = 14.63, df = 0, P = 0.10; P = 38\%$ Test for overall effect: $Z = 2.25, P = 0.02$ Local-regional recurrence 1994 Le Prise 7 41 9 45 5.1% 0.82 [0.28, 2.46] 2001 Urba 8 50 19 50 11.5% 0.31 [0.12, 0.80] 2003 An 4 48 8 49 5.2% 0.47 [0.13, 1.66] 2004 Lee 8 51 5 50 3.1% 1.67 [0.51, 5.52] 2005 Burmeister 11 128 14 128 9.2% 0.77 [0.33, 1.76] 2008 Pepper 1 30 3 26 2.2% 0.26 [0.03, 2.71] 2008 Pepper 1 30 3 26 2.2% 0.26 [0.03, 2.71] 2010 Lv 9 80 28 80 17.9% 0.24 [0.10, 0.54] 2015 Shapino 39 178 72 188 39.4% 0.45 [0.28, 0.72] Subtotal (95% Cl) 668 679 100.0% 0.49 [0.55, 6.95] 1984 Le Prise 3 35 3 42 2.9% 1.22 [0.38, 5.39] 1984 Le Prise 3 .95 3 42 2.9% 3.71 [1.33, 10.36] 2004 Lee 1 35 1.48 1.0% 1.38 [0.35, 5.39] 1984 Le Prise 3 .95 3 42 2.9% 3.71 [1.33, 10.36] 2004 Lee 1 35 1.44 1.0% 1.38 [0.35, 5.39] 1986 Watch 4 52 2.25 2.15% 2.21 [0.39, 1.260] 1987 Bosset 17 138 5 137 5.2% 3.71 [1.33, 10.36] 2004 Lee 1 35 1.44 1.0% 1.38 [0.35, 6.39] 1986 Watch 4 52 2.25 1.3% 2.21 [0.39, 1.260] 1987 Bosset 17 138 5 137 5.2% 3.71 [1.33, 10.36] 2004 Lee 1 35 1.44 1.0% 1.38 [0.36, 2.93] 2005 Burmeister 5 105 6 110 6.6% 0.87 [0.26, 2.93] 2005 Burmeister 5 105 6 110 8.6% 0.23 [0.12, 0.48] 2005 Burmeister 5 105 6 1.10 8.6% 0.23 [0.10, 2.2, 2.9] 2006 Burmeister 5 105 6 1.10 8.6% 0.23 [0.10, 2.2, 2.9] 2006 Burmeister 5 105 6 1.10 8.6% 0.23 [0.10, 2.6, 2.9] 2006 Burmeister 5 105 6 1.10 8.6% 0.23 [0.10, 2.6, 2.9] 2006 Burmeister 5 105 6 1.10 8.6% 0.23 [0.10, 2.6, 2.9] 2006 Burmeister 5 105 6 1.10 8.6% 0.23 [0.10, 8.24] 2010 Lv 3 33 80 60 80 41.5% 0.23 [0.11, 2.46] 2014 Mariette 6 9 81 1.97 High 1.17 Heterogeneity: Chf <sup>#</sup> = 33.76, df = 14 (P = 0.002); P = 59% Test for overail effect: $Z = 0.17, P = 0.87$ Total events 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2014 Mariette 6 98 1 97 1.1% 6.26 [0.74, 5.01] 2014 Bass 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2014 Mariette 6 98 1 97 1.1% 6.26 [0.74, 5.01] 2014 Bass 15 104 9 107 8.9% 1.84 [0.77, 2.132] Total events 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2			668		679	100.0%	0.76 [0.60, 0.97]	•	
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Local regional recurrence           1994 Le Prise         7         41         9         45         5.1%         0.82 [0.28, 2.46]           2001 Urba         8         50         19         50         11.5%         0.31 [0.12, 0.80]           2003 An         4         48         8         49         5.2%         0.47 [0.13, 1.86]           2004 Lee         8         51         5         50         3.1%         1.67 [0.51, 5.52]           2005 Burneister         11         122         1         23         0.7%         0.49 [0.15, 163]           2008 Peng         5         40         9         40         5.7%         0.49 [0.16, 163]           2008 Tepper         1         30         3         26         2.2%         0.26 [0.03, 2.71]           2016 Shapino         39         178         72         188         3.4.%         0.45 [0.26, 0.72]           Subtotal (95% C1)         668         679         100.0%         0.49 [0.36, 0.65]           1992 Nygaard         9         9         3         5         32         2.03 [0.59, 6.95]           1994 Le Prise         3         35         3         4.2         2.96         2.21% 2.2 6.48] </td <td></td> <td></td> <td></td> <td></td> <td>= 38%</td> <td></td> <td></td> <td></td>					= 38%				
