

Electrochemotherapy - supplementary treatment for loco-regional metastasized breast carcinoma administered to concomitant systemic therapy

Eva-Maria Grischke, Carmen Röhm, Eva Stauß, Florin-Andrei Taran, Sara Y. Brucker, Diethelm Wallwiener

Department of Gynecology, University Hospital of Tübingen, Tübingen, Germany

Radiol Oncol 2017; 51(3): 317-323.

Received 29 March 2017
Accepted 18 June 2017

Correspondence to: Prof. Eva-Maria Grischke, M.D., Department of Gynecology, University Hospital Tübingen, Tübingen, Germany.
E-mail: eva-maria.grischke@med.uni-tuebingen.de

Disclosure: No potential conflicts of interest were disclosed.

Background. Electrochemotherapy (ECT) is an established procedure for treating breast cancer loco-regional recurrences following surgical intervention and/or radiotherapy. Limited information is available on ECT application as a concomitant procedure to systemic therapy in recurrent breast cancer. The primary objective of this study was to determine if the application of ECT in close temporal relation to systemic chemotherapy could lead to increased local and/or systemic side effects. For this purpose we evaluated the safety of ECT as a supplemental local therapy to systemic therapy. ECT local and systemic toxicity and side effects were recorded and whether the anticipated local therapeutic effect of ECT would be influenced by the concomitant use of systemic therapies was investigated. **Patients and methods.** This is an observational study. Thirty three patients with loco-regional metastasized breast carcinoma were treated and observed over a period of three years with 46 ECT applications for local tumour control in addition to established systemic therapy. A specific timeline for ECT administration was not fixed up, but was generally performed one week before the following chemotherapy administration with the aim to avoid the so called nadir, this means the peak period with risk of neutropenia.

Results. Data was collected over a period of three years on a population of 33 metastatic patients. Fifteen patients, received neo-adjuvant therapy as part of their primary treatment, but still had an advanced stage tumour. Some patients received repeated ECT applications. Objective tumour response was observed in 90% of the treated patients. Patients showed no increased local toxicity, especially no higher dermal toxicity, e.g. formation of local necrosis.

Conclusions. ECT proved to be an effective supplement to a cytotoxic systemic therapy, especially for high-risk patients who did not respond well to systemic therapy of loco-regional metastases, without creating any greater systemic or loco-regional toxicities.

Key words: electroporation; loco-regional metastases; local control; local toxicity; supplement systemic therapy; concomitant systemic therapy

Introduction

About 2–20% of the time, breast carcinoma recurrences are loco-regional.¹ In most cases, the recidivism is not exclusively an isolated local problem, but rather one associated with other distant metastases, in particular for long courses of the disease.^{2,3}

In spite of operative intervention and radiotherapy, loco-regional relapses can occur repeatedly, persist, or exhibit therapy-resistance, often in a highly disseminated form. Currently, in such situations, systemic therapy is the only available approach following usual ones, like local radiation and operative intervention. In these cases, other therapies

come into consideration, which may be applied concomitantly to systemic therapy.⁴ In such situations, the high probability of recurrence arising from the local manifestation of disease demands further local treatments to achieve rapid therapeutic response.

Furthermore, a proportion of patients show progression of the cutaneous loco-regional recurrences despite good clinical responses of visceral metastases, *e.g.* lung or liver metastases, to systemic therapy. Although patients often do not perceive organ manifestations as restraining, in most cases they see loco-regional cutaneous recurrences as negatively affecting their quality of life to a greater extent. The reasons for this are often weeping ulcerations with an odour and secretion, or possibly unpleasant and itchy lymphangitic changes. Hence, it is crucial to effectively control the loco-regional manifestation of the disease while managing the overall disease progression.

Electrochemotherapy (ECT) is a proven procedure for treating loco-regional metastases following surgical intervention and/or radiotherapy; having shown higher efficacy and limited toxicity it compares favourably with other skin treatments. Its potential for expansion from its current rather limited use to first line, widespread treatment is supported by recent publications.^{5,6} Available data suggests that the effectiveness of ECT would be higher, in terms of response rate and duration of local response, if used early in the treatment pathway, in conjunction with multimodality regimens.^{7,8} There is significant amounts of data on the outcome of ECT as the sole procedure, but limited information is available on ECT feasibility, safety and activity in combination or as a concomitant procedure to established cytotoxic systemic therapy in recurrent breast cancer.

ECT combines the antitumor activity of non-permeant (*e.g.* bleomycin) anticancer drugs with short electrical pulses that enhance the drug uptake into tumour cells, thus increasing the intracellular concentration and local toxicity of the cytostatic agent.⁹ The electric field is applied precisely and directly with needle electrodes to the tumour, and the appropriate cytotoxic effect is achieved locally on the diseased tissue.

