# Quality of meta-analyses and why they sometimes lead to different conclusions

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# Conflicts of Interest: none

# Meta-analyses of randomized trials in oncology*
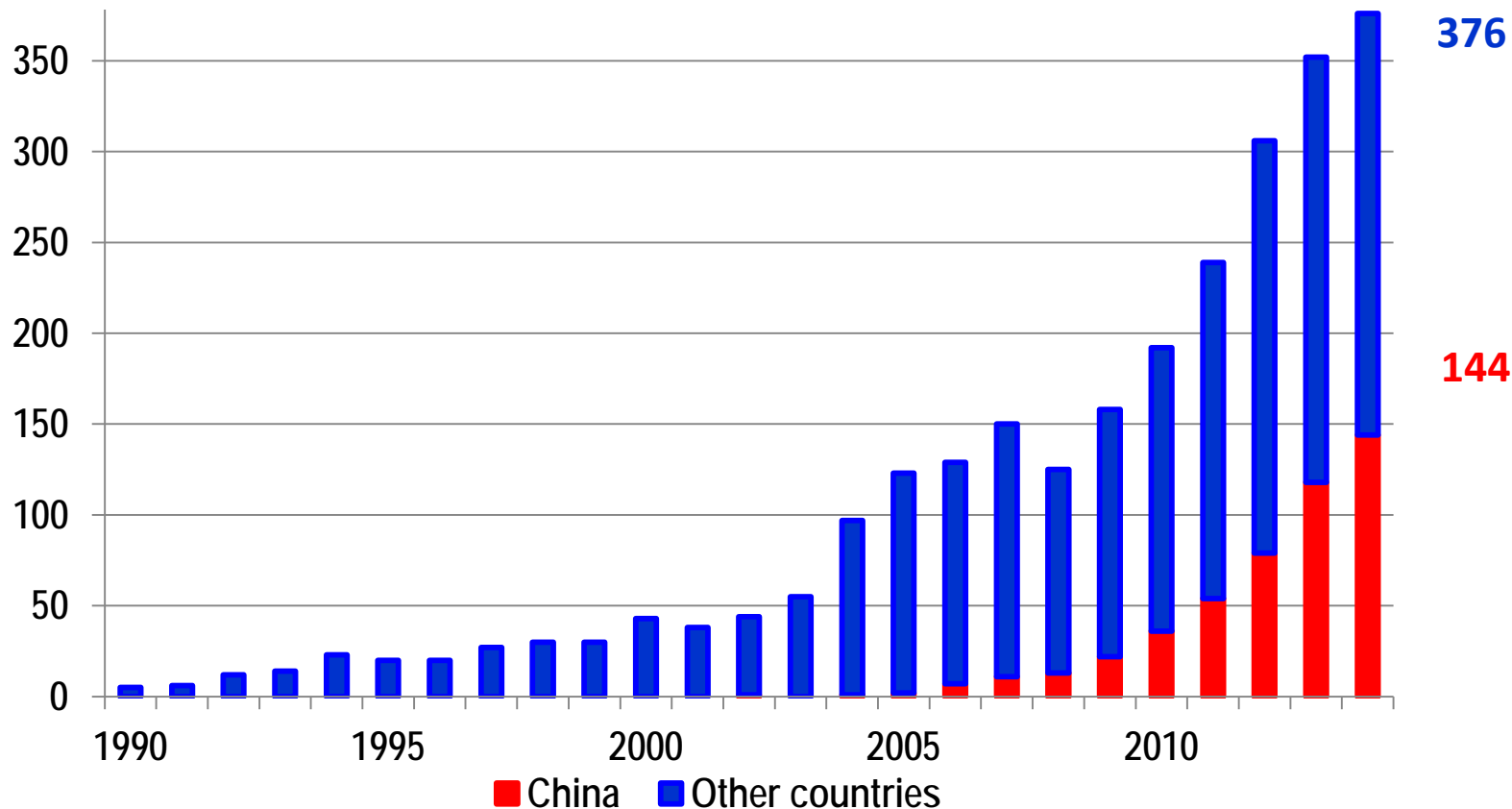


*meta-analysis[Publication Type] AND (cancer OR oncology)
AND (randomised clinical trial OR RCT) AND China

# Meta-analyses of randomized trials in oncology

- **Increase in number (376 publications in 2014)**
- **More often overlapping** i.e. evaluating same intervention
- **Quality varies**
- There is **no good meta-analysis without systematic review**
- Most use **time dependent endpoint**

# Overlapping meta-analyses (MAs)
## (from Siontis et al. BMJ 2013;347)

- Survey of a sample of 73 MAs published in 2010 on effectiveness of a medical intervention, identified 138 other MAs of the same intervention until Feb 2013

- 67% (49/73) had at least one overlapping MA, 50% had 2 and 5% had 8 or more

- Among the 49 interventions with more than 2 MAs, 17 had at least one author in common for at least 2 MAs:

  corresponding either to an update (7), a partial overlap (9), or an exact duplicate (1)

