Matching the model with the evidence: comparing discrete event simulation and state-transition modeling for time-to-event predictions in a cost-effectiveness analysis of treatment in metastatic colorectal cancer patients

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ABSTRACT

Background: Individual patient data, e.g. from clinical trials, often need to be extrapolated or combined with additional evidence when assessing long-term impact in cost-effectiveness modeling studies. Different modeling methods can be used to represent the complex dynamics of clinical practice; the choice of which may impact cost-effectiveness outcomes. We compare the use of a previously designed cohort discrete-time state-transition model (DT-STM) with a discrete event simulation (DES) model.

Methods: The original DT-STM was replicated and a DES model developed using AnyLogic software. Models were populated using individual patient data of a phase III study in metastatic colorectal cancer patients, and compared based on their evidence structure, internal validity, and cost-effectiveness outcomes. The DT-STM used time-dependent transition probabilities, whereas the DES model was populated using parametric distributions.

Results: The estimated time-dependent transition probabilities for the DT-STM were irregular and more sensitive to single events due to the required small cycle length and limited number of event observations, whereas parametric distributions resulted in smooth time-to-event curves for the DES model. Although the DT-STM and DES model both yielded similar time-to-event curves, the DES model represented the trial data more accurately in terms of mean health-state durations. The incremental cost-effectiveness ratio (ICER) was €172,443 and €168,383 per Quality Adjusted Life Year gained for the DT-STM and DES model, respectively.

Conclusion: DES represents time-to-event data from clinical trials more naturally and accurately than DT-STM when few events are observed per time cycle. As a consequence, DES is expected to yield a more accurate ICER.

1. Introduction

Healthcare expenditures have increased importantly over the last decades, especially in oncology due to expensive novel targeted agents and personalized treatments based on molecular markers in order to provide patients with the best possible care [1,2]. Cost-effectiveness analysis of such novel medical technologies is becoming increasingly relevant, as it may inform treatment, resource allocation, and research prioritization decisions. This is illustrated by the standardized approaches to value cancer treatment options in terms of efficacy and costs for clinicians [3,4] and guidance for performing cost-effectiveness analysis alongside clinical trials [5].

High quality individual patient data (IPD) on health outcomes, resource use, and care procedures, e.g. obtained from randomized controlled trials (RCTs), are the preferred source of evidence for cost-effectiveness analysis. However, single individual patient datasets do not always provide all (or the only) evidence required for estimating the (long-term) cost-effectiveness of medical technologies [6,7], indicating

the need for cost-effectiveness models to synthesize evidence from additional sources or to extrapolate beyond the time horizon of e.g. RCTs [5,8]. Such cost-effectiveness models should adequately represent clinical practice and, therefore, reflect the true nature of the evidence used to define them, including evidence obtained from RCTs and other sources of IPD. In other words, *the model should match the evidence.*

The primary outcome of many clinical oncology studies is the time until an event of interest occurs, e.g. the patients' overall survival or progression-free survival from the moment of randomization, which are typically recorded continuously over time. However, the most frequently applied cost-effectiveness modeling method, i.e. discrete-time state-transition modeling (DT-STM) [9], uses transition probabilities over discrete time cycles with a fixed length to represent the progression of time. For example, in an DT-STM with time cycles of three weeks patients can only progress to another health state after this predefined and rigid time length, even though in daily practice patients may progress at any time instead of only at a multiple of three weeks. The length of these time cycles needs to be chosen so that the complex dynamics of clinical practice are appropriately represented [9]. For DT-STM to represent clinical practice better, shorter cycle lengths would be preferable [10]. Although half-cycle corrections may be applied to avoid bias and to better approximate clinical practice [11], this still insufficiently allows complex clinical dynamics if the cycle length is too long [12].

Using shorter cycles lengths can be disadvantageous, mainly because of increase in number of cycles that needs to be simulated. Besides increasing the computational burden of the simulation [9,12], the larger number of cycles makes it more challenging to represent the uncertainty in the transition probabilities, as the uncertainty in the numerous cycle-specific probabilities needs to be reflected while also maintaining the correlation between them. Furthermore, because the expected number of observations within a cycle decreases with decreasing cycle length, the likelihood of substantial irregularities in transition probabilities between successive cycles is expected to increase. These irregularities are likely to impact the simulation outcomes and do not correspond to clinical practice, as the probability of an event is commonly expected to be similar between successive moments, i.e. the transition-curves follow a smooth pattern over time.

