RESEARCH ARTICLE

Simultaneous Comparison of Efficacy and Adverse Events of Interventions for Patients with Esophageal Cancer: Protocol for a Systematic Review and Bayesian Network Meta-analysis

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Abstract

Background: Esophageal cancer is one of the most serious malignancies. Due to the aggressive nature of this cancer, the prognosis is poor. A network meta-analysis with simultaneous comparison of multiple treatments can help determine better treatment options that have higher effects on overall survival of patients with lower adverse events. The aim of this review is to simultaneously compare efficacy and adverse events of treatment interventions for esophageal cancer. Materials and Methods: In this review, only randomized control trials (RCT) will be considered for network meta-analysis. All international electronic databases including Medline, Web of Sciences, Scopus, Cochran's library, EMBASE and Cancerlit will be searched to find randomized control trials which compared two or more treatment interventions for esophageal cancer. A network plot will be drawn for visual representation of all available treatment interventions. Bayesian approach will be used to combine the direct and indirect evidence. Treatment effects (e.g. hazard ratio for time to event outcomes, risk ratio for binary outcomes, and rate ratio for count outcomes with 95% credible interval) will be reported. Moreover, cumulative probability of the treatment ranks will be reported using the surface under the cumulative ranking (SUCRA) graphs. Consistency assumption will be assessed by the loop-specific and design-by-treatment interaction approaches. Conclusions: The results of this study may be helpful for the patients, clinicians and health policy makers in selecting treatments that have the best effect on survival and lowest adverse events.

Keywords: Esophageal cancer - treatment outcomes - network meta-analysis

Introduction

Esophageal cancer, with regard to its lethal outcome, is one of the most serious malignancies (Umar and Fleischer, 2008). Esophageal cancer, with more than 4.5 million new cases and the death of about 400,000 ones annually, is the eighth common cancer and sixth cause of death from cancers throughout the world (Ferlay et al., 2010; Pennathur et al., 2013). The common risk factors of this cancer included opium consumption, drinking hot tea, eating of hot foods, tobacco use (cigarettes, hookah, and nass), and alcohol drinking (Alaeddini et al., 2001; Nasrollahzadeh et al., 2008; Islami et al., 2009). Due to the aggressive nature of this cancer, the prognosis is poor and in spite of the progress in the management, five-year survival rate of the disease is approximately 20 percent (Ferlay et al., 2010; Mao et al., 2011; Shibata et al., 2011). Randomized control trials have reported different adverse events rates for treatment interventions and there

is controversy about the adverse events rates of esophageal cancer treatment options. Network meta-analysis with simultaneous comparison of multiple treatments can help determine better treatment options that have higher effect on the overall survival of patients while with lower adverse events (van Hagen et al., 2012; Hara et al., 2013b; Lu et al., 2014). About 80% of esophageal cancer cases occur in developing countries (Enzinger and Mayer, 2003). The highest age standardized incidence of esophageal cancer is found in countries of east Africa, Iran, Afghanistan and China (Mosavi-Jarrahi and Mohagheghi, 2006; Arnold et al., 2014).

Up to now, different therapies have been developed for treatment of patients with esophageal cancer that have improved the survival. However, despite these progresses, treatment is not satisfying and prognosis, even in developed countries, is poor. Preoperative chemotherapy, chemotherapy plus radiotherapy, and surgery have been all assessed for treatment of esophageal cancer. Some of

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randomized clinical trials have shown that preoperative chemotherapy, in comparison to only-surgery, increases the overall survival of patient but its adverse events are significantly more than only-surgery option (Tepper et al., 2008; van Hagen et al., 2012). In addition, there is controversies about selection the therapeutic strategies of the disease, especially in the case adenocarcinoma and squamous-cell carcinoma (Siewert and Ott, 2007; Hara et al., 2013a).

The five-year survival rate, as one of the measures for evaluation of treatment effect, has been different in various studies conducted around the world. The rate ranges from 5 to 47 percent in different countries. The rate has been 14%, 8%, 3.3% and 5% in United States, England, China, and in developing countries respectively (Holakouie-Nieni et al., 1989; Chen et al., 1998; Samadi et al., 2007; van Hagen et al., 2012). In addition to different survival rates, randomized control trials and pair-wise meta-analysis, which compares treatments two by two, have reported different adverse events rates for therapeutic options of esophageal cancer and there are controversies about reported adverse events (van Hagen et al., 2012; Hara et al., 2013a; Lu et al., 2014).