1994 Le Prise       7       41       9       45       5.1%       0.32 [0.22, 2.4]         2001 Urba       8       50       19       50       11.5%       0.31 [0.12, 0.80]         2003 An       4       4.8       8       49       5.2%       0.47 [0.13, 1.68]         2004 Lee       8       51       5       50       3.1%       1.67 [0.51, 5.52]         2005 Burmeister       11       122       1       22       0.76 (0.33, 1.76]         2006 Natsugoe       1       22       1       23       0.7%       0.49 [0.15, 16.3]         2008 Perper       1       30       3       26       2.2%       0.26 [0.03, 2.71]         2010 Lv       9       80       28       17.9%       0.24 [0.10, 0.54]         2015 Shapio       39       188       Heterogeneity: Chi"= 10.59, df= 9 (P = 0.30); P = 15%         Test for overall effect: Z = 4.98 (P < 0.00001)	Test for overall effect. Z	. = 2.25 (	P = 0.0.	2)					
1994 Le Prise       7       41       9       45       5.1%       0.32 [0.22, 2.4]         2001 Urba       8       50       19       50       11.5%       0.31 [0.12, 0.80]         2003 An       4       4.8       8       49       5.2%       0.47 [0.13, 1.68]         2004 Lee       8       51       5       50       3.1%       1.67 [0.51, 5.52]         2005 Burmeister       11       122       1       22       0.76 (0.33, 1.76]         2006 Natsugoe       1       22       1       23       0.7%       0.49 [0.15, 16.3]         2008 Perper       1       30       3       26       2.2%       0.26 [0.03, 2.71]         2010 Lv       9       80       28       17.9%       0.24 [0.10, 0.54]         2015 Shapio       39       188       Heterogeneity: Chi"= 10.59, df= 9 (P = 0.30); P = 15%         Test for overall effect: Z = 4.98 (P < 0.00001)	Local-regional re	currence	0						
2001 Urba       8       50       19       50       11.5%       0.31       0.12       0.60         2003 An       4       48       8       49       5.2%       0.47       (0.13, 1.66)         2003 Loe       8       51       5       50       3.1%       1.67       (0.51, 5.52)         2005 Burmeister       11       128       1.4       128       9.2%       0.77       (0.33, 1.76)         2006 Natsugoe       1       22       1       23       0.7%       0.050       (0.6, 17.85)         2008 Peng       5       40       9       40       6.7%       0.49       (0.15, 1.5.2)         2008 Tepper       1       30       3       28       2.2%       0.26       (0.03, 2.71)         2010 Lv       9       80       28       0.17, 9%       0.24       (0.10, 0.54)         2015 Shapino       39       178       72       188       39.4%       0.45       (0.29, 0.72)         Subtotal (9% CI)       668       6.79       100.0%       0.45       (0.36, 0.65)       0.65         Test for overall effect: Z = 4.98 (P < 0.00001)				9	45	5.1%	0.82 10.28 2.461		
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2005 Burmeister       11       128       14       128       9.2%       0.77       0.33       1.76         2006 Natsugue       1       22       1       23       0.7%       1.05       [0.06, 17.86]         2008 Perper       1       30       3       26       2.2%       0.26       [0.03, 2.71]         2010 Lv       9       80       28       0.79       0.28       [0.10, 0.54]         2015 Shapino       39       178       72       188       39.4%       0.45       [0.20, 0.72]         Subtotal (95% CI)       668       679       100.0%       0.49       [0.36, 0.65]       Total events       93       168         Heterogeneity: ChP= 10.59, df = 9 (P = 0.30); P = 15%       Total events       33       53       42       2.9%       1.22       [0.39, 12.60]         1992 Nygard       8       34       5       38       4.3%       2.03       [0.59, 6.96]       1.21       1.23       1.23       1.48       1.38       1.38       1.38       1.38       1.38       1.38       1.38       1.38       1.38       1.38       1.38       1.38       1.31       1.31       1.31       1.31       1.31       1.31       1.31 <t< td=""><td>2003 An</td><td></td><td>48</td><td></td><td>49</td><td></td><td></td><td></td></t<>	2003 An		48		49				
