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Local recurrence of esophageal squamous cell carcinoma after treatment: Comparison of frequentist and Bayesian network meta-analysis

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ABSTRACT

Background: We aimed to compare the treatments of esophageal cancer in association with the risk of disease recurrence, and to compare the frequentist and Bayesian methods in data analysis.
Methods: Web of Science, Medline, Scopus, the Cochrane Library and EMBASE were searched. We assessed statistical heterogeneity, and the assumption of consistency was assessed using loop-specific and design-by-treatment interaction methods. The Markov chain Monte Carlo method was used to obtain the pooled estimates of effect size in the Bayesian approach. The random effect model was used to report the pooled Risk Ratios (RR). The results of this study were reported with 95% Confidence Interval (CI), and Credible interval (CrI).
Results: We included 17 randomized controlled trials (RCTs) that reported the local recurrence of esophageal cancer. The RR of local recurrence for surgery plus paclitaxel, cisplatin, and radiotherapy (SPCRT) compared to surgery alone was 0.42 (95% CI: 0.21, 0.88). The RR for SPCRT compared with surgery plus cisplatin and vindesine (SCV) was 0.38 (95% CI: 0.12, 1.18). Compared to cisplatin, fluorouracil, and radiotherapy plus surgery (CFRTS), SPCRT was a better treatment (RR = 0.46, 95% CI: 0.17, 1.24).
Conclusions: This network meta-analysis indicated that SPCRT compared to surgery alone and other treatments was a better treatment. In terms of ranking, SPCRT and radiotherapy plus surgery (RTS) were the first and second treatments in the network. It seems the precision of frequentist is better than Bayesian approach, however, the results of the ranking of treatments were same in both frequentist and Bayesian approaches.

1. Introduction

Esophageal cancer is the eighth most common cancer in the world, with more than 450000 new cases and 400000 deaths annually.[1,2] Due to its aggressive nature, the prognosis of the disease is weak.[3] Different therapeutic regimens such as chemotherapy, radiotherapy, surgery, adjuvant chemo-radiotherapy and neoadjuvant chemo-radiotherapy have been developed to treat patients.[4,5] Some randomized controlled trials have shown that neoadjuvant chemotherapy compared with surgery alone increases the overall survival rate of patients, but that its complications are significantly more than surgery alone.[5]

In spite of the advances in treatment options for this type of cancer, the overall survival of patients is low.[3,6] One reason behind the low survival rates is the high rate of cancer recurrence. The recurrence rates following treatment were reported at 50% to 84% among different patients.[7,8] The recurrence of esophageal squamous cell carcinoma (ESCC) was categorized into three groups, including, loco-regional, hematogenous, and mixed type.[8,9]

The most common type of recurrence reported in randomized controlled trials (RCTs) is the local (or loco-regional) type. The incidence of local recurrence is different following therapeutic interventions in published RCTs[10–14] and there is no single consensus on which therapeutic regimens have lower incidences of local recurrence. A network meta-analysis with simultaneous comparing of all available treatments

Abbreviations: NMA, network meta-analysis; RCT, randomized control trials; RR, risk ratio; CI, confidence Interval; CrI, credible interval; ESCC, esophageal squamous cell carcinoma; RT, radiotherapy; S, surgery; SPCRT, surgery plus paclitaxel, cisplatin and radiotherapy; CFRTS, cisplatin, fluorouracil, and radiotherapy plus surgery; 3-DCRT, 3-dimensional conformal radiotherapy; CFS, cisplatin, fluorouracil plus surgery; SCV, surgery plus cisplatin, vindesine; SRT, surgery plus radiotherapy; CE, cisplatin, etoposide; CFRT, cisplatin, fluorouracil plus radiotherapy; RTH, radiotherapy plus hyperthermia; CRT, cisplatin plus radiotherapy; RTPCS, radiotherapy, paclitaxel, cisplatin plus surgery; SRTPC, Surgery plus radiotherapy, paclitaxel, cisplatin; 3DCRT, 3-dimensional conformal radiotherapy; RTS, radiotherapy plus surgery; DCRT, docetaxel, cisplatin, radiotherapy

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is a useful tool in the selection of better treatments,[15] and producing the highest level of evidence in the ranking of treatments and clinical guidelines.[16] The two approaches of data analysis included frequentist and Bayesian have been used in the previous published network meta-analysis.[17] According to the current literature the Bayesian frameworks are more flexible and their results more interpretable, but these approaches require more caution and there are some challenges in the selection of prior distribution.[17]

Therefore, the primary aim of this NMA was to simultaneously compare treatment interventions in terms of the risk of recurrence in patients with ESCC. The secondary aim was to compare the results of frequentist and Bayesian approaches to the data analysis and ranking of treatments.