Discrete event simulation (DES) is an alternative modeling technique to which the challenges associated with discrete time cycles do not apply. Events can occur at any time in a DES model, because the time to these events are typically modeled using smooth time-to-event distributions, e.g. Gamma or Weibull distributions [13]. In DES, the behavior of a system is translated into an ordered sequence of well-defined events, which comprise specific changes in the system's state at a specific point in time [13]. DES is well suitable for modeling clinical processes, as it is able to incorporate patient-level characteristics and clinical histories, competing resources, and interactions between different actors, e.g. physicians and patients [14]. Although originating from the operations research field, DES is increasingly being used for cost-effectiveness modeling [15].

Several studies have compared the use of DT-STM and DES for cost-effectiveness analyses of medical technologies. Using the same model structure and evidence, quantitative outcomes such as the incremental cost-effectiveness ratio (ICER), are unlikely to be substantially different between these modeling methods [16,17]. However, substantial differences in outcomes may occur, if the use of DES results in a more appropriate representation of clinical practice compared to DT-STM, for example by including patient characteristics or considering resource constraints [18]. Especially in the scenario in which insufficient observations are available for the chosen cycle length, and irregularities in the cycle-specific transition probabilities are substantial when using DT-STM, the use of DES might be preferable.

The objective of this study is to compare the evidence structure and outcomes of a recently published cost-effectiveness DT-STM [19] with those of a newly developed DES model. The comparison will be performed based on the dataset of the randomized clinical phase III CAIRO3 study, in which maintenance treatment with capecitabine and bevacizumab (CAP-B) or observation in metastatic colorectal cancer patients after six induction cycles of capecitabine, oxaliplatin, and bevacizumab (CAPOX-B) was evaluated [20]. The results of this study should facilitate a better understanding of the potential impact of selecting a modeling method for cost-effectiveness modeling studies informed by IPD.

2. Methods

2.1. Maintenance treatment in metastatic colorectal cancer

The CAIRO3 study (NCT00442637) is a randomized clinical phase III study, which was carried out by the Dutch Colorectal Cancer Group (DCCG) in 64 hospitals in the Netherlands. A total of 558 metastatic colorectal patients with stable disease or better after six cycles of CAPOX-B induction therapy were randomized to either receive CAP-B maintenance treatment or observation until progression, which is referred to as the post-induction stage. CAPOX-B treatment was to be re-introduced upon progression on either maintenance or observation, and continued until second progression (primary end-point), which is referred to as the reintroduction stage. Although second progression was the primary end-point of the CAIRO3 study, the cost-effectiveness analysis of the CAIRO3 study also considered additional lines of treatment after second progression [19], which is referred to as the salvage therapy stage. Study results have been previously published [20].

2.2. State-transition model

A cohort DT-STM, i.e. Markov model, was originally developed for the cost-effectiveness analysis of the CAIRO3 study and included four health states: post-induction, reintroduction, salvage therapy, and death (Fig. 1a). The model was defined using cohort level cycle-specific transition probabilities, which were estimated from the CAIRO3 trial using Life Tables in IBM SPSS Statistics software, version 23, IBM Corp. (Armonk, NY, USA). This indicates that the probability of moving from one state to another depended only on the time passed since the start of the simulation, e.g. time from randomization until first progression. Half-cycle correction was applied and 100 cycles of three weeks were simulated in total. The DT-STM was built using TreeAge Pro Healthcare v.2014, TreeAge Software (Williamstown, MA, USA), and is described in detail elsewhere [19].

To facilitate an adequate comparison between the two modeling methods, the DT-STM was first replicated in AnyLogic multi-method simulation software, v.7.3, The AnyLogic Company (Chicago, IL, USA), the environment also used for developing the DES model. This replicated DT-STM was then compared to the original DT-STM to assess potential variation in outcomes due to the use of different software environments. In total, 100 events were generated at intervals of three weeks, corresponding to the setup in the original DT-STM. Following each event, the occupation of the health states was recorded and used to calculate health and economic outcomes at the corresponding point in time. The model was validated by structured "walk-throughs", comparing (intermediate) results with calculations by hand, extreme value analysis, trace analysis, and cross validation with the original DT-STM during model development, and sensitivity analysis using the final model [21,22].

