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A Comparison of Partitioned Survival Analysis and State Transition Modelling Approaches – Findings from a Case Study in Oncology

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Background

- To establish the economic value of novel medicines, a cost-effectiveness analysis is usually required, part of which typically involves the development of a decision-analytic model
- The most common model structure constructed to make a value judgement in oncology is the partitioned survival analysis (PartSA), followed by state transition models (STMs) – typically based on three health states: pre-progression, progressed disease and death[1,2]
  - The three-state PartSA only requires two outcomes (progression-free survival [PFS] and overall survival [OS]), with occupancy of the 'progressed' state calculated by the difference between OS and PFS.
  - The three-state STM requires information relating to the three transitions possible between the health states. STMs can further divided based on discrete-time/continuous-time, Markov/semi-Markov or cohort/patient-level. Multi-state modelling (MSM) falls under the STM bracket and is an applicable model structure where there are a series of "competing" events and when these events can occur sequentially.
- While there are a number of different model structures available, often justification of model structure is not discussed in detail. This is particularly concerning as there is a growing body of evidence highlighting the impact of different model structures on the cost-effectiveness results[3,4]
- The traditional PartSA model structure is associated with a number of restrictive assumptions, which are often not tested or validated. Furthermore, these assumptions are more heavily relied upon with immature data – which is often the case in health technology assessment (HTA). The MSM approach offers a more flexible model structure.
- Though the MSM may offer some advantages over a traditional PartSA model, few studies have actively constructed and directly compared both models constructed using the same source data
  - In reality, this may be due to lack of understanding of the differences in the approaches, data availability, knowledge of software packages, or (perhaps most commonly) time and budget constraints
  - However, the construction of both models enables a comparison of cost-effectiveness results produced using alternative structures, as well as the ability to understand the strengths and limitations of both approaches

Objective

- To construct and compare a PartSA and a semi-Markov MSM to estimate the cost-effectiveness of a novel cancer treatment from a UK perspective
- To investigate the key similarities and differences between the modelling approaches and the corresponding cost-effectiveness results

