Partitioned survival analysis for decision modelling in health care: a critical review

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Origin of Technical Support Document

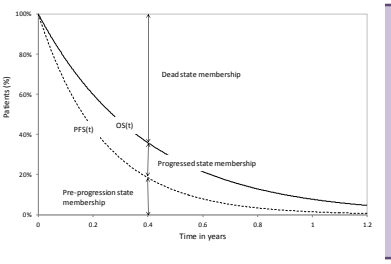
- Validity of decision models highly reliant on appropriate estimates of time spent in different health states for each comparator
- Partitioned Survival Analysis (PartSA) (*Area Under the Curve*) widely used in oncology P&R decisions
  - Method not subject to formal evaluation
- NICE technical support document (TSD) commissioned to provide:
  - Description of method
  - Review of applications in NICE TAs
  - Critique of approach and discussion of alternatives
  - Recommendations

Partitioned survival analysis approach

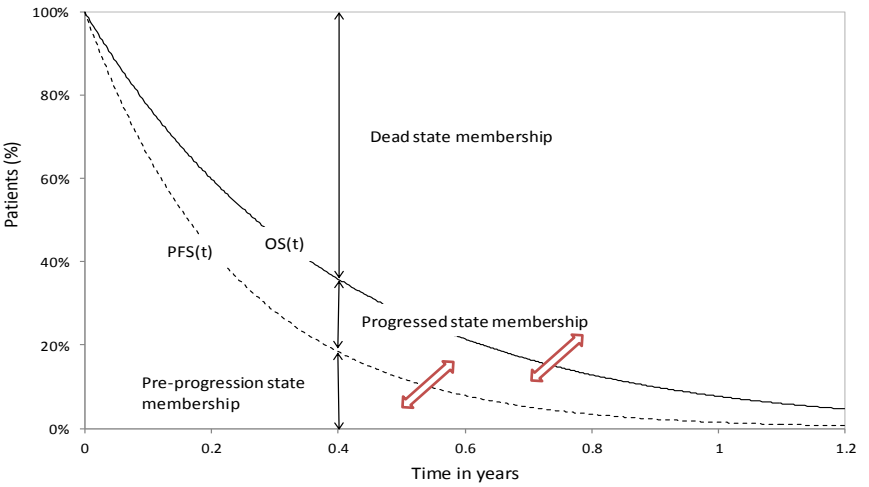
Independent survival analysis: for each health state survival analysis of time from model entry to transiting to any health state further along the sequence

- Example for three state model: pre-progression, progressed, dead
- Two independent survival endpoints
  - Progression free survival (PFS)
  - Overall survival (OS)

Decision model: simple manipulations used to derive proportion in each health state over time



Partitioned survival analysis approach



Review findings: use, description, and justification of PartSA method

- 30 most recent cancer appraisals (May 2013-Feb 2016)
- Used in 22/30 (73%) of cancer appraisals
- Predominantly advanced/metastatic

Description and justification for use of PartSA	n/N (%)
Correctly described by manufacturer (AG)	12/22 (55%)
Correctly described by ERG/AG	12/22 (55%)
Justification for method provided by manufacturer (AG)	7/22 (32%)
Assumption of independence discussed by manufacturer/ERG/AG	4/22 (18%)

Review findings: implementation

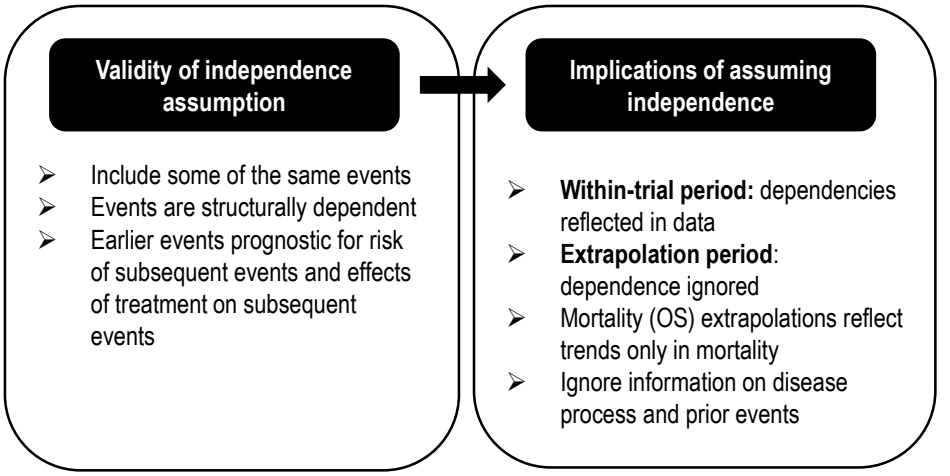
- Modelled endpoints: PFS/TTD, OS
- For comparators included within pivotal trial(s):
  - Individual patient data generally available
  - Survival curves modelled using range of methods
  - Included parametric extrapolation
- For additional comparators
  - Only aggregate data available
  - Information from meta-analyses, indirect comparisons, network meta-analyses
- Treatment effects typically applied to all endpoints for time horizon
- External data also used to inform long-term extrapolations

