Stepwise-Hierarchical Pooled Analysis for Synergistic Interpretation of Meta-analyses Involving Randomized and Observational Studies: Methodology Development

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Original Paper

Stepwise-Hierarchical Pooled Analysis for Synergistic Interpretation of Meta-analyses Involving Randomized and Observational Studies: Methodology Development

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Introduction

- The number of meta-analyses that include observational studies has steadily increased in recent decades.
- Controversy persists regarding the validity and utility of these meta-analyses
- Researchers are reluctant to assess the validity of the pooled results from studies of a heterogeneous nature and with less robust data.
- RCTs have the greatest influence on therapeutic advances and clinical decisions, however, not all decisions in clinical practice can be supported by clinical trials, especially in fields of rare diseases or intractable status.
- Conducting RCTs requires abundant support, which is not always available in all medical disciplines.

Introduction

- For example, in liver cancer, there is a drug that has demonstrated mild survival gain with little local effect (ie, sorafenib: response rate of ~3%) in the treatment of inoperable cases. This drug was studied in phase 3 RCTs that only proved the survival benefit of the drug for unresectable liver cancers.
- While. radiotherapy has a significant local effect, with a response rate of over 50%, no phase 3 RCTs has demonstrated a survival gain.
- In a surveillance study on 161 liver cancer clinicians, 86% of physicians stated that they would apply radiotherapy for unresectable liver cancer with major vascular involvement, compared to 66% who would prescribe sorafenib.

How were these clinical decisions reached?

- Clinicians perform a self–meta-analysis in their own way involving studies with various designs, commonly including observational studies.
- Clinicians in practice inevitably rely on case series or small observational studies, especially when facing intractable situations in which RCTs cannot support all clinical decisions.

Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. The Lancet Oncology 2009 Jan;10(1):25-34.
Rim CH, Kim CY, Yang DS, Yoon WS. Comparison of radiation therapy modalities for hepatocellular carcinoma with portal vein thrombosis: a meta-analysis and systematic review. Radiother Oncol 2018 Oct;129(1):112-122.

Objectives

- Identify points that require improvement during the process of planning and conducting meta-analyses
- Suggest a method to synergistically interpret results from both nonrandomized and randomized studies.

Methods

1. **Identifying limitations to overcome** esp. in intractable oncologic situations

- 1.1) Confounders in Observational Studies
- 1.2) The “Gray Zone”: Necessity of Combining Interpretations of Randomized and Observational Studies
- 1.3) Clinical Logic Flow in the Gray Zone

