Arguing about Cancer

A Lung CRT case study

Dr. Matt Williams
Consultant Clinical Oncologist, ICHNT
Honorary Clinical Senior Lecturer, IC

Cochrane Webinar October 2016
mhw@doctors.net.uk
Matthew.williams2@imperial.nhs.uk
About me

- Consultant Clinical Oncologist @ ICHNT
  - Brain tumours (primary & secondary)
  - PhD in CS
  - Various other bits of AI/ Stats in medicine

- IANACS
  - Interested in the use of computational tools to solve clinical problems
    - Because they scale, are transparent and reproducible
Chemo-radiotherapy for lung cancer.

- 37,000 cases of Lung cancer yr in the UK
- 35,000 deaths
- Many patients present with inoperable disease
  - Or are not fit for an operation

- Historically: Radical radiotherapy
  - Better outcomes with higher dose
  - Better outcomes with shorter treatment time
  - Better outcomes with chemotherapy as well
Chemo-RT for lung cancer

- Radiotherapy
  - Variations in dose, dose per fraction and timings
- Chemotherapy
  - Before RT (induction)
  - With RT (concurrent)
  - After RT (consolidation)

- Median OS: ~ 15 months, 2 yr OS ~ 30%
- TRDeaths: ~ 2%
Chemo-RT Literature

- Good evidence for chemo-RT in other tumours

- Lung:
  - Multiple, overlapping trials
  - Often different regimens
  - Different outcomes (OS timepoints, etc.)
  - Vary both RT and chemo

- Systematic review (Cochrane, 2010)
Literature - relations

- Cochrane Review: 25 trials
  - Search strategy from Cochrane Review
    - Adapted for pubmed
    - We updated the results of one study
    - 3 new studies and 1 update

- Therefore results from 28 trials
Data Capture

- Each trial considered as a series of 2-arm comparisons
- Extracted data on population
  - Age, country, stage
- Treatment
  - Chemo, RT
- Outcomes
  - Survival and toxicity
  - 28 trials, consisting of 4352 patients, giving 43 two-way comparisons of 54 regimens
  - (22 2-arm; 5 three arm; 1 2x2)
Reasoning Process

- Decompose each 2-arm comparison so that each considers a single outcome indicator
- Generate arguments
- Consider preferences
  - Efficacy ($E$) and Balanced ($B$)
- Consider meta-arguments
  - None, Stat sig. results, Stage II disease, Quality of trial
- Implemented in a prototype (python - TH, MW)
Displaying the results

- Generated superiority graph for the treatments, based on preferences
- Layout using GraphViz
- Briefly explored the impact of different preferences and meta-rules
  - Pref $E$: Considers only survival and response rates
  - Pref $B$: Considers both survival outcomes and toxicity
Initial thoughts

