Arguing about Cancer

A Lung CRT case study

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Cochrane Webinar October 2016

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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 ca/ 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

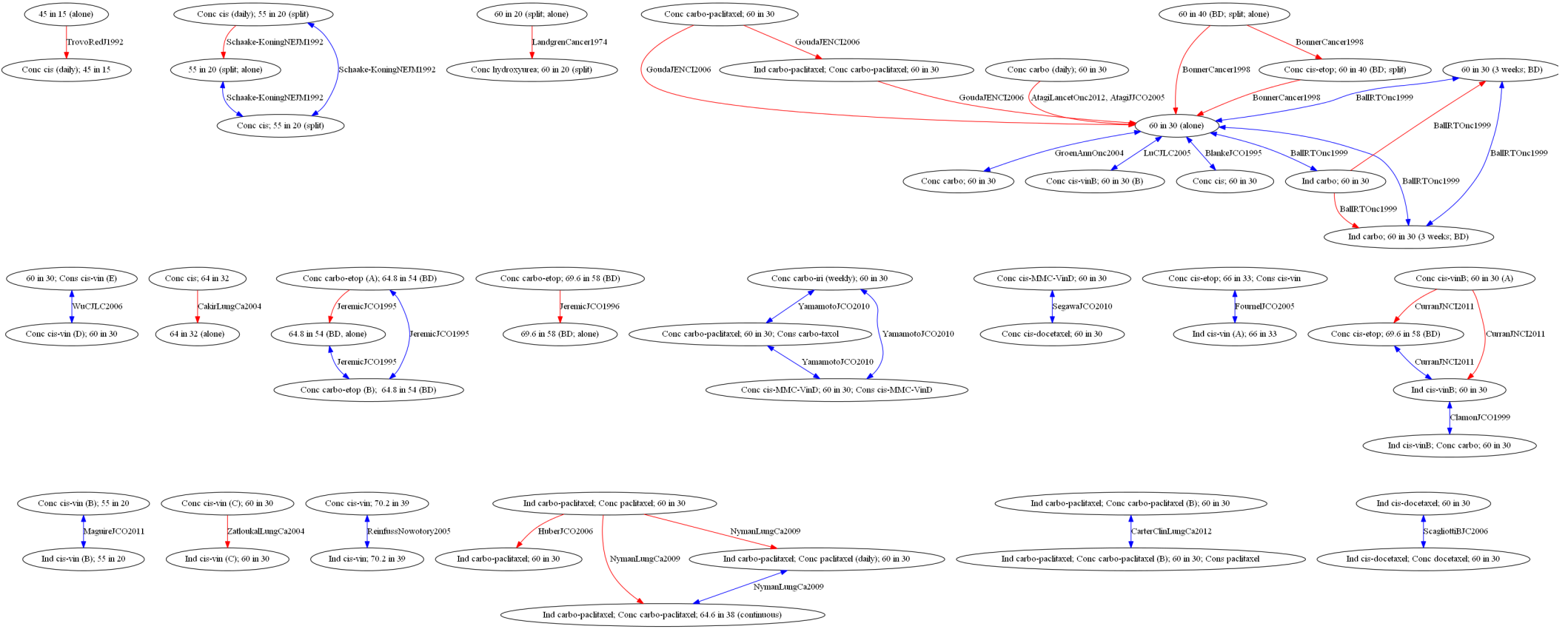
- Each trial considered as a series of 2-arm comparisons
- Extracted data on population
  - Age, country, stage
- Treatment
  - Chemo, RT
- Outcomes
  - Survival and toxicity
  - 28 trials, consisting of 4352 patients, giving 43 two-way comparisons of 54 regimens
  - (22 2-arm; 5 three arm; 1 2x2)

