Methods for Incidence Progression Estimation in Partitioned Survival Analysis: Does the Chosen Method Matter?

MSR147

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Introduction

- Partitioned survival analysis (PartSA) is widely used to evaluate the cost-effectiveness of cancer therapies. A key advantage of PartSA over traditional Markov models in oncology is its ability to directly utilize progression-free survival (PFS) and overall survival (OS) data to determine the distribution of patients across various health states.[1-3] In each cycle of the model, the probabilities of being in PFS, progressed disease (PD), and death states are estimated using PFS risk, the difference between OS and PFS risks, and OS risk, respectively.[2,3]
- A key limitation of PartSA is that it cannot directly track the proportion of patients who progress from PFS to PD in each cycle (i.e., incident progression), since it cannot differentiate pre- vs. post-progression mortality.[3] This creates a challenge in assigning costs associated with incident progression, such as subsequent therapies and one-time resource use costs. Appropriately tracking these transitions is crucial in oncology models to provide a reasonable estimation of the overall cost-effectiveness of cancer treatments.[3]

Objectives

- **Examine the impact of different incident progression calculation methods on incremental cost-effectiveness ratios (ICERs) in terms of cost per quality-adjusted life-year (QALY) gained.**

Methods

- A hypothetical PartSA model was developed, simulating an "aggressive" and a "slower progressing" cancer archetype. The methods to calculate incident progressors included equal mortality rates for PFS and PD states (approach 1), Euler's method (approach 2), using general population mortality for the PFS state (approach 3), and assuming all patients progress before dying (approach 4).[3] **Table 1** presents a summary of the approaches, including the assumptions and limitations of each identified method.
- The model was populated and parametrized using data from National Institute for Health and Care Excellence technology appraisals (TA) 557 and TA858.[2,4] Whenever data were not provided in one of these TAs, we used the corresponding data from the other TA if appropriate. Key parameters of the model are presented in **Table 2**.
- We also conducted a range of scenario analyses to evaluate the impact of various factors on outcomes for both archetypes, including:
  - Shorter time horizons of 5 and 10 years
  - Alternative discount rates of 1.5% and 5% for both costs and health outcomes
  - Alternative baseline age values (10 years lower and 10 years higher)
  - Alternative efficacy scenarios applying lower PFS/OS hazard ratios (HRs) and higher PFS/OS HRs
    - For the slower progressing cancer archetype, PFS/OS HRs of 0.3 were applied in the higher efficacy scenario and PFS/OS HRs of 0.8 in the lower efficacy scenario
    - For the aggressive cancer archetype, PFS/OS HRs of 0.5 were applied in the higher efficacy scenario and PFS/OS HRs of 0.9 in the lower efficacy scenario
  - Halving and doubling of subsequent treatment costs

Results

- In aggressive cancer, ICERs with approaches 3 and 4 were 23.3% and 23.7% lower, respectively, while approach 2 was 8.7% higher compared with approach 1. A similar pattern was observed in slower progressing cancer: ICERs with approaches 3 and 4 were 7.6% and 4.04% lower, respectively, whereas approach 2 was 9.8% higher compared with approach 1. **Table 3** summarizes the results for both cancer types.
- The four approaches differ in how they model transitions from PFS to PD or death, which directly impacts cost estimates. Approach 1 tends to underestimate progression costs, leading to lower overall costs. Approach 2 allows more dynamic transitions; however, because it uses a constant denominator for incidence calculations, it underestimates progression relative to the changing at-risk population. This results in lower overall costs, closer to those of Approach 1. Approaches 3 and 4 assume higher progression incidence, which increases PD-related costs, with Approach 4 producing the highest overall costs.
- Scenario analyses were also largely consistent with the base-case findings, again with varying magnitudes. Results of the scenario analyses are presented in **Table 4.**
  - In aggressive cancer, where survival is short, patients die earlier in the model. As a result, altering the time horizon produced minimal changes.
  - In slower progressing cancer, with longer survival, the choice of time horizon had a greater impact.
  - The discount rate also had a stronger effect in slower progressing cancer vs. aggressive cancers.
  - Changing the HRs for OS and PFS produced the largest shifts in results, as HRs directly determine survival probabilities and time spent in each health state. In aggressive cancer, modifying HRs can substantially change expected survival, with major effects on costs and QALYs. In slower progressing cancer, HR changes also lead to significant variation in outcomes due to the longer time horizon over which these differences accumulate.

