

Figure S1. Risk of bias of included studies. Risk of bias across studies assessed using the Cochrane risk of bias tool (1,2). Studies are assessed on the basis of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other sources of bias. (A) Risk of bias graph, each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary for each included study.

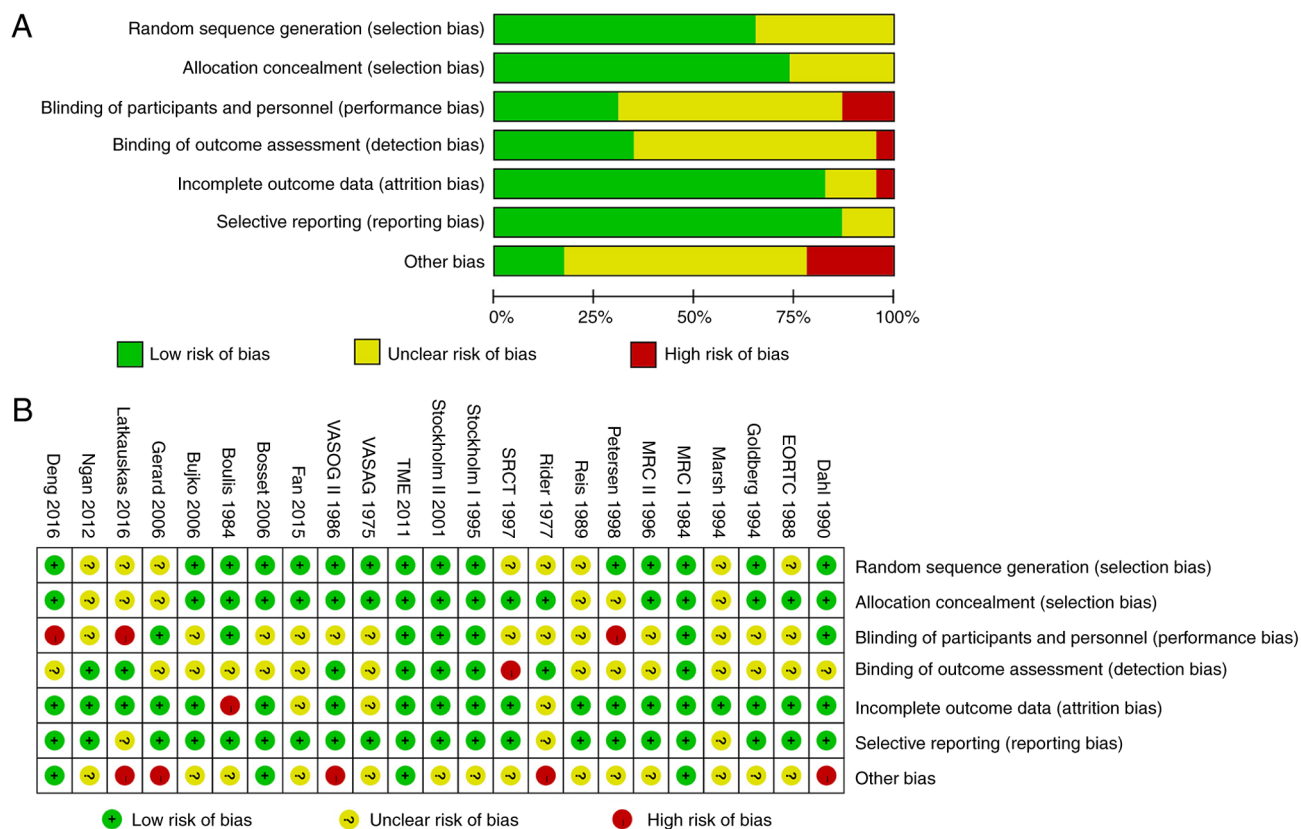


Figure S2. Network geometry for secondary outcomes in the network meta-analysis. Each node indicates a strategy and the node size is proportional to the number of patients in the treatment group. Lines represent direct comparisons between two treatments and line thickness represents the number of randomized controlled trials included in each comparison, also represented by the numbers. (A) DFS (10 trials), (B) distant metastases (13 trials), (C) pCR (7 trials), (D) organ preservation (6 trials), (E) anastomotic leak (9 trials) and (F) 30-day mortality (16 trials). DFS, disease-free survival; pCR, pathological complete response rate; S, surgery alone; RT, surgery preceded by neoadjuvant radiotherapy; CRT, surgery preceded by neoadjuvant chemoradiotherapy; CT, surgery preceded by neoadjuvant chemotherapy.