2. Methods

2.1. Search strategy and selection criteria

This study is part of a comprehensive systematic review and NMA that simultaneously compared all the treatment interventions employed for esophageal cancer in terms of survival, complications of treatment and recurrence of the disease. The protocol of this systematic review has been registered in PROSPERO (ID: CRD42015023950) and has also been published.[18] A search strategy was developed to obtain relevant RCTs regarding the evaluation of treatment interventions for esophageal cancer (Appendix Table 1). The major international databases that were searched until February 2018 included, Web of Science, Medline, Scopus, the Cochrane Library and EMBASE. In order to retrieve more articles, the reference lists of the RCTs included and relevant published meta-analyses were also scanned. The authors of the included studies were contacted via e-mail or Research Gate. In addition, the following websites of relevant conferences were searched to obtain unpublished articles:

International Gastric Cancer Association; available from: http://www. igca.info/news/dec2012_02.html

The International Society for Diseases of the Esophagus; available from: http://www.isde.net/events

Cancer Research UK; available from: http://www.cancercentre.ox.ac.uk/events/sponsored-events/symposium-on-oesophageal-cancer/

World Organization for Specialized Studies on Diseases of the Esophagus; available from: http://www.oeso.org/index.html

Gastroenterology Conference Map; available from: http://www.mdlinx.com/gastroenterology/conference-map.cfm

All RCTs that had evaluated the treatment interventions of esophageal cancer were retrieved in this systematic review. We put no restriction on the time, location and language of the RCTs. The RCTs with the following treatment interventions were included: surgery, chemotherapy, radiotherapy, adjuvant chemoradiotherapy/radiochemotherapy and neoadjuvant chemoradiotherapy/radiochemotherapy. The inclusion criterion for this section of the study was, RCTs on patients with histologically-confirmed squamous cell carcinoma only. Other types of esophageal cancer were excluded.

2.2. Data extraction and quality assessment

Two investigators (ADI & ZC) screened the titles and abstracts of the retrieved references independently, and then reviewed the full texts of relevant articles to assess the eligibility criteria of the RCTs. The following data were extracted using a predefined data sheet: year of publication, location, duration of study, stage of cancer, detailed type of treatment in each arm of the RCT, a number of randomized patients in each arm, the number of males and females, mean/median age of participants, and the numbers of local recurrences among patients in each arm of the RCT. The risk of bias was assessed using Cochrane's tools.[19]

2.3. Outcome

The interesting outcome of this study was local recurrence among patients with ESCC. Local recurrence reported as a treatment-related complication in the included RCTs. In order to the calculation of RRs, the number of patients which randomized to the treatment groups was considered as the denominators. Using the risk of local recurrence in the treatment group and the comparison group, we calculated the RRs. So, our approach for extraction of data regarding the number of local recurrence cases in the arms of RCTs and calculation of RR was an intention to treat.

2.4. Assessment of transitivity

We assessed the transitivity (similarity) assumption by comparing the distribution of effect modifier variables such as the age of patients, gender, stage of cancer, and the type of esophageal cancer.

2.5. Statistical analysis

2.5.1. Frequentist approach

In the first stage, we conducted a pairwise meta-analysis for each comparison using the random effects model. The Risk Ratio with 95% confidence interval (CI) was calculated for local recurrence in each two by two comparisons. The statistical heterogeneity was assessed using Chi^2 test; we quantified the heterogeneity across each comparison using I^2 statistics.[20] The publication bias was assessed visually by network funnel plot. The network of treatments was drawn for a visual representation of available treatments.[21] The consistency assumption was assessed using loop-specific and design-by-treatment interaction methods.[22]

The results of this NMA were summarized as Risk Ratio with 95% CI.

The cumulative rank probabilities for all treatments were calculated and illustrated visually using the surface under the cumulative ranking curve (SUCRA).[21,23] Frequentist statistical analysis was performed using both Stata 13 (Stata Corp, College Station, TX, USA), and R, version 3.3.1 (2016-06-21), with the netmeta package.

2.5.2. Bayesian approach

The Markov chain Monte Carlo method was used to obtain the pooled estimates of effect size. Four Markov chains with 90000 iterations were run simultaneously and the trace plot and Brooks-Gelman-Rubin method were used to assess the convergence.[24] The non-informative prior, two informative normal prior distributions with the mean and standard deviation (SD) (0, 0.35), and (0, 0.71) were used to obtain the posterior distribution of the risk ratios. In order to obtain the mentioned informative normal prior distributions, we calculated the means and SDs using the 95% prior probability (0.5, 2) and (0.25, 4) respectively. The following formulas were used to calculating the prior mean and SDs respectively.

$$Prior\ \ mean\ \ \ln(RR) = \frac{\ln\ (lower\ \ limit) + \ln\ (upper\ \ limit)}{2}$$

$$Prior\ \ SD\ \ \ln(RR) = \frac{\ln\ (upper\ \ limit) - \ln\ (lower\ \ limit)}{2 \times 1.96}$$

The deviance information criterion (DIC) was used to compare the fit of random effects models with different priors, and the model with lower DIC was selected for data analysis.[25] The DIC for uninformative prior, normal prior distributions N (0, 0.71), and N (0, 0.35) were 56.98, 49.21, and 49.09 respectively. So the normal prior N (0, 0.35) was used for data analysis.