2. **Rationale of Stepwise-Hierarchical Pooled Analysis**

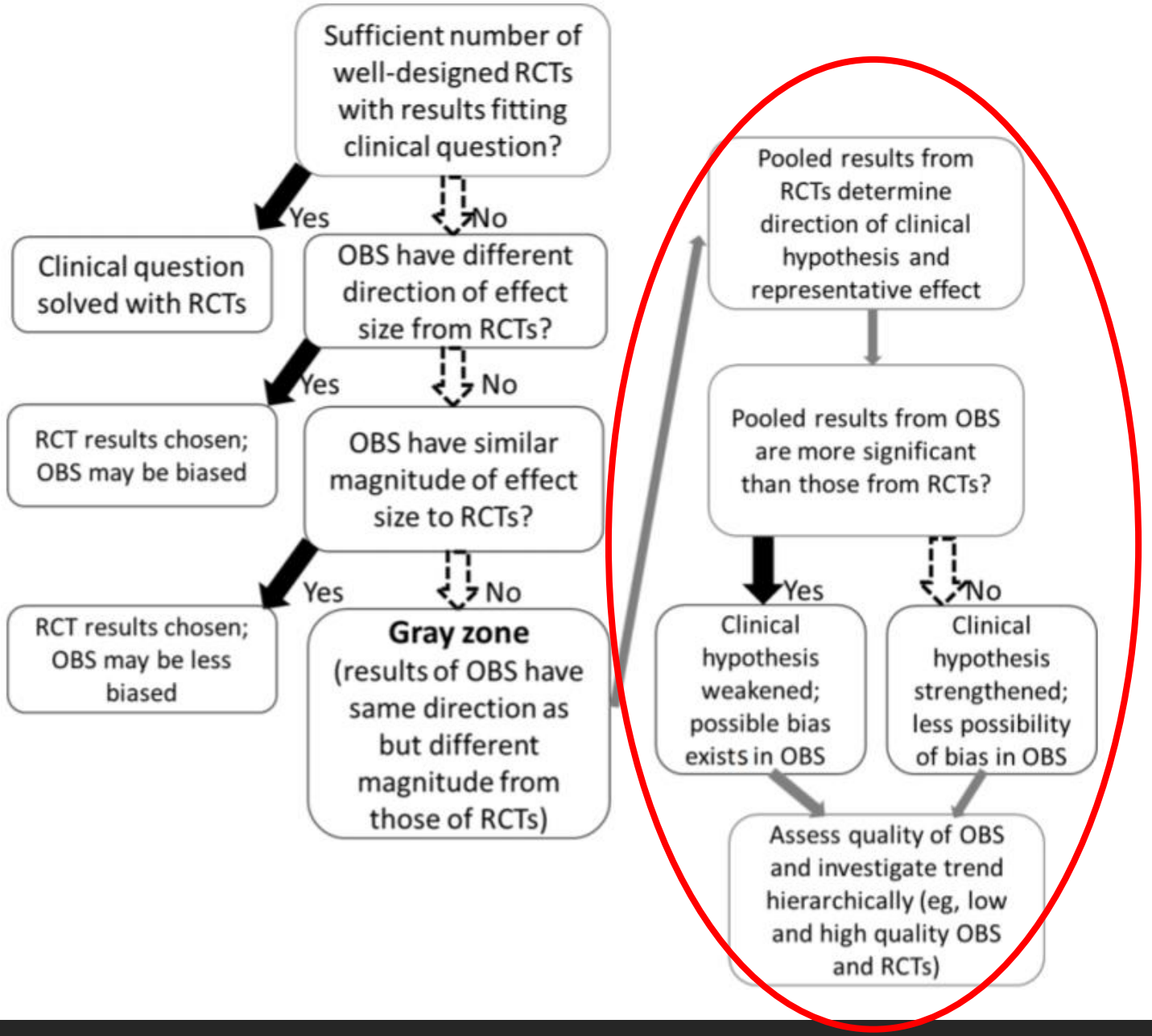
Confounders in Observational Studies

- Known and unknown confounders
- Main limitation in observational studies >>> low validity compared to RCTs
- Observational studies are more likely to be affected by confounders than RCTs. They need to be weighted differently according to their design & the degree of control for confounders.
- As methods of disease assessment advance, more factors are being identified that influence a patient's prognosis. A study in which clinical confounders were controlled using methods such as propensity matching and multiple regression analysis in a sufficient number of patients should not be analyzed at the same level as studies in which such methods were not used.
- In addition, consideration should be given to how the treatment decisions have been established.
- The Cochrane Handbook: only observational studies with at least moderate or low risk of bias should be selected in systematic reviews.

“Gray Zone”: Necessity of Combining Interpretations of Randomized and Observational Studies

- If there are enough well-designed randomized studies on a subject to be analyzed, there is little need for a meta-analysis including observational studies.
- In practice, many RCTs have difficulty recruiting a sufficient number of patients.
- Additionally, a blinding process is not possible in RCTs comparing different types of treatment (eg, comparing the effectiveness of lobectomy and radiosurgery in early lung cancer).
- These limitations necessitate the identification of clinical reasoning, complemented by meta-analyses involving observational studies.

- **“Gray zone”** is where the results of studies with different designs (randomized vs observational studies) have **the same direction, but the magnitude of the effect size differs**.
- No standard method has been established.
- It is necessary to complement clinical reasoning based on pooled results of observational studies when the number of RCTs and the numbers of patients recruited are insufficient.



Clinical Logic Flow in the **Gray Zone**

- A recommended clinical logic flow of interpretation may be as follows:
- 1. The pooled results from RCTs determine the direction of the hypothesis and the representative effect size.
- 2. In the gray zone, complementation from data synthesized from observational studies may be necessary.
  - If the pooled results from observational studies are more significant than those from RCTs, the clinical hypothesis could be weakened and confounding bias could be present among the observational studies.
  - If the pooled effect of observational studies is less significant, the clinical hypothesis can be strengthened, and there is less possibility of bias.
- 3. The quality of observational studies can be assessed, and trends of pooled effects according to study design (high and low-quality observational studies and randomized studies) can be investigated.

Rationale of Stepwise-Hierarchical Analysis

- A method of interpreting the pooled results of studies categorized according to **design & validity**.
- Dividing into 3 groups, then the individual results of each group and the trends among groups are analyzed.
- **The first level:** all studies are analyzed
- **The second level:** balanced studies in which major confounders are controlled for are analyzed.
  - Balanced studies = those in which major clinical factors are evenly distributed, based on the study design or statistical method whenever possible.
  - RCTs can also be included at this stage in the analysis as balanced studies, especially when the number of nonrandomized and balanced studies is small.
- **The final level:** analyze only RCTs
  - Randomized studies can be analyzed at one level lower if the design is suboptimal or the number of included patients is too small.

