Study design of a medical device pre-market assessment: a case study on electrochemotherapy

Zasnova študije vrednotenja novih tehnologij v medicini: študija na primeru elektrokemoterapije

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Key words: health technology assessment (HTA); cost-effectiveness analysis (CEA); Markov model; electroporation; electrochemotherapy (ECT)

Abstract

Final goal of the study is to estimate the cost-effectiveness of electrochemotherapy for the treatment of basal-cell carcinoma and skin melanoma. Paper consists of two parts: the first part presents basic principles and concepts of health technology assessment and cost-effectiveness analysis, and the second part reports an early cost-effectiveness analysis of electrochemotherapy for the treatment of basal-cell carcinoma and skin melanoma that we are developing. Few cost-effectiveness analyses of electrochemotherapy have already been done, but with a lack of information about intervention effectiveness in terms of quality of life, which may result in inaccurate or even inadequate conclusions. In order to obtain the most realistic results, two general Markov models and their reduced versions for initial calculations are presented. The models were designed specifically to assess electrochemotherapy of basal-cell carcinoma and skin melanoma. Also, data required for successful calculations have been identified, some of which are missing and will be collected within different studies which are still under way, including randomized control trials. Additionally, recommendations for data collection process and follow-up reporting are made. With this paper we want to raise awareness about the importance of numeric quality of life reporting and usefulness/meaning of EQ-5D questionnaire that might not be self-evident at first sight, but are crucial for cost-effectiveness analysis.

Izvleček

Končni cilj projekta je izdelava analize stroškovne učinkovitosti (*angl.* Cost-Effectiveness Analysis) elektrokemoterapije za zdravljenje bazalnoceličnega karcinoma in kožnega melanoma. Prispevek je sestavljen iz dveh delov. V prvem delu prispevka so predstavljeni osnovni koncepti in postopki vrednotenja tehnologij v zdravstvu (*angl.* Health Technology Assessment) in analize stroškovne učinkovitosti, v drugem delu pa poročamo o zgodnji stroškovni analizi (*angl*. early Cost-Effectiveness Analysis) elektrokemoterapije, kot terapije za zdravljenje bazalnoceličnega karcinoma in kožnega melanoma, kar je predmet naše študije. Nekaj stroškovnih analiz je že nastalo vendar zaradi pomanjkanja podatkov o učinkovitosti zdravljenja, v smislu povečanja kakovosti življenja bolnikov (*angl.* Quality of Life), zaključki ne morejo biti točni. Da bi izdelali čimbolj relevantno analizo, v članku predstavljamo dva splošna Markova modela in njuni poenostavljeni različici, ki ju bomo uporabili za začetne izračune. Modela sta bila zasnovana posebej za analizo elektrokemoterapije bazalnoceličnega karcinoma in kožnega melanoma. Dodatno so opredeljeni tudi potrebni podatki za uspešne izračune. Manjkajoče podatke bomo zbrali v okviru različnih študij, ki še vedno tečejo, vključno z randomiziranimi kliničnimi študijami. Predstavljeno je tudi priporočilo za poročanje, ki bi olajšalo zbiranje podatkov. S tem prispevkom predvsem želimo dvigniti splošno ozaveščenost o pomembnosti številčnega poročanja o kakovosti življenja in uporabnosti oziroma pomenu vprašalnikov EQ-5D, ki na prvi pogled morda nista samoumevna, vendar sta bistvenega pomena za analizo stroškovne učinkovitosti.

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1. Introduction

Electroporation is an evolving technique with many applications (1-4); in this article the focus is on one of the most successful, i.e. electrochemotherapy (ECT). ECT is an antitumor therapy that increases the cytotoxicity of chemotherapeutic drugs such as bleomycin and cisplatin by the help of applied electric pulses. Electroporator is a device that generates high-voltage electric pulses, which are delivered to the tissue trough electrodes (5). If the electric field generated between the electrodes is sufficient, the permeabilization of the target (tumor) cells is triggered and entrance of the previously injected chemotherapeutic drug into cells (within the tumor) is enabled (6). As a result, electrochemotherapy is a highly efficient treatment, with complete response rates, based on a single treatment between 60 to 70 % and objective response rates up to 80 % (7).

Basal-cell carcinoma (BCC) is the most common form of skin cancer and its incidence is still increasing mainly due to the population ageing. Worldwide, every year two to three million patients are diagnosed with non-melanoma skin cancer (8). The current gold standard for the treatment of BCC (and other skin malignancies) is surgical excision (9), but for patients that are unsuitable for conventional treatments, ECT offers a good alternative. Specifically, in the treatment of BCC, the objective response rates after a single ECT session are close to 100 % (75). Upon that, the surrounding tissue remains undamaged and, consequently, a good cosmetic outcome is obtained. In most cases, ECT can be performed as an outpatient procedure under sedation or local anaesthesia. Therefore, treatment with ECT results in a considerably shorter hospital stay, faster recovery and reduced health care costs (10). ECT diminishes the need for surgery, it can be a feasible treatment option for cutaneous lesions resistant to other therapies or can serve as an adjunct to other therapies. The UK National Institute for Health and Care Excellence (NICE) deemed that ECT was a safe treatment for primary BCC, however it also warned about the limited evidence for its efficacy (11).