The rank probabilities of all treatments were calculated and illustrated visually using bar plots of ranking probability.[23] The results of Bayesian NMA were summarized as Risk Ratio with 95% Credible

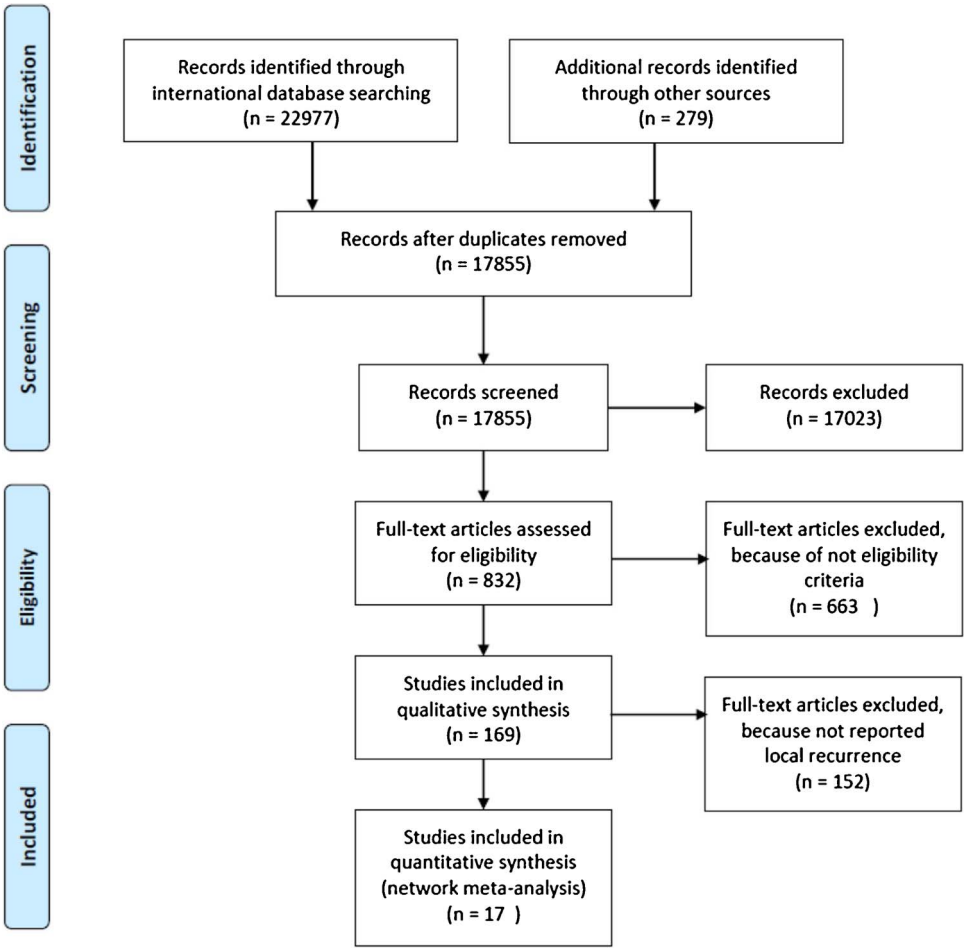

Fig. 1. A flow chart depicting the stages of retrieving RCTs and checking eligibility criteria for network meta-analysis.

Interval (CrI). Surgery and radiotherapy were considered as the reference treatments.

The Bayesian statistical analysis was performed using the R version 3.4.2 (2017-09-28) with the gemtic package version 0.8.1 (2016-09-06) for Bayesian NMA. The *rbugs* package version 0.5–9 (2015-02-20) was used for sampling posterior distribution in the Bayesian analysis.

3. Results

In all, 17855 references were retrieved after removing the duplicate references. After screening the titles and abstracts 832 RCTs remained for full-text review. Upon checking the eligibility criteria, 169 RCTs remained for assessing the risk of bias. Among these papers, 17 RCTs reported the local recurrence of esophageal cell carcinoma[10,12–14,26–38] and 152 RCTs reported other interesting outcomes in our comprehensive systematic review, the results of which will be published in the future. In this paper, we only included RCTs that had reported local recurrence (Fig. 1). Overall, the total sample size of included RCTs in this NMA was 2571 patients. The characteristics and details of treatments in each arm are shown in Table 1. Moreover, the raw data used in the network meta-analysis are shown in the Appendix Table 2.