Methods

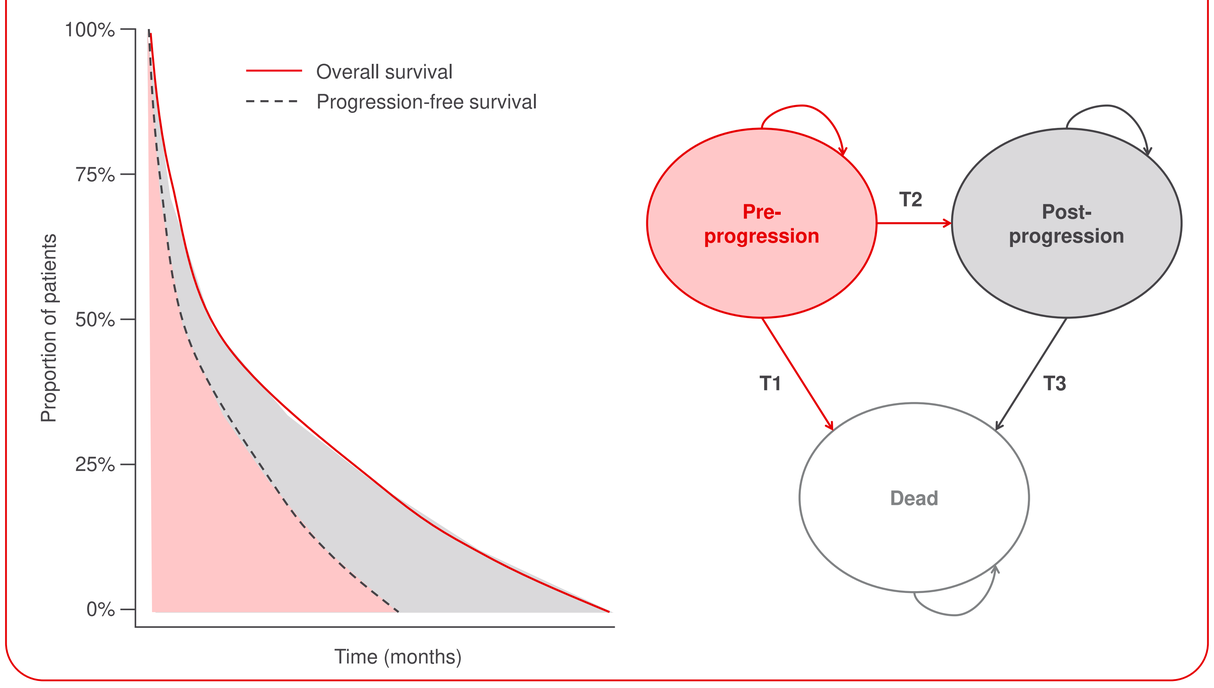
Case study

- Data were obtained from a randomised controlled trial (RCT) comparing two treatments (TX1 vs. TX2) conducted in a population of approximately n=700 patients with late-stage cancer
- Enrolled subjects had a median follow up period of ~15 months. At the end of follow-up between 54%-64% of patients had progressed and between 20%-24% had died across both the TX1 and TX2 arms, respectively.

Model conceptualisation

- **Figure 1** presents the model concept for each approach (PartSA and MSM)
  - In the PartSA, parametric survival models for OS and PFS were fitted to inform health state occupancy
    - By determining the area between the curves, patients were estimated to reside within a 'pre-progression' or 'post-progression' health state (with the remainder of patients having dead)
  - In the MSM, three transitions were modelled:
    - **T1**: 'progression-free' to 'dead'
    - **T2**: 'post-progression' to 'dead', and
    - **T3**: 'pre-progression' to 'post-progression'

Figure 1. Concept of the PartSA and MSM approaches



Statistical analysis

- Statistical analyses were performed using *R version 3.01 and R Studio*
- For the PartSA model, the parametric survival models were fitted using the 'phreg', 'aftreg' and 'flexsurv' packages
  - Six distributions were considered for both OS and PFS curves: exponential, Weibull, Gompertz, Log-logistic, Lognormal, and Generalised Gamma
- For the MSM approach, transitions were estimated using the *'mstate'* package
  - The same parametric distributions were considered for each of the MSM transitions
- Optimal model fit was determined through a combination of statistical goodness-of-fit, visual assessment of fit within the observed period, and the plausibility of long-term outcomes
  - As the MSM requires assessment of the Markovian assumption; a Markov Cox proportional hazards model was used to examine the transition from 'post-progression' to 'dead' using the time spent in the previous health state (i.e. 'pre-progression') as an explanatory variable (covariate)
  - This covariate was shown to be statistically significant, and so a semi-Markov approach was adopted

Key model settings and assumptions

- Both models were developed to compare the total costs and quality-adjusted life years (QALYs) associated with TX1 and TX2 from a UK National Health Service (NHS) and Personal Social Services (PSS) perspective, ultimately providing an ICER for TX1 vs. TX2
  - Costs and QALYs were discounted at 3.5% per annum, in line with NICE guidance, and calculated over a 15-year ('lifetime') horizon
  - Key costs included were treatment-related (initial, subsequent, and concomitant treatments), resolution of adverse events, hospitalisations and routine monitoring
  - Utilities were included according to progression status, with assumed values of 0.80 for 'pre-progression' and 0.60 for 'progressed'

Results

Headline model results

- The PartSA and MSM approaches estimated incremental cost-effectiveness ratios (ICERs) of £342,474 and £416,030, respectively (**Table 1**)

