Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 6: Model structure
6.4: Area under the curve (AUC) models and cycle length

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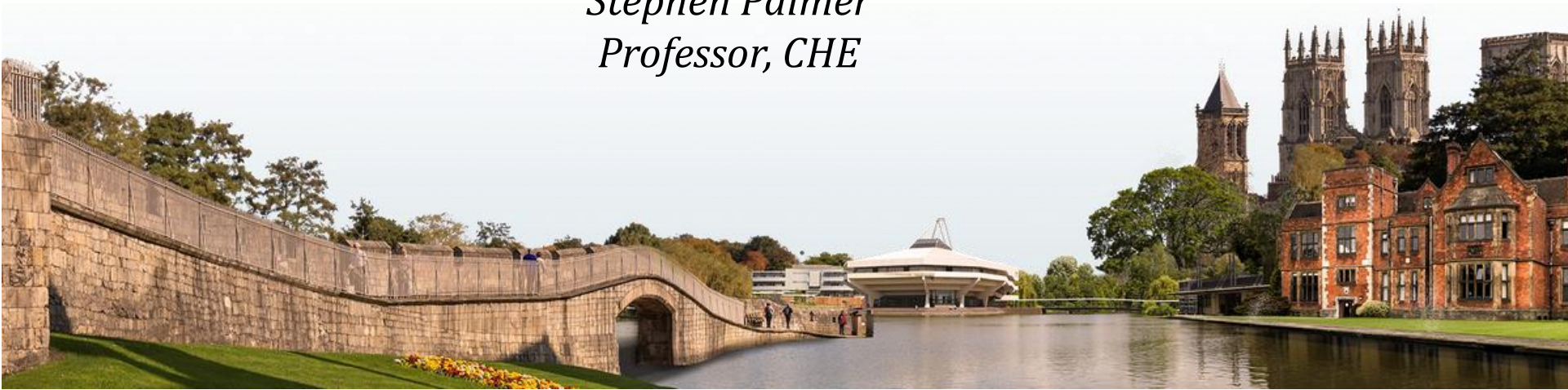


Objectives

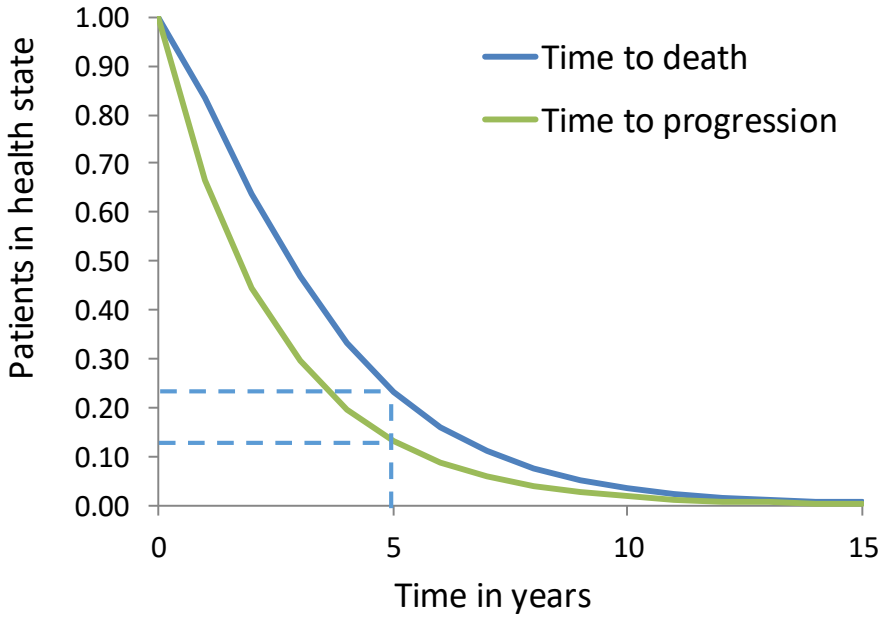
- Understand alternative state-transition approaches based on area under the curve (AUC) models
- Explore how to evaluate AUC models and determine state membership
- Understand importance of cycle length and use of corrections

Area under the curve (AUC) models

- Transitions probabilities not explicitly modelled
- Proportion in each health state over time is derived directly from survival curves
- Increasingly used in oncology based on progression-free survival (PFS) and overall survival (OS) curves
  - 3 states: (i) progression-free, (ii) progressed; (iii) death
  - Approach also referred to as partitioned survival analysis models
- As survival curves are used directly any time-dependency in the rate of events is captured