2006 Natsugoe       1       22       1       23       0.7%       1.05 [0.06, 17.85]         2008 Tepper       1       30       3       26       2.2%       0.26 [0.03, 2.71]         2010 Lv       9       80       2.2%       0.26 [0.03, 2.71]         2015 Shapiro       39       178       72       188       39.4%       0.45 [0.29, 0.72]         2015 Shapiro       39       178       72       188       39.4%       0.45 [0.28, 0.72]         Subtotal (95% CI)       668       679       100.0%       0.49 [0.36, 0.65]         Test for overall effect: Z = 4.98 (P < 0.00001)	2004 Lee	8	51	5	50	3.1%	1.67 [0.51, 5.52]		
2008 Peng       5       40       9       40       5.7%       0.49       [0.15, 1.63]         2008 Tepper       1       30       3       26       2.2%       0.26       [0.03, 2.71]         2010 Lv       9       80       28       80       1.7%       0.24       [0.16, 1.63]         2015 Shapino       39       178       72       188       38.4%       0.45       [0.29, 0.72]         2016 Lv       9       90       20       30       168         Heterogeneity: Chi <sup>m</sup> = 10.59, df = 9 (P = 0.30); P = 15%       Test for overall effect: Z = 4.98 (P < 0.00001)									
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2015 Shapiro       39       178       72       188       39.4%       0.45 [0.29, 0.72]         Subtotal (95% CI)       668       679       100.0%       0.49 [0.36, 0.65]         Total events       93       168         Heterogeneity: Ch <sup>P</sup> = 10.59, df = 9 (P = 0.30); P = 15%         Test for overal effect: Z = 4.98 (P < 0.00001)									
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1992 Nygaard       8       34       5       38       4.3%       2.03 [0.59, 6.95]         1994 Apinop       5       26       5       34       4.1%       1.38 [0.35, 5.39]         1994 Le Prise       3       35       3       42       2.9%       1.22 [0.23, 6.46]         1996 Walsh       4       52       2       55       2.1%       2.21 [0.39, 12.60]         1997 Bosset       17       138       5       137       5.2%       3.71 [1.33, 10.36]         2001 Urba       1       47       2       50       2.2%       0.55 [0.05, 5.95]         2005 Burmeister       5       105       6       110       6.6%       0.87 [0.26, 2.93]         2006 Law       0       109       4       170       4.1%       0.17 [0.01, 3.17]         2006 Natsugoe       1       29       0       23       0.6%       2.47 [0.10, 63.60]         2010 Lv       33       80       60       80       4.15%       0.23 [0.12, 0.46]									
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2010 Lv 33 80 60 80 41.5% 0.23 [0.12, 0.46] 2012 Hagen 10 188 13 188 13.6% 0.85 [0.36, 2.00] 2014 Bass 15 104 9 107 8.9% 1.84 [0.77, 4.40] 2014 Mariette 6 98 1 97 1.1% 6.26 [0.74, 53.01] Subtotal (95% CI) 1086 1205 100.0% 0.97 [0.72, 1.32] Total events 109 117 Heterogeneity: Chi <sup>P</sup> = 33.76, df = 14 (P = 0.002); I <sup>P</sup> = 59% Test for overall effect: Z = 0.17 (P = 0.87)							2.47 [0.10, 63.60]		
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Test for overall effect: Z = 0.17 (P = 0.87)			14 (P		$ ^2 = 59$	*			
0.005 0.1 1 10 200									
Exource SA Exource OPTS				1					
Exource SA Exource OPTS									
Test for subgroup differences: Chi <sup>≥</sup> = 93.91. df = 3 (P < 0.00001).   <sup>≥</sup> = 96.8%									
	Test for subgroup differ	rences: C	hi² = 93	.91. df=	3 (P < 1	J.00001).	I*= 96.8%		

