Comparison Study Based On Simulation Of Patient Pathways Using Multi-State Models In Oncology

Tamás Balázs[1], Pál Rakonczai[1], Róbert Frigyesy[1], Miklós Bacskai[1]
[1]Healthware Consulting Ltd., Budapest, Hungary

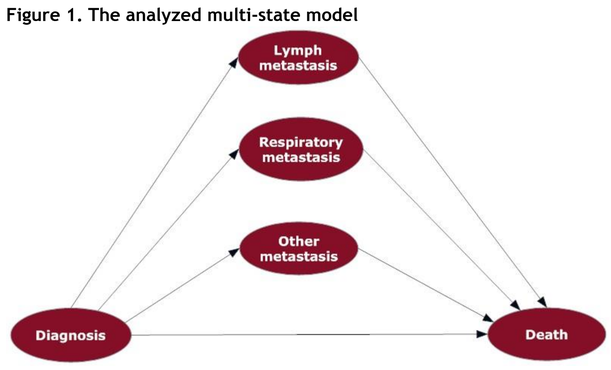
Background

- Cancer is one of the leading causes of death worldwide, and due to the increasing life expectancy it continuously requires more attention from the health care provider systems. The increasing number of new cases causes serious financial consequences through direct costs such as costs of treatment, rehabilitation or prevention and indirect costs as productivity loss and further non-medical costs. [1]
- According to WHO estimations, in 2012, the total number of cancer cases worldwide was 40.7 million. The ratio of new cancer cases was 34.6% and the mortality ratio was 20.2%. [2]
- In Hungary, the mortality ratio is one of the highest among the members of the European Union. The most frequent type of cancers among men were lung (21.8%), colorectal (17.6%) and prostate (11.7%) cancer, and breast (21.7%), colorectal (15.7%) and lung (14.4%) cancer among women. [3]
- Nowadays, in the field of oncology using multi-state models (MSM) has become increasingly popular in medical research for modelling the transitions of patients among the various states. [4, 5]
- Usually, MSM estimates, even in the case of few transitions, can only be summarized in a rather complex structure and their interpretation is often very complicated. However, simulations based on a given structure are relatively easy and fast to carry out.
- The simulated transition can be transformed into well-known utility indicators (e.g. QALY, DALY, LYG).
- The main aim of this study is to demonstrate a straightforward way of presenting results based on simulations from MSM in the field of oncology.

Methods

- **Data Source:** The study was based on the nationwide database of the Hungarian National Health Insurance Fund (NHIF), which includes all reimbursed health care services at the patient-level. The NHIF database contains demographic data on age, gender, date and location of birth/death and most importantly patient ID, type/date/place of service, International Classification of Diseases (ICD-10 codes) and International Classification of Health Interventions (ICHI) codes for in- and outpatient care or imaging technics. The actual results of laboratory tests, examinations or operations are not directly available.
- **Study Period:** Validated historical data were available from 1st January 2005 to 30th September 2015. The first two years were used as baseline period, hence the study period spanned from 1st January 2007 to 30th September 2015. The baseline period ensured that all patients had at least 2-year long history before the follow-up started (index date).
- **Study Population:** The following three cancer types were investigated in the study: lung cancer (C34), prostate cancer (C61) and kidney cancer (C64-65). Preliminarily, patients were classified into a cancer group based on the first observed health care event. In order to avoid misclassification one of the following confirming criteria were required within a year after the first observed event: dispensation of relevant medical treatment, occurrence at inpatient care, at least 3 visits at general practitioner, or death. Patients, who did not fulfill at least one of these criteria, were excluded from the study. For the sake of simplicity only two years were selected for the inclusion.
- **Statistical Methods:** The observations were structured into a longitudinal pathway for all patients from the index date to the time of death or end of study period. Some special states of the pathways were assigned for the MSM. The initial state started from the index date and lasted until the state of progression or death. Progression was identified by the occurrence of metastatic cancer, which was partitioned into the three following subcategories: lymph (C77), respiratory and digestive organs (C78), other and unspecified malignant neoplasm (C79). The distribution of transition times from one state to another were estimated by Cox proportional hazard models and were framed in a MSM (Figure 1.). The explanatory variables were gender, age, year of diagnosis and Charlson index, which categorized the patients based on their non-oncology aggregated comorbidity attributes (mild, medium and severe). The simulation of patients pathways were calculated using the hazard functions of different competing events [6].

