Bias in Meta-Analysis

Jing Yi
Genentech
Outline

- Introduction of meta-analysis
- Bias in meta-analysis
- Method for bias examination
- Example
- Recommendations
Brief Background of Meta-Analysis

○ Commonly used to obtain information that can not be derived from the individual studies

○ A useful tool to provide evidence to support clinical strategies such as
  - Hypotheses generation
  - Better estimate of treatment benefit
  - Better characterization of safety signal
Outline

- Introduction of meta-analysis
- **Bias in meta-analysis**
- Method for bias examination
- Example
- Recommendations
Publication Bias

- Studies with significant treatment benefit are likely to be
  - Published and more likely to be used in further investigation by other authors or studies.
  - Published in English and cited elsewhere.

- Studies with negative results or early termination or with non-significant results are less likely to be published.
Clinical Heterogeneity

○ Patient population
  ● Inclusion/exclusion criteria of trials
  ● Geographical location of the trials

○ Interventions
  ● Drug dose
  ● Treatment duration
  ● Various experience on treating physicians
  ● Control arm selection: placebo/none/standard care/physician’s choice

○ Outcome measure
  ● Choice of endpoint measurement
  ● Endpoint definition: definite (such as death) v.s. “softer” ones (such as progression-free survival)
Methodological Bias

○ Study designs
  ● Randomized v.s. non-randomized (e.g. observational)
  ● Study size
  ● Study population (severity, naïve, other/prior tx)
  ● Duration of follow up time
  ● Availability of subgroup information or risk factors

○ Study conduct
  ● Double blinded v.s. open-label
  ● Outcome evaluation
Statistical Bias

- Analysis population: ITT v.s. eligible
- Variation in the results of the trials
- Analysis on individual patient level v.s. total group level
  - Strategies for combining studies
    - Standardize definition for endpoints/adverse events
    - Drug exposure
    - Dosage
    - Follow-up time
    - Baseline variables
Outline

- Introduction of meta-analysis
- Bias in meta-analysis
- Method for bias examination
- Example
- Recommendations
Method for Bias Examination

- Funnel plot
- Statistical approach
Funnel Plot

- Scatter plot of the treatment effects from individual studies on the horizontal axis against a measure of sample size on the vertical axis.

- The larger the sample size is, the better precision of treatment benefit estimation. Thus results from small studies are usually presented at the bottom of the funnel plots.
Funnel Plot (cont’d)

- Funnel plot is a simple graphical test for any type of bias associated with trial size.
- Small trials are on average conducted and analyzed with low methodological quality than larger studies.
- Small trials of less rigor tend to overestimate treatment benefit in meta-analysis.
- Asymmetrical funnel plot indicates small study effect and results should be interpreted with caution.
Funnel Plot Example

**Fig 1** Hypothetical funnel plots: left, symmetrical plot in absence of bias (open circles are smaller studies showing no beneficial effects); centre, asymmetrical plot in presence of publication bias (smaller studies showing no beneficial effects are missing); right, asymmetrical plot in presence of bias due to low methodological quality of smaller studies (open circles are small studies of inadequate quality whose results are biased towards larger effects). Solid line is pooled odds ratio and dotted line is null effect (1). Pooled odds ratios exaggerate treatment effects in presence of bias.

Statistical Approach: Test for Heterogeneity

- **Cochran Q**
  - Examine whether the observed variability in effect size of included studies is within the expected range if all studies have a common population effect size.
  - Sensitivity is low when only a few studies are included.
  - Only inform the presence v.s. absence of heterogeneity.

- **$I^2$ Statistic**
  - Quantify the degree of heterogeneity
  - $I^2 = 100\times(Q-df)/Q$. df=number of studies-1.
  - No heterogeneity when $I^2=0$. Larger values show increasing heterogeneity.
Statistical Approach: Sensitivity Analysis

- To investigate the robustness of results and aid interpretation

- Options:
  - Include only studies with good quality
  - Include reasonable amount of risk factors in the model.
  - Subgroup analysis
Outline