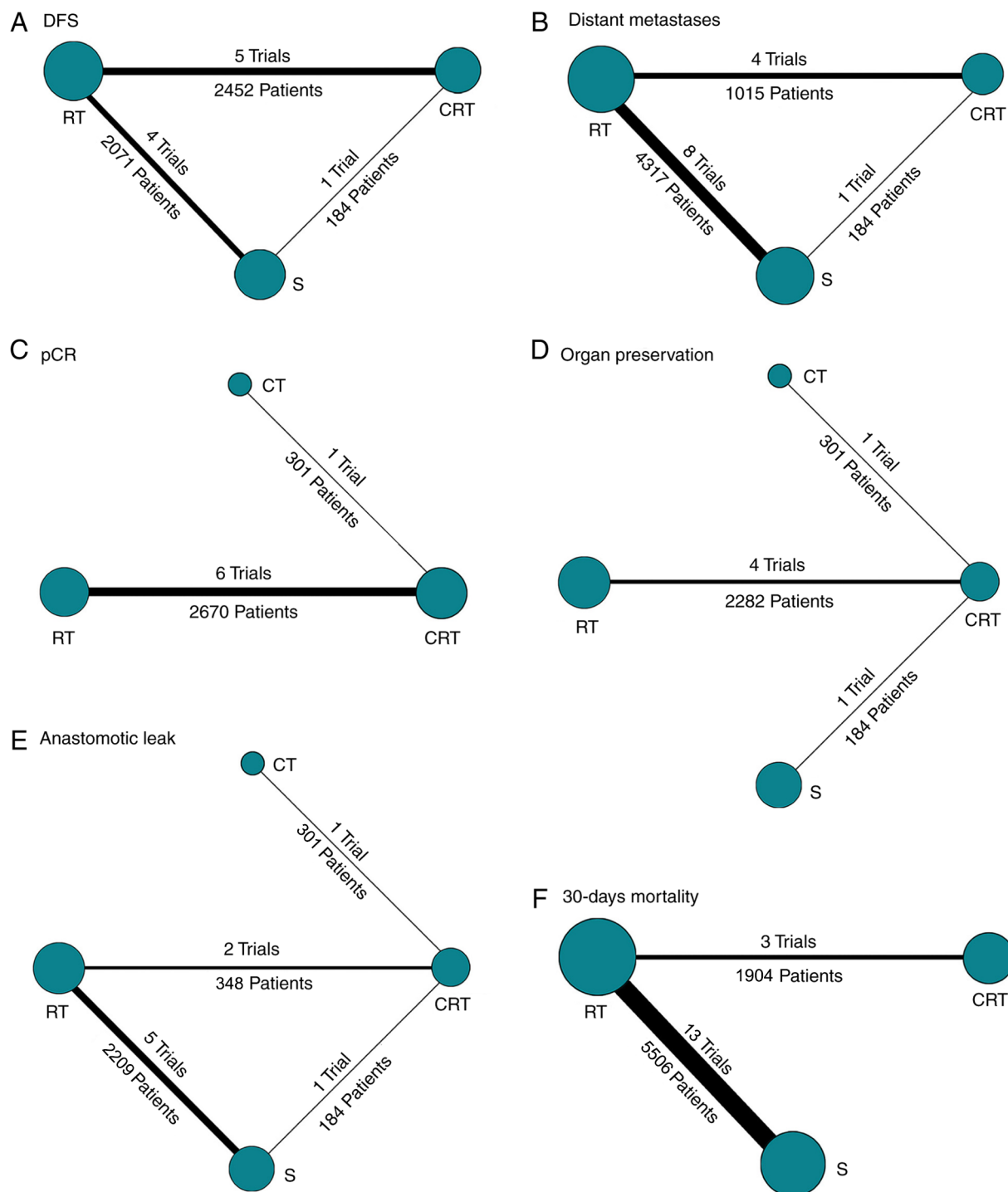


Figure S3. Ranking probability and SUCRA of strategies for secondary outcomes in the network meta-analysis of neoadjuvant treatments for resectable rectal cancer. Each line represents a treatment strategy. The x-axis indicates the ranking of strategies, with '1st' representing the best. The y-axis represents the probability of each ranking. (A) DFS, (B) distant metastases, (C) pCR, (D) organ preservation, (E) anastomotic leak and (F) 30-day mortality. SUCRA, surface under the cumulative ranking curve; DFS, disease-free survival; pCR, pathological complete response rate; S, surgery alone; RT, surgery preceded by neoadjuvant radiotherapy; CRT, surgery preceded by neoadjuvant chemoradiotherapy; CT, surgery preceded by neoadjuvant chemotherapy.

