

This is a collaboration project between SBU's Enquiry Response and the HTA unit at CAMTÖ the 4<sup>th</sup> of September 2017. SBU's Enquiry Response answer defined questions. The answer does not rely on a systematic review of literature conducted by the SBU and hence the results of the overview may be incomplete. The quality of the included studies has not been assessed. This answer has been produced by SBU's chancellery and has not been reviewed by SBU's committee.

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## Electrochemotherapy in treatment of tumours

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Electrochemotherapy is a combination therapy for cancer and consists of electroporation and treatment using cytostatic agents. Electroporation is a method that through an electric field temporarily opens the cell membrane which enhances the cytotoxic effect. Electrochemotherapy is used to a limited extent in Sweden and an essential question is if there is evidence that the method is effective and cost effective in treatment of tumours.

### Question

Is there evidence that electrochemotherapy is effective and cost effective in treatment of tumours?

### Summary

The Enquiry Response has identified three systematic reviews and one health economic study that evaluate electrochemotherapy as a cancer treatment. In the reviews skin tumours, and head and neck tumours are studied. In the systematic reviews for skin tumours the authors state that electrochemotherapy seems to be an effective method for localised treatment. In the systematic review on head and neck tumours the authors report that the response from electrochemotherapy was generally good, but that larger studies are needed as well as consensus guidelines. In the health economic study from 2008, a cost effectiveness analysis of electrochemotherapy was made with Cliniporator compared to other methods of treating skin tumours. The authors deemed electrochemotherapy cost effective. SBU has not yet taken a stand on the matter, since we have not assessed the individual studies' quality or weighed up the results. Therefore we only present the authors' individual conclusions.

## Background

Electrochemotherapy is a combination treatment for localised treatment of cancer and consists of electroporation and cytostatic treatment. Electroporation is a method which uses electrical pulses to temporarily open the cell membrane. The openings in the cell membranes last for approximately 60 to 90 seconds. During electrochemotherapy the patient receives cytostatic treatment intravenously or directly in the tumour as electrodes are placed around or within the tumour, to create an electrical field. This opens the membranes of the cancer cells. When the membrane opens up, the cancer cells take in more of the cytostatic drug. The treatment is stated to lead to selective necrosis of the dividing cancer cells. The time of treatment is dependent on how large and the frequency of tumours, and the treatment can be repeated if necessary. The treatment is given using a local anaesthetic or under general anaesthetic. Electrochemotherapy has so far only been used to a limited extent in Sweden to treat metastases of the skin.

## Method

We have made searches in the databases PubMed, Embase, Cochrane, different HTA organisations databases and other Swedish authorities' websites. We have limited the search to systematic reviews and health economic studies. For us to include an article in the response we set inclusion criteria that the article had been peer-reviewed and that it was published in English, Norwegian, Danish or Swedish.

## Results of the Search

The Enquiry Response's literature search generated a total of 94 unique hits. We read all article summaries. Out of these we deemed 9 articles relevant, which were read in their entirety. 4 articles are included in the response. The articles which are not included, were excluded on the basis that they were irrelevant to the question or because they were included in the other overviews. Observe that we did not assess the quality of the reviews or the included studies. It is therefore possible that several of the studies are of lower quality than what SBU includes in their ordinary assessments.

## Systematic Reviews

The systematic review by Aguado-Romeo et al. (2017) had the purpose of evaluating the effect of electrochemotherapy as lone treatment of advanced (inoperable or metastasising) malignant skin cancer (table 1). Electrochemotherapy was compared to other treatments such as radiation treatment, cytostatic treatment, biochemical treatment and immunotherapy. The authors included three systematic reviews and four observational studies, and write that electrochemotherapy may be effective as a local treatment of malignant tumours with complete or partial response as a result. They report that electrochemotherapy is easy to administer, economical and well tolerated,

especially if the treated tumours are less than ten and not larger than two centimetres. The treatment can be repeated with regards to the response of the tumour. The authors could not find any evidence that the method affected survivability and regard it more as a palliative treatment. They deem electrochemotherapy to be a safe method without any severe side effects. Most of the complications regarded pain, rashes, muscle cramps and local oedema.

The systematic review by Plaschke et al. (2016) includes eleven studies with data from head and neck tumours (Table 1). In most of the studies only one or two patients are of importance to the review. The purpose of the systematic review was to investigate the use of electrochemotherapy as a treatment option for head and neck tumours. None of the studies compared the results of electrochemotherapy with the standard treatment of head and neck tumours. In six of the studies electrochemotherapy was used with intratumoral injection (directly into the cancer tissue) of bleomycin and in three of the studies, the bleomycin was administered intravenously. In the two additional studies both of the methods were used depending on the size of the tumour, as larger tumours were easier to reach with intravenous administering. The times for evaluation in the studies were between four weeks and two months. The tolerance for electrochemotherapy of the mucosa in the ear, nose and throat region seemed to be dependent of the size and location of the tumour. Patients who were treated for small tumours seemed to tolerate the treatment without any severe complications, while the patients with reoccurring large tumours showed more severe and greater numbers of complications. The majority of complications were bleeding and pain. In the studies both large and small recidivating tumours were treated with electrochemotherapy with a good response to the treatment, however according to the authors no indications or recommendations for treatment can be based on these studies.