The networks of eligible comparisons for local recurrence are shown in Fig. 2. The size of each node is proportional to the number of randomized patients (sample size) and the width of lines is proportional to the number of comparisons. The comparisons of treatments in this study involved two networks. In network A and B, surgery (S) and radiotherapy (RT) were reference treatments, respectively. Network A includes 13 RCTs, 10 treatments, and 10 lines. The thickness of the lines is related to the number of included RCTs for each comparison. There was one closed loop between surgery, surgery + radiotherapy (SRT), and Surgery + Cisplatin + Vindesine (SCV).

The comparison[33] between radiotherapy + paclitaxel + cisplatin + surgery (RTPCS) and surgery + radiotherapy + paclitaxel + cisplatin (SRTPC), was excluded from the NMA because it was an independent comparison and there was no connection between this and other comparisons.

3.1. Inconsistency and heterogeneity results in the frequentist approach

In this NMA, there was one closed loop between surgery, SRT, and SCV. The inconsistency factor was 1.38 (95% CI: 0.01, 2.75). I^2 for the inconsistency of networks A and B was 29.3% and o%, respectively. The Q statistic in the network A for the whole network, within designs, and between designs were 5.7 (p = 0.226), 1.74 (p = 0.627), and 3.91 (p = 0.048) respectively.

3.2. Inconsistency and heterogeneity results in the Bayesian approach

The I^2 in the network A and B was 5% and 17% respectively. That's while in the model with the uninformative prior the I^2 was 24% and 23% respectively.

Based on the comparison-adjusted funnel plot, there was no evidence of publication bias in network A (Appendix Fig. 3).

The results of Bayesian and the frequentist NMA for local recurrence in the simultaneous comparison of treatments in the network A and B are presented in Table 2 and Appendix C respectively. In terms of lower risk of local recurrence, surgery + paclitaxel + cisplatin + radiotherapy (SPCRT) was a better treatment than surgery alone (frequentist

Table 1
Characteristics of the included RCTs in the network meta-analysis of local recurrence risk for esophageal cancer.

Author (year)	Quality *	Country	Duration of study (month)	Type of analysis**	Treatments	n 1	n 2	Male in arm 1 (%)	Male in arm 2 (%)	Age 1	Age 2	Recurrence 1	Recurrence 2
Ancona (2001) [26]	H	Italy	60	ITT	T1: Surgery (S) T2: Cisplatin (100 mg/m^2), Fluorouracil (1000 mg/m^2), Surgery (CFS)	48	48	0.79	0.79	58	58	25	21
Ando (1997) [14]	H	Japan	84	NR	T1: Surgery (S) T2: Surgery, Cisplatin (70 mg/m^2), Vindesine (3 mg/m^2) (SCV)	100	105	0.92	0.86	59.8	60.04	3	10
Anonymous (1993) [27]	I	Japan	60	NR	T1: Surgery, Radiotherapy (50 Gy) (SRT) T2: Surgery, Cisplatin (50 mg/m^2), Vindesine (3 mg/m^2) (SCV)	128	130	0.86	0.87	65	65	28	33
Boonstra (2011) [10]	H	Netherland	120	ITT	T1: Cisplatin (80 mg/m^2), Etoposide (100 mg/m^2) (CE) T2: Surgery (S)	85	84	0.74	0.75	60	60	16	21
Cao (2010) [28]	I	China	150	NR	T1: Surgery + Paclitaxel (135 mg/m^2), Cisplatin (20 mg/m^2), Radiotherapy (40 Gy) (SPCRT) T2: Surgery (S)	78	80	0.59	0.60	60	60	12	29
Chiu (2005) [29]	H	China Hong Kong	24	ITT	T1: Surgery (S) T2: Cisplatin (60 mg/m^2), Fluorouracil (200 mg/m^2), Radiotherapy (50–60 Gy) (CFRT)	44	36	0.89	0.75	62	62	14	9
Jianhua (1996) [30]	I	China	60	NR	T1: Radiotherapy (40 Gy), Hyperthermia (915 MHz) (RTH) T2: Radiotherapy (60 Gy) (RT)	59	66	0.61	0.55	51	51	52	58
Kumar (2007) [13]	H	India	84	NR	T1: Radiotherapy (50 Gy) (RT) T2: Cisplatin (35 mg/m^2), Radiotherapy (50 Gy) (CRT)	60	65	0.82	0.66	56	58	10	13
Le Prise (1994) [31]	L	France	48	NR	T1: Surgery (S) T2: Cisplatin (100 mg/m^2), Fluorouracil (600 mg/m^2), Radiotherapy (20 Gy), Surgery (CFRTS)	45	41	NR	NR	59	56	9	7
Lee (2004) [32]	H	Korea	48	ITT	T1: Cisplatin (60 mg/m^2), Fluorouracil (1000 mg/m^2), Radiotherapy (45.6 Gy) (CFRT) T2: Surgery (S)	51	50	0.90	0.94	63	63	8	5
Lv (2010)[33]	H	China	120	NR	T1: Radiotherapy (40 Gy), Paclitaxel (135 mg/m^2), Cisplatin (20 mg/m^2), Surgery (RTPCS) T2: Surgery, Radiotherapy (40 Gy), Paclitaxel (135 mg/m^2), Cisplatin (20) (SRTPC)	80	78	0.65	0.62	60	60	9	11
Ma (2010) [12]	I	China	40	NR	T1: 3-dimensional conformal radiotherapy (40 Gy) (3DCRT) T2: Conventional Radiotherapy (40 gy) (RT)	53	53	0.60	0.57	60	58	13	24
Mei (1989) [34]	H	China	60	NR	T1: Radiotherapy (4000 cGy), surgery (RTS) T2: Surgery (S)	104	102	0.70	0.72	52.2	53.6	2	5
Natsugoe (2006) [35]	H	Japan	60	NR	T1: Cisplatin (7/2 h), Fluorouracil (350 mg/m^2), Radiotherapy (40 Gy), surgery (CFRTS) T2: Surgery (S)	22	23	NR	NR	NR	NR	1	1
Xiao (2003) [36]	H	China	60	NR	T1: Surgery (S) T2: Surgery, Radiotherapy (60 Gy) (SRT)	275	220	0.73	0.85	55	55	71	35
Zhao (2012) [37]	H	China	36	NR	T1: Docetaxel (? mg/m^2), Cisplatin (75 mg/m^2), Radiotherapy (50.4 Gy) (DCRT) T2: Cisplatin (75 mg/m^2), Fluorouracil (250 mg/m^2), Radiotherapy (50.4 Gy) (CFRT)	45	45	0.56	0.64	57.4	57.4	13	12
Zieren (1995) [38]	H	Germany	36	NR	T1: Surgery, Radiotherapy (1.8 Gy/day) (SRT) T2: Surgery (S)	33	35	0.70	0.66	59.5	58.3	15	19