In western countries the incidence of melanoma has been increasing for as long as recorded (12). Melanoma spreads by lymphogenous and also by hematogenous route. ECT is a standardised procedure for the treatment of superficial metastases of melanoma resistant to other treatments. Skin metastases of melanoma occur in 2–20 % of melanoma patients (13). ECT has several advantages: the treatment can be administered in an outpatient setting under local anaesthesia and deep sedation; it can also be scheduled as a day-care or day-hospital procedure under general sedation; repeated sessions can be performed with a minimum interval of one to two weeks (14-17). Overall ECT can be considered as "patient friendly" procedure with effectiveness consistently reported throughout

the reports. Its effect can be localised, thus reducing side effects. Later in the article, the focus is mainly on the cost-effectiveness of ECT, which will facilitate a comparison of ECT to other treatment options, not only with respect to its effectiveness but also its cost effectiveness.

Screening and evaluation of medical technologies is becoming crucial, as in most of the developed countries health care expenditures are constantly increasing, while at the same time budgets are getting tighter (18). In Slovenia, health care spending is currently estimated below the European average (19,20). Between years 2002 and 2008, health care spending in Slovenia amounted to between 7.49 % and 8.08 % of GDP. It spiked in year 2009 to 8.56 % of GDP and has been between 8.5–8.73 % of GDP ever since (19,21). Unfortunately, based on demographic data, the forecast is not reassuring. In year 2017, 18.7 % of Slovenian population is older than 65 years (22). The projections show that this number is going to be approximately 33.6 % by 2060, what will unavoidably result in a significant increase in health care expenditure. Simulations show that health care expenditure will increase from 0.5 % up to 2.8 % of GDP per year, by the year 2060 (23). Independently of the relative or absolute expenditure per year, the health care national budgets are in any case limited. Therefore, decision makers have to consider carefully all public money spending, especially since, in limited budget scenarios, the introduction of a new technology may result in the exclusion of an old one. There are however cases where innovations were included into the medical practice, without any previous economical evaluations and had to be abandoned later due to economic inefficiency (73). The introduction of new technologies in the Slovenian public health care system is still relatively arbitrary. Each innovation is evaluated according to three criteria: i) health effectiveness (the more severe the disease is the more points it gets); ii) professional justification of the program (meta-analyses and systematic literature reviews get the most points, regardless of the results); iii) economic efficiency (only price is considered here, the cheaper the innovation is, the more points it gets). All innovations are than ranked on a priority list according to the number of points collected (24).

Therefore, an efficiency improvement of health care systems is necessary. Choices about providing health care interventions, based on available evidence regarding safety, effectiveness and cost effectiveness thus have to be made (18). Widely used in most developed countries is a Health Technology Assessment (HTA) evaluation process. HTA is a structured process aiming to inform decision makers about choices which can be used to allocate healthcare budget (25). In the majority of cases, HTA provides an estimate of the incremental cost-efficacy ratio (ICER), which informs decision makers about the gain in terms of quality of life per cost that the introduction of a new technology will produce (77). This article reports on an early cost-effectiveness analysis (eCEA) of ECT for the treatment of BCC and skin melanoma that we are developing. The first part of the paper introduces basic concepts of HTA and CEA, while the second part reports on a case study of electroporation based treatments, in particular ECT for BCC and skin melanoma.

2. Health technology assessment

According to the World Health Organization (WHO), *Health technology assessment (HTA) refers to the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy/decision maker* (26). The evaluation can be applied to systems, general equipment, instruments, hardware and software as well as to procedures, standards, norms, staff skills, professional knowledge, drugs, public health programs, etc. However, HTA is currently manly employed for the pharmaceuticals. Slowly it is being claimed also for biomedical devices, where slightly different methods or at least some modifications of currently used methods are required (27). Main outcome of such evaluation should provide information about the costs /economic effectiveness, savings, performance, safety, ethical and social impacts and improvements of the investigated treatment/drug. Finally, the question that needs to be answered is: "Do we really need this technology and why?".

The formal proof of HTA can be found in systematic reviews, meta-analyses and randomized controlled clinical trials (28). A multi criteria decision analysis is suggested by which one can evaluate the cost-effectiveness through the benefits of quality adjusted life years (QALY). One of these analyses is the Cost-Effectiveness Analysis (CEA); its basics concepts and principles are presented in the following section.

Unlike drugs, which cannot be commercialised if sufficient evidence on their effectiveness is not collected, medical devices can be marketed after their safety has been proven. As a consequence, decision makers are called to make choices while cost-efficacy evidence is not fully available, especially for innovative technologies. Therefore, in the past years there has been a significant diffusion of early HTA (eHTA) or early economic analyses (78,79). In those cases, the limited clinical evidence that is available is projected using statistical methods, the costs are estimated assuming the worst case (i.e., max costs) and the uncertainty is quantified using statistical techniques. As a result, an eHTA informs the decision makers about the incremental risk-opportunity ratio, where risk is considered as a potential cost and the opportunity is considered as potential effectiveness. An eHTA assumes that proper HTA analyses are preformed when sufficient clinical data are available. The alternative would be to just wait and postpone the introduction of medical devices that can potentially save lives or increase significantly life quality, but this is not feasible with medical devices because their lifecycle is much shorter than that of drugs.

2.1. Cost-Effectiveness Analysis

There is a wide variety of approaches to economic evaluations of health technologies, one of them being cost-effectiveness analysis (CEA), which measures the incremental resources required for a new intervention in monetary units and the technology impact on patient health using different scales. In this paper, the focus is on the CEA, which measures

impact on health in terms of quality of life, which is known as cost - utility analysis (29).