Description of the intervention

Different types of treatment options are developed for esophageal cancer patients. These options include surgery-alone, radiotherapy, radiotherapy plus surgery, chemotherapy plus surgery, chemoradiotherapy, laser therapy, and electrocoagulation (National Cancer Institue). Pharmacological interventions for chemotherapy includes: Epirubicin, Fluorouracil, Capecitabine, Cisplatin, Bleomycin, Vindesine, Oxaliplatin, Docetaxel, Nedaplatin, Paclitaxel and Carboplatin (Fiorica et al., 2004; Malthaner et al., 2004; Greer et al., 2005; Gebski et al., 2007). It should be noted that above-mentioned interventions are not complete; if any new treatment option is found in valid randomized control trials, it will be added to above list.

The most important clinical questions for the field of esophageal cancer treatment are as follows: which treatment has the better effect on overall survival of patients? Which treatment have the lowest adverse events? These vital questions have not been still clearly answered, although some pair wise meta-analyses have been were conducted to date (Fiorica et al., 2004; Malthaner et al., 2004; Greer et al., 2005; Gebski et al., 2007). Selecting a treatment that has the best effect on survival and lowest adverse events is very important for patients, clinicians and health policy makers. An umbrella systematic review and network meta-analysis with a simultaneous comparison of all therapeutic interventions might be useful in order to answer such questions.

Objectives

The aim of this review is to simultaneously compare efficacy and adverse events of treatment interventions for esophageal cancer. Accordingly, by using a network meta-analysis, available interventions will be ranked based on their effects on the overall survival and their adverse events.

Methods

In this review, only randomized control trials (RCT) will be considered for this Bayesian network meta-analysis. Indeed, all RCTs that have compared the treatments of esophageal cancer irrespective of the location, time and language of publication will be included. To prevent from any possible bias, other study designs such as non-randomized clinical trials and cohort studies will not be included in this network meta-analysis. The systematic review is registered at PROSPERO (ID: CRD42015023950).

In this review, RCTs that recruited participants with esophageal cancers, including squamous-cell carcinoma and adenocarcinoma, will be captured. The treatment interventions that will be considered in this study are presented in Table1.

Types of outcome measures

The treatment effects will be assessed using the survival rate of participants randomized into each arm of included RCTs. Survival rates between the arms of included RCTs will be compared and hazard ratio of death after treatment inception will be estimated. Moreover, adverse events of treatments will be compared using relative risk (RR) for binary outcomes, and rate ratio or hazard ratio for time to event outcomes.

Primary outcomes

Survival rate of people with esophageal cancer. If it is possible, we will report the six months, one, two, three,

Table 1. Treatment Intervention for Esophageal Cancer

Row	Treatment intervention
1	Surgery
2	Chemotherapy, including following drugs:
	Epirubicin
	Fluorouracil
	Capecitabine
	Cisplatin
	Bleomycin
	vindesine
	Oxaliplatin
	Docetaxel
	Nedaplatin
	Paclitaxel
	Carboplatin
3	Radiotherapy
4	Chemoradiotherapy
5	Surgery plus radiotherapy
6	Surgery plus chemotherapy

four, and five-year survival rates of participants recruited into RCTs.

Secondary outcomes

The secondary outcome is the adverse events rates of treatment interventions. The adverse events considered are as follows: *i)*. Death; *ii)*. Pulmonary complications; *iii)*. Cardiovascular complications; *iv)*. Chylothorax Mediastinitis; *v)*. Anastomotic leakage

Chemotherapy related adverse events included anorexia, alopecia, constipation, diarrhea, nausea, fatigue, rupture of esophagus, nasopharyngitis, neutropenia and thrombocytopenia, neurological complications, vomiting, and leucopenia.

Searching
Electronic searches

All international electronic databases including Medline, Web of Sciences, Scopus, Cochran's library, EMBASE and Cancerlit will be searched to find randomized control trials which compared two or more treatment interventions for esophageal cancer. In addition to identifying completed or ongoing RCTs, International Clinical Trials Registry Platform Search portal (http://apps.who.int/trialsearch/) and Iranian Registry of Clinical Trials at http://www.irct.ir/ will be searched too. A search strategy that show in Table 2 is already designed. The key words are based on the recommended treatment options for esophageal cancer (Fiorica et al., 2004; Malthaner et al., 2004; Greer et al., 2005; Gebski et al., 2007). The search strategy was initially designed for Medline, but it will be modified to cover other databases

Searching other resources

In order to attain further recourse and improve our systematic review, reference lists of selected RCTs will be scanned and corresponding authors of chosen RCTs will be contacted if it is necessary. Furthermore, following websites of conferences and congresses related to esophageal cancer will be searched for: *i)*. International Gastric Cancer Association; available from: http://www.igca.info/news/dec2012_02.html; *ii)*. The International Society for diseases of the Esophagus; available from: http://www.isde.net/events; *ii)*. Cancer Research UK; available from: http://www.cancercentre.ox.ac.uk/events/sponsored-events/symposium-on-oesophageal-cancer/; *iv)*. World Organization for Specialized Studies on Diseases of the Esophagus; available from: http://www.oeso.org/index.html; *v)*. Gastroenterology Conference Map; available from: http://www.mdlinx.com/gastroenterology/conference-map.cfm