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

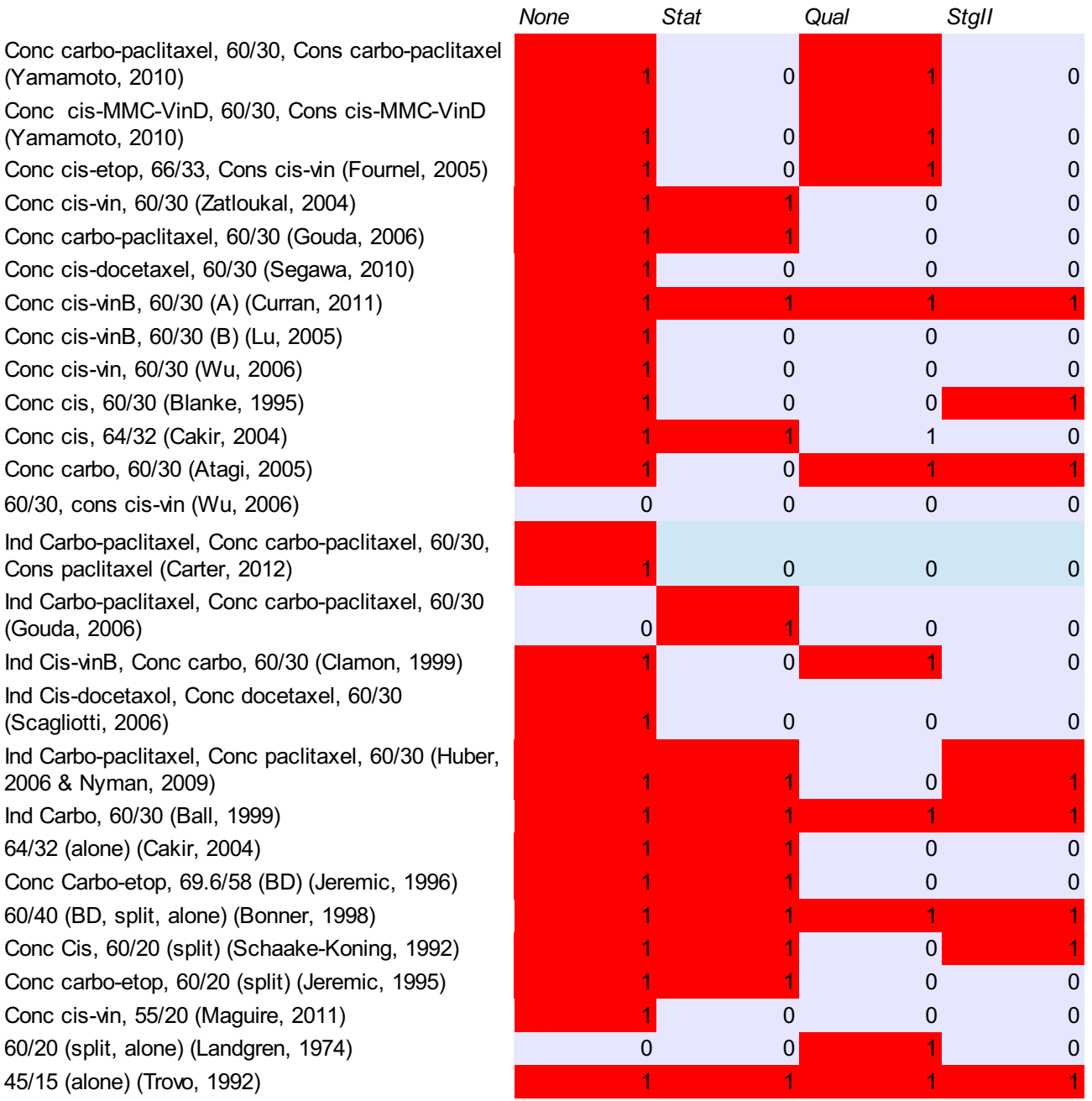
- Generated superiority graph for the treatments, based on preferences
- Layout using GraphViz
- Briefly explored the impact of different preferences and meta-rules
  - Pref *E*: Considers only survival and response rates
  - Pref *B*: Considers both survival outcomes and toxicity



Williams et al, Lung Cancer 2015

Initial thoughts

- Very disparate graphs
- Many disconnected sub-graphs
  - Clinically feels reasonable
  - Some clusters of connection around common regimens


