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Early Cost-effectiveness Analysis of Electrochemotherapy as a Prospect Treatment Modality for Skin Melanoma

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ABSTRACT

Purpose: Electrochemotherapy is increasingly entering into national and international guidelines, requiring formal evaluation of treatment costs and cost-effectiveness to ensure that its uptake provides value to budget-constrained health care systems. This study analyzed the early cost-effectiveness of electrochemotherapy in patients with Stage IIIc/IV skin melanoma in clinical practice in Slovenia. The costs of electrochemotherapy were compared to those of the standard of care, consisting of palliative treatment and therapy for symptoms.

Methods: wThe study enrolled 23 patients treated with electrochemotherapy at the Institute of Oncology (Ljubljana, Slovenia). The mean cost of electrochemotherapy was estimated using patient-specific cost data on electrochemotherapy procedures and subsequent follow-up. Quality-adjusted life-years (QALYs) were estimated by collecting EQ-5D-3L questionnaires at baseline, after complete or partial response following the treatment, and after a relapse of skin lesions. A discrete-time Markov model was built to estimate the lifetime costs and consequences of using electrochemotherapy compared to standard of care, from the perspective of the Slovenian health care system. The analysis was conducted separately in the whole patient sample and in the subset of patients with bleeding lesions. Deterministic and probabilistic sensitivity analyses were conducted to test model assumptions and to characterize the uncertainty around model parameters.

Findings: In the whole patient population, electrochemotherapy for skin melanoma Stage IIIc/IV was expected to increase QALYs by 0.29 (95% credible interval [CrI], 0.10−0.50), at the higher cost of 6568 EUR (95% CrI, 4593−8928) in comparison to the standard of care. At the cost-effectiveness threshold of 20,000 EUR/QALY, the estimated probabilities of electrochemotherapy being cost-effective compared to standard of care were 0.30 and 0.91 in the whole patient sample and in patients with bleeding lesions, respectively. In the whole sample population, a 50% reduction in the price of the electrodes was expected to increase the probability of electrochemotherapy being cost-effective from 0.30 to ~0.64.

Implications: The findings from this cost-effectiveness analysis of data from clinical practice were based on a small sample size (ie, 23 patents), which made the subgroup of patients with bleeding lesions very small. Therefore, the findings in this patient population should be carefully interpreted. (*Clin Ther*. 2020;42:1535−1548) © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Key words: cost-effectiveness, electrochemotherapy, electroporation, melanoma, skin cancer.

INTRODUCTION

Electroporation is a phenomenon by which the transport of otherwise impermeant molecules through the cell membrane is facilitated.[1–3] Electroporation is becoming increasingly recognized in medicine[4–6] and also in food technology and biotechnology.[7–9] In medicine, electroporation is used for the treatment of solid tumors, either in combination with chemotherapy (electrochemotherapy) or alone (irreversible electroporation). Electrochemotherapy is a local antitumor therapy that increases the toxicity of chemotherapeutic drugs bleomycin and cisplatin.[4] Nonthermal irreversible electroporation enables the ablation of undesirable (malignant) tissue, with minimal damage to blood vessels and nerves.[10] Electroporation is also a promising delivery method in the introduction of genetic material, and in DNA vaccination.[11] Published studies have demonstrated that the electric field established by applied high-voltage, short-duration electric pulses increases the permeability of the plasma membrane.[2] Electroporation can be classified as reversible or irreversible. In reversible electroporation, the cells fully recover after electric-pulse application, while in irreversible electroporation, after the pulse application, cells die due to the loss of cell homeostasis. The device that generates, and enables the delivery of (via application-specific electrodes), electroporation pulses to biological tissue is named an *electroporator*.[12,13]

With the development of the electroporation field, new medical therapies, new clinical electroporators, and innovative delivery systems, questions regarding cost-effectiveness have arisen. In fact, while the technology is entering into national and international guidelines,[14] its value remains largely unexplored in mostly all settings. Indeed, not many electrochemotherapy cost-effectiveness analyses have been published to date,[15] and due to a lack of information obtained, especially with regard to its effects on quality of life, results are incomplete.[16] The UK National Institute for Health and Care Excellence (NICE) deemed electrochemotherapy is a safe treatment of primary basal cell carcinoma and primary squamous cell carcinoma; however, it also warned about the limited evidence on its efficacy.[17] A recent randomized study by Clover et al[18] provided further evidence of the efficacy of electrochemotherapy in the treatment of basal cell carcinoma in relation to surgery.

Even though the use of electrochemotherapy in the treatment of skin melanoma and basal cell carcinoma has been accepted in Slovenian clinical practice, evidence on its clinical effectiveness and cost-effectiveness in this indication is still sparse. Therefore, there is a need to discuss whether the use of electrochemotherapy in this patient population is cost-effective for the Slovenian health care system, and whether the overall cost of the procedure is acceptable. Based on the results from a small study in clinical practice, the present study evaluated the early cost-effectiveness of electrochemotherapy using the Cliniporator (IGEA S.p.A., Capri, Italy) as a treatment modality for Stage IIIc and IV skin melanoma in Slovenia. Electrochemotherapy was compared to the standard of care, consisting of palliative treatment and the treatment of symptoms.

