Building an open-source semi-Markov state transition model for use in economic evaluations of early-stage cancer treatments

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Introduction

- For many cancers, the stage of disease can be categorised as early or late/advanced. While this classification can differ between cancer types, early-stage disease is often characterised by a smaller volume of disease than the advanced stage and the absence of metastasis to other organs[1]. In most cases, diagnosis and treatment at an early stage leads to better long-term outcomes[2].

- Across many cancer types, novel therapies that have shown clinical benefit for advanced disease are being tested in an earlier setting, with an increasing number undergoing health technology assessment (HTA) requiring cost-effectiveness evaluation.

- Cost-effectiveness studies in early cancer may require a more complex model than for the advanced stage due to the need to capture the downstream consequences of treatment in avoiding or delaying the onset of advanced disease. The development of these models can be both time-consuming and prone to error, requiring specialised programming.

- Our aim was to review existing models submitted to HTA for early cancer and develop an open-source framework that can be used to model outcomes across multiple early-stage cancer settings.

Methods

- We performed a targeted literature review of decision models used in HTAs (up to March 2023) for treatments of early-stage cancer.

- HTA submissions to CADTH, INESSS, PBAC, ICER, HAS and SMC were reviewed. Key modelling features were identified and summarized, including HTA model criticisms.

- An Excel-based template model was then created incorporating the common features of existing models. This is an open-access model template created for use in future HTA submissions. The model is available by request: robert.hettle1@astrazeneca.com.

Results

- The review identified 36 appraisals (Fig. 1).

- The vast majority used a Markov or semi-Markov structure with at least four health states (event-free, death, and separate health states for locoregional versus metastatic recurrences).

Fig. 1 HTA appraisals in early-stage cancer

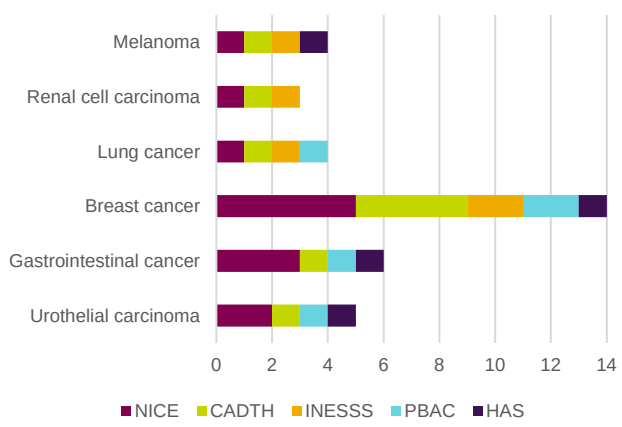
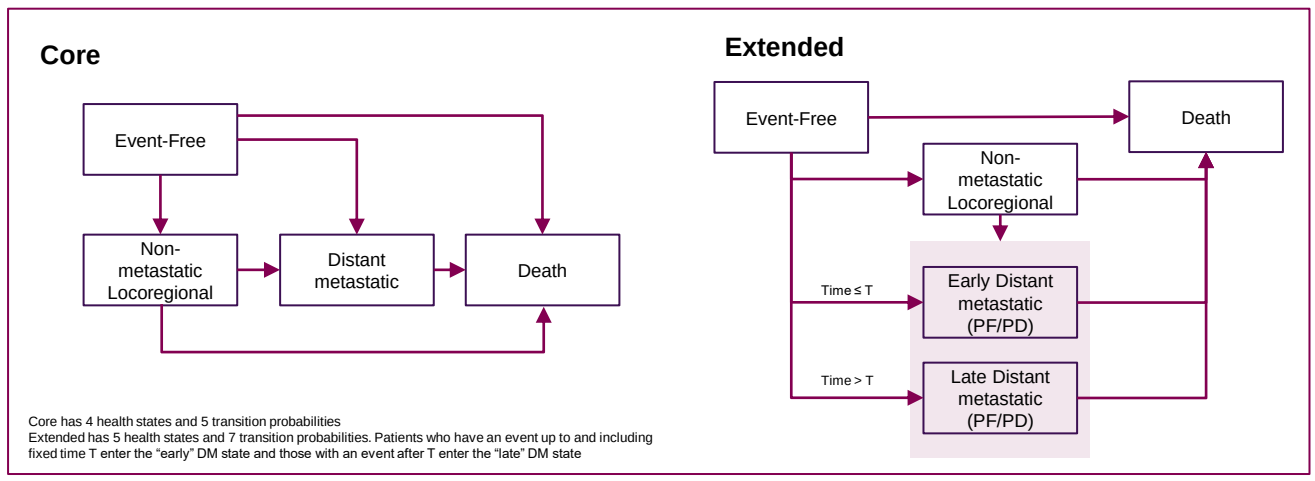