Table 1. Overview of approaches to calculate incidence of disease progression

Approach	Assumptions and Limitations
Approach 1	Approach 1 assumes that patients in the PFS and PD states have the same mortality risk. Patients in the PD state typically have a worse prognosis and higher mortality rates compared to those in the PFS state.[3] Assuming equal mortality rates may overestimate survival in the PD state, leading to inaccurate survival predictions.
Approach 2	We applied Euler's method, a numerical technique for solving ordinary differential equations, to model the rates of change of the proportions of individuals in each health state over time. While Euler's method offers a straightforward approach for calculating incident progression, it can result in cumulative errors over multiple steps, affecting the precision of the incidence progression calculation.
Approach 3	Approach 3 assumes that patients in the PFS state can either progress to PD or die according to the general population mortality risk. Patients in the PFS state, while healthier than those in the PD state, may still have a higher mortality risk compared to the general population due to underlying cancer or treatment-related factors.[3]
Approach 4	Approach 4 assumes that all patients in the PFS state will eventually progress to the PD state before dying, with no possibility of transitioning back to PFS. In reality, not all patients will progress before dying. Some patients may die while still in the PFS state due to other causes or complications.[3] We commonly assign terminal care costs to incident death to account for the costs of the last months of life. Therefore, assuming everyone receives subsequent treatment may result in double counting these costs.

Abbreviations: ICER = incremental cost-effectiveness ratio; PD = progressive disease; PFS = progression-free survival

Table 2. Key settings

Input	Aggressive Cancer[4]	Slower Progressing Cancer[2]	Reference
Time horizon	50*	50*	2,4
Baseline age, years	64	62	2,4
Discount rates	3.5%	3.5%	2,4
Efficacy: PFS curve	Log-normal distribution for SOC, constant HR of 0.7 for treatment A Median PFS in SOC: 3 months	Exponential distribution for SOC, constant HR of 0.4 for treatment A Median PFS treatment A: 23.90 months	2,4, assumption
Efficacy: OS curve	Log-normal distribution for SOC, constant HR of 0.8 for treatment A Median OS in SOC: 5 months	Exponential distribution for SOC and a constant HR of 0.65 for treatment A median OS in SOC: 34 months	2,4, assumption
Efficacy: Treatment discontinuation	Exponential distribution**	Exponential distribution**	Assumption
Subsequent treatment cost	Treatment A: £3,416 SOC: £6,551	Treatment A: £20,494 SOC: £39,307	2, assumption
Drug cost (per month)	Treatment A: £1,800 SOC: £780	Treatment A: £10,500 SOC: £4700	2,4

* A 50-year horizon was used to capture lifetime outcomes; background mortality ensures patients do not survive beyond a rational period.
** Discontinuation Rule: Treat until progression (up to 24 months).
Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival; SOC = standard of care

Table 3. Base-case results

	Approach 1	Approach 2	Approach 3	Approach 4
Aggressive cancer				
Total cost: Treatment A	£15,490	£15,218	£17,930	£18,256
Total cost: SOC	£7,990	£7,059	£12,178	£ 12,509
Total QALY: Treatment A	0.68	0.68	0.68	0.68
Total QALY: SOC	0.48	0.48	0.48	0.48
ICER treatment A vs. SOC	£38,535	£41,918	£29,551	£29,526
% changes in ICER (compared to approach 1)		8.78%	-23.31%	-23.38%
Slower progressing cancer				
Total cost: Treatment A	£160,991	£156,343	£163,579	£169,997
Total cost: SOC	£103,786	£93,518	£110,734	£115,094
Total QALY: Treatment A	3.68	3.68	3.68	3.68
Total QALY: SOC	2.49	2.49	2.49	2.49
ICER treatment A vs. SOC	£48,032	£52,750	£44,371	£46,098
% changes in ICER (compared to approach 1)		9.8%	-7.6%	-4.03%