2.3. Discrete event simulation model

The DES model was defined on patient-level using AnyLogic software and according to the ISPOR-SMDM Modeling Good Research Practice Task Force guidelines [14]. The model was defined to have the same health states as the DT-STM (Fig. 1b). Although DES allows for constrained resources to be accounted for, resource use was not
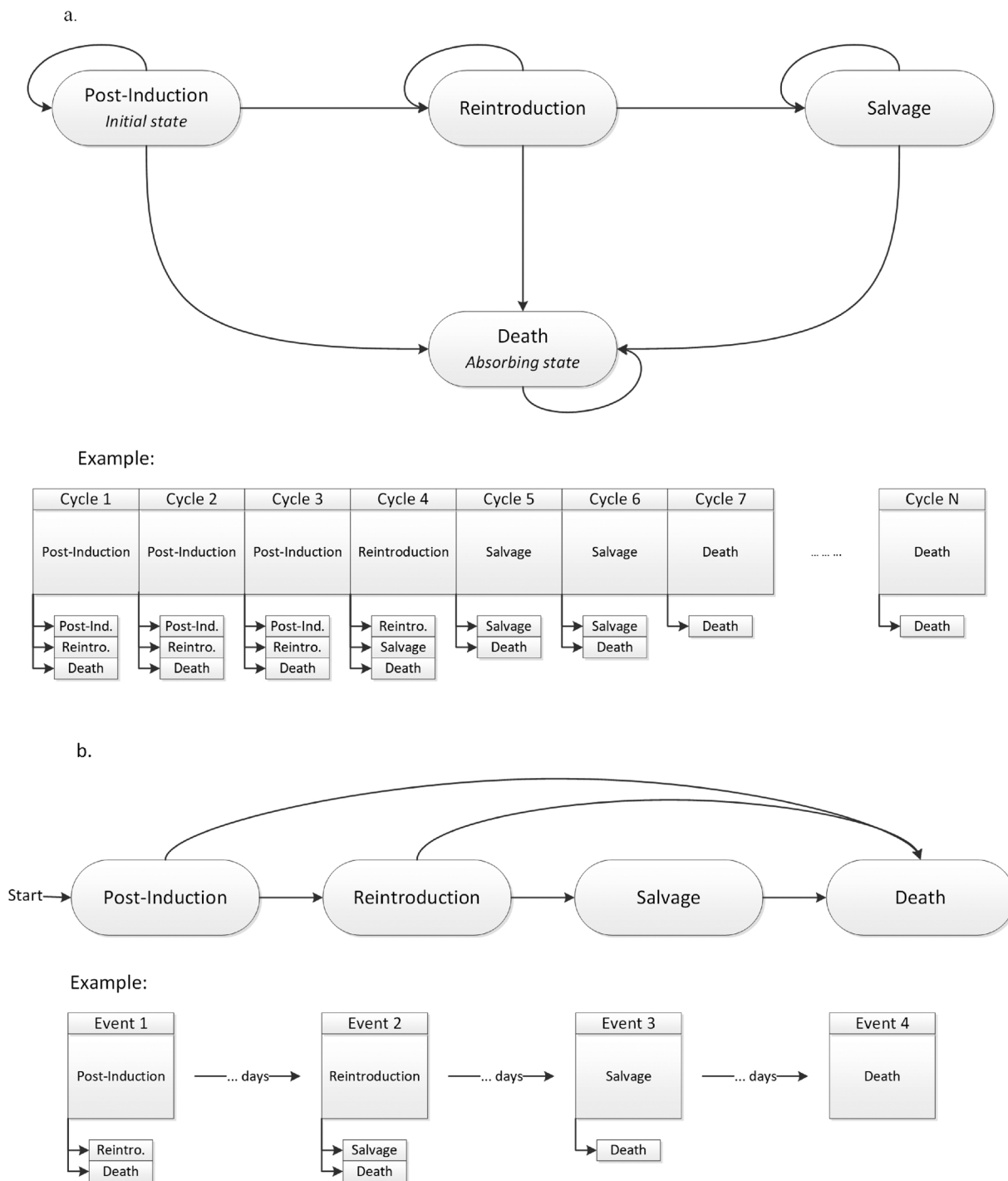
a.

b.

Fig. 1. Graphical representation of the health states defined in the Discrete-Time State-Transition (a) and the Discrete Event Simulation (b) model.

considered in the DT-STM and, consequently, also not in the DES model.

Both Weibull and Gamma parametric distributions [13] were estimated from the CAIRO3 trial data with maximum likelihood estimation (MLE), or methods of moments estimation (MME) where MLE was not successful, using the *fitdist* function of the *fitdistrplus* [23] package in R Statistical Software [24]. Estimated parametric distributions were compared graphically based on density plots, Q-Q plots, and P-P plots, and numerically based on the Akaike information criterion and Bayesian information criterion. Since performance was similar without meaningful differences, and all Weibull distributions could be estimated with MLE, whereas MME was required for some Gamma distributions,

Weibull distributions were assumed for all health state-specific time-to-event parameters in the DES model. Transitions between health states, i.e. events, were based on patient-level processing times, which were randomly drawn from Weibull distributions. Competing risks were handled by stratifying state-specific time-to-event distributions according to the two competing events that were considered, i.e. progression and death, and selecting the event to occur based on the respective observed probabilities of progression and survival [25]. To illustrate this, for a patient entering the reintroduction state a randomly drawn value compared to the chance of progression determined whether the patient would survive and progress to the salvage therapy state. Next, the time to the selected event, i.e. progression or death, was

randomly drawn from the corresponding Weibull distribution.

