Estimating Incidence Progressed Patients in Partitioned Survival Models - a Comparison of Three Methodologies

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INTRODUCTION

- Partitioned survival analysis (Part SA) is a useful modelling technique and is commonly used to model cost-effectiveness of cancer therapies.[1,2,3,4]
- The key advantage of Part SA over Markov modelling for oncology is that it can directly utilize progression-free survival (PFS) and overall survival (OS) data to estimate health state membership.
- Part SA models typically consist of three mutually exclusive health states: PFS, progressed disease (PD), and death, where health state membership in each model cycle is estimated by the PFS risk, OS-PFS risk, and OS risk, respectively.
- Incident progression in Part SA models is defined as "proportion of patients who progressed from PFS to PD state during a model cycle".
- A key limitation of Part SA modelling is that it cannot precisely track the number of patients who have progressed in each cycle (i.e., it cannot estimate 'incident progression').
- The tracking of incident progressed patients is important in oncology models as it is used to estimate the cost of subsequent therapies and one-off resource use costs associated with progression (such as CT/PET scan, ultrasound, etc.).

OBJECTIVE

The current study explores three different methods of estimating incident progression in Part SA models and their implications on cost effectiveness models.

METHODS

A hypothetical Part SA model presented in Figure 1 was developed in Microsoft Excel 2016 (Redmond, WA, USA) to apply all three methodologies of estimating incident progressed patients described below and interpret the findings from each method:

1. Approach 1- Assuming all patients progress before dying

- This approach assumes that each patient in PFS will have disease progression and move to the PD health state before dying. Assuming patients cannot transition back from PD to PFS health state, in this methodology, the incident progressed patients per cycle are simply the number of patients who left the PFS health state in each cycle
- Incident progression in each cycle using this approach can be estimated as follows:

Incident progressed = PFSx-1 – PFSx; where
PFSx-1: Number of patients in PFS health state in Cycle x-1
PFSx: Number of patients in PFS health state in Cycle x

2. Approach 2 - Assuming same mortality for PFS and PD health states

- This approach estimates the incident progressed patients per cycle based on the assumption that patients in the PFS and PD health states have equal mortality risk
- Incident progression in each cycle using this approach can be estimated as follows:

Incident progressed = PFSx-1 – PFSx – Mortality from PFS; where
PFSx-1: Number of patients in PFS health state in Cycle x-1
PFSx: Number of patients in PFS health state in Cycle x

3. Approach 3 - Assuming the general population mortality for PFS health state

- This approach estimates the incident progressed patients per cycle based on the assumption that patients in the PFS health state can either move to the PD health state or can die as per general population mortality risk from the PFS health state
- Incident progression in each cycle using this approach can be estimated as follows:

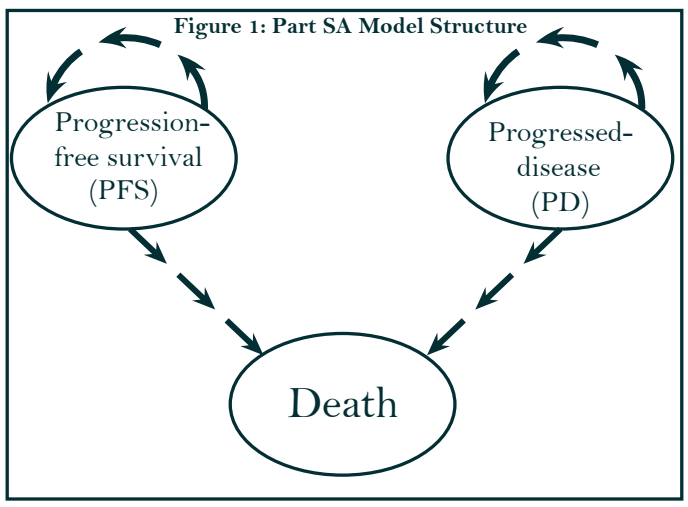
Incident progressed = PFSx-1 – PFSx – rx PFSx-1;* where
PFSx-1: Number of patients in PFS health state in Cycle x-1
PFSx: Number of patients in PFS health state in Cycle x
rx: rate of general population mortality in Cycle x;

The model used a weekly cycle and a 35-year time horizon. In the base case, a hypothetical Weibull distribution was created to simulate PFS and OS curves. OS estimates were compared to the most recent age- and gender-specific mortality rate data (years 2016-2018) for the Australian population and the higher of the two mortality estimates is used in the model. This approach therefore makes sure that the survival of the cancer patients can never be greater than the general population.