Electrochemotherapy for Skin Melanoma

Of all skin cancer types, cutaneous melanoma is the most deadly and the sixth most common cancer type in Slovenia (3.84% among all cancer types).[19] Melanoma spreads by the lymphogenous and hematogenous routes. The American Joint Committee on Cancer defines the stages of skin melanoma as follows: Stages I and II, localized melanoma, meaning a primary tumor only; Stage III, regional metastatic melanoma (IIIa/b includes primary tumor and metastases in the lymph nodes); Stage IIIc combines a primary tumor, local metastases, and metastases with predominantly cutaneous symptoms; the most severe, Stage IV, indicates a primary tumor and distal metastases.[20] Disease progression and survival rate highly depend on the stage at which melanoma is diagnosed and treated.[21] Cutaneous metastases of melanoma occur in 2%–20% of patients with skin melanoma[22] and are one of the most common malignancies in the world. Electrochemotherapy is, at the time of this writing, mainly used in the treatment of Stage IIIc/IV.[23,24]

Electrochemotherapy is a standardized procedure for the treatment of superficial metastases of

melanoma resistant to other treatments. The European Standard Operating Procedures of Electrochemotherapy were established in 2006[25] for the treatment of cutaneous and subcutaneous tumors, and were updated in 2018.[26] NICE, in the United Kingdom, has recognized electrochemotherapy as an integral part of the multidisciplinary treatment of patients with skin metastases of nonskin origin and melanoma (NICE Interventional Procedure Guidance 446).[27] Electrochemotherapy of skin melanoma is a highly effective treatment, with a complete response rate, based on a single treatment, of between 60% and 70%, and an objective response rate of up to 80%.[14,28] The main advantages of this treatment are that: (1) it can be administered in an outpatient setting, under local anesthesia or deep sedation and is therefore simple to perform; (2) the procedure is assumed as daily intervention, as it can be completed within a half-hour; (3) in cases of low or no response, it can be repeated after a month (however, a cumulative dose of bleomycin of 400,000 IU should not be exceeded) or later if a new metastasis develops; and (4) it has a good cosmetic outcome, because the surrounding tissue remains undamaged.[29,30] Overall, electrochemotherapy is considered a safe procedure with few or no associated adverse events.[28,31,32] Electrochemotherapy diminishes the need for surgery and is a feasible treatment option for cutaneous lesions resistant to other therapies.

This study analyzed the early cost-effectiveness of electrochemotherapy in patients with Stage IIIc/IV skin melanoma in clinical practice in Slovenia. The costs of electrochemotherapy were compared to those of the standard of care, consisting of palliative treatment and therapy for symptoms.

METHODS AND MATERIALS

Patients

We enrolled patients treated with electrochemotherapy at the Institute of Oncology (Ljubljana, Slovenia) between June 2014 and March 2019. Patients were treated according to the Slovenian recommendations for the treatment of patients with cutaneous melanoma and the standard operating procedures for electrochemotherapy.[26] Inclusion criteria were: (1) cutaneous melanoma metastases that were symptomatic (eg, bleeding, ulceration, oozing, odor, or pain); (2) progression of cutaneous metastases in which the development of these symptoms was expected; (3) primary skin cancers, including recurrent tumors, for which other treatment modalities (surgery, radiotherapy, and systemic therapies) have failed or are not possible; (4) receipt of systemic therapy, but having cutaneous metastases that are progressing or not responding despite satisfactory response to systemic therapy in internal organs; and (5) patient preference for electrochemotherapy, after other treatment possibilities have been thoroughly explained to the patient.

Patients were excluded from receiving electrochemotherapy if they were/had one or more of the following criteria: (1) pregnancy; (2) breast-feeding; (3) allergy or hypersensitivity to bleomycin; or (4) a lifetime dose of bleomycin exceeding 400,000 IU.

Eligible patients were diagnosed with Stage IIIc/IV malignant melanoma not amenable to other treatments. Patients' characteristics are presented in Supplemental Table I (see the online version at https://doi.org/10.1016/j.clinthera.2020.06.13). In the Slovenian guideline on the treatment of skin melanoma, electrochemotherapy is indicated as a modality for the treatment of recurrence at the extremities in which simple excision is not possible (>3−5 metastases) or for recurrent relapses (sooner than 3−6 months).[33] Patients were treated with electrochemotherapy, in accordance with standard operating procedure, with the Cliniporator device.[25,26] Follow-up examinations were conducted 14 days after the intervention and after 1, 2, 4, 8, and 12 months. At each electrochemotherapy procedure, all skin lesions present at the time of procedure were treated. Electrochemotherapy was repeated when new lesions were presented or when only a partial response was obtained.

Cost-effectiveness Analysis

An analysis of cost-effectiveness in clinical practice was conducted to estimate the lifetime costs and consequences of using electrochemotherapy in the target patient population from the perspective of the Slovenian health care system. The model used a time horizon of 10 years, which was considered to appropriately reflect the mean survival time in this patient population. All future costs and consequences were discounted at a rate of 3.5%.

Electrochemotherapy was compared to the standard of care, consisting of palliative treatment and therapy for symptoms. The cost-effectiveness of electrochemotherapy compared to standard of care was expressed in terms of incremental net health benefit (iNHB), which was calculated as $\Delta QALY - \Delta Cost/k$, where $\Delta QALY$ and $\Delta Cost$ were the differences in the expected quality-adjusted life-years (QALYs) and costs, respectively, between electrochemotherapy and standard of care, and k was a constant value representing the cost-effectiveness threshold.[34] Electrochemotherapy was considered cost-effective if $iNHB > 0$. The value of the cost-effectiveness threshold in Slovenia was assumed to be equal to the 2018 Slovenian real gross domestic product (GDP) per capita, and was set to 20,000 EUR/QALY.[35]

Cost-effectiveness analyses for the whole patient sample were conducted separately from that of the subset of patients with bleeding lesions, because higher procedure costs and greater improvement in quality of life were expected.