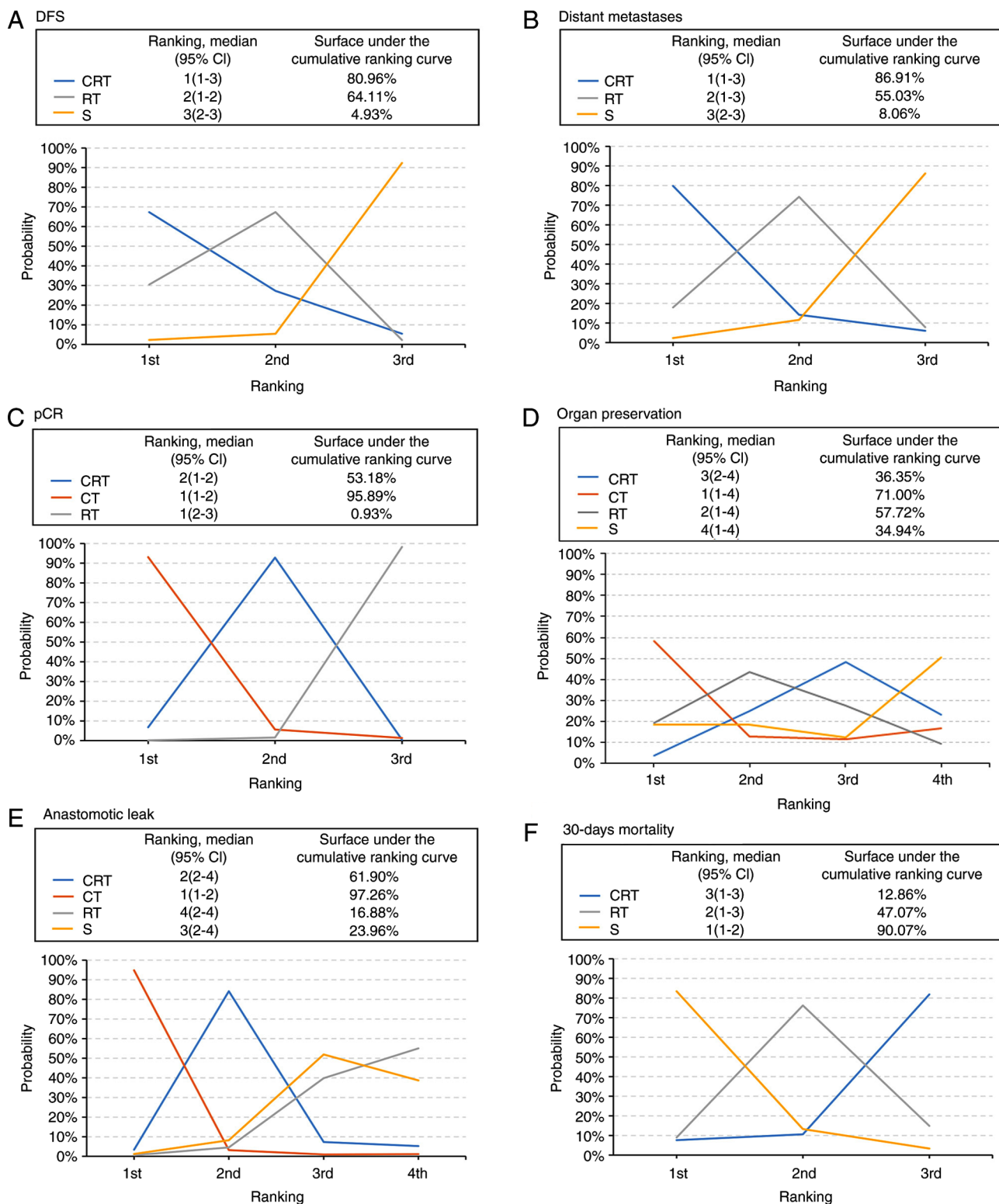


Table SI. Literature search strategy.