A total of 10,000 patients were simulated per treatment strategy in the DES model, resulting in relative standard errors for the mean costs and effects of approximately 0.5%. No fixed runtime was assumed, so the simulation terminated when all patients had left the model, i.e. reached the death state. Patient-level outcomes were calculated using the time spent in each health state and summarized to enable comparison of the two treatment strategies. The DES model was validated by structured "walk-throughs", comparing (intermediate) results with calculations by hand, extreme value analysis, trace analysis, and cross validation with both DT-STMs during model development, and by sensitivity analysis [21,22].

2.4. Model comparison

First, the original DT-STM and the replicated DT-STM were compared based on the cost-effectiveness outcomes of the CAIRO3 case study, to assess potential variation in outcomes due to differences in software environments. For this analysis, the incremental cost-effectiveness ratio (ICER) expressed in incremental costs per Quality Adjusted Life Year (QALY) gained served as the primary outcome. Costs and effects were discounted at discount rates of 4% and 1.5% per year, respectively, according to Dutch pharmacoeconomic guidelines [26]. Probabilistic sensitivity analysis (PSA) was performed using Monte Carlo simulation with 10,000 samples to assess the effect of the uncertainty surrounding the input parameters on the primary outcome measure [27]. Since the original cost-effectiveness analysis did not account for uncertainty in the correlated cycle-specific transition probabilities [19], uncertainty in the correlated distribution parameters used to represented the time-to-event evidence in the DES model, was also not considered to maintain comparability between both models. Parameter values used to populate both models, including their distributions, are listed in the publication of the original CAIRO3 cost-effectiveness analysis [19], as well as in Supplementary Materials 1.

Subsequently, the replicated DT-STM and the DES model were qualitatively and quantitatively compared based on the case study, to assess potential differences between the two modeling methods. The models were qualitatively compared based on the evidence structure. Thereafter, modeling methods were quantitatively compared based on cost-effectiveness outcomes and simulation outcomes, i.e. the simulated health-state durations. All results were graphically represented, using Kaplan-Meier curves for the simulation outcomes and incremental cost-effectiveness planes and cost-effectiveness acceptability curves (CEAC) for the cost-effectiveness outcomes.

3. Results

The replicated DT-STM developed for this study yielded comparable cost-effectiveness outcomes as the original DT-STM developed in a different software environment. The results for the original DT-STM have been previously published elsewhere and are not presented here for the sake of readability [19]. The replicated DT-STM will be referred to just as "DT-STM" in the subsequent part of this manuscript.

3.1. Simulation of health state-transitions

Health state-transitions in the DES model yield smooth time-to-event curves defined using Weibull distributions estimated based on the CAIRO3 data. In contrast, the time-dependent probabilities used for health state-transitions in the DT-STM become irregular (non-smooth) when only few events are observed for some transitions. The irregularities in these transition probabilities are caused by a decreasing number of patients retained in a health state over time, causing large variations in the observed subsequent probability of a health state-transition. An example of this is presented in Fig. 2, which depicts the difference between the DT-STM and DES model in health state-

transitions from the post-induction state to the reintroduction state for the maintenance treatment strategy.

The Kaplan-Meier curves for the health state-durations simulated in the DT-STM and DES model, compared to the CAIRO3 data, demonstrate that both modeling methods represent the clinical data well (Fig. 3). However, when the mean time-to-transition presented in the descriptive statistics below the figure are considered, the DES model seems to represent the trial data more accurately. In example, the mean health-state duration of the post-induction state for the observation strategy was 175.7 days, 207.5 days and 173.4 days for the trial data, DT-STM and the DES model, respectively.

3.2. Cost-effectiveness analysis

The cost-effectiveness outcomes obtained from the DT-STM and the DES model are presented in the incremental cost-effectiveness planes of Fig. 4. The incremental effectiveness estimates, including their 95% confidence intervals (CI), for CAP-B maintenance therapy compared to the observation strategy are 0.21 (CI: 0.015; 0.430) and 0.18 (CI: 0.006; 0.374) QALYs, and the incremental costs are €35,536 (CI: 19,945; 54,629) and €30,053, (CI: 17,047; 46,132) for the DT-STM and DES model, respectively. The mean ICERs are €172,443 and €168,383 per QALY gained for the DT-STM and DES model, respectively.

The PSA for both models only demonstrated a small difference in the amount of uncertainty surrounding the mean ICER point-estimates (Fig. 4). This is illustrated by the magnitude of the 95%-confidence ellipses surrounding these estimates, being slightly smaller for the DES model. However, as both mean ICER point-estimates and corresponding confidence ellipses are located rather similarly compared to the willingness-to-pay (WTP) threshold, the CEACs for both models are similar (Fig. 5).