In the past decade, clinical use of ECT gained acceptance and its effectiveness has been widely demonstrated in several cutaneous pathologies such as metastatic melanoma, cutaneous recurrences from breast cancer, basal cell carcinoma, squamous cell carcinoma, Kaposi sarcoma, and head and neck cancers.¹⁰ The publication of validated standard

operating procedures^{9,11} allowed the dissemination of ECT across Europe and improved the clinical outcome of the therapy.¹⁰

Although adequate experience has been gained on this method for loco-regional procedures involving breast carcinoma, and for other kinds of tumours, there is scarce clinical data to definitively answer the question of whether ECT can safely supplement cytotoxic systemic therapy. Therefore, the main objective of this study was to determine if the application of ECT in close temporal relation to systemic chemotherapy could lead to increased local and/or systemic side effects, when compared to historical toxicity profile of ECT and systemic therapies. Furthermore, this study investigated whether it is feasible and safe to apply ECT as a concomitant local therapy to established systemic therapy in patients with metastasized breast carcinoma who previously did not respond adequately to systemic therapy to treat loco-regional metastases.

Patients and methods

Study design

This observational study was approved by the Institutional Review Board of our Institute and was conducted according to the declaration of Helsinki. Informed consent has been obtained from all patients included in the trial.

The primary objective was to determine local and systemic toxicity and evaluate if the application of ECT in close temporal relation (*e.g.* in between consecutive chemotherapy administrations) to systemic chemotherapy could lead to increased local and/or systemic side effects. Whether the anticipated local therapeutic effect of ECT is influenced by the concomitant use of systemic therapies was also considered as a secondary endpoint.

Patients

The study included treatment and analysis of data on 33 patients over a period of three years (December 2012, December 2015) with loco-regional breast carcinoma, for whom other operative intervention or radiotherapy was neither possible nor appropriate because of highly extended local findings and/or disseminated tumours.

These 33 patients were subjected to a total of 46 individual ECT sessions. The indications were extended lymphangitic changes, ulcerations, or nodular skin metastases, disseminated over a very wide area or in several regions of the body.

Inclusion criteria were written informed consent, presence of symptomatic local metastasis without response to usual therapy like surgery, radiotherapy or other systemic anticancer therapy. Patients were offered ECT as a therapeutic option based on poor general condition, age, cardiac deficit not related to electrical malfunction, comorbidities, or that whether surgical procedure was not possible.

Exclusion criteria were reduced WHO performance (WHO score > 2) status clinically manifested arrhythmia, interstitial lung fibrosis, epilepsy, an active infection, a known allergy to bleomycin, kidney failure, and previous treatment with bleomycin at the maximum cumulative dosage. In case of clinical symptoms of impaired pulmonary function a lung capacity test was performed.

The patients underwent routine follow-up visits. In case of pulmonary metastases or pleural effusion, a CT of the thoracic area was performed. If necessary, a thoracic drainage was carried out.

Local response to the therapy was evaluated, along with the current systemic therapy, the tumour biology, and the tumour stage upon initial diagnosis. In addition to local response of the tumour, the study observed possible local toxicities and additional systemic reactions during the ongoing systemic therapy.

Treatment procedure

ECT has been performed according to the established ESOPE SOPs.⁹ Briefly, bleomycin was administered intravenously (15,000 IU/m² in a bolus in 30–60 s). Within 8–28 min after intravenous administration of bleomycin, electroporation of the tumour nodules was completed. Electric pulses were applied using sterile, single use hexagonal needles N-10-HG and N-20-HG, 10 or 20 mm long needle electrodes respectively, using the clinical electroporation device Cliniporator™ (Igea S.p.a., Italy). The type of electrode to be used was selected according to the physical characteristic of the lesion, *i.e.* lesion area and thickness.

In order to minimize the pain associated with the delivery of electric pulses, the procedure was performed under general anaesthesia. In most of the cases, the procedure was performed in 1 or 2 days hospitalization.

Results

Twenty four patients underwent a single ECT procedure. Nine patients received repeated ECT ap-

TABLE 1. Data on 33 patients at time of the first electrochemotherapy

Metastasis localization	N. of patients (%)
Loco-regional – exclusively	12 (36.3)
Loco-regional + distal	21 (63.6)
Distant metastasis	
1 organ affected	15 (45.4)
2 organs affected	3 (9)
> 2 organs affected	3 (9)
Distant metastasis and organs affected	
Metastases → pulmonary/pleural	11 (33)
Metastases → bone	10 (30.3)
Metastases → cerebral	3 (9)
Metastases → hepatic	3 (9)

plications: seven patients underwent 2 ECT procedures, one patient had ECT 3 times and one patient underwent ECT 5 times. Intervals between applications ranged from 6 weeks to a maximum of 11 months.