Figure 1. The analyzed multi-state model



Results

- MSM parameters were fitted to the data of 13 781 lung cancer patients, 6 009 prostate cancer patients and 2 566 kidney cancer patients. The comparison study was based on simulated patient pathways. For the simulation there were three different MSM scenarios used assuming certain modifications of population characteristics and model parameters. Each scenario was generated 100 times and the results were compared in terms of changes in the burden of disease. The following scenarios were analyzed in the study:

ORIGINAL – In the first scenario the population characteristics were identical with the observed population and the MSM parameters were kept unchanged.

NO COMORBIDITY – In the second scenario the population characteristics were changed, namely patients with mild and severe comorbidities were replaced by patients having exactly the same characteristics and no comorbidity. MSM parameters were kept unchanged.

FUTURE – In the third scenario the population characteristics were identical with the observed population and the MSM parameters were changed. Namely, all RRs related to the year of diagnosis covariate were uniformly set as 0.5.

- Figure 2 shows the simulated migration of lung cancer patients in the original and future scenarios over 1201 days from the initial state. The average of the simulated transitions are also presented and the averages are considered as point estimates for the expected number of patients at a given time. According to the original scenario the MSM for lung cancer predicts that there are 19% (2626) patients alive at the 601st day and this ratio decreases to 6% (877) at the 1201st day. According to the original scenario, at 361 days there are 22% (3004) in initial state, 4% (568) in C78 metastatic state, 6% (787) in C77 metastatic state, 1% (116) in C79 metastatic state and 67% (9304) died. In the future scenario these numbers are 27% (3753), 5% (671), 6% (867), 1% (133) and 60% (8356).

- Differences in number of patients between the two scenarios are shown in Figure 3 as a function of elapsed time from the diagnosis. It seems clear that the dynamics of the two compared scenarios are different. In the future scenario the patients stay longer in the initial state, i.e. the progression appears later. Similarly, after progression the survival time is longer too. The largest difference in initial state is around half year, in death around 1 year.

- Utility indicators as life years (LY) and disability adjusted life years (DALY) were computed for the three scenarios and three cancer groups for 1 and 2 years. Differences in LY and DALY indicators between the original and future scenario are presented in Figure 4 and Figure 5, respectively. Future scenario predicts 1574 gained LY and 1076 gained DALY in lung cancer, 164 gained LY and 131 gained DALY in prostate cancer and 175 gained LY and 110 gained DALY in kidney cancer during a 2 year period of time. Comparison between original and no comorbidity scenarios lead to similar results. Trends in transitions were analogous, but the actual differences in LY and DALY were smaller due to the fact that modification were not as substantial as in the other case. In general, 21-22% of the cancer groups had developed medium comorbidity and 3-4% had developed severe comorbidity.

