To model or not to model, what is the question?

How modelling choices affect extrapolation

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Disclosure

No conflicts to declare

I do not speak on behalf of Cancer Care Ontario – Views are my own
Outline

• What is the issue?

• Two modelling approaches – what’s the difference?

• Implications and conclusions – which is better?
Getting from clinical trial to economic model

![Graph showing overall survival (OS) over time for two treatments: New treatment and Comparator. The graph indicates that the median OS for the New treatment is 9 months, compared to 6 months for the Comparator.]
Issue with modelling/extrapolation/time horizons

When model survival seems to be overestimated

Overall Survival

OS New treatment
OS Comparator

Median OS = 9 months vs. 6 months (short!)

10% still alive after 10 years
## Two modelling approaches

- **Estimate survival (life years):**

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<tr>
<th>Indirectly</th>
<th>Directly</th>
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<tr>
<td>Indirectly</td>
<td>Directly</td>
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<tr>
<td>Estimate risks of progressing from health states until reaching absorbing death state</td>
<td>Estimating (extrapolating) OS curves</td>
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<tr>
<td>Adding up time spent in the living health states</td>
<td>Adding up area-under-the-curve</td>
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- Markov model
- Partitioned survival analysis
Markov model

- Health states to represent different costs, quality of life, and risk
- Risks at each time point of moving to another state \((a, b, c)\)
- Patients move through time – sum to get average life years (LYs)

![Markov model diagram]

- \(a\) Risk of progression
- \(b\) Risk of death while progression-free
- \(c\) Risk of death after progression

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Partitioned survival analysis

- Directly estimate overall survival for the cohort from OS curve
- Allocate into finite number of health states to adjust for costs and quality of life

Living

Progression-free

Progressed

Dead

OS

PFS

PFS-OS

1-OS

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So what’s the difference?

• Data needed (three risks vs. two curves)
• Assumptions needed (what happens after progression)

- **PFS**
  - Progression-free
  - Risk of progression
  - Risk of death while progression-free
  - Risk of death after progression

- **Progressed**
- **Dead**
  - $1-\text{OS}$
Survival beyond progression

• In a partitioned survival analysis, not modelling progression directly
  – Time in progression is difference between independent OS and PFS curves

• Risk of death in model is dependent only on time, not on health state
  – Clinically, risk of death depends on both *time and health state*
  – After progression, stopping treatment → Risk of dying likely to change!

• Problems from OS extrapolation
  – Assuming OS risk follows same pattern indefinitely (does not account for more in the progressed state)
Problem when model produces post-progression survival benefits

— OS New treatment
— OS Comparator

Overall Survival

Time (months)

Life years

New treatment
Comparator

ΔE

0.00 0.20 0.40 0.60 0.80 1.00

0 20 40 60 80 100 120

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What happens (hazards or risks) might change over time

Could assume HR=1

—OS New treatment
—OS Comparator

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Other survival distributions may be more plausible long term

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OS New treatment

OS Comparator

Overall Survival

Time (months)

Life years

New treatment

Comparator

ΔE

0.00

0.10

0.30

0.50

0.70

0.90

1.10

0.00

0.10

0.20

0.30

0.40

0.50

0.60

0.70

0.80

0.90

1.00

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Progression risks in Markov models

- Control where risks differ and where treatment effects occur
  - New treatment can have lower risk of progression than comparator, but same risks of death as the comparator after progression

A) Risk of progression

B) Risk of death while progression-free

C) Risk of death after progression
Do Markov models address concerns related to partitioned survival models?

• Markov models explicitly specify risks from each state
  – Account for changes in risk from progression
  – Can control where treatment effects occur and test alternatives

• But with more data requirements (and/or assumptions)
  – Partitioned survival and Markov models (usually) handle time in the PFS state equally
  – Don’t always have data for (C) – use external data, assume equal risks, often no time-dependence for this probability

• Both models require assumptions about risks of death
  – Differ in how they estimate risks of death, and thus, total survival time
Implications and conclusions

• The two methods make different assumptions
  – How (or whether) risks change over time
  – Where the treatment effects are applied

• Benefits to doing both
  – The two methods characterize and extrapolate risk of death differently
  – Explore impact of assumptions

• Additional methods may better address these issues
  – Incorporating external data into extrapolation
  – Competing risks and multi-state models
Thank you

Questions?

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