Meta-analysis: clinician’s point of view

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CONFLICT OF INTEREST

• NONE TO DECLARE RE. FUNDING (e.g. INDUSTRY)

• BUT (!)

• PART OF SEVERAL META-ANALYSIS EFFORTS
META-ANALYSIS

• A SUPREME PROOF OF EVIDENCE?
• UNDISPUTED PROOF?
• EXCLUSIVE TOOL FOR PRACTICING EBO?
• TEACHING TOOL?
DO WE NEED META-ANALYSES (I)?

NO! WE DO NOT NEED IT!!

NCI ALERT IN GYNAE, NOT META-ANALYSIS
several PRCTs published

TEMOZOLOMIDE TRIAL IN GBM
only one trial to change clinical practice?

PCI IN ED SCLC
only one trial to change clinical practice?
DO WE NEED META-ANALYSES (II)?

YES! WE NEED IT!!

- Warde et al, 1992; Pignon et al, 1992
  TRT in LD SCLC

- Auperin et al, 1999
  PCI in LD SCLC

- Auperin et al, 2006
  CONCURRENT RT and CHT in LA NSCLC

- IGR and collaborators, 2007
  SEQUENCING RT and CHT in LA NSCLC
DO WE NEED META-ANALYSES (III)?

- QUALITY OF DATA
- CONSISTENCY OF FINDINGS
- STUDY TIME PERIOD
- VERIFICATION IN CLINICAL PRACTICE
- PERSONAL MATTERS
EVIDENCE-BASED vs. EXPERT-BASED

I KNOW BETTER THAN THEY DO

“I have had a patient 17 years ago with advanced NSCLC and she lived for 4 years”

TRUE!

Advanced NSCLC can (extremely rarely, though!) live that long even with RT alone!
EXCUSES AGAINST EVIDENCE

KNOWLEDGE
INSTITUTIONAL POLICY
REALITY
COMPETING EVIDENCES
PERSONAL INTERESTS
META-ANALYSIS

Meta-analysis

Systematic Review

Practice Guideline

Randomized Controlled Trial

Cohort Study

Case Control Study

Case Report
WHAT IS META-ANALYSIS (I)?

Quantitative approach for systematically combining results of previous research to arrive at conclusions about the body of research.
WHAT DOES IT MEAN?

- **Quantitative**: numbers
- **Systematic**: methodical
- **combining**: putting together
- **previous research**: what's already done
- **conclusions**: new knowledge
WHAT IS META-ANALYSIS (II)?

- a subset of systematic reviews
- a method for systematically combining study data from several selected studies to develop a single conclusion that has greater statistical power
- this conclusion is “statistically stronger” (?) than the analysis of any single study, due to increased numbers of subjects, greater diversity among subjects, or accumulated effects and results
WHAT IS META-ANALYSIS (III)?

• Meta-analysis would be used for the following purposes:
  
  • To establish statistical significance with studies that have conflicting results
  
  • To develop a more correct estimate of effect magnitude
  
  • To provide a more complex analysis of harms, safety data, and benefits
  
  • To examine subgroups with individual numbers not statistically significant
Steps in a Meta-Analysis

• Formulate the *Problem*

• Review the *Literature*

• Select the *Studies*
  • Based on quality
  • Based on subject matter
  • Decide if unpublished studies are to be included

• Decide on *Dependent variables* or *Summary measures*

• Select the *Model*
IDENTIFY YOUR STUDIES

• Be methodical: plan first

• List of popular databases to search
  • Pubmed/Medline
  • Embase
  • Cochrane Review/Trials Register

• Other strategies you may adopt
  • Hand search (go to the library...)
  • Personal references, and emails
  • web, eg. Google (http://scholar.google.com)
HOW TO SEARCH LITERATURE

• Formulate your question appropriately

• If you are searching pubmed
  • Use Medical Subject Headings (MeSH) [1]
  • Lookup word in text word, abstract, title [2]
  • Set up proper filters

• For Others, use text word, abstract

Huh?!, what is boolean logic??
Boolean Logic: AND

this is **AND** zone, covering common area between two ellipses
Boolean Logic OR

this is boolean OR,
covering the two ellipses
Let's say we want to know whether **Radiotherapy** is efficient in curing **nonsmall cell lung cancer** in **patients with stage IIIIB** disease. How should we set up a search strategy? We will search **Pubmed** only.
The Search