Markov Model for Electrochemotherapy of Skin Melanoma

A discrete-time Markov model was used for modeling patients' lifetime costs and consequences of either electrochemotherapy or standard of care. A Markov model of skin melanoma[16] was suggested; however, it had to be modified to better fit disease progression in patients with Stage IIIc/IV skin melanoma after electrochemotherapy. The model used in the study is presented in Fig. 1. In the initial state (state 1), patients had predominantly cutaneous symptoms and were treated with electrochemotherapy; they either did not respond (ie, they remained in the same state) or moved to a response state (state 2) if they experienced a partial or complete response to electrochemotherapy. Patients then remained in the response state, unless they developed new metastases, in which case they were moved to a relapse state (state 3) and could again receive repeated electrochemotherapy, or die (state 4). The cycle duration used in the model was 2 months.

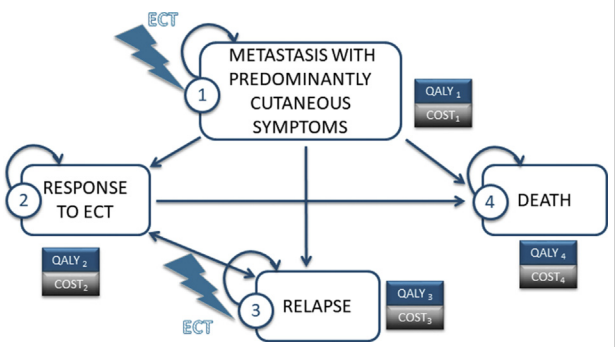

Figure 1. Four-state Markov model of skin melanoma, adopted for electrochemotherapy (ECT) for Stage IIIc/IV melanoma. QALY = quality-adjusted life-year.

Bimonthly probabilities of transition between states were directly derived from fully observed patient-level data collected during the study. First, the total person-months of exposure in each state and the number of transitions to any other state were used to calculate a 4 × 4 transition-rate matrix Q in a Bayesian framework using the data from the study and uninformative prior distributions. The model was run using OpenBugs Markov Chain Monte Carlo (MCMC) software[36] (see Appendix A in the online version at https://doi.org/10.1016/j.clinthera.2020.06.13). In the model, an initial run of 10,000 iterations was considered as "burn-in" (these values were discarded). Subsequently, 2 independent chains, starting from randomly assigned values, were run, and convergence was monitored by a look at the ratio of the within-chain to between-chain variance to be ~1, and by using Heidelberger-Welch[37] and Gelman-Rubin[38] diagnostics. Second, the transition-probability matrix $P(t)$ was estimated using the matrix exponential $P(t) = \text{Exp}(Qt)$ using the *exmp* package in Rstudio.[39]

In the absence of electrochemotherapy, since standard of care provides only palliative care, patients were assumed to remain in state 1 until they died, with probability, which was assumed to be equal to the one of relapsed patients in the electrochemotherapy group (state 3 to state 4). This assumption was discussed and validated with expert clinicians at the Institute of Oncology. Lastly, transition probabilities were assumed to be the same both in the whole sample and in the subgroup of patients with bleeding lesions.

The estimated transition probabilities and their credible intervals for electrochemotherapy are provided in Table I.

Cost Analysis

Cost of Electrochemotherapy

The mean (SD) cost of a single electrochemotherapy procedure was estimated using patient-specific data on resource consumption during the electrochemotherapy procedure and subsequent follow-ups and by attaching the corresponding unit costs. All of the costs are presented in EUR and valid for Slovenia. Costs related to the hospital and procedure were obtained from the Institute of Oncology, whereas the manufacturer of the Cliniporator provided prices related to the medical device. The overall costs of electrochemotherapy are presented in Table II.

The estimated mean (SD) cost of a single electrochemotherapy procedure was 2757 (707.30) EUR. In addition to the individual costs of specific items reported in Table II, the Institute of Oncology provided an exact expense for 8 electrochemotherapy procedures. The error between the exact amount and our evaluation was <10%; therefore, we concluded that the assessment method was appropriate.

General anesthesia was used in 25 of 38 treatments. Means of 1.5–2 bleomycin vials and 1 cisplatin bottle per patient were used, and the cost of bleomycin was thus set to 52.50 EUR per procedure. The cost of cisplatin was less, but was used in only 2 electrochemotherapy procedures. Electrodes represent almost half of the price of electrochemotherapy procedures, and new versions of electrodes (EPSA series) are even more expensive, with a price of 1600 EUR per single electrode (Value Added Tax (VAT) excluded). All electrochemotherapy electrodes manufactured by IGEA S.p.A. are for single use, meaning 1 electrode can be used in 1 patient, but for multiple metastases, in some cases >1 electrode geometry is used due to the difference in metastases. In the scope of our study, a mean of 1.19 electrodes per patient were used (range, 1–2 per procedure). Also, other patient-specific costs were analyzed and evaluated, such as for analgesics or antibiotics, but because these costs did not exceed 10 EUR per treatment, they were neglected in the analysis. Follow-up specialist visits were conducted at 1, 2, 4, 8, and 12 months following the intervention, with an estimated cost of 22.50 EUR per examination.

The Cliniporator is an essential part of electrochemotherapy. The price of the Cliniporator model EPS02 is 100,000 EUR (VAT excluded). The maintenance cost is 3000 EUR, with maintenance due every 24 or 36 months according to the specified country (eg, Germany, 24 months; Italy, United Kingdom, and Slovenia, 36 months). The Cliniporator is considered as a highly stable device; therefore, the manufacturer requires maintenance only every 36 months. The device lifetime is specified as 500 treatment sessions or 10 years according to the user manual.

Table I. Two-month transition probabilities in patients receiving electrochemotherapy.