None
Stat
Qual
StgII
Conc carbo-paclitaxel, 60/30, Cons carbo-paclitaxel (Yamamoto, 2010) 1 0 1 0
Conc cis-MMC-VinD, 60/30, Cons cis-MMC-VinD (Yamamoto, 2010) 1 0 1 0
Conc cis-etop, 66/33, Cons cis-vin (Fournel, 2005) 1 0 1 0
Conc cis-vin, 60/30 (Zatloukal, 2004) 1 1 0 0
Conc carbo-paclitaxel, 60/30 (Gouda, 2006) 1 1 0 0
Conc cis-docetaxel, 60/30 (Segawa, 2010) 1 0 0 0
Conc cis-vinB, 60/30 (A) (Curran, 2011) 1 1 1 1
Conc cis-vinB, 60/30 (B) (Lu, 2005) 1 0 0 0
Conc cis-vin, 60/30 (Wu, 2006) 1 0 0 0
Conc cis, 60/30 (Blanke, 1995) 1 0 0 1
Conc cis, 64/32 (Cakir, 2004) 1 1 1 0
Conc carbo, 60/30 (Atagi, 2005) 1 0 1 1
60/30, cons cis-vin (Wu, 2006) 0 0 0 0
Ind Carbo-paclitaxel, Conc carbo-paclitaxel, 60/30, Cons paclitaxel (Carter, 2012) 1 0 0 0
Ind Carbo-paclitaxel, Conc carbo-paclitaxel, 60/30 (Gouda, 2006) 0 1 0 0
Ind Cis-vinB, Conc carbo, 60/30 (Clamon, 1999) 1 0 1 0
Ind Cis-docetaxol, Conc docetaxel, 60/30 (Scagliotti, 2006) 1 0 0 0
Ind Carbo-paclitaxel, Conc paclitaxel, 60/30 (Huber, 2006 & Nyman, 2009) 1 1 0 1
Ind Carbo, 60/30 (Ball, 1999) 1 1 1 1
64/32 (alone) (Cakir, 2004) 1 1 0 0
Conc Carbo-etop, 69.6/58 (BD) (Jeremic, 1996) 1 1 0 0
60/40 (BD, split, alone) (Bonner, 1998) 1 1 1 1
Conc Cis, 60/20 (split) (Schaake-Koning, 1992) 1 1 0 1
Conc carbo-etop, 60/20 (split) (Jeremic, 1995) 1 1 0 0
Conc cis-vin, 55/20 (Maguire, 2011) 1 0 0 0
60/20 (split, alone) (Landgren, 1974) 0 0 1 0
45/15 (alone) (Trovo, 1992) 1 1 1 1

Under Pref *E*

	None	Qual	Grade	StgII
Conc carbo-paclitaxel, 60/30, Cons carbo-paclitaxel (Yamamoto, 2010)	0	0	0	0
Conc cis-MMC-VinD, 60/30, Cons cis-MMC-VinD (Yamamoto, 2010)	1	0	1	0
Conc cis-etop, 66/33, Cons cis-vin (Fournel, 2005)	1	0	1	0
Conc cis-vin, 60/30 (Zatloukal, 2004)	1	1	0	0
Conc carbo-paclitaxel, 60/30 (Gouda, 2006)	0	1	0	0
Conc cis-docetaxel, 60/30 (Segawa, 2010)	1	0	0	0
Conc cis-vinB, 60/30 (A) (Curran, 2011)	1	1	1	1
Conc cis-vinB, 60/30 (B) (Lu, 2005)	1	0	0	0
Conc cis-vin, 60/30 (Wu, 2006)	0	0	0	0
Conc cis, 60/30 (Blanke, 1995)	1	0	0	1
Conc cis, 64/32 (Cakir, 2004)	0	1	0	0
Conc carbo, 60/30 (Atagi, 2005)	1	0	1	1
60/30, cons cis-vin (Wu, 2006)	1	0	0	0
Ind Carbo-paclitaxel, Conc carbo-paclitaxel, 60/30, Cons paclitaxel (Carter, 2012)	1	0	0	0
Ind Carbo-paclitaxel, Conc carbo-paclitaxel, 60/30 (Gouda, 2006)	0	1	0	0
Ind Cis-vinB, Conc carbo, 60/30 (Clamon, 1999)	0	0	0	0
Ind Cis-docetaxol, Conc docetaxel, 60/30 (Scagliotti, 2006)	0	0	0	0
Ind Carbo-paclitaxel, Conc paclitaxel, 60/30 (Huber, 2006 & Nyman, 2009)	1	0	1	1
Ind Carbo, 60/30 (Ball, 1999)	1	1	1	1
64/32 (alone) (Cakir, 2004)	1	0	1	0
Conc Carbo-etop, 69.6/58 (BD) (Jeremic, 1996)	1	1	0	0
60/40 (BD, split, alone) (Bonner, 1998)	1	1	1	1
Conc Cis, 60/20 (split) (Schaake-Koning, 1992)	1	1	0	1
Conc carbo-etop, 60/20 (split) (Jeremic, 1995)	1	0	0	0
Conc cis-vin, 55/20 (Maguire, 2011)	1	0	0	0
60/20 (split, alone) (Landgren, 1974)	0	0	1	0
45/15 (alone) (Trovo, 1992)	1	0	1	1