Fig. 2 Health state structure of the open-source model (core and extended)



Core has 4 health states and 5 transition probabilities
Extended has 5 health states and 7 transition probabilities. Patients who have an event up to and including fixed time T enter the "early" DM state and those with an event after T enter the "late" DM state

State structure

Based on findings from the literature review, a Semi-Markov discrete-time state transition model containing four core health states of event-free, non-metastatic/locoregional recurrence, distant metastatic (DM) and death, with a 1-month cycle length, was developed (Fig. 2):

- Patients enter the model in the event-free state.
- Forward transitions to more severe disease states are allowed between all disease states.
- Transitions to death can occur from any state.

The open-source model also contains several additional features identified from previous HTAs:

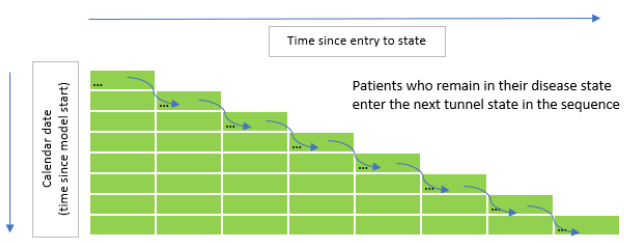
- The DM state can be partitioned into sub-states representing progression-free (PF) and progressed disease (PD) for advanced cancer using a nested partitioned survival method. This approach uses the ratio of progression-free (PFS) and overall survival (OS) probabilities over time from a metastatic disease setting, to estimate the proportions in the DM state that are PF versus PD. The PFS:OS ratio is a function of time since entry to the DM state and is applied to the tunnel states that track time in state (see Fig. 3).

- Additional states for 'early' and 'late' distant metastases (extended model) provide flexibility to model different pathways and outcomes based on time of recurrence. These states may help to capture re-treatment with novel therapies in advanced stage, which often depends on the time of first recurrence (Fig. 2).

Semi-Markov structure

All transition risks are dependent on time since entry to state and modelled via tunnel states[3]. Each tunnel state represents the disease state, and the number of cycles spent in this state.

Fig. 3 Illustration of tunnel states



In Excel, the tunnel states are represented by a large lower triangular matrix with each row capturing each month of calendar time (since model start) and each column capturing the time since state entry (Fig 3).

Input parameters

Characteristics of the starting population include age and sex distribution. The template model inputs include the parameters for survival models for each transition, age- and gender-specific mortality lifetables, and a standardised mortality ratio for modelling excess mortality.

Transition probabilities are calculated from parametric survival models fitted to cause-specific hazards for each transition in the model[4]. The cause-specific hazard is defined as the time to an event (or cause) with all other events censored. The survival parameters can be estimated from clinical trial, observational or other data sources.

Standard survival functions including Generalised Gamma, Gompertz, Weibull, Exponential, Lognormal and Log-logistic are estimated using an open-source custom Excel VBA function, based on the flexsurv package in R.

Model outputs

Model outputs include a state trace display of the proportion of patients in each state over time and estimates of the median and mean life years.

Discussion

An open-source model framework was developed to support future cost-effectiveness studies in early cancer by reducing the burden of de-novo model build.

The model is designed with a view to enabling future adaptations and improvement, for example the inclusion of cure modelling.

As an open-source resource, our hope is it will improve consistency and transparency as well reduce the presence of technical errors in the health state modelling of early cancer treatment for health technology developers and decision-makers.

References

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