- radiotherapy [text word] AND “nonsmall cell lung cancer” [text word] AND “stage IIIB” will capture only those subsets that have BOTH radiotherapy AND nonsmall cell lung cancer AND stage IIIB anywhere in the text – restrictive, few

- “radiotherapy”[text word] OR “nonsmall cell lung cancer”[text word] OR “stage IIIB”[text word] produces all articles that contain EITHER radiotherapy OR nonsmall cell lung cancer OR stage IIIB anywhere in the text – inclusive, many

Next, we shall look at the PUBMED Screen …
Choose your DATABASE here

Remember to choose both PUBMED, and MESH for formulating search. Choose PUBMED CENTRAL for free articles!
Keep some, throw out others

• Cannot include all studies

• Keep the ones with
  • high levels of evidence
  • good quality
  • check with QUOROM guidelines

• Meta-Analysis usually done with Randomized Trials

• Case series, and case reports definitely out

• Selection problems are major problems

• Should abstracts whose results cannot be confirmed in subsequent publications be included in the review?
# Quality Control in MA: QUOROM Table

<table>
<thead>
<tr>
<th>Heading</th>
<th>Subheading</th>
<th>Descriptor</th>
<th>Reported? (Y/N)</th>
<th>Page number</th>
</tr>
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<tbody>
<tr>
<td>Title</td>
<td></td>
<td>Identify the report as a systematic review (meta-analysis) of RCTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstract</td>
<td></td>
<td>Use a structured format</td>
<td></td>
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</tr>
</tbody>
</table>

**Objectives**

The clinical question explicitly

**Data sources**

The databases (ie list) and other information sources

**Review methods**

The selection criteria (ie population, intervention, outcome and study design); methods for validity assessment, data abstraction, and study characteristics; and quantitative data synthesis in sufficient detail to permit replication

**Results**

Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie point estimates and confidence intervals); and meta analyses

**Conclusion**

The main results

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**Introduction**

The explicit clinical problem, biological rationale for the intervention, and rationale for review

**Methods**

Searching

The information sources, in detail (eg databases, registers, personal files, informants, agencies, hand-searching) and any restrictions (years considered, publication status, language publication)

Selection

The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)

Validity assessment

The criteria and process used (eg masked conditions, quality assessment, and meta analysis)

Data abstraction

The process or processes used (eg completed independently, in duplicate)

Study characteristics

The type of study design, participants' characteristics, details of intervention, outcome definition, etc, and how clinical heterogeneity was assessed

Quantitative data synthesis

The principal measures of effect (eg relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias

**Results**

Trial flow

Provide a systematic review profile summarising trial flow (see Fig. 1)

Study characteristics

Present descriptive data for each trial (eg age, sample size, intervention, dose, duration, follow-up period)

Quantitative data synthesis

Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome; present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2x2 tables of counts, means and SDs, proportions)

Discussion

Summarise key findings; discusses clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg population bias); and suggest a future research agenda

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- Detailed Guidelines
- A Good Checklist
- Use it for reporting
- Meta Analysis
- Systematic reviews
ARE THE STUDIES ELIGIBLE FOR MA (STEP I)?

- NO → DISCARD
- YES

ABSTRACT THE DATA

ENTER INTO A SPECIFIED FORMAT
TO CONSIDER THE FOLLOWING:

• **Eligibility criteria:**

  • **Characteristics of participants:** where a majority but not all people in a study meet an age range, should the study be included?
  
  • **Characteristics of the intervention:** what range of doses should be included in the meta-analysis?
  
  • **Characteristics of the comparator:** what criteria are required to define usual care to be used as a comparator group?
  
  • **Characteristics of the outcome:** what time-point or range of time-points are eligible for inclusion?
  
  • **Study design:** should blinded and unblinded outcome assessment be included, or should study inclusion be restricted by other aspects of methodological criteria?
What data should be analysed (I)?

- **Time-to-event data:** what assumptions of the distribution of censored data should be made?

- **Continuous data:** where standard deviations are missing, when and how should they be imputed? Should analyses be based on change scores or on final values?

- **Ordinal scales:** what cut-point should be used to dichotomize short ordinal scales into two groups?
What data should be analysed (II)?