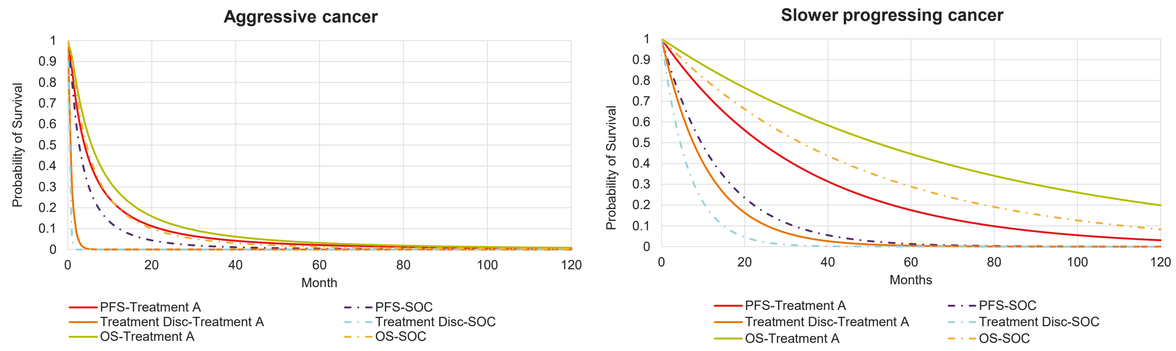
Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care

Table 4. Scenario analyses: % Difference in ICER compared to Approach 1

	Aggressive Cancer			Slower Progressing Cancer		
Scenario/Approach	**Approach 2**	**Approach 3**	**Approach 4**	**Approach 2**	**Approach 3**	**Approach 4**
Scenario 1: Change time horizon to 5 years	8.67%	-23.22%	-23.69%	12.7%	-7.64%	-6.5%
Scenario 2: Change time horizon to 10 years	8.76%	-23.29%	-23.47 %	10.49%	-7.50%	-4.49%
Scenario 3: Change discount rate (health and cost outcomes) to 1.5%	8.78%	-23.19%	-23.15%	9.51%	-7.62%	-3.52%
Scenario 4: Change discount rate (health and cost outcomes) to 5%	8.78%	-23.40%	-23.54%	10.12%	-7.71%	-4.41%
Scenario 5: Decrease baseline age by 10 years	8.78%	-23.34%	-23.38%	9.88%	-5.30%	-4.05%
Scenario 6: Increase baseline age by 10 years	8.78%	-20.93%	-23.38%	9.98%	-10.71%	-4.04%
Scenario 7: Lower setting for HR*	3.95%	-17.98%	-15.96%	6.69%	-9.80%	-5.75%
Scenario 8: Higher setting for HR*	9.00%	-39.94%	-42.40%	10.00%	-14.64%	-15.29%

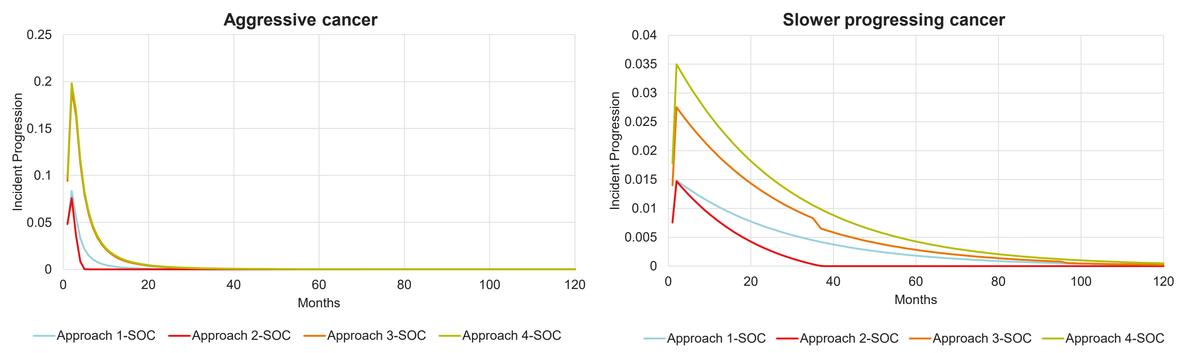
*Slower progressing Cancer: Lower Setting: HR = 0.3, Higher Setting: HR = 0.8; Aggressive Cancer: Lower Setting: HR = 0.5, Higher Setting: HR = 0.9;
Abbreviation: HR = hazard ratio

Figure 1. State membership in PartSA models under different severity assumptions



Abbreviations: OS = overall survival; PFS = progression-free survival; SOC = standard of care

Figure 2. Incident progression over time by approach and treatment arm



Abbreviations: SOC = standard of care

Conclusions

- **Estimating incident progression in PartSA models requires clinical assumptions, and the choice of incident progression estimation method can potentially significantly affect ICER results.**
- **Transparent reporting and careful selection of estimation methods are essential for accurate interpretation and comparison of cost-effectiveness results in oncology. Moreover, considering scenario analyses with alternative assumptions can support robustness of the economic analysis outcomes.**

References

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