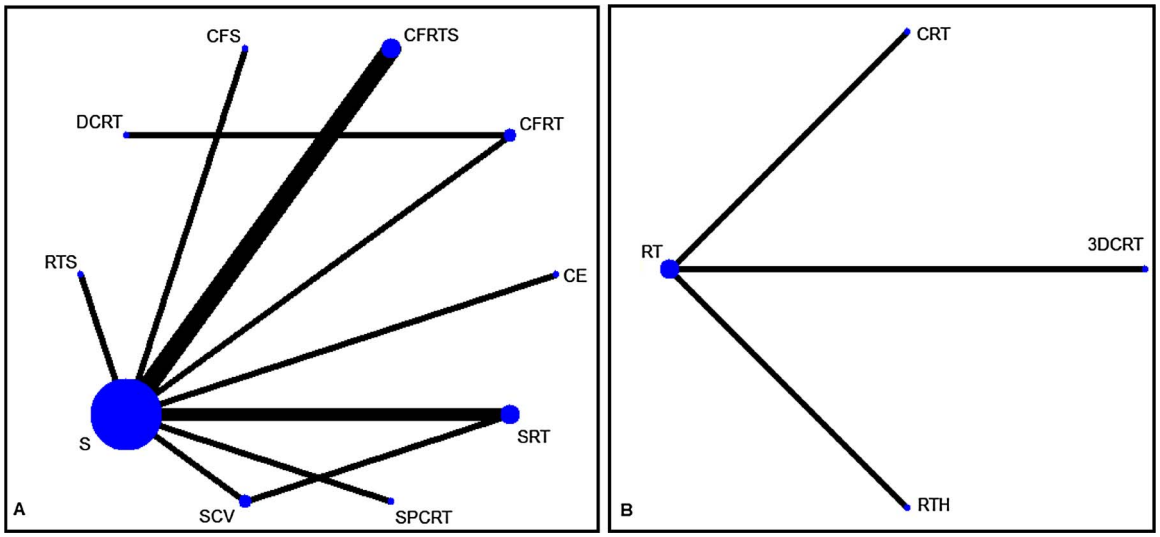

Fig. 2. Networks of eligible comparisons for local recurrence in esophageal squamous cell carcinoma.

RR = 0.42, 95% CI: 0.28, 0.88, and Bayesian RR = 0.41, 95% CrI: 0.11, 1.6). The frequentist and Bayesian RRs for SPCRT compare with SCV were 0.38 (95% CI: 0.12, 1.18), and 0.34 (95%CrI: 0.05, 1.16). Compared to CFRTS, SPCRT was a better treatment (frequentist RR = 0.46, 95% CI: 0.17, 1.24, and Bayesian RR = 0.31, 95% CrI: 0.05, 1.54). The risk of local recurrence for SPCRT versus RTS was not statistically different. The frequentist and Bayesian RRs were 1.08 (95% CI: 0.18, 6.67) and 0.74 (95% CrI: 0.08, 8.32) respectively. Overall, SPCRT was a better treatment in comparison to other treatments in the network A (Table 2 and Appendix Table 3).