4. Discussion

Smooth health state-transition curves served as input for the DES model, presenting the data in an informative manner. Conversely, it is more complicated to interpret the time-dependent health state-transitions probabilities used as input for the DT-STM. We have shown that these probabilities are irregular over time, due to scarce observations in many of the time cycles. Therefore, the health state-transition curves used in the DES model were much more representative of a "natural" patient flow through health states over time. Additionally, the Kaplan-Meier curves per health state simulated from the DES model matched the original study Kaplan-Meier curves slightly better, especially with regard to the mean time to transition from one health state to another, e.g. from randomization to the start of therapy reintroduction. The increasing difference between the trial data and STM over time, suggests a cumulative effect over successive health states, which may be amplified by a combination of irregularities in transition probabilities and their time-dependency.

Cost-effectiveness outcomes were comparable for the DT-STM and the DES model (ICER €172,443 and €168,383, respectively). The rather small differences observed, can be explained by the disparities in simulated mean time to transitions between both models. Furthermore, the magnitude of uncertainty surrounding the mean ICER point-estimate was smaller for the DES model. The observed difference in the uncertainty might be caused by the irregularities in the health state-transition probabilities in the DT-STM, consequently causing more extreme effects compared to the smooth health-state transition curves of the DES model. Results of this study did not alter the previously published conclusion that CAP-B maintenance may not be regarded as cost-effective [19].

These results confirm that cost-effectiveness outcomes are not expected to be substantially different between DT-STM and DES models, if both models are based on the same evidence [16,17]. It is, however, imaginable that ICER outcomes closer to a country's willingness to pay
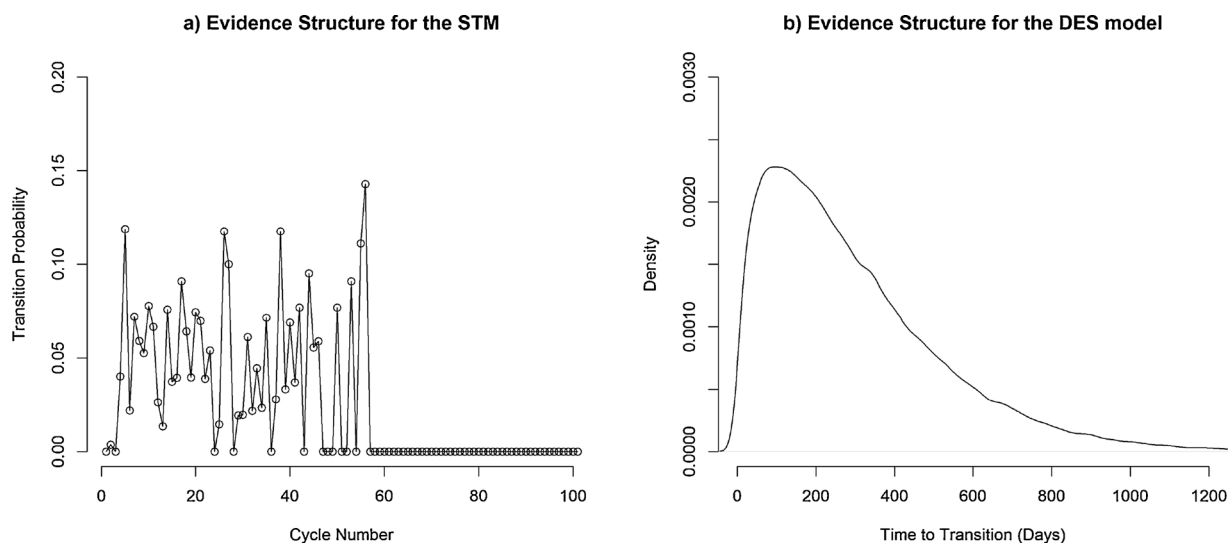
Fig. 2. a) probability curve for the time to transition of the post-introduction to the reintroduction health state for the maintenance strategy per cycle (with a 3-week duration) for the DT-STM, and b) probability density curve for the time to transition of the post-introduction to the reintroduction health state for the maintenance strategy in the DES model.

threshold might incur different conclusions on cost-effectiveness depending on the choice of modeling method. This was previously demonstrated by Jahn et al comparing a DES model and a DT-STM evaluating decision tools for adjuvant chemotherapy treatment in breast cancer [28].