Group/State	Mean	95% Credible Interval
Electrochemotherapy group		
From state 1 to:		
State 1	0.15	0.06–0.28
State 2	0.61	0.48–0.72
State 3	0.11	0.07–0.16
State 4	0.13	0.06–0.26
From state 2 to:		
State 1	0	–
State 2	0.73	0.64–0.81
State 3	0.20	0.13–0.27
State 4	0.08	0.04–0.13
From state 3 to:		
State 1	0	–
State 2	0.24	0.13–0.36
State 3	0.54	0.39–0.68
State 4	0.22	0.11–0.36
Standard of care group* from state 1 to state 4	0.22	0.11–0.36

* In the absence of electrochemotherapy, since standard of care only provides palliative care, it was assumed that patients would remain in state 1 until death.

Cost of Skin Melanoma

Following an extensive literature review, we could not identify baseline cost data for skin melanoma in the Slovenian setting. However, an extensive cost-of-illness study from Croatia was available.[40] Because Croatia and Slovenia are neighboring countries and, not long ago, were even both part of the same

Table II. Costs included in the evaluation of the cost of electrochemotherapy in Slovenia.

Unit	Cost per Unit, EUR
Overnight stay in the hospital (1 night after electrochemotherapy + 1 day)	240.00
Price of intervention and cost of staff (mean duration: 45 min to 1 h)	
Staff 1 h of procedure	128.25
Supplies for personnel and venue	66.13
Consumables during operation	99.25
Depreciation of apparatus in an operating room	22.57
Chemotherapeutic drug	
Bleomycin vial	30.00
Cisplatin bottle	23.00
Anesthesia	
General anesthesia	225.88
Local anesthesia	4.40
Sedation	14.60
Spinal block	15.90
Electrodes EPSA series	1200.00

country, the data collected from Croatia were considered in this study. For the calculations, the mean cost per single patient with Stage IV melanoma was set to 4333 EUR per year. This value was also in accordance with the European mean[41] and similar to a value available from Italy.[42] With the help of Slovenian palliative experts, we evaluated the worst-case cost of care in a patient with bleeding lesions to be 3450 EUR per patient per year (includes only the care of bleeding wounds). This cost can be completely eliminated after the electrochemotherapy procedure; however, only 5% of patients with melanoma develop bleeding lesions.[43]

Quality-of-Life Assessment

Patients were given an EQ-5D-3L questionnaire at each examination, and the following results, which present health utilities, were obtained: before the procedure, the mean QALYs were 0.65; patients that responded to electrochemotherapy had an increase to 0.72 QALYs, and in cases of relapse of metastases, the QALYs were decreased to 0.66. A significant increase in quality of life was expected only in patients with bleeding nodes, which after electrochemotherapy gained the most; however, only 5% of all patients with melanoma have bleeding lesions, meaning 1.15 patients in our study. Thus, the quality of life in patients with bleeding lesions was, in that initial state (state 1 in Fig. 1), reduced to minimal obtained quality of life, which was equal to 0.4 QALYs. The baseline mean estimates (95% CrI) of cost and QALY data used in the model are reported in Table III.

Scenario and Sensitivity Analysis

Probabilistic sensitivity analysis was performed by assigning probability distributions to all parameters used in the cost-effectiveness model. For transition probabilities, samples were taken directly from the joint posterior distribution of the transition probability matrix, calculated with the MCMC simulation in OpenBugs. For cost and QALY data, samples were derived from γ and β distributions, respectively, which were previously characterized using mean (SD) estimates from the study data and the literature. The results of the probabilistic sensitivity analysis were then reported in a cost-effectiveness plane and used for calculating cost-effectiveness acceptability curves for electrochemotherapy compared to standard of care.

Table III. Costs and QALYs values and credible intervals used in the model (1-year values).

Parameter	Mean	95% Credible Interval
Cost, EUR		
State 1		
All patients	4333.00	4139.00–4533.00
Patients with bleeding lesions	7784.00	7586.00–7978.00
State 2	4333.00	4139.00–4533.00
State 3	4333,00	4139.00–4533.00
ECT	2757.00	2095.00–3690.00
QALYs		
State 1		
All patients	0.66	0.54–0.74
Patients with bleeding lesions	0.40	0.23–0.58
State 2	0.72	0.66–0.80
State 3		
All patients	0.66	0.54–0.74
Patients with bleeding lesions	0.40	0.23–0.58

ECT = electrochemotherapy; QALY = quality-adjusted life-year.

In addition, the probability of electrochemotherapy being cost-effective was estimated as a function of the cost of the electrodes used for each electrochemotherapy procedure in both patient groups, because the cost of 1 electrode geometry represents almost half of the estimated electrochemotherapy procedure cost. Lastly, since electrochemotherapy is usually considered to be a day-procedure not requiring hospitalization, the results of a scenario analysis are reported, in which electrochemotherapy procedures were assumed to be provided in an outpatient care setting, without any hospitalization costs.

RESULTS

Patient Sample

We enrolled 23 patients; at the time of this writing, 8 patients were still undergoing follow-up, while 15 had died or refused further treatment. The mean (SD) patient age at the first electrochemotherapy procedure was 78.1 (12.3) years (range, 48–96 years). All together, 38 electrochemotherapy procedures were performed, meaning that each patient was treated a mean of 1.6 times (range, 1–5 procedures per patient).

