CAN WE DETERMINE THE OPTIMAL CYCLE LENGTH FOR WHICH HALF-CYCLE CORRECTION SHOULD ALWAYS BE APPLIED?

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Objectives

When modeling long-term costs and health effects using Markov models, choosing the time of transition to another state (progression of a disease) seems to influence the final results. Various approaches can be adopted, i.e. transitions at the beginning, at the end or in the middle of the cycle. Our aim is to measure influence of cycle length and progression rates on differences between final results obtained using those methods and to establish whether there is an optimal cycle length for which half-cycle correction (HCC) should always be applied.

Introduction

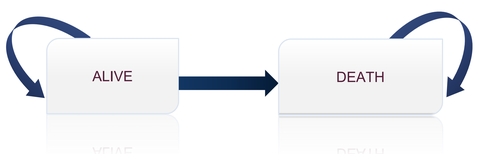
Because of the discrete nature of Markov models the problem of the time of transition arises. When specific cycle length is adopted, it allows to change the status of a disease (progression, regression or death) only in specific moments of time which does not reflect fully the real course of the disease. The simplest solution is to assume that transitions take place at the beginning or at the end of the cycle. However, these solutions result in over- or underestimation of total costs/health effects. Another way to deal with the problem is application of a 'life table' method in which the number of patients in particular state is calculated as the average of the number of people at the beginning and at the end of the time interval (cycle) [1]. The most commonly used method is half-cycle correction which assumes that transition occurs halfway through each cycle. The practical implementation of the method consists in assuming that all transitions take place at the end of the cycle and cutting off first half of the first cycle. As a result, the first half of each 'new' cycle patient/cohort spend in 'initial' state (the same as at the beginning of original cycle) and second half in 'target' state (the same as at the end of original cycle). If the horizon of the analysis is shorter than lifetime, this action will result in underestimation of the results, therefore, an additional correction must be made by modeling patient/cohort life one cycle longer then assumed time horizon and taking into account results obtained in first half of last cycle considered [2]. The half-cycle correction and the 'life-table' method are equivalent in some situations: if costs/utilities are equal in each cycle and there is no discounting. The differences between described methods depend on the cycle length and progression rates.

Methods

A simple two-state Markov model (alive or dead) was developed in order to analyze the influence of cycle length on differences between analyzed methods.

The time horizon was set to be 70 years (lifetime), initial age – 30, the discount rate was 0–5% and costs/utilities were held constant in time.

Figure 1. ***Structure of Markov model considered in the analysis***



Assuming different death rates (0.05–0.90 annually), three methods were compared:

- transitions at the beginning of the cycle ('beginning'),
- transitions at the end of the cycle ('end'),
- transitions in the middle of the cycle (HCC).

The progression rates were assumed to be constant in time. For each rate the threshold values were determined, i.e. the maximal cycle lengths for which the differences between half-cycle correction and 'beginning'/'end' methods were not greater than 5%. We propose that cycles longer than the estimated threshold should imply the application of HCC.

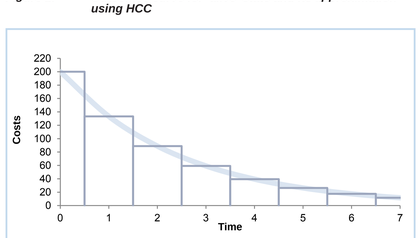
Additionally, the relationship between threshold cycle lengths and incremental results was analyzed.

Results

The problem of calculation of the costs/health effects for a cohort of patients may be illustrated by curves which link survival curves with costs/utilities. Such curves may be created for every state, however in more complicated models it is not always easy. The final result would be the sum of the areas under the curves. An example for the analyzed model is presented on Figure 2.

A mathematical approach to the problem of calculating area under the curve would be solving a respective integral. When discrete Markov models are used, the approximate area is calculated as the sum of areas of rectangles (see Figure 2). All three methods ('beginning', 'end', HCC) provide approximate outcomes, which are the more accurate the smaller rectangles are used. Using Markov models language, it means that the shorter cycle we choose the more accurate outcome we obtain.