Data collection and analysis

Identification of the studies

In order to ensure the correct selection of RCTs, two authors (ADI and ZC) will independently identify the

RCTs based on their eligibility criteria by scanning the titles and abstracts. The name of the authors of articles, journals, and results of studies will not be blind for these two authors. In the case of disagreement between authors about inclusion of RCTs, the issue will be resolved by discussion and adjudication of other colleagues (MAM, KHN and ARF). In the next stage, based on the evaluation of full texts of selected RCTs, inclusion in the network meta-analysis will be decided. All excluded full texts along with the reasons for their exclusion will be described in a table titled "characteristics of excluded RCTs".

Data extraction and management

After selection of the RCTs, two authors (ADI and ZC) will independently extract the following data.

i). Data related to characteristics of RCTs included:

first author of study; publication date of study; conduction date of study; language of publication; location

Table 2. Search Strategy for MEDLINE via PubMed

Row	Key words
#1	Epirubicin
#2	Fluorouracil
#3	Capecitabine
#4	Cisplatin
#5	Bleomycin
#6	Vindesine
#7	Oxaliplatin
#8	Docetaxel
#9	Nedaplatin
#10	Paclitaxel
#11	Carboplatin
#12	antineoplastic agents
#13	Placebo
#14	Radiochemotherapy
#15	Radiotherapy
#16	Chemotherapy
#17	Surgery
#18	Esophagectomy
#19	Gastrectomy
#20	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21	Clinical trial
#22	Randomized control trial
#23	Randomized clinical trial
#24	Randomly
#25	Meta-analysis
#26	Systematic review
#27	(OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
#28	Esophageal Neoplasms
#29	Esophageal cancer
#30	Esophageal squamous cell carcinoma
#31	Esophageal carcinoma
#32	Gastro-esophageal junction neoplasms
#33	(#27 OR #28 OR #29 OR #30 OR #31)
#34	(#20 AND #27 AND #33)

of study (the countries that RCT is performed in it); duration of follow-up (date of RCT starting and ending, if possible); method of data analysis (intention to treat or per-protocol); type of esophageal cancer (squamous-cell carcinoma or adenocarcinoma)

ii). Interventions data: type of used interventions in the arms of RCTs

iii). Outcome data: number of randomized participants in each arm; number of included participants in the analysis in each arm; number of participants with events for binary outcomes; person-time and number of participants with events for time to event outcomes; mean and standard deviation for continuous outcomes.

iv). Effect modifier data: age of participants in each arm; sex of participants in each arm; dosage of used drugs for chemotherapy interventions; stage of esophageal cancer in RCT commencement; risk of biased data that will be evaluated by Cochrane's tool

Corresponding authors of included studies will be contacted in the case of missing or unclear data.

Risk of bias assessment

To assess the risk of bias in selected RCTs, two authors (ADI, ZC) will independently use the Cochrane guideline (Higgins and Green, 2008). Cochrane guideline considers seven criteria for assessment of the risk of bias. Any disagreement will be resolved by adjudication of other colleagues (MAM, KHN and ARF).

Cochrane tools for assessment the risk of bias include the following items:

1. Selection bias: *i)*. Random sequence generation: the method of randomization explained adequately; *ii)*. Allocation concealment: method for concealment of treatment allocation explained adequately.

2. Performance bias: *i)*. Blinding of participants and personnel in the arms of RCTs

3. Detection bias: *i)*. Blinding in the outcome assessment stage

4. Attrition bias: *i)*. Incomplete outcome data assessment for each outcome

5. Reporting bias; authors of RCTs explained whether reported outcomes were selective or not.

6. Other biases; other biases not mentioned above but important in RCTs related to treatment interventions for esophageal cancer.

Finally, RCTs that fulfill all criteria will be categorized as low risk studies; RCTs that do not meet only one criterion will be classified as intermediate, and RCRs that do not meet more than one criteria will be classified as high-risk studies.

Measures of treatment effect

Relative treatment effect

Survival of patients in each arm of RCTs and in different time durations are of the salient treatment effects that will be considered. Adverse event rates of interventions are other measures of treatment effect.

To be exact, the following measures will be used for assessment of treatment effect:

For time to event outcomes, pooled Hazard Ratio (HR) will be calculated. For count data (e.g. Number of adverse events for each treatment), pooled Rate Ratio with 95% credible interval will be estimated. For binary outcomes related to adverse events, pooled Relative Risk or Odds Ratio (OR) with 95% credible interval will be estimated. For continues outcome, standardized mean difference with 95% credible interval will be used.