Evaluating AUC models

- 3 states: (i) progression free, (ii) progressed, (iii) dead
- Proportions derived from time to progression (PFS curve) and time to death (OS curve)



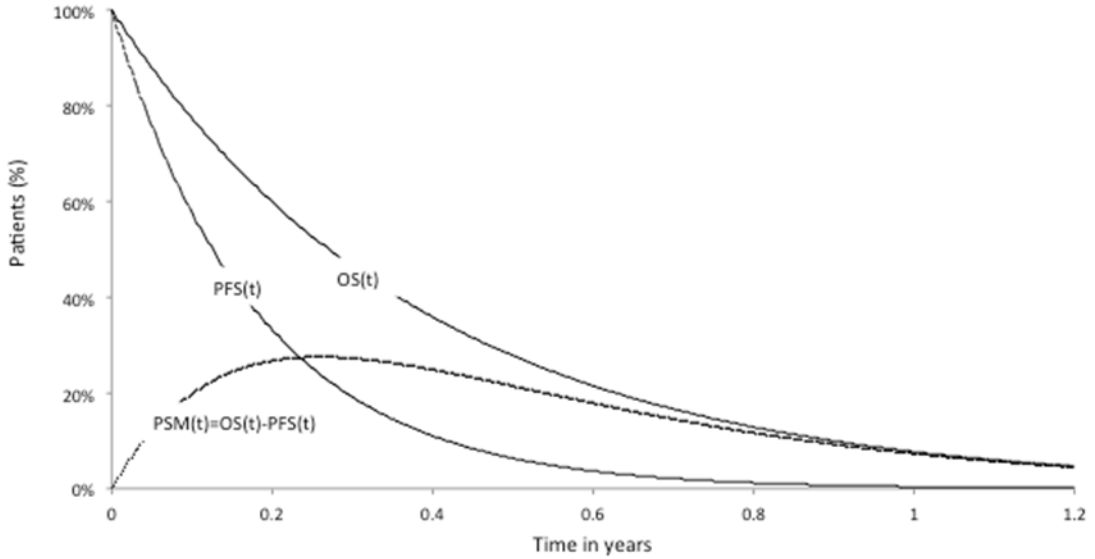
At t=5 years

- 13% patients have not yet progressed
- 23% of patients have not yet died

State membership is therefore

- Progression free: 0.13
- Progressed: 0.23-0.13 = 0.10
- Dead: 1-0.23 = 0.77
- Check: 0.13+0.10+0.77=1.0

Determining state membership in an AUC model



PSM = Progressive state membership – derived from OS and PFS curves

Issues with AUC models

- Simple to implement, consistent with published survival data and readily captures time dependency
- Not underpinned by explicit model of disease process
- May not provide robust predictions if data are incomplete (e.g. if a significant proportion of patients have not died)
- OS and PFS modelled independently
- Logical issues may arise in extrapolations/probabilistic analysis
- Less transparent/flexible than Markov model (e.g. impact of alternative assumptions in pre and post-progression periods)

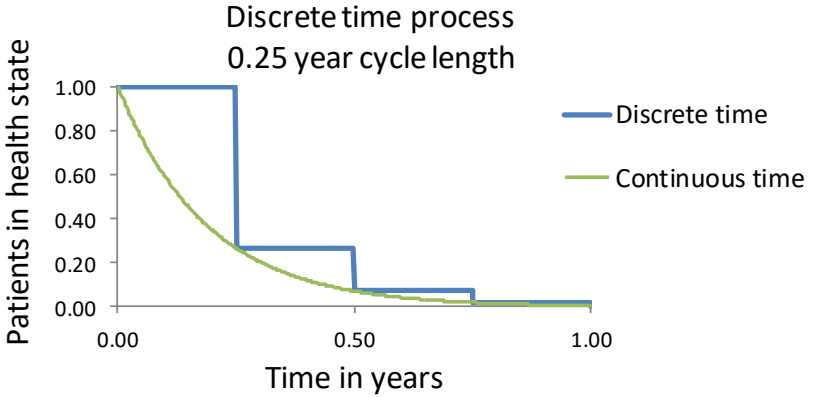
Extensions to AUC model – More explicit assessment of heterogeneity

- AUC based approaches
  - Splines/fractional polynomials
  - Landmark approach (e.g. responders, non-responders)
  - Independence still assumed between endpoints
  - Extrapolations still driven by time