Results: Descriptive Interpretation

- 4 representative patterns

Pattern type	Results	All studies included	[a]Balanced studies	[b]Randomized studies	Hypothesis	Confounder in OBS	Effect size of OBS	Further interpretation
Ascending patterns 1	Effect size				Strongly true	Possibly	May be smaller than the true effect	OBS may be affected by confounders negative to the hypothesis.
	Significance	Non-significant		Significant				
2	Effect size				Strongly true	Less likely		
	Significance	Significant		Significant				
Descending patterns 3	Effect size				Not true	Very likely	Less reliable	OBS may be affected by researchers' bias, or confounders positive to hypothesis.
	Significance	Significant		Non-significant				
4	Effect size				True	Possibly	May be larger than the true effect	
	Significance	Significant		Significant				

[a]Designed to reasonably control for possible confounders, including randomized studies.
[b]Studies with a flawed design or too few subjects might be downgraded.

cancers IF 6.639

MDPI

Article

Oncologic Benefit of Adjuvant Chemoradiation after D2 Gastrectomy: A Stepwise Hierarchical Pooled Analysis and Systematic Review

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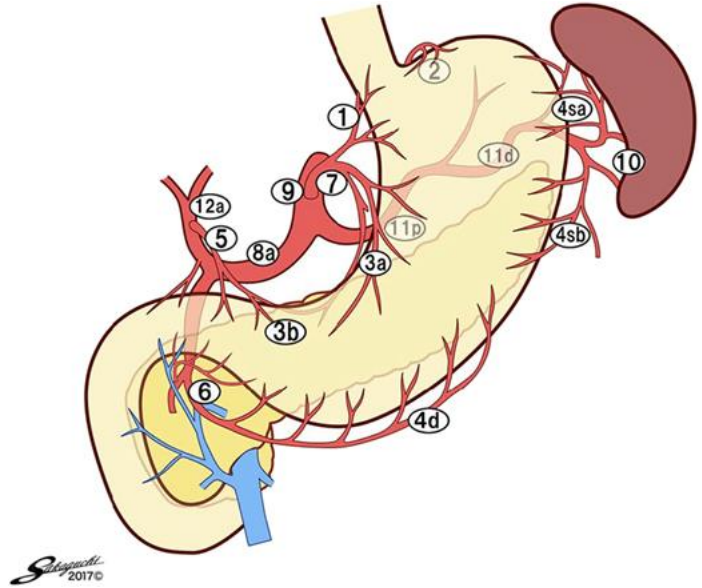
Example 1

- Role of additional radiotherapy has not been accepted widely after D2 gastrectomy, including extensive lymphatic dissection because the result for the primary endpoint (disease-free survival) of the only phase 3 RCT on the subject was marginally non-significant.
- However, several observational studies and small randomized trials have reported the oncologic benefit of radiotherapy.
- “Is there an oncologic benefit of adjuvant chemoradiotherapy (CRT) compared to chemotherapy (CT) after D2 resection for gastric cancer in a real-world clinical setting?”



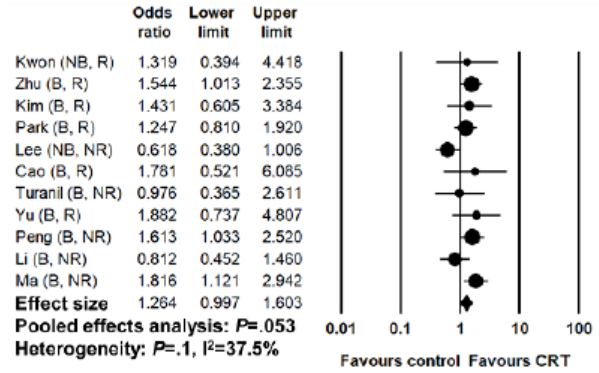
Methods

- A review included controlled clinical trials aimed at comparing chemoradiation (CRT) and chemotherapy (CT) after D2 resection for gastric cancer.
- 13 studies were included: 6 RCTs and 7 non-RCTs
- 9 studies balanced between 2 arms

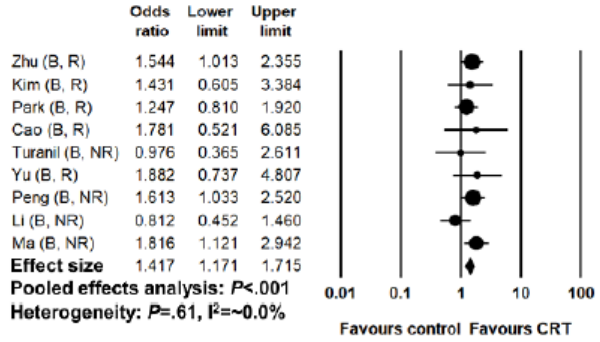
Balanced studies without significant differences in the patients' clinical profiles (i.e., age, histologic type, and TNM stage).