Figure 2. ***Outcomes curve for 'alive' state and its approximation using HCC***

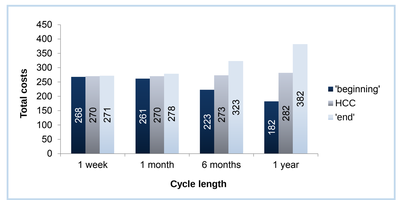


Assumptions: constant progression rate – 0.3,annual costs – 200, discount rate – 5%;

It is intuitive: if a short cycle is used, we are able to describe more precisely the moments of transitions between states. However, it is not always possible to adopt very short cycles as their length depends on the type of the disease and available data and in practice it is a compromise between accuracy of the results and computational time. The illustrative results for probability of death equal to 0.5 are presented on Figure 3. The exact result in this example (calculated using integrals) is 269.56.

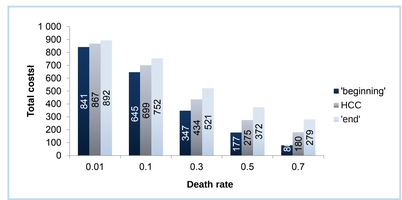
If the horizon of analysis is finite (i.e. not lifetime), the accuracy of the approximation depends also on the slope of the curve (progression rates in Markov models). The steeper the slope, the less precise the approximation of the area (Figure 4).

Figure 3. ***Comparison of differences in total costs between methods for various cycle lengths***



Assumptions: progression rate – 0.05, annual cost for 'alive' state – 200, annual cost for death state – 0, discount rate 5%

Figure 4. ***Comparison of differences in total costs between methods for various progression rates***



Assumptions: horizon 5 years, cycle length 1 year, annual costs 200, discount rate 5%; The exact results (obtained using integrals) are 866.32, 697.16, 428.30, 262.96, 159.34 .for rates 0.01, 0.1, 0.3, 0.5, 0.7, respectively

In case of lifetime horizon the differences between adopted methods are associated with the differences in approach to cycle 0. As a result, the difference between results obtained using different methods is equal to the difference obtained in cycle 0 and does not depend on the progression rate (assuming the rate is constant). However, the percentage difference between results obtained using HCC and other methods depends on the rate because the total outcomes are strictly connected with the probability of transition. In example presented in Table 1 the differences between HCC and other methods are 100 for both probabilities of death and the percentage differences are 56% and 68% for probabilities 0.7 and 0.8, respectively.

Table 1. ***Costs for different methods depending on the progression rate for 1-year cycle***

Cycle	Annual probability of death 0.7			Annual probability of death 0.8		
	Beginning	End	HCC	Beginning	End	HCC
0		200.00	100.00		200.00	100.00
1	57.14	57.14	57.14	38.10	38.10	38.10
2	16.33	16.33	16.33	7.27	7.27	7.27
3	4.66	4.66	4.66	1.38	1.38	1.38
4	1.33	1.33	1.33	0.26	0.26	0.26
5+	0.53	0.53	0.53	0.06	0.06	0.06
Total	80.00	280.00	180.00	47.06	247.06	147.06
Percentage difference		56%			68%	

Assumptions: annual cost for 'alive' state – 200, annual cost for death state – 0, discount rate 5%

The percentage differences between results obtained using different methods do not depend on the magnitude of costs/health effects. In the example illustrated in Table 1 annual costs of 'alive' state equal to 200 were assumed, however any other costs would provide the same results for percentage difference. Therefore the results described further are general and the only important assumptions are two-state model and constancy of costs/utilities and death rates in time.

In Table 2 threshold cycle lengths for various transition probabilities are presented. The threshold was defined as cycle length for which the difference between HCC and other methods is equal to 5%. Adopting cycles shorter than the threshold provides more accurate approximation of outcomes.

Costs/utilities are usually not constant in time, e.g. utilities may depend on age. In Table 3 the comparison of threshold cycle lengths is presented for constant utilities and utilities dependent on age (using the age specific multipliers according to Polish tariff [3] and hypothetical 50% decrease of utility at the age of 55). The thresholds for decreasing utilities are slightly lower, the largest differences are observed for slower progression rates. In opposite situation, e.g. if costs of health care increased, the thresholds would be slightly higher.