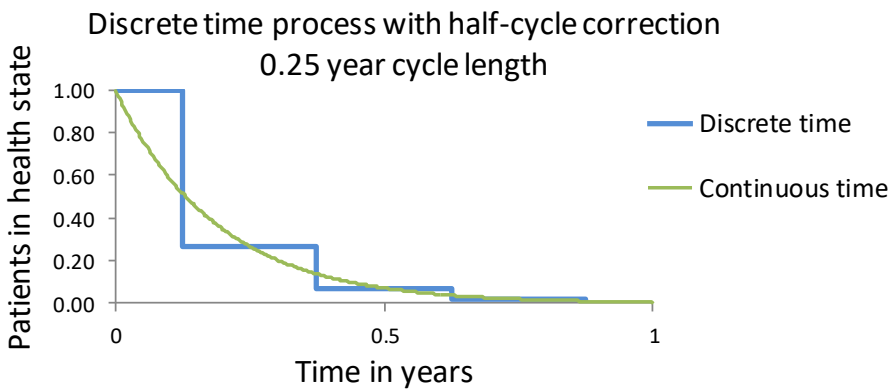
- Mixture cure models
  - Study population includes ‘cured’ and ‘uncured’ patients
  - Estimate probability that a patient is cured
  - Predict survival of patients who are not cured
  - Avoids grouping heterogeneous populations and using single mean value
  - Extrapolation and assumptions for ‘cured’ patients still required

Choice of cycle length and half-cycle correction

- Using discrete cycle lengths introduces bias in to estimates of time in state (and therefore costs and QALYs)
- To minimise - reduce cycle length and apply a half-cycle correction (HCC)



True survival = 0.19
Estimated survival = 0.34

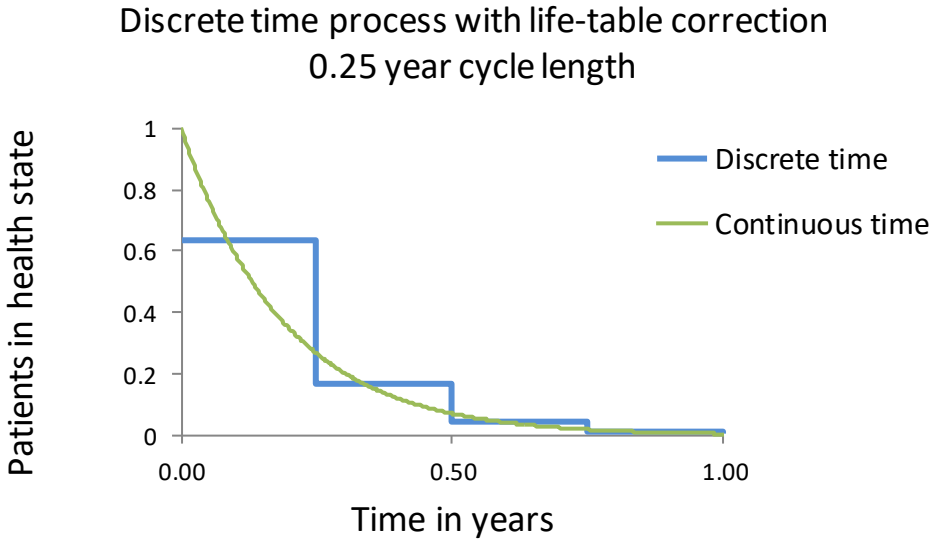


True survival = 0.19
Estimated survival = 0.21

- The **HCC** subtracts (or adds) one half cycle's worth of cost and outcomes from first (or last) cycle – *transitions assumed at end (beginning) of cycle*

Alternative correction methods - Life-table

- **Life-table method:** average of the start and end state membership



True survival = 0.19
Estimated survival = 0.21

- Implemented at each cycle (within-cycle correction)
- Within-cycle approach now recommended

ICER with different correction methods and cycle length

	ICER				
Method	**Annual cycle (n=1)**	**Semiannual cycle (n=2)**	**Monthly cycle (n=12)**	**Weekly cycle (n=52)**	**Daily cycle (n=365)**
Right Riemann	60,333	51,042	47,881	47,795	47,790
Trapezoidal rule	60,333	51,042	47,881	47,795	47,790
Simpson's 1/3 rule	51,224	48,075	47,790	47,790	47,790
Simpson's 3/8 rule	53,594	48,371	47,791	47,790	47,790
Gold standard	47,790	47,790	47,790	47,790	47,790

Source: Elbasha and Chhatwal (2016)

Summary

- AUC approach increasingly common in oncology
  - Important differences compared with other state-transition approaches
- Various extensions proposed to AUC model
  - Novel mechanisms
  - Heterogeneity in survival
- Use of discrete cycles introduces bias
  - Minimise cycle length
  - Half-cycle correction