In network B, 3-DCRT was a better treatment than the others in the network were. The RR for 3-DCRT to RT, RTH, and CRT alone was 0.54 (95% CI, 0.31 to 0.95), 0.54 (95% CI: 0.30, 0.96), and 0.45 (0.18, 1.15) respectively. In the Bayesian approach these RR were 0.58 (95% CrI: 0.01, 68.51), 0.58 (95% CrI: 0.02, 18.16), and 0.45 (95% CrI: 0.01, 61.62) respectively (Table 3 and Appendix Table 4).

In terms of ranking probabilities for the lower risk of local recurrence, the frequentist cumulative SUCRA values for ten active treatments in the network A were as follow: SPCRT (86.2%), RTS (78.3%), CE (53.4%), SRT (52.7%), CFRT (49.9%), CFS (45.4%), DCRT (44.1%), CFRTS (37.7%), S (27.5%), and SCV (24.9%) (Appendix Fig. 2). In addition, plots of Bayesian rank probabilities for all treatments in the network A are shown in Fig. 3. The results of ranking the treatments in both frequentist and Bayesian approaches were same. The first and second-ranked treatments in both approaches were SPCRT and RTS respectively.

4. Discussion

In this NMA, we synthesized the available data on local recurrence of esophageal squamous cell carcinoma following treatment using frequentist and Bayesian approaches. As an adjuvant chemo-radiotherapy, SPCRT was a better treatment compared to other treatments in network A. In network B, 3-DCRT was a better treatment. In network B, surgery was not considered a component of the therapeutic regimen. We compared the results of frequentist and Bayesian methods in this NMA. The results of both mentioned methods were same in terms of point estimates and rankings of the treatments. However, the 95% Credible Intervals in the Bayesian were wider than 95% confidence intervals in the frequentist methods. Therefore, it seems the precision of the RRs in the frequentist is better than Bayesian in this NMA. On the other, another study that compared these approaches showed the frequentist model tends to underestimate the random effect variability relative to the Bayesian, and the 95% CIs in frequentist were narrower than Bayesian.[17]

According to the results of a meta-analysis conducted by Urschel et al, neoadjuvant chemoradiation compared with surgery alone reduced the risk of loco-regional cancer recurrence (OR = 0.38, 95% CI: 0.23, 0.63).[39] However, this result is in line with ours.

In this NMA, we compared all types of neoadjuvant and adjuvant chemoradiotherapy/chemotherapy with surgery alone. Upon comparing SPCRT as an adjuvant chemoradiotherapy with surgery alone, the risk of local recurrence dropped by 0.42 (0.21, 0.88) in the frequentist and 0.41 (0.11, 1.16) in the Bayesian approach. As a neoadjuvant chemotherapy, cisplatin + fluorouracil + surgery (CFS) reduced the risk of local recurrence. Moreover, adjuvant radiotherapy (SRT) and neoadjuvant radiotherapy (RTS) both reduced the risk of local recurrence compared with surgery alone.

A meta-analysis that compared neoadjuvant chemotherapy and surgery with surgery alone showed that the odds ratio of loco-regional recurrence was lower in the neoadjuvant chemotherapy group (OR = 0.71, 95% CI: 0.36, 1.42), but that it was not statistically significant.[40] This finding is in line with our results of comparing CFS with surgery alone in both frequentist and Bayesian approaches.

Another meta-analysis[41] showed that the odds of local recurrence were lower in patients that received neoadjuvant chemo-radiotherapy compared with surgery alone (OR = 0.64, 95% CI: 0.41, 0.99). The meta-analyses conducted to date have compared all neo-adjuvant chemo-radiotherapies with surgery only, but we compared each neoadjuvant-based type of chemotherapy on the therapeutic regimens network. So, apparently, we have provided more informative evidence than the traditionally conducted meta-analyses.

In network B, we found that 3-dimensional conformal radiotherapy (3-DCRT) is a better treatment compared to CRT, RT alone and Radiotherapy + Hyperthermia (RTH).