- **Cluster-randomized trials:** what values of the intraclass correlation coefficient should be used when trial analyses have not been adjusted for clustering?

- **Cross-over trials:** what values of the within-subject correlation coefficient should be used when this is not available in primary reports?

- **All analyses:** what assumptions should be made about missing outcomes to facilitate intention-to-treat analyses? Should adjusted or unadjusted estimates of treatment effects used?
How to Abstract Data: Guidelines

1. Create a spreadsheet (Excel, or OpenOffice Calc)
2. For each study, create the following columns:
   - name of the study
   - name of the author, year published
   - number of participants who received intervention
   - number of participants who were in control arm
   - number who developed outcomes in intervention
   - number who developed outcomes in control arm

Let’s do that to our Radiotherapy in Stage IIIB Nonsmall cell lung cancer, next …
Spreadsheet Data for RT Study

We got e.g. 22 studies to do our meta analysis, after all

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
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<td>8595</td>
<td>1029</td>
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</tbody>
</table>

We created seven columns:
- **trial:** trial identity code
- **trial name:** name of trial
- **year:** year of the study
- **pop1:** study population
- **deaths1:** deaths in study arm
- **pop0:** control population
- **deaths0:** deaths in control arm
Analyze Data Statistically

- Combine data to reach a summary, 3 measures
  - Effect Size (Odds Ratio)
  - Variance with 95% Confidence Interval
  - Test of heterogeneity
- Two Graphs
  - Forest Plot
  - Funnel Plot
- Examine why studies are heterogeneous (if yes)
- Use Statistical Packages, several choices

Let’s see what we got for RT in stage IIIB NSCLC
Summary Estimates for RT Study

Mantel Haenszel OR = 0.77

95% Confidence Interval
[0.72, 0.83]

Test of Heterogeneity:
Chi-square (df=21) = 31.5
P-Value = 0.07

The pooled Odds Ratio shows that those receiving RT in stage IIIB NSCLC are about 77% at risk of death (23% less likely to die)

That in 95 out of 100 such meta analyses, the pooled Odds Ratio would lie between 0.72 and 0.83, indicating a statistically significant protective effect

That these studies were not significantly heterogeneous
The dotted line passes across null, or 1.0
The Risk Estimate of each study is lined up on each side of the dotted line, with 95% CI spread as the line
The diamond in the below is the summary estimate
The two ends of the diamond indicate 95% CI

The size of the black square box indicates weight of the study

They call it a forest plot so that you don’t miss the wood for the trees!
LIMITED DISEASE  SMALL CELL LUNG CANCER
TIMING OF  ADMINISTRATION OF RT AND CHEMO
SYSTEMATIC REVIEWS/META-ANALYSES

- EARLY/LATE ARMS WITH SIMILAR % OF PTS RECEIVING ALL CHEMO
  \[ HR = 0.73 \quad P < 0.001 \quad \text{OS (2 yr), } P < 0.001 \]

- EARLY ARM WITH LESS % PTS RECEIVING ALL CHEMO THAN LATE ARM
  \[ HR = 1.07 \quad P = 0.17 \quad \text{OS (2 yr), } P = 0.36 \]

- TOTAL
  \[ HR = 0.96 \quad P = 0.58 \quad \text{OS (2 yr), } P = 0.29 \]

- ** a test for heterogeneity, \( P = 0.002 \) ! (HR estimates differ from the overall estimates)

Spiro et al, JCO, 2006
Forest plot for treatment effect

- **RECEIVED ALL CHEMO CYCLES**
  - similar % in both arms  
    early better  
  - lower % in early arms  
    late better  

- **HYPERFRACTIONATED RT**
  - yes  
    early better  
  - no  
    late better  

- **PLATINUM-BASED CHEMO**
  - yes  
    early better  
  - no  
    late better

---

Spiro et al, *JCO*, 2006
Issues in meta analysis

- Choosing a model
  - Fixed effects model or random effects?