- Very disparate graphs
- Many disconnected sub-graphs
  - Clinically feels reasonable
  - Some clusters of connection around common regimens
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Stat</th>
<th>Qual</th>
<th>StglII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc carbo-paclitaxel, 60/30, Cons carbo-paclitaxel (Yamamoto, 2010)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-MMC-VinD, 60/30, Cons cis-MMC-VinD (Yamamoto, 2010)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Conc cis-etop, 66/33, Cons cis-vin (Fourmel, 2005)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vin, 60/30 (Zatloukal, 2004)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc carbo-paclitaxel, 60/30 (Gouda, 2006)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-docetaxel, 60/30 (Segawa, 2010)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Conc cis-vinB, 60/30 (A) (Curran, 2011)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vinB, 60/30 (B) (Lu, 2005)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vin, 60/30 (Wu, 2006)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis, 60/30 (Blanke, 1995)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis, 64/32 (Cakir, 2004)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc carbo, 60/30 (Atagi, 2005)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc carbo-paclitaxel, 60/30 (Carter, 2012)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc carbo-paclitaxel, 60/30 (Gouda, 2006)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ind Cis-vinB, Conc carbo, 60/30 (Clamon, 1999)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ind Cis-docetaxol, Conc docetaxel, 60/30 (Scagliotti, 2006)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ind Carbo-paclitaxel, Conc paclitaxel, 60/30 (Huber, 2006 &amp; Nyman, 2009)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ind Carbo, 60/30 (Ball, 1999)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>64/32 (alone) (Cakir, 2004)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc Carbo-etop, 69.6/58 (BD) (Jeremic, 1996)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc Carbo-paclitaxel, 60/40 (BD, split, alone) (Bonner, 1998)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Conc Cis, 60/20 (split) (Schake-Koning, 1992)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Conc carbo-etop, 60/20 (split) (Jeremic, 1995)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Conc cis-vin, 55/20 (Maguire, 2011)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>60/20 (split, alone) (Landgren, 1974)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>45/15 (alone) (Trov, 1992)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Under Pref E
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Study</th>
<th>Grade</th>
<th>Stage II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbo-paclitaxel, 60/30, Cons carbo-paclitaxel</td>
<td>(Yamamoto, 2010)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-MMC-VinD, 60/30, Cons cis-MMC-VinD</td>
<td>(Yamamoto, 2010)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-etop, 66/33, Cons cis-vin</td>
<td>(Fournel, 2005)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vin, 60/30</td>
<td>(Zatloukal, 2004)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Conc carbo-paclitaxel, 60/30</td>
<td>(Gouda, 2006)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Conc cis-docetaxel, 60/30</td>
<td>(Segawa, 2010)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vinB, 60/30 (A)</td>
<td>(Curran, 2011)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vinB, 60/30 (B)</td>
<td>(Lu, 2005)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vin, 60/30</td>
<td>(Wu, 2006)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis, 60/30 (Blanke, 1995)</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis, 64/32</td>
<td>(Cakir, 2004)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Conc carbo, 60/30</td>
<td>(Atagi, 2005)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>60/30, Cons cis-vin</td>
<td>(Wu, 2006)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ind Carbo-paclitaxel, Conc carbo-paclitaxel, 60/30, Cons paclitaxel</td>
<td>(Carter, 2012)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ind Carbo-paclitaxel, Conc carbo-paclitaxel, 60/30</td>
<td>(Gouda, 2006)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ind Cis-vinB, Conc carbo, 60/30</td>
<td>(Clamon, 1999)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ind Cis-docetaxol, Conc docetaxel, 60/30</td>
<td>(Scagliotti, 2006)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ind Carbo-paclitaxel, Conc paclitaxel, 60/30</td>
<td>(Huber, 2006 &amp; Nyman, 2009)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ind Carbo, 60/30</td>
<td>(Ball, 1999)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>64/32 (alone)</td>
<td>(Cakir, 2004)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc Carbo-etop, 69.6/58 (BD)</td>
<td>(Jeremic, 1996)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>60/40 (BD, split, alone)</td>
<td>(Bonner, 1998)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Conc Cis, 60/20 (split)</td>
<td>(Schaae-Koning, 1992)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc carbo-etop, 60/20 (split)</td>
<td>(Jeremic, 1995)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Conc cis-vin, 55/20</td>
<td>(Maguire, 2011)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>60/20 (split, alone)</td>
<td>(Landgren, 1974)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45/15 (alone)</td>
<td>(Trovo, 1992)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Relaxation

- Many of the differences between regimens are minor
  - Minor differences in RT or chemotherapy
  - Splitting the chemo doses, slightly different dose levels
  - Seems reasonable to try and “relax” our definition of what we consider to be the same
Relaxation

- Re-wrote the treatment data
- Grouping treatments
- RT
  - Conv. Fractionated/ Hyper# or BD treatment/ Hypo-fractionated
- Chemo
  - Platinum or Taxane-containing

- These definitions are not exclusive
Results

- Grouping the treatments made the graphs more cohesive
- Both RT and chemo had an obvious effect
- Greatest when both were grouped
What have we learnt?

- Lots of things are better than 60/30#
  - Under multiple preferences and meta-rules
  - Hyper# is better than 60/30#, and so is CRT
  - There are lots of options....

- Chose the group that has the best support, and then look for the best treatment in that group
- Gives us more than the CSR
Summary

- Novel method for representing and reasoning with clinical trial results
- Complex, real-world example
  - Difficult to handle
  - Computational approach offers us a way to understand and shape the literature
- We think this should be more commonly used
Development

- Better display of the data
- More clinically relevant preferences and M-R
- Sensitivity analysis
- Better handling of relaxation
- Cross-validation with other approaches
- New domains

- Where does this fit into current approaches to knowledge aggregation?
Current work

- Expanding & updating lung work
  - CSR criteria exclude many trials
  - We can begin to include some these of a systematic basis

- New diseases:
  - Primary brain tumour (Glioblastoma; GBM)
  - Brain metastases
    - Cochrane NMA
    - Novel computational work - parallel analyses
Current work

- New clinical domains drive new theory
  - Biomarker-based sub-graphs
    - MGMT-methylation or Age in GBM
  - Non-inferiority trials
Further work

- Expand formalism to consider other forms of knowledge
  - <10% patients in RCTs; Unrepresentative

- RCTs
- Case-series
- IPD
  - How can we use the three of these is a sensible way?