A, Search strategies for MEDLINE [Ovid MEDLINE (R) 1946 to June 1st, 2018]

Search no.	Search term
#1	Rectal neoplasms/
#2	Rectal cancer.mp.
#3	Rectum cancer.mp.
#4	#1 OR #2 OR #3
#5	Chemotherapy/
#6	Antineoplastic agents/
#7	(Chemotherapy or chemoradiotherapy or chemoradiation or adjuvant or neoadjuvant or surgery).mp.
#8	#5 OR #6 OR #7
#9	(Overall survival or OS or disease-free survival or DFS or mortality or recurrence or Hazard ratio or HR or risk ratio or Kaplan–Meier curve*).mp.
#10	Comparative study/
#11	(Compare or comparison or comparing or comparative or vs. or vs. or side by side).mp.
#12	#10 OR #11
#13	Limit #12 to clinical trial, all
#14	Limit #12 to (meta analysis or systematic reviews)
#15	#13 or #14
#16	#4 and #8 and #9 and #15

B, Search in EMBASE

Search no.	Search term
1	'Rectal neoplasms'/exp OR 'rectal neoplasms'
2	'Rectal cancer'/exp OR 'rectal cancer'
3	'Rectum cancer'/exp OR 'rectum cancer'
4	#1 OR #3
5	'Chemotherapy'/exp OR chemotherapy
6	'Antineoplastic agents'/exp OR 'antineoplastic agents'
7	(Chemotherapy OR chemoradiotherapy OR chemoradiation OR adjuvant or neoadjuvant OR surgery)
8	#5 OR #6 OR #7
9	'Overall survival' or OS or 'disease free survival' or DFS or mortality or recurrence or 'Hazard ratio' or HR or 'risk ratio' or 'Kaplan Meier curve'
10	'Comparative study'/exp
11	Compare OR comparison OR comparing OR comparative OR vs. OR vs. OR side by side
12	#10 OR #11
13	#12 AND ('clinical trial'/de OR 'controlled clinical trial'/de OR 'randomized controlled trial'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'systematic review'/de OR 'phase 1 clinical trial'/de)
14	#4 and #8 and #9 and #13

C, Search strategies for CENTRAL

Search no.	Search term
1	'Rectal neoplasm' (Word variations have been searched)
2	'Rectal cancer' (Word variations have been searched)
3	Rectal carcinoma (Word variations have been searched)
4	MeSH descriptor: [Rectal Neoplasms] explode all trees
5	#1 or #2 or #3 or #4
6	Surgery or surgical or chemo* or chemo rad or radiotherapy or radiation or adjuvant or neoadjuvant
7	#5 and #6

Database, MEDLINE [Ovid MEDLINE (R) 1946 to June 1st, 2018]. Mp., indicates a search of title, original title, abstract, name of substance word and subject heading word. exp, 'explodes' controlled vocabulary term. B) Database, Embase Classic+Embase 1947 to 2018. Mp., indicates a search of title, original title, abstract, name of substance word and subject heading word. exp, 'explodes' controlled vocabulary term. de, limit-controlled vocabulary heading. C) Database, EBM Reviews-Cochrane Central Register of Controlled Trials <May 2018>.

Table SII. GRADE evidence profile table for direct comparisons and network meta-analysis.