2.1.1. Quality of life (QoL) and QALY

In HTA it is assumed that people in their life move through different health states, each of those states has a specific value attached to it - Quality of life (QoL). QoL describes a quality of individual's daily life, including social, emotional and physical aspects. For evaluating QoL, health care indices that provide information how health care influences patients, known as Health Adjusted life Years (HAYs), are used. One of them is Quality Adjusted Life Years (QALY), which is a general index (i.e., not disease specific), and a unit of health care outcome that merges length of life with quality of life. QALYs are used in the Cost Effectiveness Analysis (CEA) to determine the ratio of incremental costs (i.e., new technology versus a benchmark) to QALY gained. The index is defined as the value-weighted time-life-years, weighted by their quality-accumulated over the time (30). QoL is normalized to a standardized scale with ranges from 0.0 (death) to 1.0 (perfect health). According to some authors, negative values can also be reached, describing states worse than dead (e.g., dementia and coma are often considered equal to or worse than death (31)). Widely used and translated into most languages is the EuroQol (EQ-5D) evaluation tool (questionnaire), which is a standardized instrument for use as a measure of health outcome (The study/trial/project that use EQ-5D should be registered; see also: https://euroqol.org/support/how-to-obtain-eq-5d/) (32,33). It is also one of the measures recommended for use in cost-effectiveness analyses by the Washington Panel on Cost Effectiveness in Health and Medicine (34) and NICE (National Institute for Health and Care Excellence) (35). The health status is measured in five dimensions: mobility (walking ability); self-care (ability to wash or dress); usual activities (such as "work, study, housework, family or leisure activities"); pain/discomfort; and anxiety/depression. The respondents rate each dimension. There are two versions with a three-level (EQ-5D-3L, which rate each dimension using three values: '0', indicating no problems, '1' indicating some problems, or '2' indicating huge problems) and a five-level (EQ-5D-5L) scale. On the basis of patients' evaluation of their physical, social and cognitive functions final index – value is calculated. Therefore, the EQ-5D-3L defines 243 potential health states (i.e., 3^5), which together with two additional states for dead or unconscious give a total of 245 health states. For example, a year of perfect health is worth 1 and all non-perfect health years are worth less than 1, depending on the burden of the disease to the patient (36). Thus an intervention that generates six additional years in a health state valued at 0.65 will generate more QALYs than comparable technique that generate seven years in health state estimated at 0.5. There are also some other measurement instruments available that are frequently used in parallel or alternatively, such as Nottingham health profile, Quality of life Scale (QUOLS) and others (37-40). Since healthcare budget is always limited (sometimes scarce) and the introduction of a new technology may result in the exclusion of another, it is important to use a general index (e.g. QALY) in order to quantify the benefit on the whole national population (41,73).

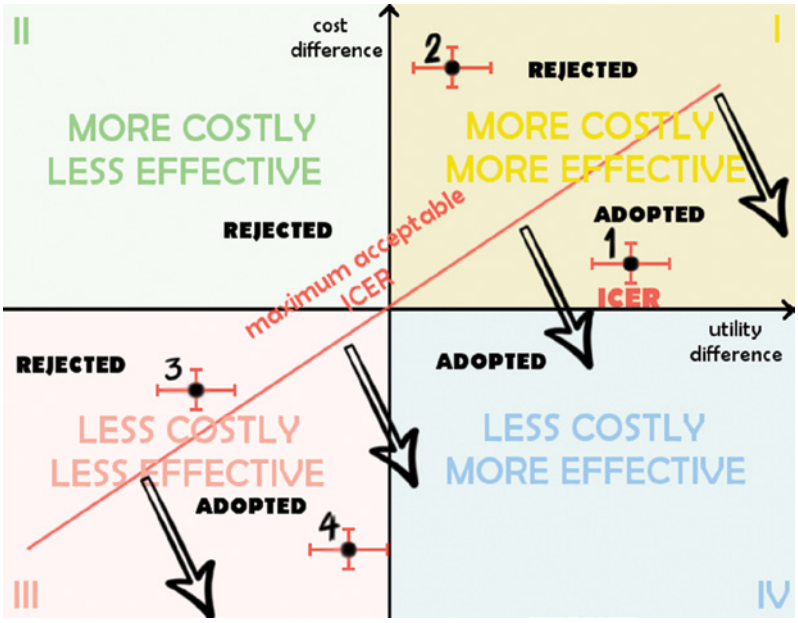

Figure 1: Incremental cost-effectiveness plane/diagram (70). The resulting ICERs are presented graphically as a ratio between costs and the effectiveness/utility or as a distribution with uncertainty in cost-effectiveness plane. Four quadrants represent all combinations of possible outcomes. The more effective outcomes are located further right on the x-axis, and with the rise of y-axis the cost of the outcome rises (69). An ICER of an innovation that is more costly and more efficient then the benchmark is located in the first quadrant; in case of a more costly and less efficient technology, ICER is in second quadrant. Other options can be derived from the figure.

2.1.2. Incremental cost ratio (ICER)

The result of CEA is presented with incremental cost ratio (ICER). ICER is defined as the additional cost per additional benefit/utility that is measured in QALY. Because QALY has a normal distribution and a sum of two normal variables is also normally distributed, ICER can be calculated as a ratio of two asymptotically normal variables (42). In the following equation (Eq. 1) treatment B represents a gold standard or benchmark to which new treatment X, e.g. electrochemotherapy, is compared.

$$RATIO = \frac{cost_{treatment\ X} - cost_{treatmentB}}{utility_{treatmentX} - utility_{treatmentB}} \quad (1)$$

The visualization of ICER is a distribution over a sample population, it is presented with a four quadrant cost--effectiveness plane that illustrates the relation between an incremental levels of effectiveness (utility gained) of an outcome and additional total cost of implementing this outcome (Figure 1). In case when new technology is more effective and cost efficient (fourth quadrant in Figure 1), compared to the benchmark, i.e. treatment B, than the innovation, i.e. treatment X, is for sure more suitable and worth of adopting. More commonly the outcomes of CEA of new technologies are divergent, for example the innovation is more effective but also more costly (case 1 and 2 in Figure 1). It should be decided whether the incremental utility is worth the cost and sustainable (43).