Quality of Life

In the whole sample, electrochemotherapy was expected to add 0.29 QALYs (95% CrI, 0.10–0.50) (Table IV) over a patient's lifetime, at an increased cost of 6568.00 EUR (95% CrI, 4593–8928). The expected iNHB of electrochemotherapy compared to standard of care was –0.04 QALYs (95% CrI, –0.19 to 0.11), meaning that at the used cost-effectiveness threshold of 20,000 EUR/QALY gained, electrochemotherapy was slightly less cost-effective compared to standard of care, although the uncertainty over this estimate is quite large. In the subgroup of patients with bleeding lesions, electrochemotherapy was expected to yield 0.34 QALYs (95% CrI, 0.18–0.56) (Table IV) at a higher cost of 4863 EUR (95% CrI, 2479–7177). Compared to the whole sample, providing electrochemotherapy only to patients with bleeding lesions was expected to be more cost-effective, with an expected iNHB of 0.11 (95% CrI, –0.06 to 0.27).

Table IV. QALYs, costs, and NHBs in each patient group.

Parameter	ECT		Standard of Care		Incremental Results	
	All Patients	Patients With Bleeding Lesions	All Patients	Patients With Bleeding Lesions	All Patients	Patients With Bleeding Lesions
QALYs	0.74	0.62	0.45	0.27	0.29	0.35
Costs, EUR	9,539.00	10,198.90	2971.30	5,335.90	6,567.70	4,863.00
NHB	0.26	0.11	0.30	0	–0.04	0.11

NHB = net health benefit; QALYs = quality-adjusted life-years.

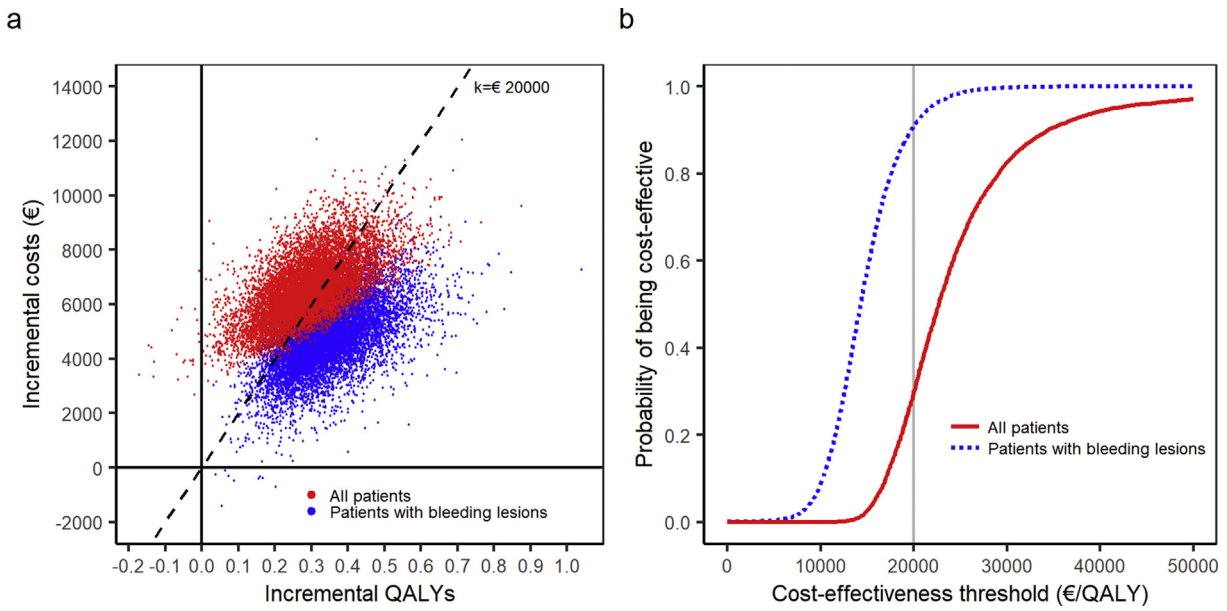

Figure 2. A, Cost-effectiveness plane. B, Probability of electrochemotherapy being cost-effective in all patients and in patients with bleeding lesions. QALYs = quality-adjusted life-years.

Cost-effectiveness

The probabilistic sensitivity analysis showed considerable uncertainty with regard to the incremental costs and QALYs of electrochemotherapy in both patient groups, with the simulated costs and QALY pairs being spread widely in the cost-effectiveness plane. However, it must be noted that most of the simulations remain in the first quadrant of the cost-effectiveness plane, meaning that electrochemotherapy is highly likely to be more effective and more costly compared to standard of care (Fig. 2A). The estimated probability of electrochemotherapy being cost-effective in the whole sample was 0.3, and 0.91 in patients with bleeding lesions (Fig. 2B).

A reduction in the cost of the electrodes used in the electrochemotherapy procedure is not expected to greatly affect the probability of cost-effectiveness in patients with bleeding lesions, since in this patient population, electrochemotherapy is already highly likely to be the best treatment option even at the base-case cost of the electrodes. However, the cost of the electrodes had a considerable impact when the whole patient sample was considered (Fig. 3). For example, a 50% reduction in the mean cost of the electrodes used during the electrochemotherapy procedure would increase the probability of cost-effectiveness from 0.30 to ~0.64.

Finally, in the scenario without hospitalization costs, the expected incremental costs of electrochemotherapy were estimated to be 16% lower compared to the base-case analysis, which in turn resulted in a higher iNHB of 0.014 (95% CrI, –0.12 to 0.15) and a higher probability of being cost-effective, 0.58 (Fig. 4), in the whole patient sample.