Even though the DES methodology may initially seem more complex for novices, its model structure and evidence structure more closely match transitions and events as observed in clinical trials, compared to that of DT-STM. Once familiar with the DES methodology, the parametric distributions used to describe time-to-event data are straightforward to estimate and interpret. Furthermore, these parametric distributions enable uncertainty in their parameter estimates to be included in the PSA more easily than the (correlated) uncertainty that is present in every individual time-dependent transition probability [29]. However, by discretizing parametric time-to-event distributions into transition probabilities that can be used to populate a DT-STM, uncertainty in these transition probabilities can be represented. Additionally, by discretizing a parametric distribution rather than directly estimating transition probabilities from individual patient data, issues with regard to irregularities in these time-dependent transition probabilities may also be addressed. Furthermore, extrapolation beyond the time horizon of RCTs, although challenging, can be performed by fitting these parametric distributions [30]. Although parametric distributions can be used to address these general and DT-STM related challenges, doing so can be considered suboptimal due to the required discretization, whereas these parametric distributions can be incorporated directly in DES. In this respect, issues regarding appropriately reflecting uncertainty surrounding health economic outcomes, scarce events, and extrapolation may more easily be addressed using DES methodology. Regardless of these advantages to DES, DT-STM typically is computationally simpler, can be implemented using spreadsheets, and requires limited (programming) skills to do so, whereas implementation of DES is mainly limited to specialized simulation and statistical software [15,17,31]. Hence, regarding external review of models, DT-STM currently has an advantage, while experience with DES in health economics is developing [15,31].

DES seems the preferable modeling method compared to DT-STM for the evaluation of individual patient time-to-event data, which is also supported by the health economic modeling literature [15,31]. In particular when time cycle size needs to be very small to adequately reflect dynamic treatment and monitoring processes, leading to irregularities in the estimated time-dependent transition probabilities due to a lack of observed events. However, DT-STM is still the most commonly used modeling method in cost-effectiveness modeling, for which different reasons can be identified. Firstly, as mentioned before, DES might initially be thought of as a more complex methodology requiring more evidence. This study demonstrated that DES models do not necessarily require more evidence or are more complex. Secondly, comprehensive guidance is available on how to use a (cohort) DT-STM for the evaluation of healthcare interventions [9], whereas the available guidance on the use of DES is less specific [14]. Researchers and clinicians with interest in health economics alike, however, should be aware of the potential advantages of DES compared to DT-STM, especially with regard to cost-effectiveness analyses informed by patient-level time-to-event data obtained from e.g. obtained from clinical trials.

This study compared a cohort state-transition model qualitatively and quantitatively based on an extensive health economic evaluation informed by patient-level time-to-event data obtained from the CAIRO3 study. Both models were developed in the same software environment and analyzed according to health economic good practices guidelines, optimizing the validity of our results. However, the generalizability of these single case study results is limited, though the results found are in line with literature [16,17,28]. Furthermore, the full potential of DES was not utilized, since no patient-level characteristics were incorporated and, deliberately, parameter uncertainty in the time-to-event distributions parameter estimates themselves were not considered. The inclusion of patient-level characteristics in DES models undoubtedly allows for even better representation of clinical practice. Finally, Weibull distributions were assumed for representing health state durations in the DES model, which may potentially influence health economic outcomes. To assess the impact of this design choice, simulations were additionally performed with Gamma distributions instead of Weibull distributions, which did not result in meaningfully different results.