Maximum acceptable ceiling ratio (max ICER) is the threshold or the maximum amount that a decision-maker is prepared to pay for one incremental QALY. It is drawn in the cost-effectiveness plane, as a threshold line (Figure 1, red line). If the calculated ICER falls below this line, the new technology is considered cost effective and is adopted (cases 1 and 4 in Figure 1), otherwise it is rejected based on its cost-ineffectiveness (cases 3 and 2 in Figure 1) (44). Decisions, which apply to the public health care thresholds and acceptable outcomes of maximum ICER, are suggested by the WHO, however the problem remains how to apply these thresholds to each specific case. As analyses are often made by commercial entities with vested interests, the results may favor the new technology. It thus needs to be taken into account that the evaluator's subjective impact is always present. Another question that is also present is, how much the society shou-

ld pay for a QALY. According to the generally present opinion, e.g. in the UK, a QALY is worth somewhere between £20,000 and £30,000 (44). In Slovenia, rather than having a maximum value defined, each innovation is placed on a priority list of admission based on the evaluation of the following criteria: health effectiveness; quality of justification of recommended program; economic effectiveness (high scores correlate with lower costs); population perspective (more patients more points); and organizational efficiency. The quality of life is not considered in the evaluation.

CEA always includes a comparison of a new technology to the benchmark technology, if available. The innovation cannot be cost effective by itself, it has to be cost effective compared to the benchmark. In a CEA, a treatment producing an additional 0.5 QALY at an incremental cost of €3,000 per patient, is considered having a cost of €6,000 per QALY (i.e. €3,000 /0.5 QALY = €6,000 / QALY) (36).

2.1.3. Discounting

It should always be taken into account that values of costs and outcomes change with time (29). Because the CEA are projected through a certain period of time discounting is necessary. Cost and outcomes should be discounted relative to their present value at the rate of 3 % or up to 5 %, per year (29). The cost discount rate can be estimated from the equation (Eq. 2). Some authors suggest a common rate for costs and outcomes and others prefer a lower rate for outcomes. NICE discounting guidance for cost effectiveness analysis (45) requires that both costs and health outcomes are discounted at 3.5 % (46).

$$present\ value = \sum_{n+1}^{n} \frac{future\ cost\ at\ n\ years}{(1 + annual\ discounting\ rate)^{n}} \quad (2)$$

For example, if the present value of cost is €2,500 and a 5 % discount rate is used, one year in the future, the cost will be €2,375 and 5 years in the future the expense will be only €1,875. The same procedure is used for the discounting of health care outcomes.

2.1.4. Sensitivity analysis

The degree of uncertainty is a subject to variables used in CEA. To estimate plausible variations, a sensitivity analysis should always be performed. Such sensitivity analysis provides information on how a variation of a certain variable affects the result of the CEA. We distinguish between deterministic and probabilistic sensitivity analysis. Deterministic sensitivity analysis uses an approach in which one or more parameters are changed manually across a pre-specified range (range should correspond to the uncertainty defined in literature). Results are than analysed and the extent of the impact of input parameter variation on the output values is defined. Probabilistic sensitivity analysis captures uncertainty of all input variables, it is characterized through the use of probability distributions, translated to uncertainty and results in means and standard error for the incremental costs (47). If a correlation of input variables is present and available, it should also be considered and incorporated into the model (48).

2.1.5. Data collection and decision-making models

Most often, data collection methods used in HTA are: systematic literature review; meta-analysis; modelling; group judgment; unstructured litera-

ture review; and expert's opinions (29). Sometimes it happens that for a specific new medical device or an innovative technique there is not yet sufficient evidence available, apart from data proving its safety. When only few or low quality studies are available, potential source of bias must always be considered and documented (29). Additionally, in order to incorporate conditionality and uncertainty of data collected, decision models are used to simulate adjustments of projections of the existing primary data. With modeling patients conditions, treatment efficacy, treatment and maintenance costs and incidence of the disease, projections to a future costs and outcomes of the treatments or innovations can be made. Decision making trees, fuzzy logic and state transition modeling, such as Markov model and Monte Carlo simulation, are most often used (49). Markov models are widely used in HTA and health-economy studies, and recently Craven et al. (50) showed that this approach can also be used in pre-market HTA studies for medical devices.

In the CEA, each state in the model represents a specific state of health, or stage of disease between which the patient migrates. There is always one state that represents death, which is considered an absorbing state as it does not have a return path. Each state is associated with an average QALY, reflecting the quality of life of patients in this health status, a cost that is reflecting the cost needed to maintain the patient in this state (e.g., avoid deteriorations) and the probability to move from the current health state to another, or the stay in the same state in the following period of time (usually one year). Health states are defined according to the disease being studied. The model's structure should be as simple as possible, as it is not necessary to model the full complexity of the disease. Moreover, since the CEA focuses on incremental costs and QALY, only those states in which the technology under assessment is making real differences are relevant for the model. Model complexity (i.e. number of parameters and model order) should always be limited by the quantity and quality of data available (51). However, more aggregated structure that still includes fundamental disease process and interventions is often the best solution (47).