DISCUSSION

Ten percent of patients with skin melanoma develop in-transit melanoma metastases during the course of cutaneous melanoma treatment.[44] Most often, in-transit metastases develop on the lower limbs. Conventional methods of treatment differ among countries and include surgery, radiotherapy, topical imiquimod, isolated limb perfusion, systemic therapy, and therapy for symptoms. Surgical excision is a reasonable treatment option only in cases in which a

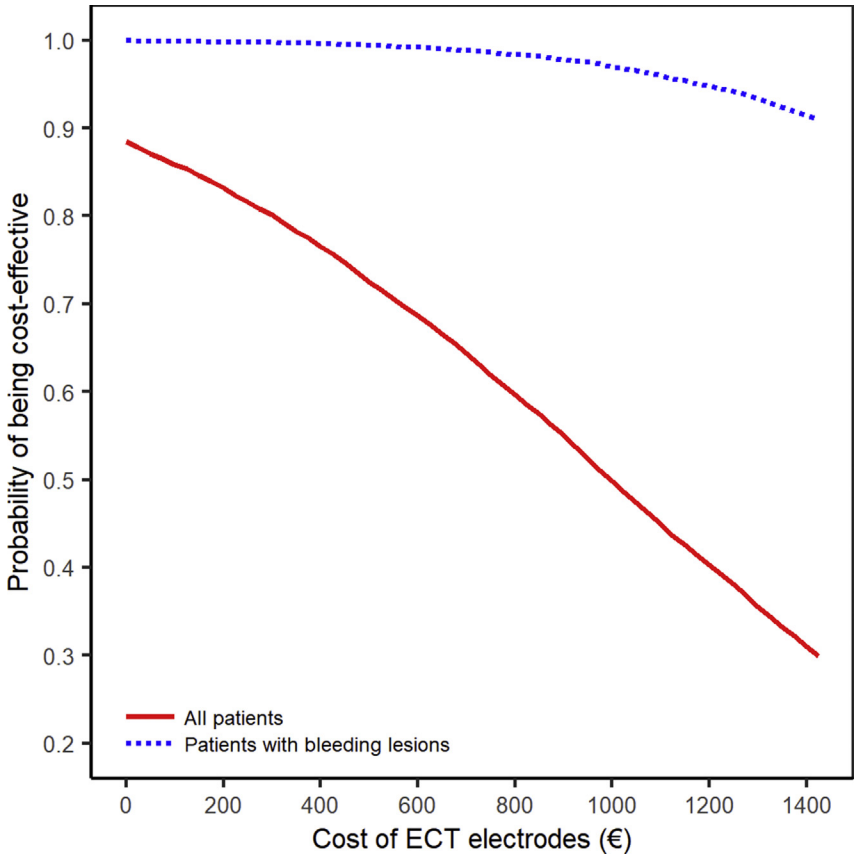

Figure 3. Probability of electrochemotherapy (ECT) being cost-effective as a function of electrode cost in all patients and in patients with bleeding lesions.

patient has a small number (<3) of skin lesions. However, research has shown that even then, only 19% of patients remain without evidence of recurrence, within a median follow-up of 40 months.[45] Other treatment options, including electrochemotherapy, are thus used in cases of a higher number of skin lesions. New systemic therapies are promising; nonetheless, due to the high cost, as well as to the treatment-related adverse events, it is still advised to treat skin lesions locally, for as long as possible.[46]

The mean age of the patients included in our study was 78.1 years. Elderly patients are often not suitable candidates for new systemic treatments due to comorbidities. For them, topical or local therapy, like electrochemotherapy, is recommended, as it is safe, has no associated adverse events, and can improve quality of life in comparison to therapy for symptoms or palliative treatment (natural course of the disease). However, the cost of electrochemotherapy is relatively high, the main contributor being electrodes and the electroporation device (Table II). In the future, a greater need for electrochemotherapy can be expected, despite the promise of new systemic therapies. Due to different cell clones in cutaneous metastases, the management of individual strains that do not respond to systemic therapy remains necessary.

In the scope of this article, the first cost-effectiveness analysis of electrochemotherapy based on the clinical practice is presented. To our knowledge, this is the first study to report detailed primary data on the costs and QALYs associated with electrochemotherapy in this patient population. Previous studies have reported increases in quality of

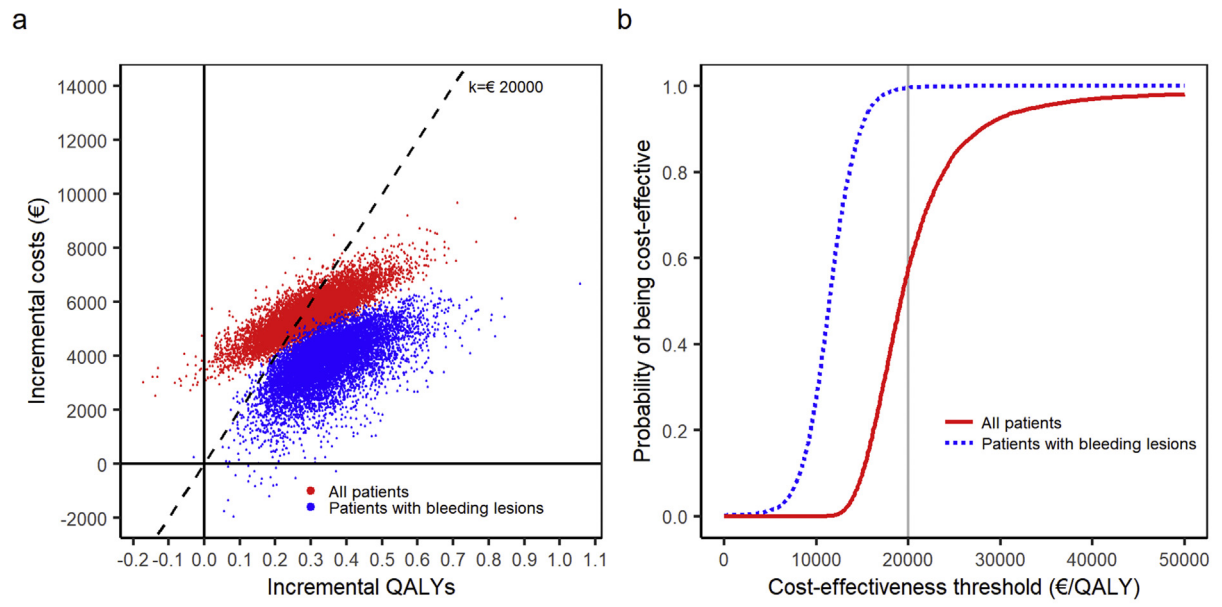

Figure 4. A, Cost-effectiveness plane, in case of elimination of hospitalization price. B, Probability of electrochemotherapy being cost-effective in all patients and in patients with bleeding lesions, without hospitalization costs. QALYs = quality-adjusted life-years.