Figure 2. Lung cancer example – number of patients in the different states

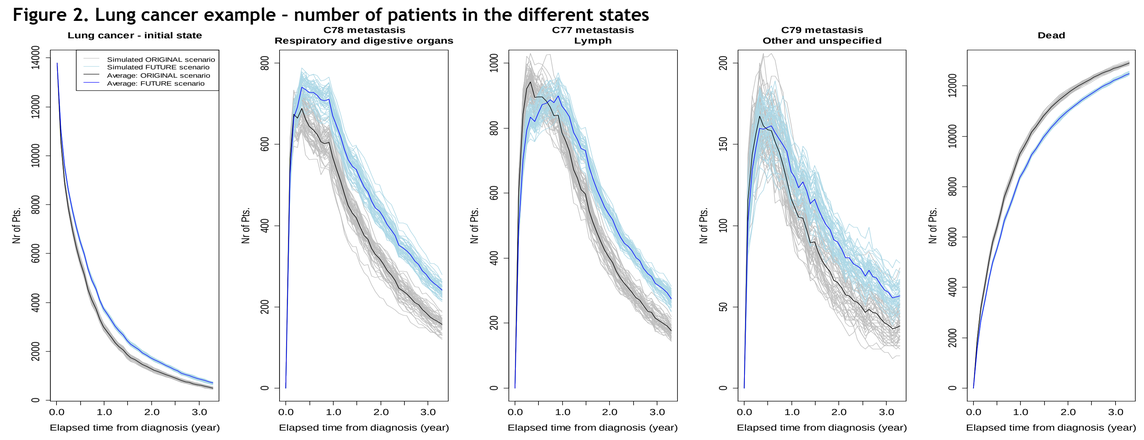


Figure 3. . Lung cancer example - differences in the different states

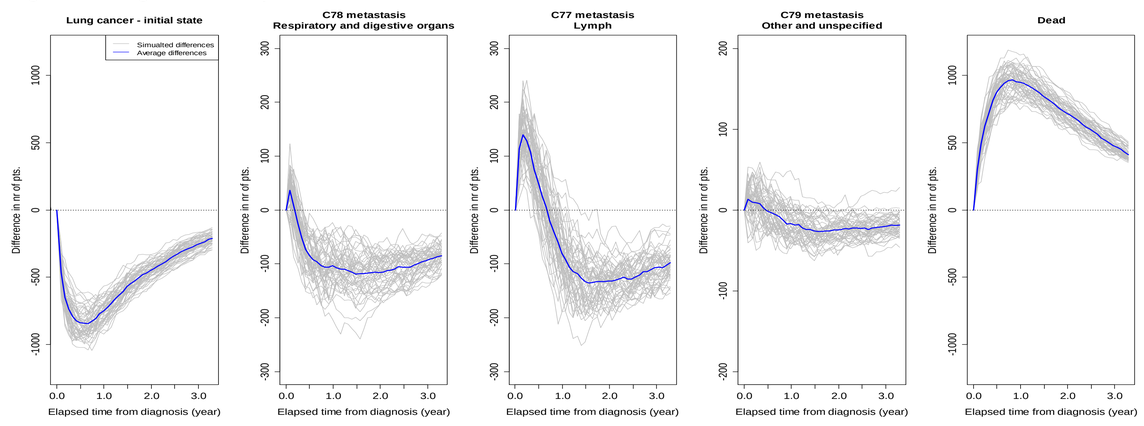


Figure 4. Estimated LY – lung, prostate and kidney cancer

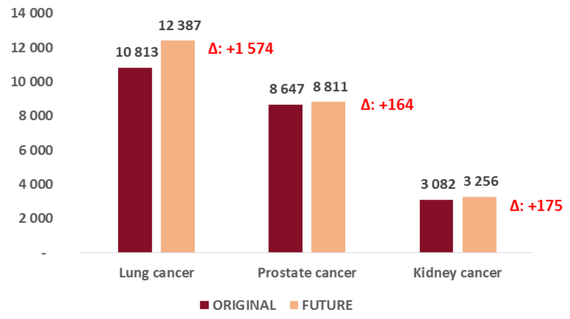
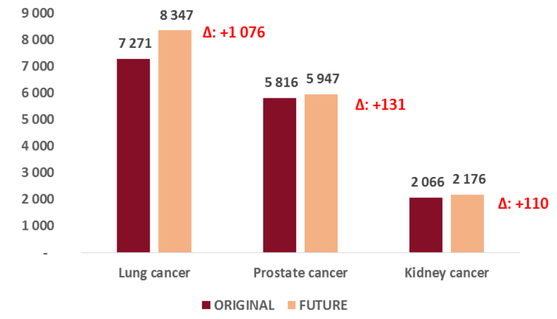


Figure 5. Estimated DALY* – lung, prostate and kidney cancer



*: used disability weights - cancer 0.288, - metastasis 0.451

Conclusions

- MSM can serve as appropriate and flexible framework for different types of time-dependent Markov chain models used in multiple cohort simulations. These models are essential in supporting the planning of interventions of healthcare and public health systems at the population level.
- Including further relevant covariates e.g. smoking, medical treatments, disease-specific indicators can improve the performance of the MSM model, and its applicability can be expanded.

References

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Poster code: PRM127