3. Case study on electrochemotherapy (ECT)

Electroporation is an evolving technique with many applications (1-4). In our study the focus is on electrochemotherapy of basal-cell carcinoma (BCC) and skin melanoma, as these two therapies are used for the longest time and have a very high success rate. Few cost-effectiveness analyses have already been done (52,53), but due the lack of information obtained, especially about QoL increase, the results are incomplete, inadequate and/or inaccurate. Numerical data about QoL increase are not available, QoL is reported only as "better", "highly improved", "significantly better", or using similar descriptors. Most probably the main reason that QoL was not acquired in previous studies is due to poor reporting. Our study originates from a previous one (52) and uses innovative eCEA methods (54). In order to facilitate result comparisons with benchmark technologies, cancer type specific analyses are done. For the scope of this paper, models for

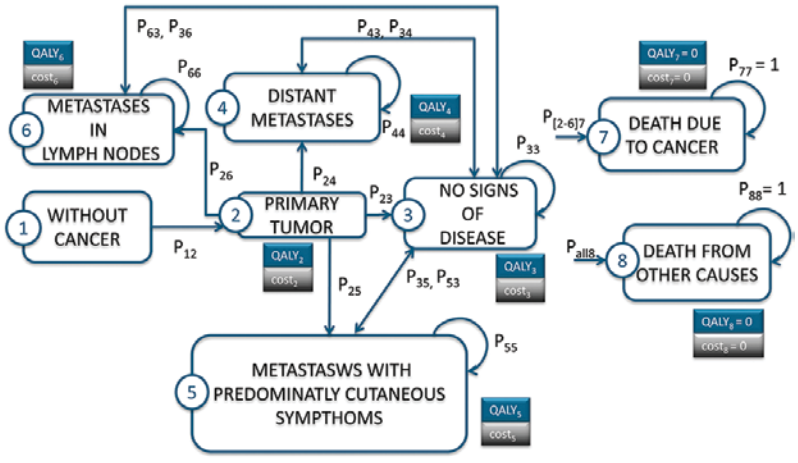

Figure 2: A general eight state Markov model of skin melanoma. The model should always reflect the essential features of the disease and its outcomes (40).

both studied cancer types are designed and presented. In addition, required and missing data are defined and presented (Table 1). In the near future we plan to collect all missing data trough randomized control trials and different studies which are still under way. With this paper we also want to raise general awareness about the importance of numeric QoL reporting and usefulness/meaning of EQ-5D questionnaires that might not be self-evident at first sight. If despite our effort the data will still not be available, simulations will be done to acquire the missing data. Our main aim is to build a general model that will allow us – with minimal changes – to also simulate/project the cost efficiency for patients with better initial survival options and to also stimulate similar studies for other cancer types treated with ECT.

Cancer patients that are treated with innovative technologies (which have not yet been introduced into clinical practice) in most cases have severe cancers and are not suitable for any other already established treatment. In fact they are usually without other treatment options. However, the goal of several emerging applications in oncology, such as ECT, is to be used in early-diagnosed patients with better survival options. Measurement of QoL increase in patients with severe cancer is more demanding and biased. QoL of a patient with severe cancer and poor survival options after the therapy cannot be equally compared with the QoL of patients, with better survival options before the procedure. Their quality of life before treatment was not the same, therefore we can assume that only a minimum increase in the quality of life could be observed (56).

Regarding the benchmark, there are different options. Some authors compare the innovative technology with the most recent cost-effective technology while others compare it with the gold standard/benchmark in order to make the analysis more replicable. For skin cancer, competitive technologies are: surgical excision, topical intralesional therapy, photochemotherapy and radiotherapy (14,55). In our study, the ECT treatment of BCC and skin melanoma will be compared to surgery and radiotherapy. We assume ECT is considerably cheaper than radiotherapy while having at least comparable effect (10,14,52).

3.1. Constructing the model

While the structure of the model should reflect the essential features of the disease and its interventions irrespective of data availability, it is expected that in some cases data availability may affect choices regarding model structure (29). In order to

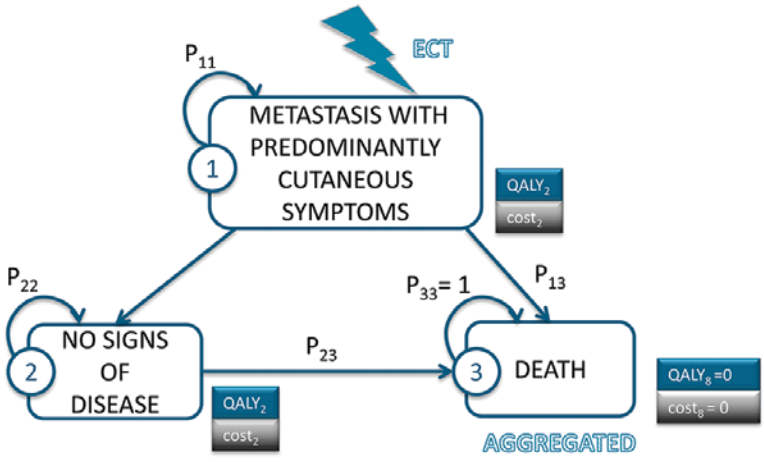

Figure 3: A reduced – initial Markov model for skin melanoma, only the states that are relevant for the new technology, in this case ECT, are included.

use the most appropriate models that would give the most realistic results, models are designed in advance and the data needed will be obtained subsequently in the near future (56). Two general models, for each cancer type, are presented in this paper (Figure 2, 4), covering whole complexity of the disease and its essential features. Those two models will be used for final simulations that could provide the cost-effectiveness evaluation of electrochemotherapy as a treatment also used in patients with less severe cancer stages. For the initial analysis, however, models are simplified/reduced (e.g. aggregating states) (Figure 3, 5), in order to facilitate the calculations and focus only on states that are relevant for the new technology (i.e. where ECT is currently used). Models for different cancer types differ from each other with respect to the number of states; their definition and flow through the model are conditioned by disease characteristics and possible outcomes.