- Bias in meta analysis
  - poor quality of trials
  - publication bias

- Quality control in meta analysis
  - QUOROM guidelines

- Statistical Software for meta analysis
Model Selection (I)

Fixed effects model

• Overall effect = weighted average of study estimates

• Weight = inverse of variance of the study estimate

• Large studies dominate

• Not to be used if heterogeneity between studies is present
Random effects models

• Used for combining heterogenous results

• Weighting = 2 steps
  • Inverse variance weighting
  • Unweighting by random effects variance components
  • More heterogeneity = more unweighting = simple averaging of study results

• Der-Simonian Laird approach vs REML → No real difference
Model Selection (III)

Quality-effects model

- combines evidence from a series of trials comparing 2 interventions
- incorporates heterogeneity of effects in the analysis of the overall interventional efficacy
- adjustment is based on measured methodological heterogeneity between studies is done
- simple noniterative procedure used for computing combined effect size
- could represent a more convincing alternative to the random effects model
Bias in Meta Analysis

• Poor Quality of Trials
  • to avoid them, learn more at CONSORT statement
    [http://www.consort-statement.org]

• Publication Bias
  • study showing beneficial effects of new treatment more likely to be published than one showing no effect
  • negative trials assumed to contribute less; never show up in the literature base
  • use several approaches to avoid this
  • use Funnel Plots to examine the influence of publication bias
Funnel Plot: what and how to read

Plots the effect size against the sample size of the study

To study a funnel plot, look at its LOWER LEFT corner, that’s where negative or null studies are located

If EMPTY, this indicates “PUBLICATION BIAS”

Here, the plot fits in a funnel, and the left corner is not all that empty, but we cannot rule out publication bias
Statistical Software for Meta Analysis

• Huge Checklist [http://faculty.ucmerced.edu/wshadish/]

• Free Software:
  • EpiMeta: from Epi Info
  • Revman: from Cochrane Collaboration
  • “meta” package in R for statistical computing

• Non-free
  • meta module in STATA
ADVANTAGES

• Greater statistical power

• Confirmatory data analysis

• Greater ability to extrapolate to general population affected

• Considered an evidence-based resource
DISADVANTAGES

• Difficult and time consuming to identify appropriate studies

• Not all studies provide adequate data for inclusion and analysis

• Requires advanced statistical techniques

• Heterogeneity of study populations
• Studies pooled for review should be similar in type (i.e. all PRCT)
  • *Are the studies being reviewed all the same type of study or are they a mixture of different types?*

• Analysis should include published and unpublished results to avoid publication bias
  • *Does meta-analysis include any appropriate relevant studies that may have had negative outcomes?*
  • *File drawer problem and publishing bias*
A LITTLE MORE ON THE PITFALLS

• Meta analysis of several small studies *does not* predict the results of a single large study

• “Good” meta-analysis of badly designed studies, *does not* result in “good statistics”
PUBLICATION BIAS

• Exaggerated outcomes of meta analyses occur because it is far harder to publish negative results

• Most negative results are never even reported

• Creates a base rate fallacy: results may not be as significant as they appear since only 20% of studies are published

• Visualized by means of funnel plots: Study size vs Effect size
REALITY CHECK (I)

IMPORTANT OUTCOME
NOT ADDRESSED PROPERLY
Concomitant RT-CHT vs RT + sequential CHT
Auperin et al, JCO, 2010

Summary of analyses

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
<th>3-year benefit with concomitant CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>0.83</td>
<td>0.73 - 0.94</td>
<td>0.0026</td>
<td>6.6%</td>
</tr>
<tr>
<td>EFS</td>
<td>0.89</td>
<td>0.78 - 1.00</td>
<td>0.0585</td>
<td>3.5%</td>
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<tr>
<td>LRP</td>
<td>0.76</td>
<td>0.62 - 0.94</td>
<td>0.011</td>
<td>decrease of 6.1%</td>
</tr>
<tr>
<td>Distant P</td>
<td>1.04</td>
<td>0.86 - 1.25</td>
<td>0.669</td>
<td></td>
</tr>
</tbody>
</table>

- Concomitant CT improves survival as compared to sequential CT, mainly by the decrease of loco-regional progression
- No heterogeneity
- No clear evidence of any benefit or detriment of treatment in any pre-specified patient subgroup
- Concomitant CT increases acute oesophageal toxicity as compared to sequential CT
IMPLICATIONS?

• *All* radiochemo more toxic (esophagus)?

• Data available?

• 2D vs 3D vs else?

• High-dose RT vs moderate-dose RT?