- The authors performed pooled analyses in a stepwise-hierarchical manner; ORs calculated from the comparison of endpoints between the CRT and CT arms were pooled and analyzed for **all studies, RCTs alone, and balanced studies alone.**
- Considering the range of clinical diversity, the different institutions with distinct treatment modalities, and the inclusion of studies (NRCTs and RCTs) of different designs, a random effects model was used for the pooled analysis of endpoints.
- Heterogeneity: I^2 at 25% (low), 50% (moderate), 75% (high)

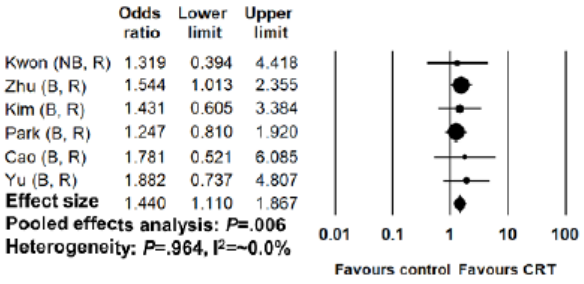
(A) All studies included



(B) Balanced studies



(C) Randomized studies



Disease free survival (DFS)

ES: 1.26, *P*: Nonsignificant (.053) Moderate heterogeneity

ES: 1.42, *P*: Significant (<.001) Low heterogeneity

ES: 1.44, *P*: Significant (.006) Very low heterogeneity

The effect size of only RCTs.

The trend of these results correlates with the 1st pattern.

- Considering only balanced or randomized studies strengthened the validity of the hypothesis.
- The results of observational studies may have underestimated the true effect size due to the influence of confounders (eg, patients assumed to have greater risk of recurrence underwent radiochemotherapy).
- The low heterogeneity in the analyses of balanced and RCTs suggests that the pooled results of those studies are reliable and well designed, and less affected by possible confounders.
- The authors concluded that the study clearly demonstrated the benefit of CRT after D2 gastrectomy in terms of DFS.

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Benefits of local consolidative treatment in oligometastases of solid cancers: a stepwise-hierarchical pooled analysis and systematic review

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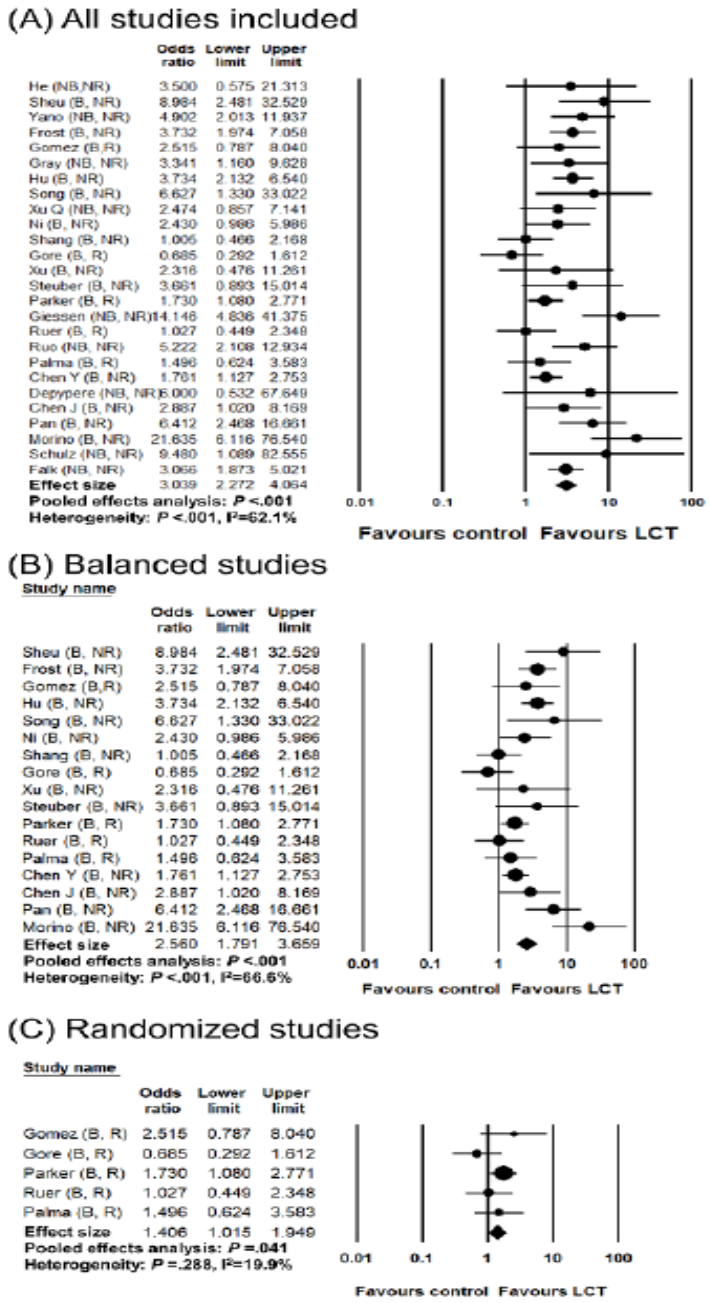
Example 2