Because cancer may be a recurrent disease, Markov model approach is used for modeling (57). The first general model was made for BCC (Figure 4). It is simple, it has only seven states and much less possible state transitions than the second general model that was made for skin melanoma (Figure 2) which has nine states. The initial states in both general models represent population without cancer. (These two states will be eliminated at the initial calculations, because they are not relevant for the new technology - ECT.) The following states represent different cancer stages, such as primary tumor, distant metastases, metastases in the lymph nodes, distant metastases with predominantly cutaneous symptoms and distant metastases without predominantly cutaneous symptoms in case of skin melanoma. Because all patients are not diagnosed with cancer at its initial state, some might enter the model with the disease that combines several states in the model. Clinical stages of skin melanoma are defined as follows: at stages I and II patients only have a primary tumor; stage IIIa,b means that a patient has a primary tumor and metastases in the lymph nodes; stage IIIc combines a primary tumor, local metastases and metastases with predominantly cutaneous symptoms. The last and most severe stage IV includes a primary tumor and distant metastases (76).

Electrochemotherapy is at the time of writing manly used in stage IIIc and IV patients (10,14), therefore a reduced - initial models for initial calculations consist only of states relevant for those two cancer stages. A reduced BCC model is slightly different and simpler. There are only three possible outcomes: complete response, residual disease and progressive disease. In the case of BCC, electro-

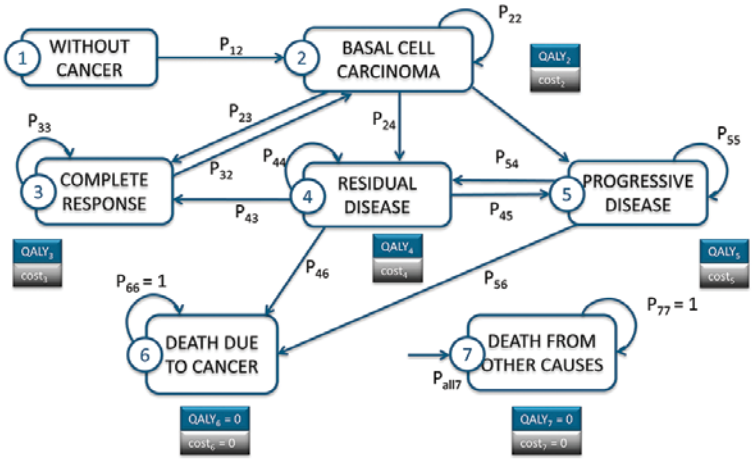

Figure 4: A seven state general Markov model of basal-cell carcinoma (BCC).

chemotherapy is used only in patients with bigger and recurrent tumors (10,14). Both general models also have the same two absorbing states, one is death due to cancer and the other is death from other causes; for initial calculations these two states will be merged into one state (patients can move to these two states from any other state, arrows are not drawn in the models for clarity (Figure 2, 4)). The probability of staying in dead state is always one and the cost zero. As seen from the model, all states are numerated and have two additional parameters: QALY and cost. The time step at which patients migrate between states is set in accordance with disease characteristics (58). Because significant changes in QoL of patients treated with electrochemotherapy are detected already within few months after the treatment (34,59), the time step for the study is set to three months. In all models (Figure 2–5) numbers in the circles enumerate states, for example the state without cancer in both general models designates the state 1. The letter P in both general models (Figure 2, 4) represents a probability of transition between two states. The first undersigned number represents the state from which a transition is made and the second undersigned number provides the information to which state it is moving. Finally, in order to correctly include data in the model, a conditioned probability calculation will be performed (58).

3.2. Data collection approach

For each state represented in the model, three data are needed for a successful cost-effectiveness analysis:

1. The probability of transition between different states in a defined time step (Example$_{\text{BCC g. model}}$: P_{23} represents the probability of a complete response three months after the treatment.);
2. The cost of staying for three months in each state (Example$_{\text{BCC g. model}}$: $cost_2$ represents the sum of all expenses a health care provider has in the selected time step, such as medical examinations, medications, therapies, etc. in case patient has an untreated BCC);
3. The utility of patients in each state, expressed in QALY (Example$_{\text{BCC g. model}}$: $QALY_3$ represents the average result of an EQ-5D questionnaire filled out by the patients with complete response).