According to the frequentist results of this NMA, the 95% CI of effect size (Risk ratio) in the comparison of treatments, except SPCRT, with surgery as the reference treatment in network A, and RT compared with RTH and CRT in the network B involved the null value. Also in the Bayesian approach, the 95% CrI Risk Ratios involved the null value. A reason might due to the low number of included studies in the networks and consequently the low sample size for two-by-two comparisons, which can be lead to spars-data bias.[42] However, upon simultaneously comparing and ranking all treatments, in both frequentist and Bayesian methods, it seems SPCRT and 3-DCRT were better treatments in both networks. There was no notable difference in the ranking of treatments between these approaches. The overall frequents inconsistency was 29.3% and 0% in networks A and B and in Bayesian 5% and 17%, respectively, which are appropriate for NMA. The larger I2 in the network

Table 2
Bayesian network meta-analysis for simultaneous comparisons of available treatments using relative risk (95% CrI) in network A for local recurrence of esophageal squamous cell carcinoma.

CE	0.99 (0.21, 5.23)	0.51 (0.08, 3.58)	1.52 (0.32, 10.89)	1.27 (0.33, 4.85)	0.7 (0.06, 6.65)	1.09 (0.1, 12.65)	1.09 (0.17, 7.29)	1.59 (0.29, 9.42)	1.06 (0.15, 7.71)
1.01 (0.19, 4.67)	SRT	0.52 (0.1, 2.37)	1.53 (0.59, 5.07)	1.29 (0.51, 2.77)	0.7 (0.08, 5.01)	1.11 (0.12, 9.28)	1.11 (0.22, 4.75)	1.7 (0.46, 6.15)	1.08 (0.19, 5.27)
1.94 (0.28, 12.96)	1.91 (0.42, 10.15)	SPCRT	2.94 (0.62, 20.66)	2.46 (0.63, 9.48)	1.34 (0.12, 13.21)	2.13 (0.19, 23.55)	2.12 (0.32, 13.69)	3.24 (0.65, 18.28)	2.06 (0.29, 14.13)
0.66 (0.09, 3.14)	0.65 (0.2, 1.69)	0.34 (0.05, 1.61)	SCV	0.84 (0.22, 2.15)	0.44 (0.04, 3.43)	0.72 (0.06, 6.04)	0.73 (0.1, 3.25)	1.1 (0.22, 4.32)	0.7 (0.09, 3.54)
0.78 (0.21, 3.02)	0.77 (0.36, 1.96)	0.41 (0.11, 1.6)	1.19 (0.47, 4.5)	S	0.55 (0.07, 3.43)	0.86 (0.12, 6.42)	0.86 (0.24, 3.21)	1.32 (0.52, 3.74)	0.84 (0.2, 3.4)
1.44 (0.15, 15.39)	1.44 (0.2, 13.07)	0.74 (0.08, 8.32)	2.25 (0.29, 24.61)	1.83 (0.29, 13.82)	RTS	1.58 (0.1, 26.44)	1.57 (0.17, 16.95)	2.42 (0.32, 23.59)	1.53 (0.15, 18.14)
0.92 (0.08, 10.43)	0.9 (0.11, 8.46)	0.47 (0.04, 5.34)	1.39 (0.17, 16.76)	1.16 (0.16, 8.49)	0.63 (0.04, 9.6)	DCRT	1 (0.09, 10.91)	1.54 (0.17, 14.82)	0.97 (0.24, 4)
0.92 (0.14, 5.98)	0.9 (0.21, 4.58)	0.47 (0.07, 3.13)	1.38 (0.31, 9.62)	1.17 (0.31, 4.23)	0.64 (0.06, 6.04)	1 (0.09, 10.97)	CFS	1.54 (0.32, 8.31)	0.97 (0.14, 6.61)
0.59 (0.1, 2.89)	0.59 (0.16, 2.18)	0.31 (0.05, 1.54)	0.91 (0.23, 4.51)	0.76 (0.27, 1.91)	0.41 (0.04, 3.16)	0.65 (0.07, 5.73)	0.65 (0.12, 3.12)	CFRTS	0.63 (0.11, 3.39)
0.94 (0.13, 6.59)	0.93 (0.19, 5.16)	0.49 (0.07, 3.51)	1.44 (0.28, 10.63)	1.2 (0.29, 4.91)	0.65 (0.06, 6.53)	1.03 (0.25, 4.15)	1.03 (0.15, 7.11)	1.69 (0.35, 9.56)	CFRT

Table 3
Bayesian network meta-analysis for simultaneous comparisons of available treatments using relative risk (95% CrI) in network B for local recurrence of esophageal squamous cell carcinoma.