Figure 6. Traditional meta-analysis for surgical parameters of patients with EC by treatment schedule (CRTS or SA). CRTS, neoadjuvant chemoradiotherapy and surgery; SA, surgery alone; CI, confidence interval.

in a randomised controlled phase III trial indicating that preoperative CRT with cisplatin and fluorouracil did not significantly improve progression-free or overall survival in patients with resectable esophageal cancer compared with SA.

Meta-analyses on CRTS vs. SA in esophageal cancer, however, are discordant. In the most recent meta-analysis of 13 studies on CRTS compared with SA in operable patients, the hazard ratio for all-cause mortality was 0.78 (P<0.001), favoring CRTS. However, due to the large majority of locally advanced cases included in the trials and the heterogeneity in staging methods, there was no definitive conclusion regarding survival benefit for stage I or II esophageal cancer (29). A meta-analysis of those trials by Gluud and Krag (30) reported a short-term survival benefit for neoadjuvant chemoradiotherapy over surgical monotherapy in adenocarcinoma as well as squamous cell carcinoma of the esophagus. In addition, a meta-analysis by Huang et al (31) reported that CRTS with paclitaxel plus platinum appeared to be a better choice compared with platinum plus 5-fluorouracil for esophageal cancer, particularly for squamous cell carcinoma. Wijnhoven et al (32) performed a secondary meta-analysis of six published meta-analyses to compare the differences in the studies included and statistical methods applied, and found heterogeneity between the RCTs included in the meta-analyses with regard to the previously mentioned content. Of note, the majority of RCTs were conducted in the 90s; hence, the diagnostic methods, staging, treatment delivery and outcome assessment reflected the clinical practice during tha decade.

			No. of p	oatients		
Variables	Overall survival	No. of studies	CRTS	SA	OR (95% CI)	P-value
Histological type						
SCC	OSR1y	11	647	654	1.13 (0.88-1.45)	0.35
	OSR3y	10	554	556	1.57 (1.21-2.04)	0.0006
	OSR5y	8	622	698	1.69 (1.32-2.16)	< 0.0001
AC	OSR1y	4	295	302	1.55 (1.09-2.20)	0.01
	OSR3y	5	429	442	1.77 (1.34-2.36)	< 0.0001
	OSR5y	4	371	387	1.92 (1.34-2.75)	0.0004
Location						
Asia	OSR1y	8	398	403	1.05 (0.74-1.49)	0.80
	OSR3y	8	424	424	1.81 (1.37-2.40)	< 0.0001
	OSR5y	7	452	514	1.73 (1.31-2.27)	< 0.0001
Europe	OSR1y	7	669	673	1.22 (0.96-1.54)	0.10
-	OSR3y	8	847	860	1.74 (1.42-2.14)	< 0.0001
	OSR5y	5	701	719	1.69 (1.35-2.13)	< 0.0001
USA	OSR1y	2	80	76	1.75 (0.86-3.55)	0.06
	OSR3y	2	80	76	3.55 (1.68-7.49)	0.0009
	OSR5y	2	80	76	2.80 (1.19-6.61)	0.02

Table III. Survival rate by histological type and continent in EC patients treated with CRTS and SA.

The fixed-effects model was used. EC, esophageal carcinoma; CRTS, neoadjuvant chemoradiotherapy and surgery; SA, surgery alone; OR, odds ratio; CI, confidence interval; OSR, overall survival rate; y, year; SCC, squamous cell carcinoma; AC, adenocarcinoma.

Our aim was to conduct a meta-analysis combining the traditional and cumulative methods. The traditional meta-analysis revealed that CRTS may improve the long-term survival and surgical parameters, and reduce locoregional cancer recurrence and distant metastasis in adenocarcinoma as well as squamous cell carcinoma of the oesophagus, but there was no significant difference in terms of short-term survival. We focused more on the integration of various researches chronologically by using the cumulative meta-analysis. Clinical trials on a particular research topic constitute an increasing, open and continuous entity over time. Baum et al (33) first proposed the concept of cumulative meta-analysis that was first applied to clinical practice by Lau et al (34) on the basis of the traditional meta-analysis, adding studies sequentially and performing multiple meta-analyses in a sequential manner based on the time of publication, the size of the sample and the quality score of the study; whenever a new study is published, the meta-analysis may be again continued. Unlike traditional meta-analyses, which are performed only at a certain point in time, cumulative meta-analysis was performed at each time point in order to capture the variation tendency of the combined total effect, which may enable greater use of information, contribute to early detection of coherent interventions, and facilitate new research.