- Introduction of meta-analysis
- Bias in meta-analysis
- Method for bias examination
- Example
- Recommendations
In a meta-analysis of thromboembolism in randomized trials of bevacizumab in metastatic malignancies, Nalluri et al (JAMA 2008) concluded that bevacizumab treatment was associated with a 33% increase in relative risk of venous thromboembolism (VTE), with a 2% absolute increase in grade 3-4 event incidence.
<table>
<thead>
<tr>
<th>Study Name</th>
<th>Trial Phase</th>
<th>No. Enrolled</th>
<th>No. for Analysis</th>
<th>Duration of Follow-up, Median (Range), mo</th>
<th>Underlying Malignancy</th>
<th>Concurrent Treatment</th>
<th>Bevacizumab Dose, mg/kg per wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escudier et al, 2007</td>
<td>3</td>
<td>649</td>
<td>641</td>
<td>13.3 (0-25.6)</td>
<td>Renal cell carcinoma</td>
<td>Interferon alfa</td>
<td>5</td>
</tr>
<tr>
<td>Giantonio et al, 2007</td>
<td>3</td>
<td>829</td>
<td>572</td>
<td>28.0 (NA)</td>
<td>Colorectal cancer</td>
<td>Oxaliplatin, fluorouracil, and leucovorin</td>
<td>5</td>
</tr>
<tr>
<td>Herbst et al, 2007</td>
<td>2</td>
<td>122</td>
<td>81</td>
<td>15.8 (NA)</td>
<td>NSCLC</td>
<td>Docetaxel or pemetrexed</td>
<td>5</td>
</tr>
<tr>
<td>Hurwitz et al, 2004</td>
<td>3</td>
<td>813</td>
<td>790</td>
<td>18.0 (NA)</td>
<td>Colorectal cancer</td>
<td>Irinotecan, bolus fluorouracil, and leucovorin</td>
<td>2.5</td>
</tr>
<tr>
<td>Johnson et al, 2004</td>
<td>2</td>
<td>99</td>
<td>98</td>
<td>14.7 (NA)</td>
<td>NSCLC</td>
<td>Carboplatin and paclitaxel</td>
<td>2.5 or 5</td>
</tr>
<tr>
<td>Kabbinavar et al, 2003</td>
<td>2</td>
<td>104</td>
<td>102</td>
<td>17.6 (NA)</td>
<td>Colorectal cancer</td>
<td>Fluorouracil and leucovorin</td>
<td>2.5 or 5</td>
</tr>
<tr>
<td>Kabbinavar et al, 2005</td>
<td>2</td>
<td>209</td>
<td>204</td>
<td>14.8 (NA)</td>
<td>Colorectal cancer</td>
<td>Bolus fluorouracil and leucovorin</td>
<td>2.5</td>
</tr>
<tr>
<td>Karrison et al, 2007</td>
<td>2</td>
<td>115</td>
<td>108</td>
<td>15.1 (NA)</td>
<td>Mesothelioma</td>
<td>Cisplatin and gemcitabine</td>
<td>5</td>
</tr>
<tr>
<td>Kindler et al, 2005</td>
<td>3</td>
<td>602</td>
<td>525</td>
<td>11.5 (NA)</td>
<td>Pancreatic cancer</td>
<td>Gemcitabine</td>
<td>5</td>
</tr>
<tr>
<td>Manegold et al, 2007</td>
<td>3</td>
<td>1043</td>
<td>1043</td>
<td>NA</td>
<td>NSCLC</td>
<td>Cisplatin and gemcitabine</td>
<td>2.5 or 5</td>
</tr>
<tr>
<td>Miller et al, 2005</td>
<td>3</td>
<td>462</td>
<td>445</td>
<td>14.8 (NA)</td>
<td>Breast cancer</td>
<td>Capecitabine</td>
<td>5</td>
</tr>
<tr>
<td>Miller et al, 2007</td>
<td>3</td>
<td>722</td>
<td>711</td>
<td>25.9 (NA)</td>
<td>Breast cancer</td>
<td>Paclitaxel</td>
<td>5</td>
</tr>
<tr>
<td>Price et al, 2008</td>
<td>3</td>
<td>400</td>
<td>400</td>
<td>NA</td>
<td>Colorectal cancer</td>
<td>Capecitabine or mitomycin</td>
<td>2.5</td>
</tr>
<tr>
<td>Saltz et al, 2007</td>
<td>3</td>
<td>1401</td>
<td>1369</td>
<td>27.6 (NA)</td>
<td>Colorectal cancer</td>
<td>Oxaliplatin, fluorouracil, and leucovorin or capecitabine and oxaliplatin</td>
<td>2.5</td>
</tr>
<tr>
<td>Sandler et al, 2006</td>
<td>3</td>
<td>878</td>
<td>868</td>
<td>19.0 (NA)</td>
<td>NSCLC</td>
<td>Paclitaxel and carboplatin</td>
<td>5</td>
</tr>
</tbody>
</table>
Bias in the Analysis

- Unable to differentiate two different medical concepts of arterial and venous event due to lack of individual patient-level data.

- No uniform safety data collection
  - Grade $\geq 3$ v.s. all grade

  - Open-label studies only collected treatment-related AEs, which lead to possible overestimation of treatment arm difference.
Bias in the Analysis (cont’d)

- Patient follow up time is different
  - Pancreatic cancer v.s. breast cancer
  - Statistical significant prolongation of progression-free survival was observed in 2/3 of the trials. A lack of adjustment for time-on-treatment likely contributed to an overestimation of the risk.
Outline

- Introduction of meta-analysis
- Bias in meta-analysis
- Method for bias examination
- Example
- Recommendations
Summary and Recommendations

- Use data from all relevant trials with good quality.

- Only include non-randomized trials when no randomized controlled trials were available and the meta-analysis goal is for hypothesis generation or safety investigation.

- If possible, use individual patient-level data.
Summary and Recommendations (cont’d)

- Test for heterogeneity is important

- Conduct sensitivity analysis on subgroups or different methods to see if the treatment benefit is robust to various assumption on bias
Reference

- Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50:1088