A, Overall survival						
Comparison	Direct comparisons		Indirect comparisons		Network meta-analysis	
	HR (95% CI)	QoE	HR (95% CI)	QoE	HR (95% CI)	QoE
RT vs. S	0.90 (0.84-0.96)	High	1.23 (0.38-4.00)	Low	0.89 (0.82-0.97)	High
CRT vs. S	1.34 (0.43-4.21)	Low	0.91 (0.77-1.12)	Low	0.95 (0.81-1.10)	Low
CT vs. S	-		0.88 (0.40-1.90)	Low	0.88 (0.40-1.90)	Low
CRT vs. RT	1.06 (0.92-1.21)	Low	1.54 (0.48-4.76)	Low	1.10 (0.93-1.20)	Low
CT vs. RT	-		0.99 (0.45-2.20)	Low	0.99 (0.45-2.20)	Low
CRT vs. CT	1.08 (0.51-2.29)	Low	-	-	1.10 (0.50-2.30)	Low
B, Local recurrence						
Comparison	Direct comparisons		Indirect comparisons		Network meta-analysis	
	OR (95% CI)	QoE	OR (95% CI)	QoE	OR (95% CI)	QoE
RT vs. S	0.44 (0.37-0.51)	High	1.45 (0.28-7.69)	Low	0.44 (0.35-0.65)	High
CRT vs. S	1.05 (0.25-4.30)	Low	0.31 (0.21-0.50)	Moderate	0.34 (0.23-0.56)	Moderate
CT vs. S	-		0.32 (0.11-1.00)	Low	0.32 (0.11-1.00)	Low
CRT vs. RT	0.78 (0.48-1.25)	Moderate	2.44 (0.48-12.35)	Low	0.81 (0.61-1.10)	Moderate
CT vs. RT	-		0.76 (0.30-1.80)	Low	0.76 (0.30-1.80)	Low
CRT vs. CT	1.06 (0.46-2.40)	Low	-	-	1.10 (0.46-2.50)	Low
C, DFS						
Comparison	Direct comparisons		Indirect comparisons		Network meta-analysis	
	HR (95% CI)	QoE	HR (95% CI)	QoE	HR (95% CI)	QoE
RT vs. S	0.80 (0.63-1.02)	Low	1.54 (0.32-7.14)	Low	0.81 (0.64-1.00)	Low
CRT vs. S	1.48 (0.34-6.52)	Low	1.30 (0.94-1.80)	Low	0.80 (0.60-1.10)	Low
CRT vs. RT	0.92 (0.82-1.05)	Moderate	1.85 (0.40-9.10)	Low	0.99 (0.82-1.30)	Moderate
D, Distant metastases						
Comparison	Direct comparisons		Indirect comparisons		Network meta-analysis	
	OR (95% CI)	QoE	OR (95% CI)	QoE	OR (95% CI)	QoE
RT vs. S	0.87 (0.73-1.05)	Low	0.83 (0.27-2.78)	Low	0.87 (0.69-1.10)	Low
CRT vs. S	0.76 (0.30-1.90)	Low	0.77 (0.43-1.15)	Low	0.75 (0.47-1.10)	Low
CRT vs. RT	0.82 (0.51-1.30)	Low	0.83 (0.28-2.50)	Low	0.86 (0.57-1.20)	Low
E, 30-day mortality						
Comparison	Direct comparison		Indirect comparisons		Network meta-analysis	
	OR (95% CI)	QoE	OR (95% CI)	QoE	OR (95% CI)	QoE
RT vs. S	1.38 (0.89-2.12)	Moderate	-	-	1.40 (0.79-2.20)	Moderate
CRT vs. S	-		2.20 (0.67-6.90)	Moderate	2.20 (0.68-6.40)	Moderate
CRT vs. RT	1.55 (0.86-2.79)	Moderate	-	-	1.60 (0.58-4.30)	Moderate

F, Anastomotic leak						
	Direct comparisons		Indirect comparisons		Network meta-analysis	
Comparisons	OR (95% CI)	QoE	OR (95% CI)	QoE	OR (95% CI)	QoE
RT vs. S	1.12 (0.75-1.67)	Moderate	0.29 (0.03-2.27)	Low	1.10 (0.61-1.80)	Moderate
CRT vs. S	0.24 (0.05-1.18)	Low	0.83 (0.24-3.13)	Low	0.55 (0.19-1.50)	Low
CT vs. S	-		0.21 (0.04-0.95)	Low	0.21 (0.04-0.95)	Low
CRT vs. RT	0.74 (0.30-1.84)	Low	0.20 (0.02-1.15)	Low	0.52 (0.19-1.30)	Low
CT vs. RT	-		0.76 (0.31-1.80)	Low	0.20 (0.04-0.87)	Low
CRT vs. CT	2.58 (1.25-5.31)	Low	-		2.60 (0.83-8.60)	Low
G, Pcr						
	Direct comparisons		Indirect comparisons		Network meta-analysis	
Comparison	OR (95% CI)	QoE	OR (95% CI)	QoE	OR (95% CI)	QoE
CRT vs. RT	4.01 (2.24-7.18)	Low			4.90 (1.80-17.00)	Low
CT vs. RT	-		27.00 (1.80-530)	Low	27.00 (1.80-530.00)	Very low
CRT vs. CT	2.58 (1.25-5.31)	Moderate			0.18 (0.01-2.40)	Moderate
GRADE, the grading of recommendations assessment, development and evaluation; OR, odds ratio; HR, hazard ratio; CI, confidence interval; QoE, quality of evidence; RT, surgery preceded by neoadjuvant radiotherapy; S, surgery alone; CRT, surgery preceded by neoadjuvant chemo-radiotherapy; CT, surgery preceded by neoadjuvant chemotherapy; DFS, disease-free survival; pCR, pathological complete response rate.						