life after electrochemotherapy[47–53]; however, quantitative information is often lacking or not sufficiently detailed to allow for the estimation of the cost-effectiveness of electrochemotherapy in patients with Stage IIIc/IV skin melanoma. For example, even when quality-of-life estimates were reported, it was not possible to differentiate between cancer types and stages.[54,55] The primary data collected in this study aim to fulfil this gap; however, the study has a number of limitations. First, by collecting data only on patients receiving electrochemotherapy, improvements in QALYs were measured using a before-and-after evaluation, which is prone to biases. Second, the estimation of the relative effectiveness of electrochemotherapy compared to standard of care was based on the assumption that patients not receiving treatment would remain with the same baseline utility values for the rest of their lives, which may not be the case. Third, EQ-5D-3L questionnaires were collected at each examination, but some patient data were missing. Nonetheless, the QALY estimates were consistent with those from the existing literature and were considered plausible by the clinicians who collected the data in the first place.

In consideration of all patients with Stage IIIc/IV skin melanoma, electrochemotherapy is expected to be less cost-effective compared to palliative care and the treatment of symptoms (iNHB, –0.037 QALYs, with a probability of being the most cost-effective strategy, equal to 0.32). Conversely, electrochemotherapy is expected to be more cost-effective in patients with bleeding lesions, as both the relative improvement in QALYs after successful electrochemotherapy and the expected savings in management costs are expected to be higher, although with a considerable uncertainty in the model estimates. It should be also noted that the NHB estimates were calculated using a cost-effectiveness threshold of 20,000 EUR/QALY, equal to approximately the 2018 Slovenian per-capita GDP. While the use of thresholds based on GDP has been recommended by the World Health Organization,[35] other estimates have also been proposed in the literature. For example, Woods

et al[56] provided country-specific values using empirical estimates of the threshold for the United Kingdom, estimates of the relationship between country GDP per capita and the value of a statistical life, and a series of explicit assumptions. For Slovenia, the authors estimated a threshold in a range between 11,374 and 15,690 USD purchasing power parity, which corresponded to a range between 6710 and 9257 EUR. It is expected that electrochemotherapy would not be considered cost-effective in any case at these lower thresholds.

Electrochemotherapy is, in theory, a day-procedure, but due to the age of some of patients involved in this study, most patients were hospitalized for a day or two, and some patients had even longer hospitalizations of up to 8 days due to disease-related complications unrelated to electrochemotherapy. Also, an advantage of electrochemotherapy is that it can be performed under local anesthesia, but in our study, 65.8% of patients received general anesthesia due to the high number of metastases treated.

In cases in which electrochemotherapy was used in younger patients or in patients with cancer of a less advanced stage, the number of procedures would increase, and an increase in quality of life after electrochemotherapy might be higher than in patients included in our study. However, in this case, the cost-effectiveness analysis of electrochemotherapy should include other treatment options for this patient population, including surgery, radiotherapy, and immunotherapy. The cost of immunotherapy is significantly higher than the cost of electrochemotherapy, while the increase in quality of life might be comparable. For example, it was estimated that the cost of immunotherapy in Slovenia may be up to 60,000 EUR/y. Electrochemotherapy, in the case of reasonable electrode price, is also expected to be less expensive than surgery because it is a day-procedure and lasts no more than 45 min in cases of less severe cancer stages. Increases in quality of life and treatment response rates are also likely to be higher in these patient populations. Therefore, one could arguably assume that the probability of electrochemotherapy being cost-effective is potentially higher in patients with less severe cancer stages compared to their counterparts with more severe disease.

Nonetheless, the cost of electrodes remains a crucial issue that may hinder a broader adoption of electrochemotherapy in clinical practice. Indeed, electrodes represent almost half of the procedure costs, and this study showed the extent to which their price is likely to affect the value of electrochemotherapy. This study also showed that the cost-effectiveness of electrochemotherapy was highly dependent on which patient subgroups were considered in the analysis, suggesting that the optimal price of the device is likely to be a specific indication. Finally, although this cost-effectiveness analysis used data from clinical practice, it was based on a small sample size (ie, 23 patents), which made the subgroup of patients with bleeding lesions very small. Therefore, results in this patient population should be carefully interpreted.

More research is needed for estimating the cost-effectiveness of electrochemotherapy in patient populations with less severe disease. Systematic collection of EQ-5D-3L questionnaires or any other quantitative reporting of quality of life during electrochemotherapy treatment is essential for further economic evaluations of electrochemotherapy. It seems that even if it is obligatory to collect quality-of-life data (eg, due to the commitment in the study application), it is not done on a regular basis, as it is not considered important.