For the initial calculations, initial models that reflect only the impact of the technology under investigation (ECT) will be used. In case any of above listed information is not available, those data will have to be estimated using the best possible approach, including:

1. The transition probability between states or QoL data can be adapted from randomized control trials te-

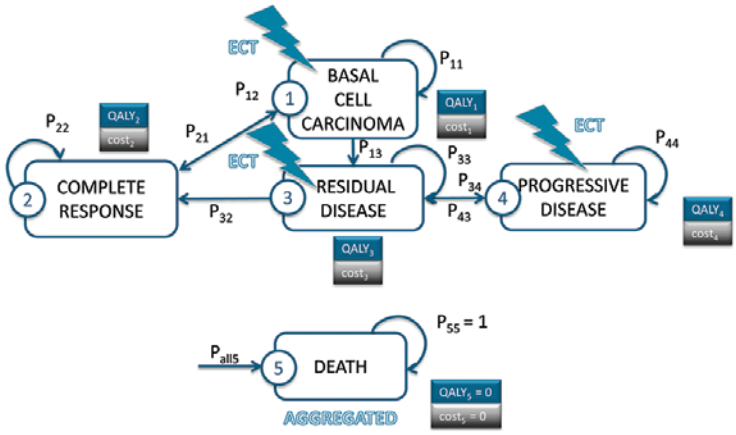

Figure 5: A reduced – initial Markov model for BCC, only the states that are relevant for the new technology, in this case ECT, are included.

sting the most similar technology in the most possible similar cancer (Figure 6: Case 1 and 2). The missing values can be estimated by fitting probabilistic distribution and then calculating mean and standard deviation, which are also useful for sensitivity analysis that will be performed later.

2. Alternatively, the missing data can be derived from interviews with expert clinicians and fitting the results with statistical distribution (Figure 6: Case 3).
3. The missing data for a general model can be simulated or predicted from initial calculations, made on reduced models that include only states relevant for the new technology. (The simulation will also provide the CEA estimation in case ECT would be used in early-diagnosed patients with greater survival options.)

Once the data for initial models will be collected, an incremental analysis will be run in order to determine the incremental cost-effectiveness ratio and its confidence interval. Finally, two steps will conclude the first stage of this study:

1. Sensitivity analysis (the model will be run using a deterministic approach by changing the input parameter value)
2. Statistical analysis (i.e. using Monte Carlo simulation, each subject will move from one state to another according to the given transition probability.)

3.3. Field of interest

1. *Probability of transition between states*: Response rates for initial calculations / probabilities for the electrochemotherapy treatments and other comparable technologies will be collected at first from different oncological trials in Slovenia. In case these data will have a high standard deviation, or there will not be enough of them for a representative pattern, we will expand our study requesting data and support from InspECT database (60). (Probability values will be defined from study reports; the use of a table (Table1) is suggested for easier data collection). Finally, we would also like to make some possible outcome predictions, in case that the technique will/would also be used in patients with earlier cancer stages and better survival options; for these purposes general models were developed. Cancer incidence data that will define the probability P12 (in both general models) for skin melanoma will be obtained from the Cancer Registry of the Republic of Slovenia (61). In case of BCC, the incidence should be multiplied by 1.3, because non-melanoma skin cancers are usually not properly included in the cancer registries (62). Also, the fact that the incidence of BCC continues to increase should be taken into account in general calculations.

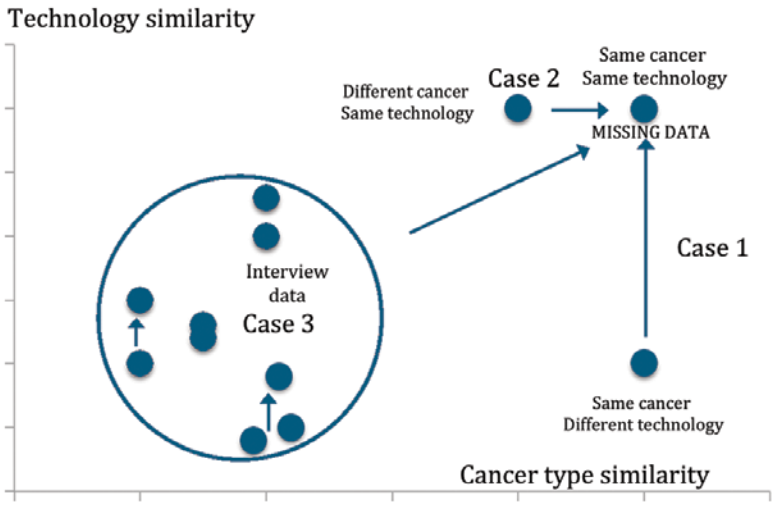

Figure 6: Visualization of data collecting and data simulating process.

Because most databases are made on an annual basis, the collected data will be projected on a three-month scale, if needed. Other probabilities will be simulated from initial calculations and expert's opinions. In case of skin melanoma, patients can be diagnosed at different cancer stages or might be in a state that is a combination of two states in the model; for example, they can have a primary tumor and distant metastases with predominantly cutaneous symptoms. In order to properly fit those probabilities in the model, statistical methods will be used.

2. *Quality of life evaluation*: already after a brief literature survey, it has become obvious that most of the relevant reports are missing data about EQ-5D results even though these should be collected as stated at clinical trial specifications (63,64). The quality of life is reported only as "better", "highly improved", "significantly better", or using similar descriptors (65,66,71,72). For the Markov model analysis, however, numeric data are required. This is one of the main reasons why we have decided to postpone the analysis, as we want to collect real data instead of implementing expert's estimations of QALY increase. It seems more rational to collect EQ-5D results, as only numerical values will provide us with adequate/useful results. At first we will try to collect the test results from already completed clinical trials. Most likely, if EQ-D5 were done, the results were collected at 3 and 8 months after the treatment, as specified in clinical trial documentation, so the rescaling on a time step basis will be necessary to fit into the model. Then we will ask physicians who are involved in trials including electroporation treatments to include the EQ-5D evaluation tool into their studies if they are not already included, and use the developed table template (Table 1) for reporting.