The following scenario analyses were also performed:

1. Exponential distribution was fitted based upon the median PFS and OS of 1.0 and 2.5 years, respectively, of angioimmunoblastic T-cell lymphoma patients reported in Ying Li et al. 2017.[5]
2. Exponential distribution was fitted to simulate PFS curve based upon hypothetical median PFS time of 4.0 years. OS curves were simulated by applying a standard mortality ratio of 1.5 to general population mortality rates.

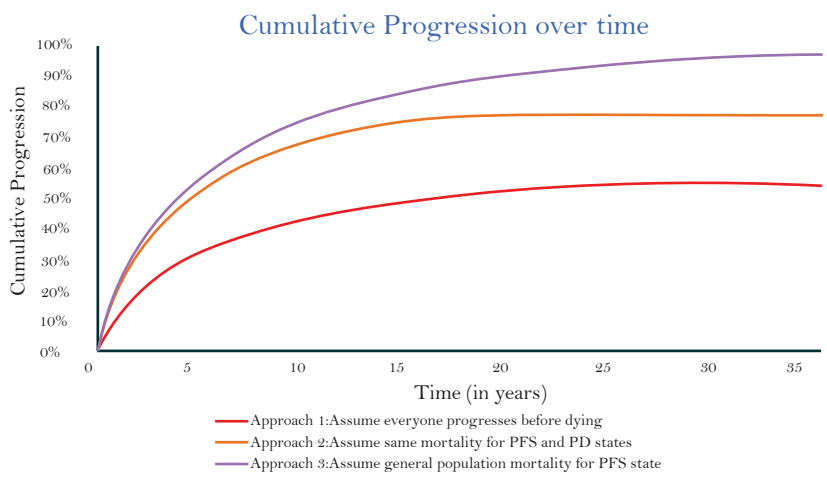
Figure 1: Part SA Model Structure



RESULTS

In the base case, the proportion of cumulative progressed patients over time--calculated by adding the incident progressed patients in each cycle estimated using the three different approaches, was 97.1% (Approach 1), 54.4% (Approach 2), and 77.5% (Approach 3) and is presented in Figure 2.

Figure 2: Cumulative Progression Over Time Using Three Alternative Approaches-Base Case



We believe that Approach 1 overestimates the incident progression whereas Approach 2 underestimates the incident progression (Figure 2). The estimates from Approach 3 lie between Approach 1 and Approach 2.

Depending upon the rate of disease progression, the estimates from Approach 3 may closely resemble the estimates from Approach 1 or Approach 2 as well. The first scenario analysis estimated cumulative progressed patients were similar using Approach 1 (100%) and Approach 3 (98.1%), while 59.8% patients progressed using Approach 2 (Figure 3). Whereas the second scenario analysis depicted that cumulative progressed patients were similar using Approach 2 (83.4%) and Approach 3 (88.6%), while 99.8% patients progressed using Approach 1 (Figure 4).