- The study was on the benefit of local treatment for oligometastases.
- Oligometastases refer to a disease state with ≤3 or ≤5 metastatic lesions.
- In the recent literature, it was proposed that local treatment for oligometastatic foci could prolong cancer survival.
- Several RCTs have been published, but the number of patients recruited is generally insufficient.
- In addition, because the studies in the literature were published according to the type of primary cancer, it was difficult to comprehensively analyze the oncologic benefit of local treatment on general oligometastases.
- Therefore, the author attempted to prove the hypothesis that local treatment for oligometastases will increase overall survival in a meta-analysis.

Methods

- 31 included studies (23 retrospective studies & 8 prospective studies)
- Pooled analyses of primary endpoints were performed (considering the study quality) in a stepwise-hierarchical manner.
- Overall analysis of **all the studies was first performed; next, pooled analyses of balanced studies (8-9 points on the Newcastle-Ottawa scale) were performed, followed by pooled analyses of the RCTs alone**.
- Considering the varying study designs, treatment modalities, and clinical characteristics, the random-effects model was used for the first two analyses.

For quality assessment, the Newcastle–Ottawa scale was used. Studies with scores of more than 8 were considered high quality, scores of 7–8 medium quality, and the remainder low quality.



ES: 3.04,
P: Significant
(<.001)
High
heterogeneity

ES: 2.56,
P: Significant
(<.001)
High
heterogeneity

ES: 1.41,
P: Significant
(.041)
Low
heterogeneity

95% CI 1.02-1.95

The trend of these results correlates with the 4th pattern.

- The hypothesis of this meta-analysis is true, referring to the analysis results of RCTs.
- The change in the effect size or P value does not increase the validity of the hypothesis.
- Observational studies may have been affected by confounders >> high heterogeneity among observational studies.
- The results from observational studies may have been larger than the true effect size.
- In subgroup analyses, the benefit of local treatment was higher in certain cancer types (eg, lung cancer, colorectal cancer) and with higher metastatic burden ($\leq$ 5 metastases).
- The authors concluded that local treatment for oligometastases is beneficial, however patients must be carefully selected with consideration of the type of disease or metastatic burden, and the design of future observational studies needs to be improved.

Discussion

- There is still no established model that can evaluate how bias or confounders of observational studies affect estimates.
- Little is known about how observational and randomized studies should be integrated and analyzed to yield actual clinical decisions.
- Limitations of observational studies are categorized and explained in the GRADE handbook: They include fundamental flaws such as inappropriate eligibility criteria, flawed measurement of exposure, inadequate follow-up, and inadequate control of confounders. In the presence of these limitations, it is suggested that the evidence grade should be lowered by one or two steps.
- However, obtaining clinically useful information by complementing the results of randomized studies with information from observational studies has not been sufficiently suggested.

Discussion

- The model proposed in this study is less difficult to apply;

  Not require additional statistical analysis or software use, easy and intuitive, even for physicians without mathematical expertise, because it is based on clinical logical flow.

- The limitations of this study are as follows:

1) 4 typical patterns described cannot explain all possible patterns and their variations.

2) Cooperation between a clinician and a biostatistician with sufficient experience in meta-analysis is recommended to successfully use our model.

- Recommend using the stepwise-hierarchical pooled analysis approach as a model for interpreting meta-analyses involving randomized and observational studies in a synergistic manner.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