From forest plots of cumulative meta-analysis (performed in chronological order), it was observed that, as the number of cases increased, the test efficacy increased and the 95% CI gradually decreased; under the  $\alpha$ =0.05 test standard, cumulative meta-analyses demonstrated there was no statistical difference between CRTS and SA in terms of OSR1y, and the P-value

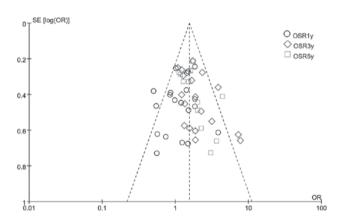


Figure 7. Funnel plot for the publication bias tests. OSR1y, 1-year overall survival rate; OSR3y, 3-year overall survival rate; OSR5y, 5-year overall survival rate; OR, odds ratio; SE, standard error.

decreased gradually and stabilized at 0.334. Therefore, it was concluded that CRTS did not improve the short-term survival benefit of patients with esophageal cancer. The difference between the two treatment approaches in terms of OSR3y was initially confirmed to be statistically significant (OR=2.10, 95% CI: 1.18-3.72, P<0.05); when adding a 113 sample size study by Walsh *et al* (10) under the selected test criteria, it was observed that the treatment regimen was the same as that of previous studies, except that the subjects were adenocarcinoma patients rather than squamous cell carcinoma patients. Thus, it was hypothesized that CRTS may be more effective in treating esophageal adenocarcinoma. The same conclusion was reached using the traditional meta-analysis, as the OR for OSR1y, OSR3y

and OSR5y in adenocarcinoma patients is higher compared with that in squamous cell carcinoma patients (1.55 vs. 1.13 for OSR1y, 1.77 vs. 1.57 for OSR3y and 1.92 vs. 1.69 for OSR5y). A meta-analysis conducted by Hai-Lin et al (35) also confirmed that CRTS may increase the survival rate of patients with esophageal adenocarcinoma. However, the P-value was >0.05 when adding a 282 sample size study by Bosset et al (11) in 1997, possibly due to the cisplatin monotherapy. The P-value again became <0.05 when a 100 sample size study by Urba et al (12) in 2001 was included (OR=1.45, 95% CI: 1.04-2.02, P<0.05), in which innovative triple therapy was used, combining vinblastine with cisplatin and fluorouracil. Liu et al (36) also reported in 2015 that cisplatin with vinorelbine may achieve a higher pathological complete response rate and better survival outcomes compared with cisplatin and fluorouracil in esophageal squamous cell carcinoma. Subsequently, the cumulative analysis of successively included studies demonstrated that the difference was statistically significant, with P-values stable at <0.05. It was demonstrated that CRTS may improve the 3-year survival benefit of patients with esophageal cancer. As regards OSR5y, cumulative meta-analyses demonstrated that the difference was initially found to be statistically significant in 2007, when a 102 sample size study was conducted by Cao et al (17) (OR=1.33, 95% CI: 1.06-1.66, P<0.05), after which the P-values were stable at <0.05. A study by Wolf et al (37) on long-term outcome of mitomycin C and 5-fluorouracil-based primary CRT for esophageal cancer demonstrated a significant increase of overall survival (P<0.0001) in the CRT vs. the radiotherapy alone group, indicating that CRTS may provide a long-term survival benefit to patients with esophageal cancer. However, it remains uncertain whether the alteration in the abovementioned treatment options is the cause of P<0.05, as this is only a monistic interpretation. From the present analysis, it was concluded that CRTS was able improve the long-term survival of patients with esophageal cancer, and may be more effective in treating esophageal adenocarcinoma. In addition, vinblastine or mitomycin combined with general chemotherapy were more likely to improve the long-term survival rate following complete resection, which may also be a future research focus.

Traditional meta-analysis may be associated with various types of bias, such as selection, implementation, exit and measurement bias; the same biases may occur at various time points in the cumulative meta-analysis and affect the determination of the overall effect trend. Furthermore, certain information could not be collected (e.g., the chronological cumulative effect of the treatment regimen, the difference in efficacy and the quality score of a single article), which is a major drawback. In addition, patients included in the present study were in various stages of the trial, such as adjuvant therapy; patient compliance was also different, which may affect the results. Furthermore, the 22 included studies differed significantly in sample size; thus, the contribution to the overall effect was not proportional, which was another limitation of the cumulative meta-analysis.

In summary, it may be concluded from the cumulative meta-analysis that CRTS may increase OSR3y and OSR5y by 38% (P<0.0001) and 42% (P<0.0001), respectively. From the forest plot, it was observed that the difference in OSR3y and OSR5y was statistically significant, with P-values stable at <0.05, indicating that CRTS may improve the patient survival

rate. Therefore, it is recommended that the CRTS regimen is routinely used for patients with early resectable esophageal cancer. There are ongoing studies on this subject and, as the results of those studies are published, it may further elucidate the role of CRTS in the treatment of early resectable esophageal cancer.

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