In conclusion, the results show that the DT-STM and DES model did not yield substantially different outcomes if they are developed based on the same health states and evidence. Which modeling method should be applied, depends on the complexity of the clinical process to be modeled, the available evidence, and the modelers' experience. In our opinion, DES is the preferable modeling method in the scenario that patient-level time-to-event data is available, e.g. from clinical studies, as its model structure and evidence structure represent the dynamics of daily clinical practice more naturally.
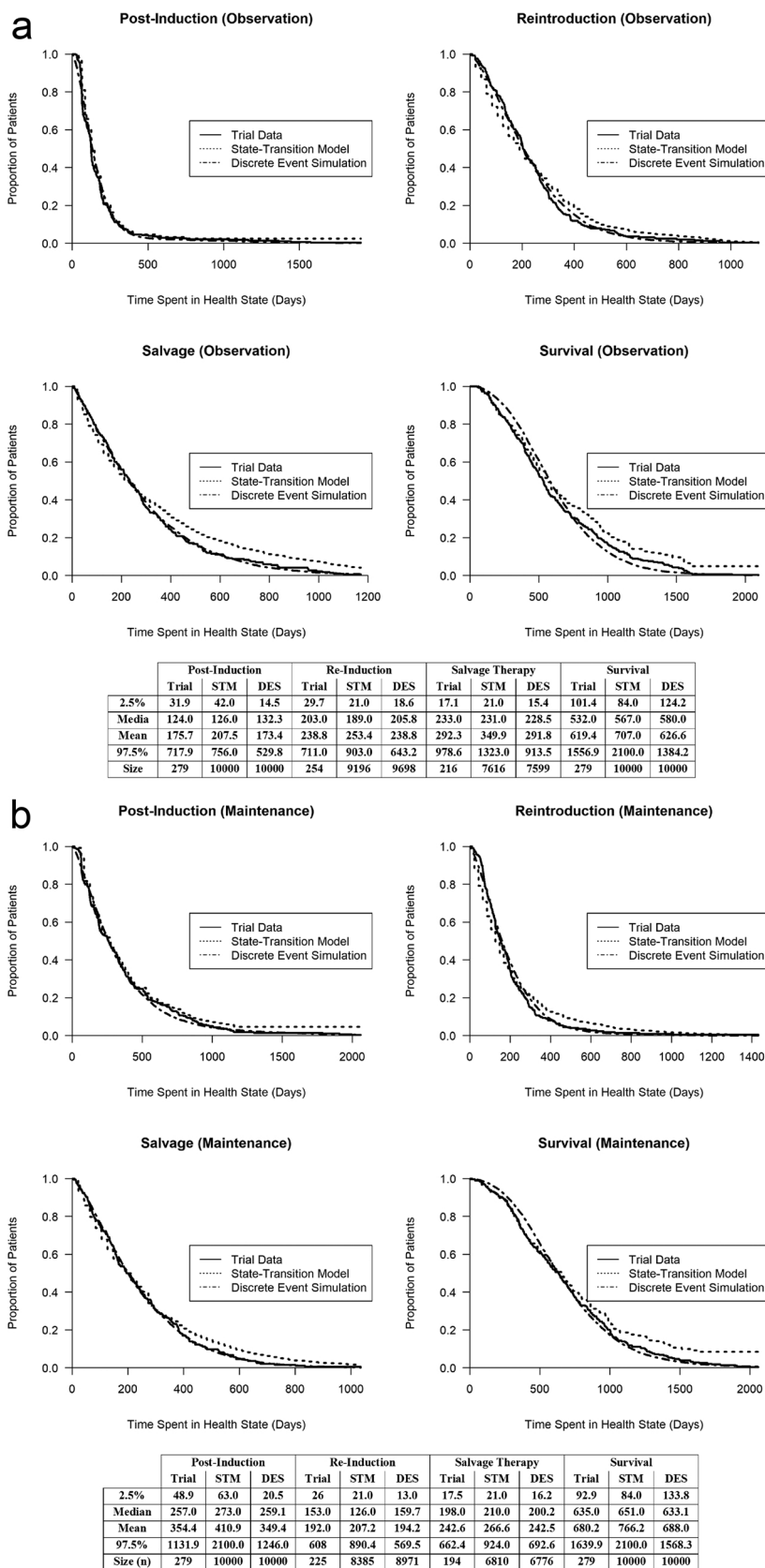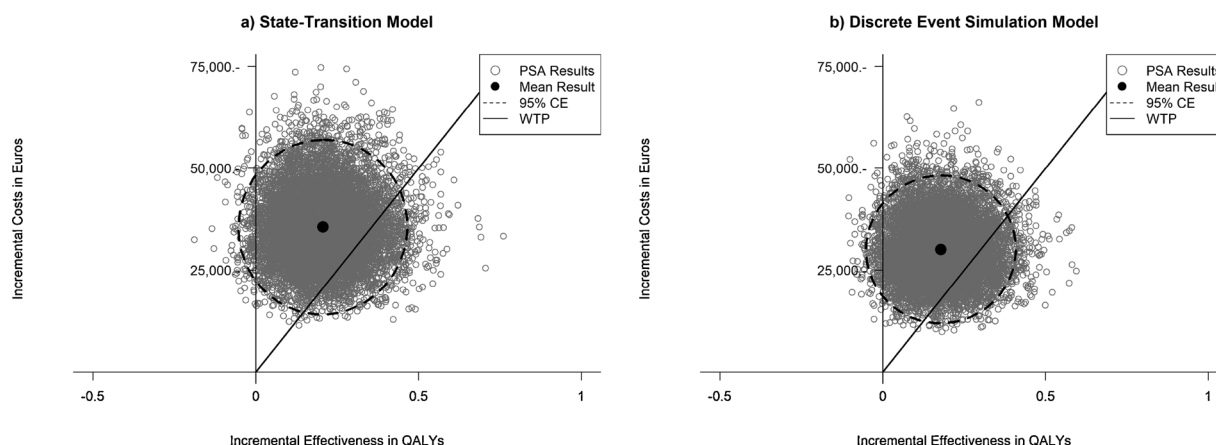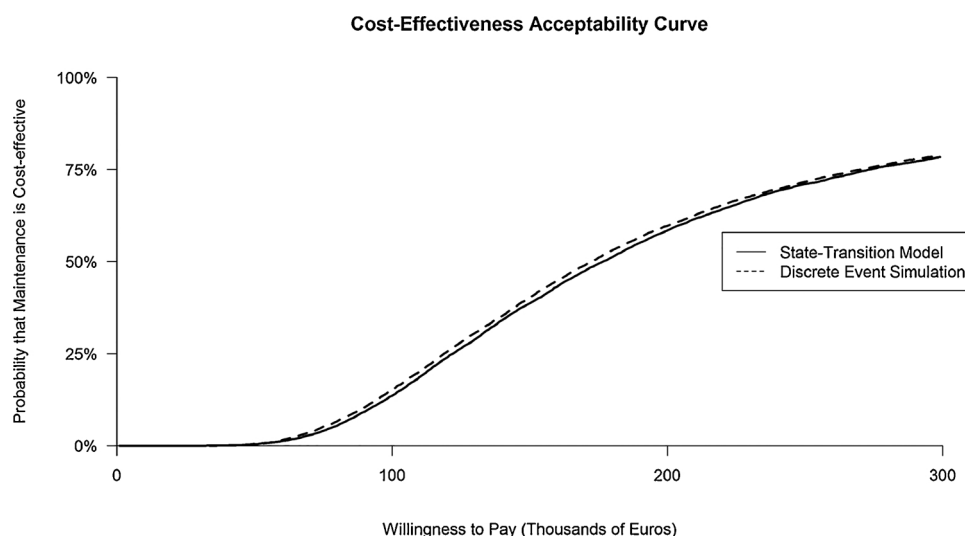
Table (a) Observation strategy:

	Post-Induction			Re-Induction			Salvage Therapy			Survival		
	Trial	STM	DES	Trial	STM	DES	Trial	STM	DES	Trial	STM	DES
2.5%	31.9	42.0	14.5	29.7	21.0	18.6	17.1	21.0	15.4	101.4	84.0	124.2
Media	124.0	126.0	132.3	203.0	189.0	205.8	233.0	231.0	228.5	532.0	567.0	580.0
Mean	175.7	207.5	173.4	238.8	253.4	238.8	292.3	349.9	291.8	619.4	707.0	626.6
97.5%	717.9	756.0	529.8	711.0	903.0	643.2	978.6	1323.0	913.5	1556.9	2100.0	1384.2
Size	279	10000	10000	254	9196	9698	216	7616	7599	279	10000	10000

Table (b) Maintenance strategy:

	Post-Induction			Re-Induction			Salvage Therapy			Survival		
	Trial	STM	DES	Trial	STM	DES	Trial	STM	DES	Trial	STM	DES
2.5%	48.9	63.0	20.5	26	21.0	13.0	17.5	21.0	16.2	92.9	84.0	133.8
Median	257.0	273.0	259.1	153.0	126.0	159.7	198.0	210.0	200.2	635.0	651.0	633.1
Mean	354.4	410.9	349.4	192.0	207.2	194.2	242.6	266.6	242.5	680.2	766.2	688.0
97.5%	1131.9	2100.0	1246.0	608	890.4	569.5	662.4	924.0	692.6	1639.9	2100.0	1568.3
Size (n)	279	10000	10000	225	8385	8971	194	6810	6776	279	10000	10000

Fig. 3. a) Kaplan-Meier curves for the time-spent in the health states for the observation strategy. b) Kaplan-Meier curves for the time-spent in the health states for the maintenance strategy.

a) State-Transition Model

b) Discrete Event Simulation Model

Fig. 4. Incremental Cost-Effectiveness Planes comparing the maintenance treatment strategy with the observation strategy at a Willingness to Pay (WTP) of €100,000.- per Quality Adjusted Life-Year (QALY) gained, for a) the discrete-time state-transition model, and b) the discrete event simulation model. CE = Confidence Ellipse.

Cost-Effectiveness Acceptability Curve

Fig. 5. Cost-Effectiveness Acceptability Curves representing the probability that the maintenance treatment strategy is cost-effective compared to the observation strategy for a range of Willingness to Pay threshold values.

Author contributions

The research design was developed as combined effort of KD, MF, AM, MK, and HK, and was revised by MO, CP, and MIJ. Models were developed, and analyses were performed by KD and MF, under the supervision of MK and HK. All authors contributed to the interpretation and discussion of the results. The initial manuscript was drafted by KD, MF, and HK, and critically revised by AM, MO, MK, CP, and MIJ. The overall guarantor of this study is HK.

Conflicts of interest

The authors declare no conflict of interest.

Funding sources

No funding was received for performing this study.

Ethics approval and consent to participate

The CAIRO3 study protocol, which includes secondary data analyses such as performed in this study, was approved by the Committee on Human-Related Research Arnhem-Nijmegen in the Netherlands.

Written informed consent was not required for this study separately, as written informed consent was obtained from all participants in the CAIRO3 study, which includes secondary data analyses such as performed in this study

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2018.09.008.

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