• High-dose chemo vs low-dose chemo?
## Locally Advanced NSCLC

### Acute High-Grade (≥ 3) Esophagitis

<table>
<thead>
<tr>
<th>Study/author</th>
<th>RT (Gy)</th>
<th>CHT</th>
<th>Sequence</th>
<th>Esophagitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 8808</td>
<td>60 (QD)</td>
<td>-</td>
<td>-</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>RTOG 8808</td>
<td>60 (QD)</td>
<td>PV</td>
<td>induction</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>RTOG 9204</td>
<td>63 (QD)</td>
<td>PE</td>
<td>induction</td>
<td>6%</td>
</tr>
<tr>
<td>LUN-27</td>
<td>60 (QD)</td>
<td>T</td>
<td>concurrent</td>
<td>17%</td>
</tr>
<tr>
<td>Jeremic et al</td>
<td>69.6 (BID)</td>
<td>CE</td>
<td>concurrent</td>
<td>10-15%</td>
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<tr>
<td>Jeremic et al</td>
<td>67.6 (BID)</td>
<td>TC</td>
<td>concurrent</td>
<td>17%</td>
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<tr>
<td>RTOG 9015</td>
<td>69.6 (BID)</td>
<td>PV</td>
<td>concurrent</td>
<td>24%</td>
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<td>TC*</td>
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<td>25%</td>
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<tr>
<td>LUN-63</td>
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PV = cisplatin/vinblastin, PE = cisplatin/etoposide; CE = carboplatin/etoposide; T = paclitaxel; *=include adjuvant TC
INTERPRETATIONS?

• UNSOLVED ISSUE
• DISREGARD REALITY
• MAY NEVER BE SCIENTIFICALLY RESOLVED
• MAY HAVE AN IMPACT ON FUTURE STUDIES
• META ANALYSIS MAY NOT REACH ITS GOAL
• DECISION TO CHANGE PRACTICE OR NOT SCIENTIFICALLY UNFOUNDED
REALITY CHECK (II)

IMPORTANT OUTCOME
NOT PUBLISHED
Summary of analyses

<table>
<thead>
<tr>
<th></th>
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<th>3-year benefit with sequential CT</th>
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<tr>
<td>OS</td>
<td>0.88</td>
<td>0.82 - 0.94</td>
<td>0.0001</td>
<td>2.6%</td>
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<tr>
<td>OS (in EFS analysis trials)</td>
<td>0.83</td>
<td>0.74 - 0.94</td>
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</tr>
<tr>
<td>EFS</td>
<td>0.85</td>
<td>0.75 – 0.96</td>
<td>0.0097</td>
<td>2.0%</td>
</tr>
<tr>
<td>LRP</td>
<td>1.18</td>
<td>0.97 – 1.43</td>
<td>0.101</td>
<td>increase of 4.3%</td>
</tr>
<tr>
<td>Distant P</td>
<td>0.73</td>
<td>0.60 – 0.88</td>
<td>0.001</td>
<td>decrease of 7.9%</td>
</tr>
</tbody>
</table>

- **RT+sequential CT improves survival and EFS as compared to RT alone by the reduction of distant progression**
- **RT+sequential CT could increase the incidence of loco-regional progression**
- **Effect of increasing age!**
Summary of analyses

• RT+sequential CT improves survival and EFS as compared to RT alone by the reduction of distant progression.

• RT+sequential CT could increase the incidence of loco-regional progression.

Effect of increasing age:

<table>
<thead>
<tr>
<th>HR</th>
<th>95%CI</th>
<th>p value</th>
<th>3-year benefit with sequential CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.88</td>
<td>0.82–0.94</td>
<td>0.0001</td>
</tr>
<tr>
<td>EFS</td>
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</tr>
</tbody>
</table>

DATA NEVER PUBLISHED
Summary of analyses

- RT+sequential CT improves survival and EFS as compared to RT alone by the reduction of distant progression.
- RT+sequential CT could increase the incidence of loco-regional progression.