In the systemic overview by Mali et al. (2013) the purpose was to reinforce the current knowledge of clinical electrochemotherapy of skin tumours and to investigate the differences in effectiveness of electrochemotherapy depending on the type of tumour, what cytostatic drug that is used and how the drug is administered (Table 1). The studies were mostly non-randomised clinical studies and case studies. The authors used meta-analysis amongst others to evaluate the difference in antitumoral effect between electrochemotherapy and traditional cytostatic treatment (13 studies) and between different types of tumours (8 studies). Meta-analysis showed that electrochemotherapy had a significantly greater effect than traditional cytostatic treatment when the same cumulative dose was given. The effect on non-melanoma skin cancers was greater compared to melanoma skin cancers. Statistical comparisons of how tumours reacted to the treatment showed that the effect was significantly greater when bleomycin was administered intratumorally compared to intravenously and that there was no difference in effect between intratumorally administered bleomycin and cisplatin when used in electrochemotherapy. Statistical comparisons also showed that electrochemotherapy was more effective against sarcomas than against melanomas or carcinomas. Treatment with just electroporation had no effect on tumoral response.

Table 1. Systematic Reviews

Included Studies	Intervention	Variables
Aguado-Romeo et al. 2017		
7 Studies (Of which 3 are reviews)	Electrochemotherapy as monotherapy and as therapy combined with isolated limb perfusion on patients with a high tumoral load	Tumour response, safety, side effects, local or systemic toxicity
<p><b>Authors' Conclusions:</b>            "Results of the meta-analyses favored electrochemotherapy over chemotherapy. Electrochemotherapy appears to be an effective procedure for the local treatment of malignant tumor nodules (evidence of intermediate or low quality). This inexpensive method is simple to apply, well tolerated, and achieves objective responses under certain circumstances. There is no evidence that electrochemotherapy alters the natural course of the disease and it should therefore be considered a palliative treatment. With an evidence level of 1- (minus), electrochemotherapy can be recommended for the palliative treatment of unresectable, locoregionally advanced melanoma (grade B recommendation)."</p>		
Plaschke et al. 2016		
11 Studies	Electrochemotherapy against head and neck tumours compared to other treatments	Tumour response and side effects
<p><b>Authors' Conclusions:</b>            "Few studies concerning electrochemotherapy on mucosal head and neck tumors are available and they are not easily comparable. Overall response to treatment is good; nonetheless, further systematic studies are warranted."</p>		
Mali et al. 2013		
44 studies	Electrochemotherapy compared to only cytostatic treatment or only electroporation	Tumour response (According to WHO's handbook, RECIST criteria, biopsy or scanning) after a single electrochemotherapy treatment
<p><b>Authors' Conclusions:</b>            "The results of this review shed new light on effectiveness of electrochemotherapy and can be used for prediction of tumor response to electrochemotherapy with respect to various treatment conditions and should be taken into account for further refinement of electrochemotherapy protocols."</p>		

\* The reviews have a few studies in common

# Health Economic Studies

Colombo et al. (2008) published a health economic study of the costs and the use of electrochemotherapy. In the study they compare Cliniporator with other methods for treating skin cancer (table 2). Resource consumption and clinical results were collected from cost evaluation data and from a literature review. The total cost for the healthcare (Including installment and service) for electrochemotherapy was calculated to be approximately 18 000 SEK (1900 euro) per treatment. The authors conclude that electrochemotherapy is more costly, but also more effective than radiation treatment, with an additional cost of approximately 20 000 SEK (2100 euro) per additional tumour response. They write that electrochemotherapy has greater effect and a lower cost than both interferon-alfa treatment and a combination of hyperthermia, radiation treatment and cytostatic treatment. According to the authors isolated limb perfusion is the most effective treatment, however it is very costly with an additional cost of 1 200 000 SEK to achieve an additional tumour response compared to electrochemotherapy. It should be noted that the cost for some drugs are lower today compared to 2008, when the study was published. Some of the treatments that were used as comparisons are no longer used and new treatment alternatives have become available, and as such these results should be interpreted with care.

Table 2. Health Economic Studies

Population	Intervention	Variables
Colombo et al. 2008		
Patients with cutaneous or subcutaneous tumours	Electrochemotherapy compared to radiation treatment, hyperthermia together with radiation treatment and cytostatic treatment, interferon-alfa treatment or isolated limb perfusion	Tumour response, cost
<p><b>Authors' Conclusions:</b></p> <p>"After sensitivity analysis, the study results confirm the favorable cost-effectiveness ratio of ECT with the Cliniporator and justify its wider use."</p>		