# Example: Chemotherapy in locally advanced head and and neck squamous cell carcinoma

- 35 meta-analyses (17 papers) by 13 groups between 1980 and 2015 with 1 to 6 meta-analyses by paper

- Three groups published 8 papers, including 2 updates and 2 partial overlap

- 14 questions according to timing, tumor site, and type of chemo

- 11 questions related to adding chemo to locoregional treatment (LRT)

- From broad questions "adding chemo to LRT" (87 RCTs)
  to very specific questions "adding induction chemo before surgery in oral cancer" (2 RCTs)

# Algorithm to interpret discordant systematic reviews (Jadad et al. CMAJ 1997)

Pragmatic guide to interpret discordant systematic reviews

Two steps:

1. <u>Are the reviews valid?</u> Major flaws ➔ unsuitable in guiding decision

2. <u>Are the differences among the discordant reviews important?</u>
"A decision maker may consider differences between 2 reviews to be unimportant if the estimated treatment effects are of different magnitude but in the same direction, and are statistically significant and clinically important"

# Quality of meta-analyses publications

- Several scales:
  - Oxman & Guyatt index (10 items),
  - AMSTAR (11 items.)
  - ROBIS ($\geq$21 items)
- To be interpreted with caution: failure in few items may be sufficient to disqualify a meta-analysis (MA)
- Different from recommendations for publication (PRISMA)
- Protocol and trial quality evaluation are systematic in Cochrane review hence Cochrane reviews are better than other meta-analyses
- Individual patient data MA is better than aggregate data MA

# Factors related to quality of meta-analyses

- Protocol , statistician & clinician authorship
- Journal with high impact factor, with peer review
- Quality of trials search: no language restriction, search of grey literature (abstract, unpublished RCT) through meeting proceedings and trial registries
- Detailed evaluation of trial quality
- PRISMA flow chart
- Use of hazard ratio and not survival rate or median survival ratio to estimate effect on survival endpoint

# Do the overlapping MAs ask the same question?

## No

- Select "the meta-analysis closest to the question to be solved " (Jadad et al); e.g., induction chemo in head & neck cancer (HNC): any chemo, platin-based or 5FU-platin?

- But meta-analysis that "considers multiple, …, available treatment options for the same condition ….can offer more complete pictures of the evidence" (Siontis et al)

  e.g., addition of chemo to loco-regional treatment in HNC, study of

  best timing by direct and indirect comparisons; network MA of loco-regional and systemic treatment in HNC

# Do the meta-analyses ask the same question?

Yes

<u>similar conclusions</u>

- Duplicate publications of the same MA (compare authors' name)
- Meta-analysis update ➜ When to update MA?
  - » Quantitative methods proposed by Moher et al (Cochrane DSR 2008)
  - » Approximate rule: <10% new data, update not useful, except if contradictory results

<u>discordant conclusions</u>

➜ include the same trials?

# Do meta-analyses include the same trials?

Yes: ➔ same quality?  Select the meta-analysis with the highest quality

No: ➔ same selection criteria? Select the meta-analysis with the largest number of trials, taking into account the quality of trials and meta-analyses

**Platin-5FU  vs. Taxane-Platin-5FU induction chemo** : *same overall conclusion*

| Reference | Number of | | Type of data | Parameters for survival |
| | Trials | Patients in survival analysis | | |
| --- | --- | --- | --- | --- |
| Qin 2012 | 3 | 1 241 | Aggregated | Risk ratio 3-year surv. rate |
| Blanchard 2013 | 5 | 1 772 | Individual patient | Hazard ratio |
| Perl 2013 | 4 | 1 454 | Aggregated | Hazard ratio |
| Qian 2015 | 5 | 1 765 | Aggregated | Hazard ratio |

# Why MA sometimes lead to different conclusions?

- Question studied, number and quality of RCTs are the main factors to explain different results in overlapping MAs (systematic review)

- Data collection, in particular for time dependent outcome (OR vs. HR) may explain some differences

- Statistical methods may explain some differences, for instance when the study lacks power, some significant results with fixed effect model may become non significant with random effect model

- Importance of sensitivity analyses for the robustness of the conclusion

- Same data + same methods ➔ same results, but their interpretation may differ

# Conclusions and recommandations (1)

- Duplicate meta-analyses are useful, in particular if concerns about existing meta-analysis (MA), but too much duplication is research waste

- Meta-analyses should be updated only when new evidence may affect the previous conclusion

- Investigators should registered meta-analyses (PROSPERO), and search MA registries before starting a new MA and at the time of its publication

# Conclusions and recommandations (2)

- <u>Investigators</u> should provide their reasons for doing a new meta-analysis (MA) and discuss the results of similar meta-analyses in their publication
- MA publications should follow PRISMA recommendations
- <u>Editors and reviewers</u> should promote registration, use PRISMA and request investigator to take overlapping meta-analyses into account

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# Back-up slides

# Overlapping MA: Jadad algorithm to interpret discordant systematic review (CMAJ 1997)

**Table 1: Sources of discordance among meta-analyses**

**Clinical question**
Populations of patients
Interventions
Outcome measures
Settings

**Study selection and inclusion**
Selection criteria
Application of the selection criteria
Strategies to search the literature