Table 2. ***Threshold cycle lengths in relation to progression rate***

Annual probability of transition	Threshold cycle length (days)		
	Discount rate = 5%	Discount rate = 3.5%	Discount rate = 0%
0.05	365	425	696
0.1	237	261	346
0.2	134	142	163
0.3	90	93	102
0.4	65	67	71
0.5	49	50	53
0.6	38	38	40
0.7	29	29	30
0.8	22	22	23
0.9	16	16	16

Table 3. ***Threshold cycle lengths in relation to utilities variation***

Annual probability of transition	Threshold cycle length (days)		
	Constant utilities	Polish tariff [3]	Decreasing utilities [a]
0.05	362	352	253
0.1	237	234	180
0.2	134	134	117
0.3	90	90	84
0.4	65	65	64
0.5	49	49	49
0.6	38	38	38
0.7	29	29	29
0.8	22	22	22
0.9	16	16	16

Assumptions: discount rate – 5%, initial age – 50 ; a) for age ≥ 55 utility equal to 50% of initial value

Table 4. ***Differences between ICERs depending on costs of 'alive' state***

Annual costs for 'alive' state		Percentage difference between total results for HCC and 'beginning'/'end' methods		
Intervention	Comparator	Total costs of intervention	Total costs of comparator	ICER
400	200	3.1%	5.0%	2.2%
700	200			2.7%
700	600			1.0%

Assumptions: 1 month cycle, probability of transition – 0.5 for intervention, 0.7 for comparator, discount rates – 5% for costs, 3.5% for utilities, utility of 'alive' state – 0.85

Other common violations of adopted assumptions are progression rates changing in time and multi-stage models. Such cases need to be analyzed individually as no general recommendation may be provided.

The challenging problem to determine the threshold cycle length occurs also when incremental outcomes are concerned. The key issue is the fact that there are differences between two interventions associated with death rates and cost/utilities variety in time. Not only differences between costs/utilities have impact on the results but also magnitude of costs/utilities for compared interventions. The example is presented in Table 4. It may be observed that although the percentage differences for costs of interventions do not depend on the annual costs of 'alive' state, the percentage differences between ICERs show a slight variety for different costs assumptions.

However, after making a few assumptions, it is possible to observe some general dependencies for ICERs:

- the initial cohort distribution among health states and the utilities for each health state are the same for both options,
- probability of death is lower for assessed intervention than for the comparator,
- annual costs of health states for assessed intervention are higher than annual costs of the states for comparator.

The first assumption implies that incremental QALY will be the same for all three methods [4]. The second assumption implies that the percentage difference between costs of intervention for analyzed methods is lower than the respective difference for comparator.

Under these assumptions the percentage difference between ICERs obtained using analyzed methods is not higher than the minimum of percentage differences between costs for both options.

If annual costs associated with the intervention are lower than annual costs associated with comparator (assumption 3 is not satisfied), percentage difference between ICERs may become large, even if the percentage differences between costs for particular interventions are low. The example is presented in Table 5.

If all the assumptions made in the Methods are satisfied, the results obtained for lifetime horizon may be generalized for finite horizon models. All thresholds calculated and presented in Table 2 are the same for any finite horizon. Remarks concerning changing costs/utilities and progression rates, multi-state models and incremental outcomes remain in force also for finite horizon models.

Table 5. ***Large difference between ICERs for specific costs data***

Category	Method	Intervention	Comparator	Intervention vs Comparator
Annual costs	-	530,000	800,000	-
Results				
Total costs (per 1 patient)	Beginning	692,490	640,490	52,000
	End	736,657	707,157	29,500
	HCC	714,574	673,823	40,750
	Percentage difference	3.1%	5.0%	27.6%
QALY (per 1 patient)	Beginning	1.133	0.689	0.444
	End	1.204	0.760	0.444
	HCC	1.169	0.725	0.444
	Percentage difference	3.0%	4.9%	0.0%
ICER	Beginning	-	-	117,126
	End	-	-	66,447
	HCC	-	-	91,787
	Percentage difference	-	-	27.6%

Assumptions: 1 month cycle, probability of transition – 0.5 for intervention, 0.68 for comparator, discount rates – 5% for costs, 3.5% for utilities, utility of 'alive' state – 0.85

Conclusions

Choice of the time of transitions in the model may have a significant impact on results. For cycles shorter than 2 weeks HCC does not seem to be necessary, however it should always be applied for cycles longer than 1 year. For cycles between 2 weeks and 1 year a general recommendation cannot be made.

References

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