Constructing a State-Transition Model for an Economic Evaluation of Cancer Treatments

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The paper gives an overview of the four fundamental elements that should be considered when constructing a Markov model of cancers, including outcome measures, health state transition, transitional probabilities, and model calibration. The construction of any model of this kind should begin by establishing transition to the death state. The probability of this transition can be estimated using overall survival data from clinical studies. Possible health states over a cycle are defined according to the natural history of diseases and treatment pathways. Validity of the constructed model is tested against real patient data and the parameters are adjusted until the survival results are consistent.

Keywords: *Health state, Markov model, Solid tumor, Survival, Transitional probability*

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Among healthcare experts, there is growing recognition of the importance of "whole disease modeling" to help inform decisions regarding prevention and treatment[1]. This paper provides an overview of the fundamentals of constructing a state-transition model (best known as a Markov model), to serve as a whole disease model for cancers and treatment pathways. Four related methodological issues are examined: 1) choice of outcome measures from clinical studies, 2) development of health state transition, 3) estimation of transitional probabilities, and 4) calibration of the constructed model.

Outcome measure

When building an economic evaluation model of cancer treatments, a crucial first step is deciding which outcome measures, derived from existing clinical and epidemiological studies, will be used in the model. In most randomised controlled clinical trials (RCTs) and comparative effectiveness research[2], overall survival (OS) or disease-free survival (DFS)-sometimes called progression-free survival (PFS)-are set as the primary end point, and treatment response is set as the secondary end point. For cancers where treatment is unlikely to increase patient survival, studies may choose to report the response rate instead.

For OS and DFS/PFS, the survival rate (measured as a 0-1.0 proportion or 0-100%) at various time points can be estimated using the Kaplan-Meier method. For ease of understanding, it is normally depicted as a survival curve, with the survival rate equal to 1.0 (or 100%) at time zero, which then declines over time as in the life table[3]. Because DFS/PFS is a combined end point, consisting of surviving patients who have no progressive disease (PD), the DFS or PFS is always lower than the OS at any given time point. Median survival data (the duration of time that passes before half of the patients have died) and time to progression data should not be used directly for estimating a transitional probability of the model parameter.

Treatment response rate is usually derived from data from patients who at baseline have at least one cancerous cell with the longest diameter (LD) no shorter than 20 mm (or 10 mm based on spiral CT scans), and who afterwards are evaluated (i.e. excluding data from patients who drop out before evaluation). It is important to note that the response rate becomes an unreliable or unstable outcome measure in studies where the number of evaluated patients is far below the number at baseline.

For patients with solid tumors, an objective response (OR) to the treatment can be classified as either complete response (CR), where all cancer cells are found to have disappeared following treatment, or partial response (PR), where fewer cancer cells are found than before treatment or where the LD of the tumor is found to be reduced by at least 30%[4]. Non-response (NR) outcomes can include stable disease (SD), where

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target lesions are found to have shrunk or enlarged by a certain degree (less than PR or PD) or progressive disease (PD), where the LD is found to have increased by at least 20% or where a new lesion is observed. PD indicates the second worst possible treatment outcome following death as a result of the disease. It is regarded as treatment failure, and often leads to death, which is referred to technically as the 'absorbing health state'.

Health state-transition

A Markov model is a state-transition model[5] that simulates the transition of health states of a hypothetical cohort of patients according to the natural history of the disease from a starting time point until the end of an adequately long time horizon[6,7]. Fig. 1 illustrates six mutually exclusive health states for cancer treatments that are possible in each Markov cycle. Markov cycles are relatively short to ensure that the probability of health state transition remains stable for the entire cycle period.

Having undergone first-line treatment, patients in the first cycle may reside in one of the following health states: CR, PR, SD, PD (and pre-progression), or death. In Fig. 1, three states-CR, PR, and SD-are combined into a single state, which can be named clinical response (clinR), standard practice when modeling for cancers that have very high fatality rates. In certain circumstances, the SD state can be separated from the CR and PR states. For instance, if the treatment is expected to be very effective, the CR should be included in the model separately.