**Data extraction**
Methods to measure outcomes
End points
Human error (random or systematic)

**Assessment of study quality**
Methods to assess quality
Interpretations of quality assessments
Methods to incorporate quality assessments in review

**Assessment of the ability to combine studies**
Statistical methods
Clinical criteria to judge the ability to combine studies

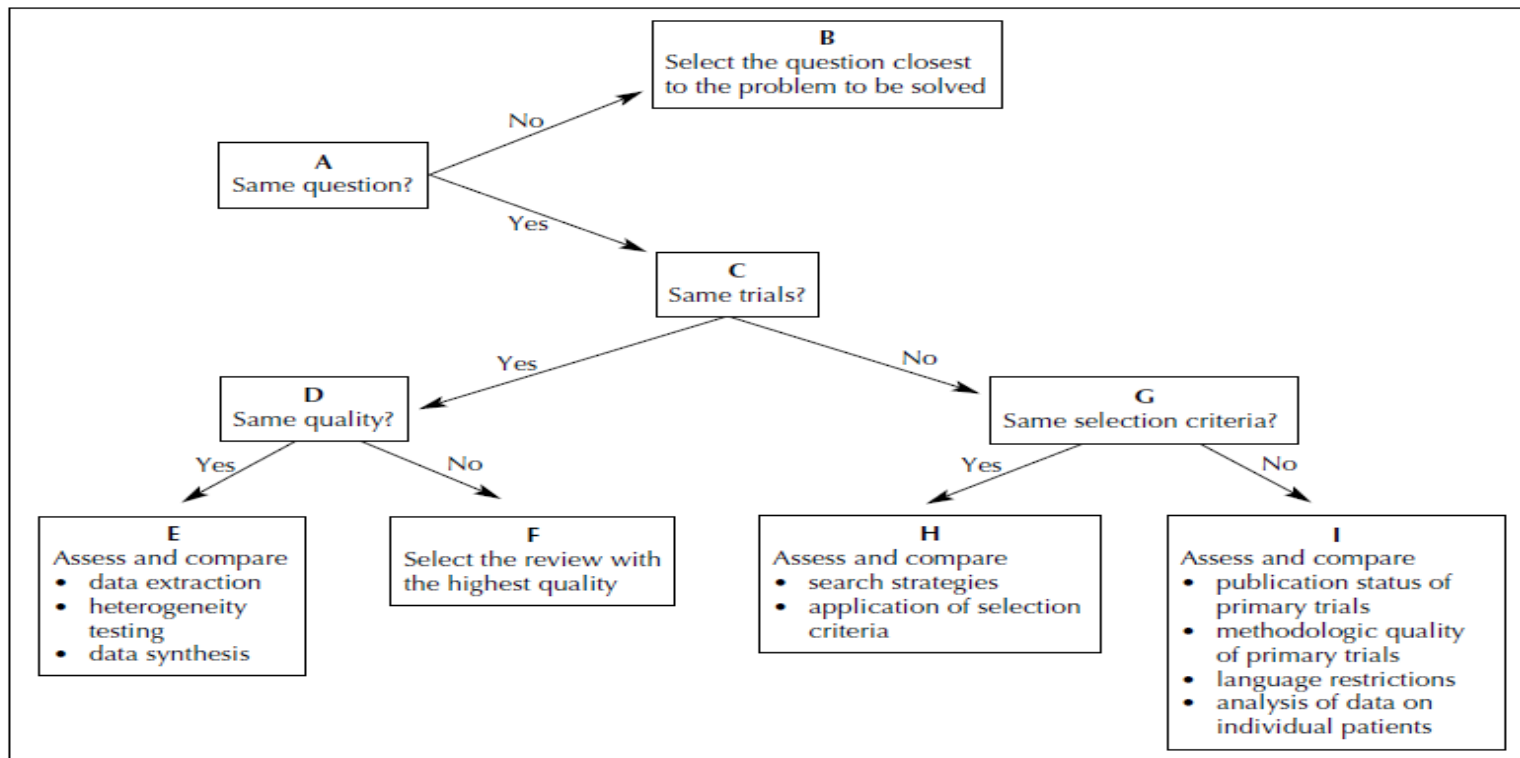**Statistical methods for data synthesis**

# Overlapping MA: Jadad algorithm to interpret discordant systematic review (CMAJ 1997)

| Table 2: Types of discordance | |
| --- | --- |
| Type | Example |
| **Results** | |
| Direction of effect | One review favours the experimental treatment and another favours the control treatment |
| Magnitude of effect | One review suggests that the intervention results in a 30% reduction in mortality and another suggests that it results in a 5% reduction in mortality |
| Statistical significance | One review shows a statistically significant difference between the experimental and the control treatments and another review shows a nonsignificant difference between them |
| **Interpretation of the results** | |

# Overlapping MA: Jadad algorithm to interpret discordant systematic review (CMAJ 1997)

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