3. *Incremental cost evaluation*: costs depend on the specific application protocol, disease stages and severity. The first necessary and inevitable cost, which is common to all applications, is staff (e.g., nurses, doctors). Local or general anesthesia is also used in some procedures. In case of electrochemotherapy, the cost of intratumoral or intravenous application of chemotherapeutics cistplatinum or bleomycin must be considered. The cost of patient's hospitalization, the necessary medical examinations before the procedure and any other specific treatment that may entail side effects must also be taken into account.

The second necessary cost is the electroporator and electrodes. IGEA S.p.A. (Italy) produces a Cliniporator device, appropriate for electrochemotherapy of smaller cutaneous or subcutaneous tumors. Cliniporator VITAE is an upgrade, which has higher pulse amplitude and can also be used for electrochemotherapy of deep-seeded tumors or irreversible electroporation (IRE).

In the USA, AngioDynamics produces NanoKnife, which is mainly used for IRE. For successful application, electrodes are needed that may be for single or multiple use. IGEA offers many different electrode types. NanoKnife has only needle electrodes; from one up to six per treatment can be used. The amortization expense or annual lease of the device must also be considered. The cost of electrochemotherapy has already been evaluated for Italy by Colombo et. al. (52), a cost-effectiveness analysis has also been done, but without the quality of life consideration. All the collected data thus must be rechecked and updated for further evaluations. The authors calculated an average use of 1.3 electrode per procedure. In a further study, the number of available electrode types may significantly change because there are several new electrode configurations available. Maintenance was estimated biannually at €6,000 and annual lease of the device at that time was €12,000. The device lifespan is 8 years, and for all further calculations Colombo et. al. (52) assumed that at least 100 patients are treated per year with a single device, which may be an overly optimistic assumption. The cost is then calculated per patient. Electroporator and electrode price must be divided by its lifespan and the number of patients treated on a yearly basis. The cost of being in each state needs to be defined. The cost evaluation of being in initial state (having cancer) will be taken from the literature; for the USA, UK estimations of specific cancer types on a yearly basis are available (67,68). In case of expanding the data collection to other countries, we should consider the issue of different living standards, as the standard of living and money value is not the same everywhere. To align the costs, data collected from all around the world will be calibrated if needed. The adjustment will be made on the basis of living costs (74).

3.4. Data collection proposal

To facilitate initial data collection, a table template (Table 1) is proposed. The table refers to reduced models; in case of BCC there are five possible states and in case of skin melanoma only three. For each patient, every three months the clinician is supposed to:

- define the medical interventions;
- assess patient state by circling the appropriate number in the table;
- obtain EQ-5D questionnaire and report numerical value;
- record all medical interventions or examinations that patient had in the last period, including the type of anesthesia during ECT, days spend in hospital, biopsy, blood analysis and radiological assessment;
- report about all drugs prescribed to the patient for his/her condition, also for the management of side effects, analgesics, wound care dressing…
- report any other potential costs.

4. Conclusion

In the scope of this paper two general Markov models for CEA have been developed, one for skin melanoma and the other for BCC. Initially, both models are reduced in such a manner that they consists only of states that are relevant for the current use of new technology, i.e. electrochemotherapy. But for a cost-effectiveness analysis, the data on quality of life increase on a time step scale are also needed, which in our case represents a problem. Researchers are currently only reporting that quality of life is increased after the treatment, but

Table 1: A table template proposed for the initial data collection.

Patient code: *0001/2017* (BCC) / Skin melanoma	**Pre-operative evaluation**	**Procedure**	**Follow-up at 3 months**	**Follow-up at 6 months**
Medical interventions	*1 visit at the specialist*	*Ect in general anesthesia, chest x-ray*	*2 visits at the specialist*	*3 visits at the specialist*
State (Reduced model)	(1),2,3,4,5	(1),2,3,4,5	1,2,3,(4),5	1,2,3,(4),5
EQ_5D	*0.45*	*0.43*	*0.38*	*0.33*
Biopsy	(Y)/ N	Y /(N)	Y /(N)	Y /(N)
Blood analysis	Y /(N)	(Y)/ N	(Y)/ N	Y /(N)
Radiological assessment	(NO) / US / CT / MR / PET-CT	(NO) / US / CT / MR / PET-CT	(NO) / US / CT / MR / PET-CT	(NO) / US / CT / MR / PET-CT
Days of hospitalization	*0*	*2*	*0*	*2*
Wound care dressing (Product name)	*NO*	*NO*	*YES: XY©*	*NO*
Prescribed drugs	*NO*	*Paracetamol 500 mg tablets 3X1*	*NO*	*NO*
Other potential costs (Describe)	*NO*	*NO*	*NO*	*NO*

the numerical data that are crucial for successful cost-effectiveness analysis are missing (65,66,71,72). In this paper, the data needed for the evaluation of cost-effectiveness of electrochemotherapy treatment of skin melanoma and BCC are clearly identified. Additionally, recommendations for data collection process and follow-up reporting are made.

Because electrochemotherapy is an emerging technology, it is still not used in all patients, but as the proof of concept rises, it is gradually moving up the cancer staging scale. A realistic cost-effectiveness analysis for a specific cancer type will facilitate equipment purchase and clinical practice implementation. Additionally, the prediction of cost effectiveness can also influence the next round of fund raising. In our opinion, an additional incentive from a good cost--effectiveness analysis would definitely also benefit other electroporation-based therapies. The biggest obstacle is Quality of life data, which will be overcome by obtaining the EQ-5D questionnaires in the near future. Because the time step is set to three months, we believe a two-year data will give a representative pattern. Furthermore, specific models should be developed for each disease separately in order to include all specific phenomena in a specific cancer type. Electrochemotherapy must be compared to well established procedures that are cancer-type, location and size dependent.

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