Relative ranking of treatments

At first, relative ranking probability of available treatment interventions for esophageal cancer will be calculated. Then, by using the surface under cumulative ranking curve (SUCRA), probability of the best treatment intervention will be obtained (Salanti et al., 2011).

Unit of analysis

The unit of analysis for this study will be patients with esophageal cancer who were randomized into each arm of RCTs.

Dealing with missing data

A simple and common method to encounter with missing data is to limit the analysis to participants with complete data (Complete case analysis). However, estimates of treatment effect with complete case analysis are biased (Mavridis et al., 2014). Therefore, if any missing data in the included RCTs is faced in present study, missing data model in meta-analysis and missing data model in the network meta-analysis will be used. We will calculate the informative missing odds ratio (IMOR) to quantify the association between informative messiness and a dichotomous outcome. If IMOR equals one, it indicates that missing data is at random, if it equals zero, all missing data will be a failure, and if equals infinite, it indicates that all missing data will be a success (White et al., 2008; Spineli et al., 2013).

Assessment of heterogeneity

Statistical heterogeneity will be assessed using Chi-square test for pair-wise comparisons. In addition, amount of heterogeneity will be obtained using I^2 test. The variance of between studies will be calculate by a tau-squared test (Higgins et al., 2003; Huedo-Medina et al., 2006). If a considerable heterogeneity is found, it will be explored further by using a meta-regression (Baker et al., 2009), and if the source of heterogeneity is identified, a subgroup analysis will be conducted based on the source.

Assessment of transitivity and consistency across treatment comparisons

Transitivity assumption will be assessed by comparing the distribution of potential effect modifier variables in pair-wise comparisons (Baker and Kramer, 2002). Consistency assumption will be assessed by the loop-specific and design-by-treatment interaction approaches. By the loop-specific approach, inconsistency assumption

in each closed loop in the network will be assessed. Overall inconsistency in the network of treatments will be assessed by using a design-by-treatment interaction approach (Veroniki et al., 2013). If we encounter with inconsistency in the network of treatment interventions, following strategies will be performed. (1) Assessment of extracted data, because the inconsistency may be due to errors in data extraction (Veroniki et al., 2013). (2) Bypass operation, i.e. we will change the measure of treatment effect for dichotomous outcomes. Indeed, the relative and standardized measures (i.e., odds ratio, risk ratio, mean difference, and ratio of means) may be more homogenous than difference measures such as mean difference and risk difference (Lu and Ades, 2006; Veroniki et al., 2013). (3) We will explore it using network meta-regression (Salanti et al., 2009).

Assessment of reporting biases

To examine reporting bias in RCTs for a direct comparison, a funnel plot will be used that assesses visual asymmetry to explore the publication bias (Sterne and Harbord, 2004). In addition, a linear regression Egger test (Egger et al., 1997) and Begg test (Begg and Mazumdar, 1994) will be used to quantitatively assess the reporting bias.

Statistical analysis

Network meta-analysis will be conducted to simultaneously compare the available treatment interventions for esophageal cancer. We will compare interventions in the primary and the secondary outcomes of this review. A network plot will be drawn for visual representation of all available treatment interventions using Stata software (Stata Corp, College Station, TX, USA) (Chaimani et al., 2013). As a result, the linked RCTs (via treatments) and RCTs that are not connected to the network will be identified. Not connected RCTs will be excluded then. Bayesian approach will be used to combine the direct and indirect evidence (Jansen et al., 2008). A Bayesian network meta-analysis will be conducted in WinBUGS 1.4 using Markov Chain Monte Carlo method (Gilks, 2005).

The difference between treatment effects in subgroups, based on gender of patients, age groups, disease stage, type of esophageal cancer (carcinoma or adenocarcinoma), geographic location of study, risk of bias (low risk, unclear and high risk), and type of analysis in RCTs (intention to treat or per-protocol), will be assessed too.

Sensitivity analysis will be assessed using the best-case and the worst-case scenarios in the following situations. (1) If RCTs with high-risk of bias are encountered, (2) If any missing data is found even after imputation of missing values in RCTs (we will test if imputation of missing value affects the results of pooled estimations of treatment effects), (3) If RCTs with per-protocol analysis are encountered.

Presentation of results

Treatment effects (e.g. Hazard Ratio for time to event outcomes, Risk Ratio for binary outcomes, and Rate Ratio for count outcomes with 95% credible interval) will be reported. Moreover, cumulative probability of the treatment ranks will be reported using the surface under the cumulative ranking (SUCRA) graphs (Salanti et al., 2011).

Acknowledgements

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