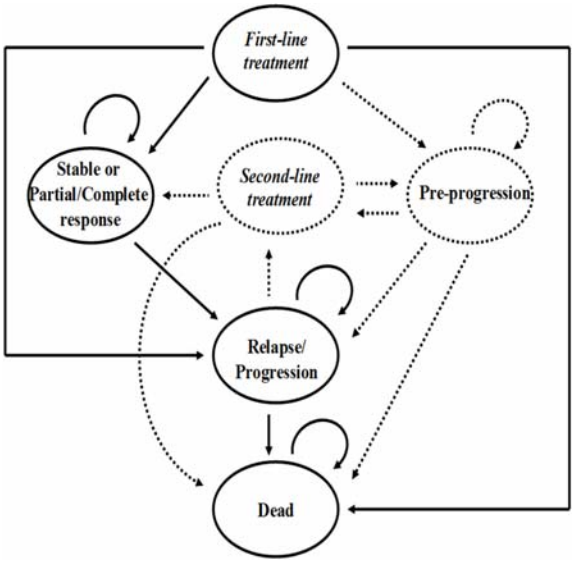

Fig. 1 Health state transitions after cancer treatment.

In the second cycle, surviving patients for whom first-line treatment failed may be switched to the second-line treatment before their disease progresses further. Some of these patients who do not receive next-line treatment enter the PD state and some of them die. The rest of the patients return to recursive pre-progression state.

Some patients who respond to first-line treatment or who stay in the SD state enter the relapse state in subsequent cycles, and some remain there until death, as a result either of disease progression or being switched to second-line treatment. The rest of the patients stay in the recursive response or stable state. Those who receive second-line treatment follow a similar pattern of health state transition in the subsequent cycles. For models that do not allow patients to be switched to the next-line treatment, the health state transition, indicated by the dashed line, can be omitted from the model.

Transitional probability

In order to ensure the model parameters include health outcomes that are similar to those used in clinical studies, the first step with any model of a potentially terminal disease, like cancer, is to calculate the probability of transitioning to the death state from the comparator arm. The probability of dying, P (D), in the first cycle can be calculated using an OS derived from a single study, over a duration comparable to the cycle length, as shown in equation 1.

$$P(D) = 1 - OS \quad (1)$$

If the data were obtained from several studies (k = 1, 2, …, K), an average for the P (D) should be derived using the weighted average, $P(D)_{avg}$, by placing a higher weight on data from studies with larger sample sizes (n). Because probability (P) is non-linear, pooling the studies need to be done through a transformation and retransformation of the linear parameter rate (r), as shown in equations 2-4[3].

$$r(D)_k = - \ln (1 - P(D)_k) \quad (2)$$

$$r(D)_{avg} = (n_1 r(D)_1 + n_2 r(D)_2 + ... + n_K r(D)_K)/(n_1 + n_2 + ... + n_K) \quad (3)$$

$$P(D)_{avg} = 1 - \exp(- r(D)_{avg}) \quad (4)$$

For the treatment of interest, estimating P(D) directly from the treatment arm of a study, as shown in equation 1, is not recommended. Instead, the relative efficacy of OS should be used to enable the treatment

to be compared with the control. For example, the treatment's P(D) should be derived from the hazard ratio (HR), as shown in equation 5. In this case, the HR can be obtained from a meta-analysis as well.

$$P(D)_{treatment} = HR_{OS} \times P(D)_{control} \quad (5)$$

Estimating the probability of the disease progressing, P(PD), is slightly more complex. It is not exactly equal to 1 - DFS (or 1 - PFS), since the DFS or PFS is a combined end point, which includes death or P(D), as shown in equations 6 and 7.

$$DFS = 1 - P(D) - P(PD) \quad (6)$$
$$P(PD) = OS - DFS \quad (7)$$

To distinguish between those patients for whom treatment failed and those for whom it did not, using the treatment comparator, the probability of having a clinical response, P(clinR) for the whole cohort is used. This can be estimated using the objective response rate (ORR), which is based on the data from surviving patients, as reported by clinical studies (equation 8).

$$P(clinR) = (1 - P(D)) \times ORR \quad (8)$$

For the treatment of interest, an estimation of the P(clinR) should not be derived directly from the ORR of the study's treatment arm. Instead, relative efficacy of DFS or PFS, derived from comparison of the treatment with the control should be used for this purpose, as shown in equation 9.

$$P(clinR)_{treatment} = (1/HR_{DFS}) \times P(clinR)_{control} \quad (9)$$

The probability of a patient's treatment failing or of a patient being in the pre-progression state, P(pre PD) of whom some would continue onto next-line treatment, is estimated in equation 10.

$$P(pre\ PD) = 1 - P(D) - P(clinR) \quad (10)$$

Model calibration

Before using the hypothetical cohort simulation to conduct further calculations on cost and effectiveness, the constructed model should be examined for its validity. This can be done by examining whether the results of the cohort simulation are consistent with findings from the referent clinical studies or the established epidemiology of the disease[8]. Frequently, a number of parameters need to be calibrated again to refine the model, until the simulation result is close to the real patient data.