Figure 3: Cumulative Progression Over Time Using Three Alternative Approaches-Scenario Analysis #1

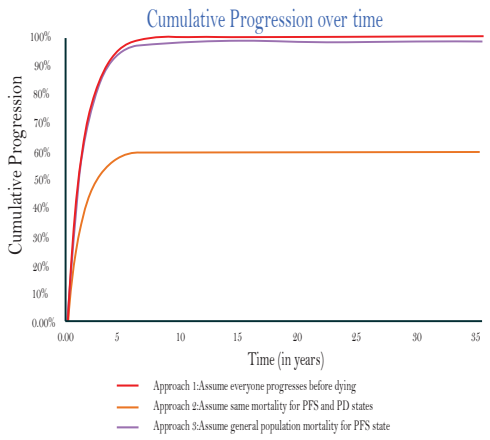
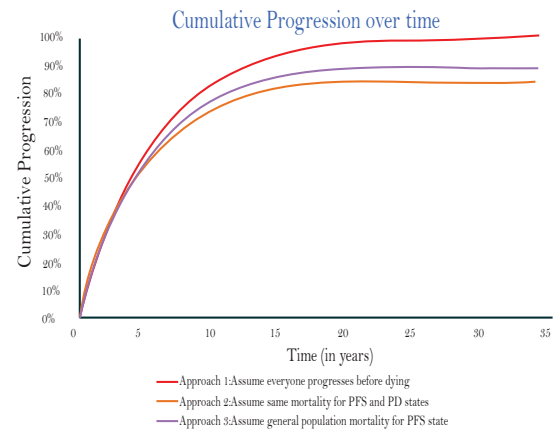


Figure 4: Cumulative Progression Over Time Using Three Alternative Approaches -Scenario Analysis #2



DISCUSSION

- Approach 1 disregards the possibility of transition of patients directly from PFS to the Death health state and assumes that patients in the PFS health state would necessarily progress first before dying. This methodology may overestimate the incident progression patients for advanced or metastatic cancers, or for later line of treatment where a patient can die from the PFS state as well.
- Approach 2 may underestimate true incident progressed patients in each cycle as it assumes equal mortality risk for PFS and PD patients. This may not hold true in a real-world setting as patients in the PD health state with more severe disease are likely to have a higher mortality risk compared to PFS patients. However, in some rare cases for advanced stages of cancer, where the risk of mortality is the same for both PFS and PD patients, this approach can precisely estimate the incident progression per cycle.
- Approach 3 may lead to the closest approximation of the 'true' incident progressed patients in Part SA modelling as this approach does not 'force' every patient to progress before dying (as in Approach 1) nor assume a similar rate of mortality for PFS and PD health state (as in Approach 2).
- The magnitude and direction of the results will vary depending upon the rate of disease progression, baseline characteristics, and the statistical distribution function used for extrapolation of PFS and OS. For example, if the cancer is rapidly progressing and the median time spent by patients in the PFS health state is small, then the results yielded by Approach 1 and Approach 3 are similar. The results of the scenario analyses validate this finding. External data from trials, observational studies or national cancer statistics may assist in validating the base-case approach.
- Patient-level simulation models may give the precise estimate of incident progressed patients, but they are not commonly used in HTA submission for oncology because such granular level of data is not readily available, the complexity in the programming required and the higher run time of these models.

CONCLUSION

- Ideally, a Part SA model should implement all the three approaches to estimate incident progressed patients' and present the results with all three scenarios.
- The base case approach to estimate incident progression could be selected based upon the cancer severity, line of treatment under evaluation, and the mortality risk associated with cancer.
- We acknowledge that neither of the three approaches represents the true incident progressions but only the approximate incident progressed patients.
- Pharmaceutical companies and HTA bodies need to carefully examine the methodology used to estimate the incident progressed patients in a Part SA model, since it can substantially impact the model results.

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REFERENCES

1.Woods B, Sideris E, Palmer S, et al.[Available from http://www.nicedsu.org.uk]
2.Mistry R, May JR, Suri G, et al.e. J Manag Care Spec Pharm.2018 Jun;24(6):514-523.
3.Wang J, Chmielowski B, Pellissier J, et al. J Manag Care Spec Pharm. 2017 Feb;23(2):184-194.
4.Chouaid C, Bensimon L, Clay E, et alLung Cancer. 2019 Jan;127:44-52.
5.Li Y, Yang C, Mao L, et al. Medicine (Baltimore). 2017 Sep;96(39):e8091