PartSA advantages

- Stem from direct correspondence between frequently reported trial endpoints and survival functions used to derive state membership
  - Easy to construct and communicate
  - Can use published summary/aggregate data
    - Less of a consideration for pivotal trial (IPD)
    - Major consideration for external data
  - Generally validates well against trial data

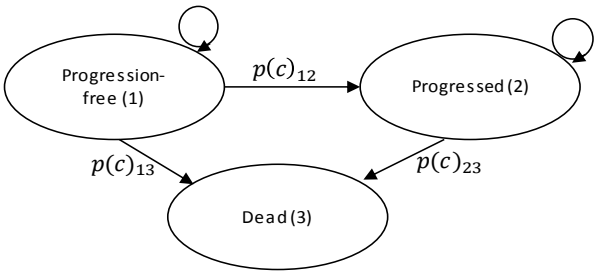
PartSA disadvantages

- Stem from structural independence of modelled endpoints

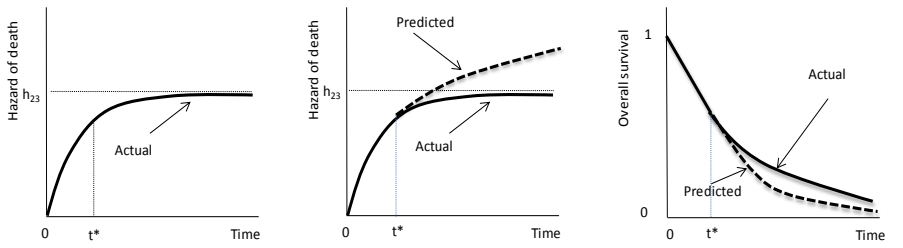


Implications of ignoring disease process when extrapolating OS

- Simple illustrative example
  - Start with a single comparator
  - Constant transition probabilities
  - Risk of death elevated in progressed patients
  - Risk of death depends on proportion who have progressed



Implications of ignoring disease process when extrapolating OS



(a) Actual hazard of death

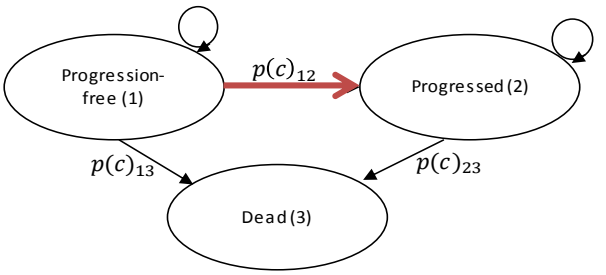
(b) Hazard of death predicted by PartSA approach

(c) Implications for overall survival curve

Ignoring information on disease process (here, progression) and focusing on within-trial mortality rates may produce inappropriate extrapolations

Extension to consider treatment effects

- Treatment modifies probability of progression (conforms to the proportional hazards assumption)
- Differences between treatments in mortality rates depend on differences in proportion of patients in progression-free and progressed health states



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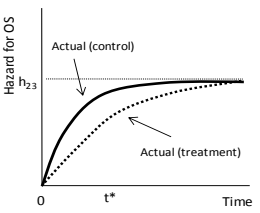
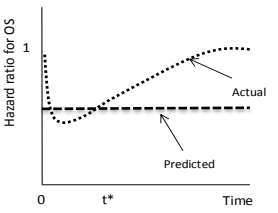
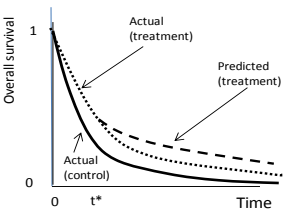


(a) Actual hazards for OS



(b) Actual and predicted hazard ratio



(c) Implications for overall survival curve

Ignoring information on disease process (here, progression) and focusing on within-trial hazard ratio on OS may produce inappropriate extrapolations

Assessing extrapolation uncertainties to support decision making

- NICE methods guidance recommends assessing the *clinical and biological plausibility* of extrapolations and consider *alternative scenarios*
- Possible to review mean time spent in health states
- Not possible to review or modify individual transitions
  - Can't identify whether extension to post-progression survival supported by trial data or generated via extrapolation
  - Can't modify post-progression survival via sensitivity analyses
- Probabilistic Sensitivity Analysis less meaningful