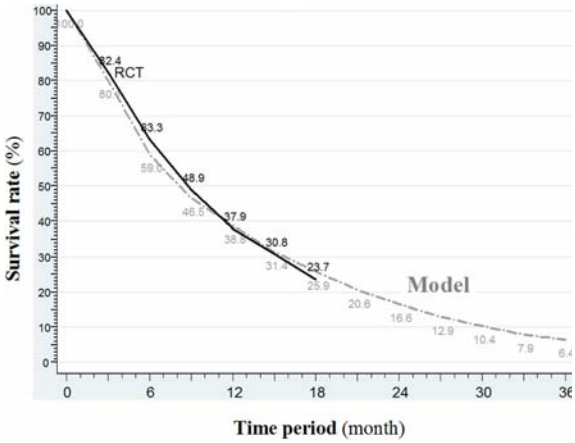

Fig. 2 Overall survival of non-small cell lung cancer for docetaxel, Markov model and RCT results[9].

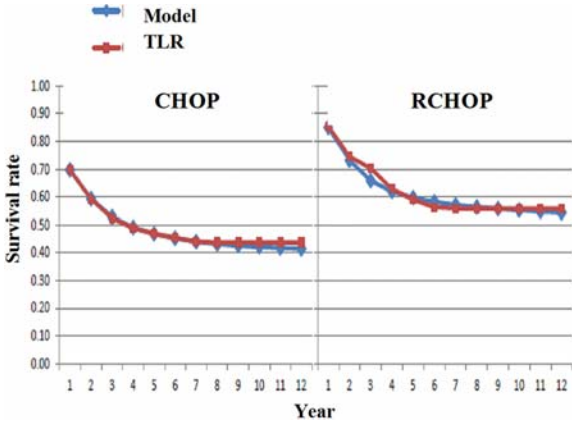

Fig. 3 Overall survivals of non-Hodgkin Lymphoma for CHOP and RCHOP, model-based and Thai Lymphoma Registry (TLR)[10].

For cancers, the best indication of a valid model is the survival curve, which most clinical studies use as a primary endpoint. Fig. 2 and 3 compare the survival at various time points between data obtained from the models and data reported by the RCT[9] or national registry[10]. Notice that the survival curves are comparable, even though in Fig. 2 the follow-up period in most RCTs is shorter than the time horizons used in the models.

Guidelines for Health Technology Assessment in Thailand (second edition): Recommendations for economic evaluation of cancer treatment

The authors have presented a summary of

each of the four key aspects that should be taken into account when constructing a Markov model of cancers: 1) choice of outcome measures, 2) health state transition, 3) transitional probabilities, and 4) model calibration. In developing a Markov model for cancer, the first step should be the clarification of the probability of transition to the death state. This can be estimated using the OS, obtained directly from the end point of existing clinical studies. For models that permit next-line treatment, a secondary end point, usually in terms of response to the first-line treatment, can also be included. Validity of the constructed model should then be verified by examining the survival results of the models and comparing them with data from existing databases. The parameters should then be adjusted accordingly, until the model findings are close to reality.

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Potential conflicts of interest

None.

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การสร้างตัวแบบการเปลี่ยนสถานะสุขภาพสำหรับการประเมินทางเศรษฐศาสตร์ของการรักษาโรคมะเร็ง

จุฬาภรณ์ ลิมวัฒนานนท์, สุพล ลิมวัฒนานนท์

บทความนี้อธิบายพื้นฐานสำคัญ 4 ประการ ในการสร้างตัวแบบมาร์คอฟสำหรับโรคมะเร็งได้แก่ มาตรวัดผลลัพธ์ การเปลี่ยนสถานะสุขภาพ ความน่าจะเป็นของการเปลี่ยนสถานะสุขภาพ และการปรับตัวแบบ การเปลี่ยนเข้าสู่สถานะการเสียชีวิต เป็นขั้นตอนแรกที่ควรทำโดยคำนวณความน่าจะเป็นตามข้อมูลอัตรารอดชีพซึ่งได้จากการศึกษาทางคลินิก การกำหนดสถานะสุขภาพที่เป็นไปได้ในแต่ละรอบจะกำหนดตามลักษณะการดำเนินโรค และแบบแผนการรักษา ความตรงของตัวแบบที่สร้างขึ้นควรได้รับการทดสอบโดยเปรียบเทียบกับข้อมูลของผู้ป่วยจริงโดยมีการปรับค่าพารามิเตอร์จนกระทั่งได้ผลที่ใกล้เคียงกัน