Under Pref *B*

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

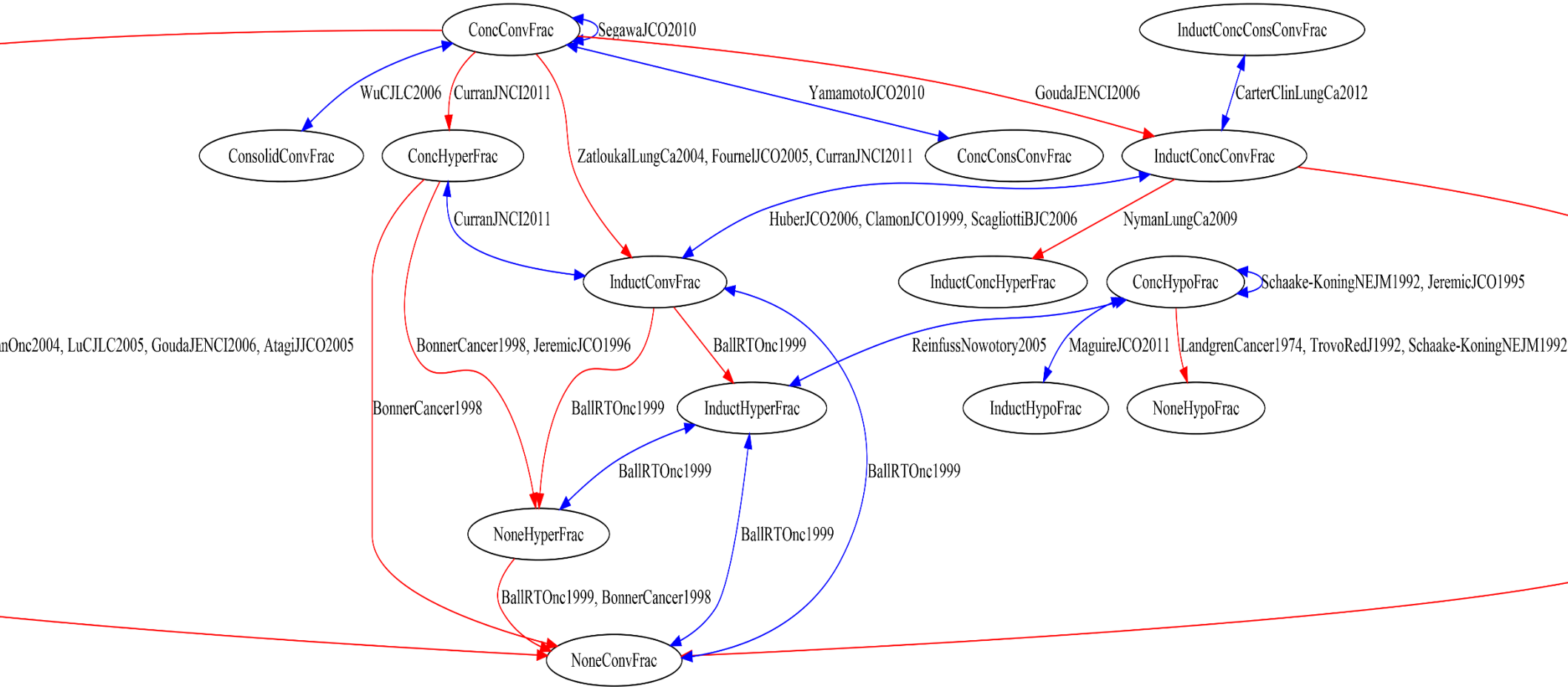
- Re-wrote the treatment data
- Grouping treatments
- RT
  - Conv. Fractionated/ Hyper# or BD treatment/ Hypo-fractionated
- Chemo
  - Platinum or Taxane-containing

- 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

Figure 2


ConcConvFrac
SegawaJCO2010
InductConcConsConvFrac
WuCJLC2006
CurranJNCI2011
YamamotoJCO2010
GoudaJENCI2006
CarterClinLungCa2012
ConsolidConvFrac
ConcHyperFrac
ZatloukalLungCa2004, FournelJCO2005, CurranJNCI2011
ConcConsConvFrac
InductConcConvFrac
CurranJNCI2011
HuberJCO2006, ClamonJCO1999, ScagliottiBJC2006
NymanLungCa2009
InductConvFrac
InductConcHyperFrac
ConcHypoFrac
Schaake-KoningNEJM1992, JeremicJCO1995
nOnc2004, LuCJLC2005, GoudaJENCI2006, AtagiJJCO2005
BonnerCancer1998, JeremicJCO1996
BallRTOnc1999
ReinfussNowotory2005
MaguireJCO2011
LandgrenCancer1974, TrovoRedJ1992, Schaake-KoningNEJM1992
BonnerCancer1998
BallRTOnc1999
InductHyperFrac
InductHypoFrac
NoneHypoFrac
BallRTOnc1999
BallRTOnc1999
NoneHyperFrac
BallRTOnc1999
BallRTOnc1999, BonnerCancer1998
NoneConvFrac

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?