CONCLUSIONS

In this analysis of the cost-effectiveness of electrochemotherapy for Stage IIIc/IV skin melanoma, quality of life was increased after the procedure. The probability of electrochemotherapy (with hospitalization) being cost-effective in patients with Stage IIIc/IV skin melanoma was just above 30%, which implies that the prices of the device and electrodes should be reduced for the successful implementation of electrochemotherapy into clinical practice. However, in patients with bleeding lesions, electrochemotherapy was more likely to be cost-effective (probability increased to 0.91). In order to simulate the probability of electrochemotherapy being cost-effective in patients with less severe cancer stages, the hospitalization cost was removed from the cost of the procedure, as electrochemotherapy can be performed as a day-procedure. The probability of cost-effectiveness in all patients included in the study was increased; however, cost-effectiveness could be easily increased with a reduction in the electrode price, which in our study represented almost half of the procedure cost.

DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Eva Pirc: Investigation, Data curation, Formal analysis, Writing - original draft, Visualization. **Carlo Federici:** Methodology, Formal analysis, Writing - original draft. **Maša Bošnjak:** Resources, Data curation, Writing - original draft. **Barbara Perić:** Resources, Validation, Writing - review & editing. **Matej Reberšek:** Writing - review & editing, Supervision. **Leandro Pecchia:** Methodology, Writing - review & editing, Supervision. **Nebojša Glumac:** Resources. **Maja Čemažar:** Supervision. **Marko Snoj:** Resources. **Gregor Serša:** Supervision, Writing - review & editing. **Damijan Miklavčič:** Conceptualization, Writing - review & editing, Supervision.

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APPENDIX A. CODE USED IN OPENBUGS TO ESTIMATE THE TRANSITION-RATE MATRIX

```
model{
   #estimate rates from fully observed data
   #loop for any state except for the death state
   for (i in 1:3){
   # model transitions from each state to any other state as a poisson distribution
   temp[i]<-lambda[i]*E[i]
   m[i]~dpois(temp[i])
   #estimate conditional probability to go to one of the two possible other states (conditional on leaving state i)
   tr[i,1]~ dbin(condP[i],m[i])
   }
   #define rate-transition matrix
   G[1,1]<–G[1,2]-G[1,4]
   G[1,2]<-lambda[1]*condP[1]
   G[1,3]<-0
   G[1,4]<-lambda[1]*(1-condP[1])
   G[2,1]<-0
   G[2,2]<–G[2,3]-G[2,4]
   G[2,3]<-lambda[2]*condP[2]
   G[2,4]<-lambda[2]*(1-condP[2])
   G[3,1]<-0
   G[3,3]<–G[3,2]-G[3,4]
   G[3,2]<-lambda[3]*condP[3]
   G[3,4]<-lambda[3]*(1-condP[3])
   #define priors for rates and conditional probabilities
   for (s in 1:3){
   lambda[s]~dgamma(0.1,0.1)
   condP[s] ~dbeta(1,1)}
   }
   #data
   list(m=c(24,27,19),

   E=c(724,4271,1635),
   tr=structure(.Data=c(22,24,
   11,2,3,8),.Dim=c(3,2)))
```

PATIENTS' CHARACTERISTICS.

	Gender	Age	Previous local/ regional treatments	Previous systemic treatment	Systemic treatment at ECT	Location of nodules	No oe ECT session	Number of nodules	Route and drug for ECT	Used electrodes
1	M	80	surgery, RT	No	No	armpit	2	5/5*	i.v. bleomycin	H
2	F	73	surgery	No	No	cheek	1	4	i.v. bleomycin	P
3	F	94	surgery, RT	No	No	foot	1	1	i.v. bleomycin	H
4	F	79	surgery, ILP	No	No	calf and tight	1	30	i.v. bleomycin	P
5	F	84	surgery	No	No	scalp	1	6	i.v. bleomycin	H
6	F	96	surgery	No	No	calf	1	34	i.v. bleomycin	H
7	M	62	surgery	No	No	neck	1	14	i.v. bleomycin	H + N
8	F	88	surgery	No	No	calf	1	1	i.t. bleomycin	P
9	F	83	surgery	No	No	calf and tight	3	20/19 (2*)/25(3*)	i.v. bleomycin	H/H + P/H
10	F	60	surgery, RT	adjuvant interferon-α	No	calf	1	18	i.t. cisplatin	P
11	F	82	surgery, ILP	No	No	tight	1	115	i.v. bleomycin	P
12	F	82	surgery	No	No	calf	1	12	i.v. bleomycin	P + N
13	F	79	surgery	No	No	calf	1	6	i.v. bleomycin	H/N
14	F	79	surgery, RT	No	No	calf	1	36	i.v. bleomycin	P
15	F	84	surgery, RT, ILP	No	No	calf and tight	5	18/23/ 27/41/20	i.v. bleomycin	P/P/HG + P/P/N + P
16	M	58	surgery	No	No	tight	1	10	i.v. bleomycin	P
17	F	48	surgery	pembrolizumab	pembrolizumab**	breast	1	1	i.v. bleomycin	H
18	M	86	surgery	No	No	shoulder	2	1	i.t. cisplatin	P
19	M	93	surgery, RT	No	No	cheek	1	1	i.t. bleomycin	N
20	M	75	surgery, RT	No	No	cheek	1	1	i.v. bleomycin	P
21	F	63	surgery, RT, ILP	pembrolizumab, dacarbazine	dacarbazine**	tight	2	13/3*	i.v. bleomycin	H
22	F	84	surgery	No	No	calf and tight	1	107	i.v. bleomycin	P
23	M	86	surgery, RT	No	No	calf	1	9	i.v. bleomycin	H

ECT-electrochemotherapy, RT – radiotherapy, ILP – isolated limb perfusion, * same nodules as in previous session were treated, i.v. – intravenous, i.t. – intratumoral, ** therapy not working on skin lesions, H – hexagonal electrode, P – plate electrode, N – needle row electrode.