<table>
<thead>
<tr>
<th>Effect</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
<th>Benefit OS (in EFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.88</td>
<td>0.82 - 0.94</td>
<td>0.0001</td>
<td>2.6%</td>
</tr>
<tr>
<td>OS</td>
<td>0.83</td>
<td>0.74 - 0.94</td>
<td>0.0044</td>
<td>3.2%</td>
</tr>
<tr>
<td>EFS</td>
<td>0.85</td>
<td>0.75 - 0.96</td>
<td>0.0097</td>
<td>2.0%</td>
</tr>
<tr>
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<td>0.001</td>
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</tr>
</tbody>
</table>

DATA NEVER PUBLISHED

**WHY?**
NEW FINDING

IMPACTS STANDARDS OF PRACTICES

THIS MEANS MAJORITY OF PATIENTS

THIS MEANS MUCH LESS CHEMO

THIS MEANS MUCH LESS MONEY

YES! FOR BOTH DOCTORS AND INDUSTRY
REALITY CHECK (III)

SEVERAL META-ANALYSES WITH DIFFERENT RESULTS
SEVERAL META-ANALYSES WITH DIFFERENT RESULTS

Better Get With the Program
**SYSTEMATIC REVIEWS/META-ANALYSES**

<table>
<thead>
<tr>
<th>Author</th>
<th>Time</th>
<th>OS RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huncharek/McGarry</td>
<td>2 yr</td>
<td>1.60</td>
<td>1.29 – 1.99</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>3 yr</td>
<td>1.49</td>
<td>1.15 – 1.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fried et al</td>
<td>2 yr</td>
<td>1.17</td>
<td>1.02 – 1.35</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>3 yr</td>
<td>1.13</td>
<td>0.92 – 1.39</td>
<td>0.2</td>
</tr>
<tr>
<td>Pijls-Johannesma et al</td>
<td>2-3 yr</td>
<td>0.84</td>
<td>0.56 – 1.28</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>0.80</td>
<td>0.47 – 1.38</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Jeremic B, *IJROBP*, 2006
HOW AND WHERE TO LOOK?
LIMITED DISEASE SMALL CELL LUNG CANCER  
TIMING OF ADMINISTRATION OF RT AND CHEMO  

SYSTEMATIC REVIEWS/META-ANALYSES  

- DIFFERENT DEFINITION OF LD SCLC  
- DIFFERENT DEFINITION OF “EARLY” AND “LATE” RT/CHT  
- INCLUSION OF “GREY “ LITERATURE  
- DIFFERENT NUMBER OF PATIENTS  
- NO INDIVIDUAL PATIENTS DATA PROVIDED  

Jeremic B, *IJROBP*, 2006
LEUCOPENIA MORE FREQUENT IN “LATE” RT/CHT

FAVORABLE EFFECT OF SHORT OTT (≤ 30 DAYS)

FAVORABLE EFFECT OF BID FRACTIONATION

FAVORABLE EFFECT OF PE CHEMOTHERAPY

NEGATIVE EFFECT OF SPLIT-COURSE RT

Jeremic B, *IJROBP*, 2006
WHERE TO GO FROM HERE???

BELIEVERS vs NON-BELIEVERS?
WHERE TO GO FROM HERE???

BELIEVERS

- PRACTICE AND PREACH
- MASTER THE TECHNIQUE
- IMPROVE QUALITY
- BASE OWN PRACTICE ON IT
WHERE TO GO FROM HERE???

NON-BELIEVERS

• PRODUCE HIGH-QUALITY PRCTs

  Or

• PRACTICE EXPERT-BASED ONCOLOGY

  Or

• LOOK TO THE FUTURE
PROPOSED EXPANSION OF THE NIH ROADMAP

**Figure.** “Blue Highways” on the NIH Roadmap

- **BENCH**
  - Basic Science Research
    - Preclinical Studies
    - Animal Research
  - T1
    - Case Series
    - Phase 1 and 2 Clinical Trials

- **BEDSIDE**
  - Human Clinical Research
    - Controlled Observational Studies
    - Phase 3 Clinical Trials
  - T2
    - Delivery of Recommended Care to the Right Patient at the Right Time
    - Identification of New Clinical Questions and Gaps in Care

- **PRACTICE**
  - Clinical Practice
  - T3
    - Dissemination Research
    - Implementation Research

**T2**
- Guideline Development
- Meta-analyses
- Systematic Reviews
- Practice-Based Research
- Phase 3 and 4 Clinical Trials
- Observational Studies
- Survey Research

**Translation to Patients**

Westfall et al, JAMA, 2007
THANK YOU