Sensitivity analysis

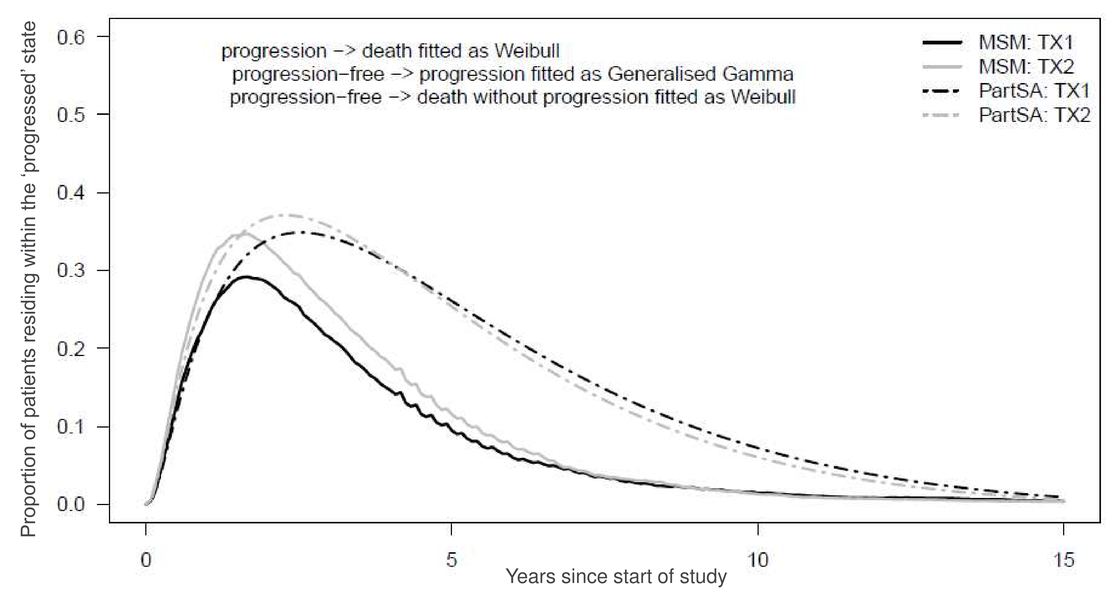
- Scenario analyses exploring alternative parametric forms provided incremental discounted life-year estimates that ranged from +0.15 to +0.33 for the PartSA approach, compared with -0.13 to +0.23 for the MSM approach
  - This variation was reflected in the range of ICERs. PartSA produced ICERs between £234,829 and £522,963, whereas MSM results were more variable and included instances where the intervention was dominated and ICERs above £7 million (caused by very small incremental QALYs)

Table 1. Model results

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
PartSA					
TX1	£265,693	3.14			
TX2	£187,648	2.91	£78,045	0.23	£342,474
Semi-Markov MSM					
TX1	£239,499	2.57			
TX2	£161,300	2.38	£78,199	0.19	£416,030

- The driving difference behind the different model results is the occupancy in the 'progressed' health state over time – this was notably different between the two model structures
  - For example, the estimated LYs gained within the 'progressed' health state for TX1 were 1.97 (for both treatment arms) and 1.07-1.26 for the PartSA and semi-Markov MSM, respectively
- A comparison of the 'progressed' health state occupancy for both treatments and both modelling approaches is presented in **Figure 2**
- The occupancy of the 'progressed' state is shown to be much greater within the PartSA model structure after approximately 1-2 years

Figure 2. Progressed disease state occupancy over time



Conclusions

- The use of progression-based models for cancer treatments is relatively commonplace. However, a comparison of model structures is seldom undertaken (and presented in the public domain). This may be due to time and/or resource limitations.
- The comparison of structural approaches presented within this study indicates that the choice of structure may have a profound impact on cost-effectiveness results
  - This highlights the importance of a carefully considered model conceptualisation process, and the need for further research to ascertain when it may be most appropriate to use each approach
    - For example, it may be preferable to use a MSM structure where transitions from intermediate states are expected to be of high importance (e.g. to capture costs incurred upon documented disease progression); however, this may not be possible if only published survival curves are available for implementation within the model (e.g. for a comparator treatment)
  - If the data were complete then the results from the PartSA and the semi-Markov MSM should be extremely similar. However, often complete data are not available. Therefore, the implications of model specification need to be explored further and the impact of structural uncertainty should be considered in decision-making.

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Abbreviations

PartSA, partitioned-survival analyses; HTA, health technology appraisal; STA, single technology appraisal.

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