3DCRT	1.74 (0.06, 49.35)	1.74 (0.01, 189.62)	2.2 (0.02, 232.29)
0.58 (0.01, 68.51)	RT	1 (0.03, 30.48)	1.27 (0.04, 35.91)
0.58 (0.02, 18.16)	1 (0.03, 28.93)	RTH	1.27 (0.01, 146.06)
0.45 (0.01, 61.62)	0.79 (0.03, 24.07)	0.79 (0.01, 98.2)	CRT

A in the frequentist than Bayesian is in the line of another study that compared the I2 of these approaches.[17] In the network B, because of the low number of studies, it seems the I2 in the Bayesian approach is more rational than frequentist. Moreover, in the mentioned study showed that the Bayesian estimates of inconsistency, are more accurately truer than the frequentist estimates.[17]

Because of the difference in the sampling of the included studies and different locations of RCTs, we used the random effects model for data analysis in the network A. Thus the choice of the model was not based on the results of heterogeneity and inconsistency tests.[43]

One strength of this NMA was the lack of heterogeneity in pairwise comparisons and low inconsistency in both frequentist and Bayesian methods. A further strength of the study was the analysis of data based on the exact type of neo-adjuvant or adjuvant chemotherapy/chemoradiotherapy in therapeutic regimens. This may interest clinicians or patients in selecting better treatments, as some traditional meta-analyses have compared neoadjuvant or adjuvant treatments in general. Moreover, network meta-analyses that simultaneously compare all treatments and raise the precisions of effect sizes have been recommended as the highest levels of evidence in treatment guidelines.[16]

In addition, we included RCTs that involved only patients with ESCC. Other meta-analyses[39–41] however, have included RCTs with both histologic types (adenocarcinoma *and* SCC) in their analyses.

Our study had some limitations. Firstly, despite conducting a comprehensive systematic review and searching all potential databases it is possible that we missed some RCTs. These limitations may have increased the risk of selection bias. Secondly, a limitation was the low and average quality of some RCTs. Among the 17 RCTs included, five had low and average quality; this may have increased the risk of information bias. Another limitation of this study was the difference in the duration of included RCTs. The lowest duration (24 months) was reported in one study and also the highest duration was reported in one study (150 months). Our concern regarding the low durations studies is an underestimate of the risk of local recurrence. However, duration of more studies, 14 RCTs, was more than 40 months.

The RCTs included in this review were published from 1989 to 2012, so an important point is related to the improvement in surgical techniques and other treatment interventions in recent years. Therefore, the results should be interpreted with caution.

5. Conclusions

This NMA exhibited low inconsistency. Compared to surgery alone, as the reference treatment and other treatments in the network A, SPCRT and RTS seem to be better options. In addition, compared with other treatments in network B (RTH, and CRT), it seems that 3-DCRT, is a better option. In the comparison of frequentist and Bayesian methods for data-analysis, it seems the precision of frequentist is better than Bayesian approach. But there was no notable difference in the ranking of treatments in the network. However, more research is needed to explore the benefits of these approaches in terms of precision in the analysis of network meta-analyses.

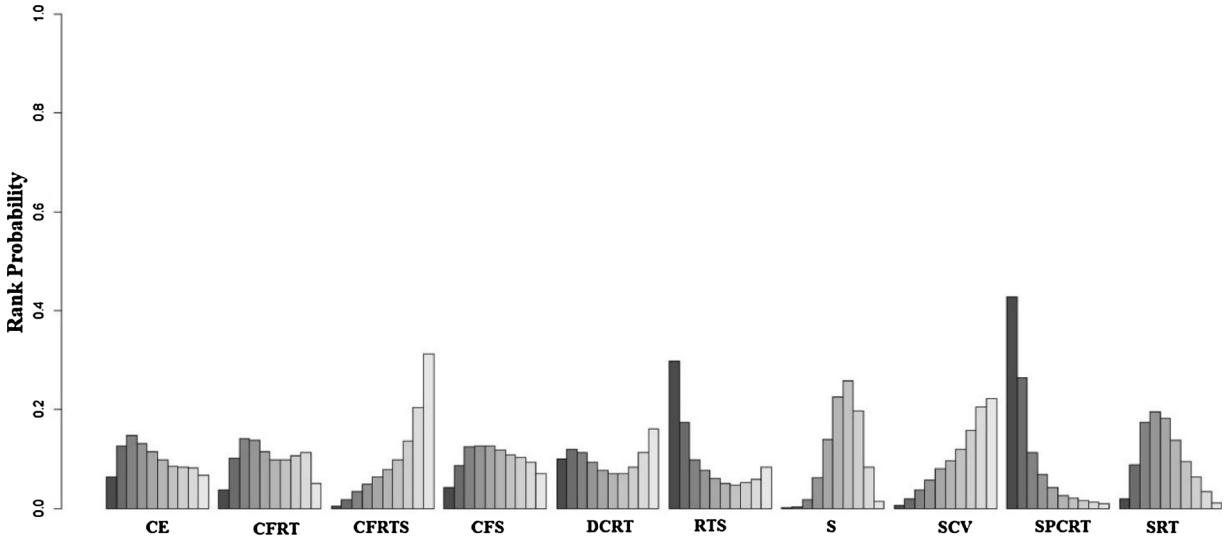

Fig. 3. plot of rank probability for all treatments in the network A in the Bayesian approach.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cegh.2018.02.009.

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