Twelve (36.3%) of the patients exhibited only extended loco-regional metastases, with at minimum area of 10 x 8 cm. The cutaneous metastases in most cases were confluent, only in 3 cases disseminated. Further specificities were ulceration or lymphangiosis. Twenty-one (63.3%) patients also had distant metastases; additional metastatic localizations are summarized in Table 1.

In most cases, systemic monotherapies were used: 8 patients received eribulin, 4 received taxane, 3 received vinorelbine, 3 patients were treated with capecitabine, 1 with mitomycin, and 1 with pegylated liposomal doxorubicin. Four patients received combi - chemotherapy; 3 of them a combination of carboplatin and gemcitabine, and 1 was given vinorelbine and capecitabine. Four patients were treated with bevacizumab and 6 with trastuzumab as an antibody therapy. Patients given endocrine treatment received an aromatase inhibitor, antiestrogen in the form of fulvestrant, and in 1 case exemestane in combination with everolimus. Thus, 5 patients were treated solely with endocrine therapy (Table 2). The sequence of metastasis treatments ranged from first line (because of distant metastases) to fifth line. Systemic treatment was given for distant metastasis and/or repeated local recurrent tumour (characterizing can be seen Table 1).

In all cases, loco-regional recidivism concerned the thoracic wall and/or cutaneous area of the contra-lateral thoracic wall or mammary gland. In 23



FIGURE 1. Patient with triple negative breast cancer under chemotherapy before ECT. The patient was previously under treatment with taxanes, carboplatin and eribulin. In contrast to response in liver and lung metastasis, skin metastasis showed progression.



FIGURE 2. Two month after ECT. Good tumour control in the pretreated area was obtained but progression in the border is visible and partially with tumour-free area. Typical hyperpigmentation following ECT treatment is visible.

cases (69.7%), the tumour occurred on one side, and in 7 (21.2%) cases on two sides. The axillary region was also affected in 5 patients, the dorsal thoracic wall in 5, and the upper arm in 3. One patient had an extended supra/ infraclavicular tumour (Table 3). In all cases, the changes covered large areas, partly lymphangitic, partly with ulcerations and large nodular areas. Especially the tumours in the axilla exhibited large nodules.

Local tumours, especially with lymphangitic changes, showed good response 3 months after

TABLE 2. Systemic therapy at the time of electrochemotherapy

Monochemotherapy	N. of patients
Eribulin	8
Taxane	4
Vinorelbine	3
Capecitabine	3
Mitomycin	1
Pegylated liposomal doxorubicin	1
Combo-chemotherapy	
Carboplatin & gemcitabine	3
Vinorelbine & capecitabine	1
Antibody therapy	
Trastuzumab	6
Bevacizumab	4
Endocrine monotherapy	
AI with everolimus & fulvestrant	5

TABLE 3. Findings of locoregional recidivism prior to electrochemotherapy

Areas of treated thorax wall	N. of patients (%)
On one side	23 (69.7)
On two sides	7 (21.2)
+ axilla	5
+ upper arm	3
+ dorsal	5
+ supra/infraclavicular	1

ECT. The redness improved rapidly or disappeared completely, and exudation of weeping areas either declined significantly or stopped fully. In terms of complete or partial remission, tumour response was observed in 90% of the treated patients. Necrosis occurred exclusively in large nodules, with consecutive healing of the changes. The hyperpigmentation of the treated area is a common skin toxicity following ECT treatment but the extent and intensity is variable.^{6,16} In almost a third of the patients, new lesions appeared primarily in peripheral areas, depending on the remaining disease dynamics (Figures 1, 2).

Analysis of the primary tumour stages and primary tumour biology showed that the patients treated were part of a high-risk group (Table 4). Almost half of the patients, namely 15 of the 33 (45.5%), received neo-adjuvant therapy (as first-

TABLE 4. Findings on patient characterization at initial diagnosis and after systemic therapy

	N. of patients (%)	N. of patients (%)	N. of patients (%)
Tumour stage	pT1	pT2	pT3/4
Total 18 patients	7 (38.9)	7 (38.9)	4 (22.2)
Post-PST	ypT1	ypT2	ypT3/4
Total of 15 patients	2 (13.3)	8 (53.3)	5 (33.3)
Nodal stage	pNo	pN1	pN2/3
Total of 22 patients	8 (36.3)	6 (27.2)	8 (36.3)
Post-PST	Nodal stage not determined		ypN2/3
Total of 11 patients	4 (36.3)		7 (63.6)

PST = primary systemic therapy

line systemic therapy) as part of their primary treatment. In spite of responsive chemotherapy, 13 of the 15 (86.7 %) patients still had an advanced stage tumour in the form of ypT2 and/or ypT3 and ypT4. Eight of the 33 patients (24.2%) exhibited a triple negative breast carcinoma. The HER2 status was positive for 6 of the 33 patients (18.2%), while a positive receptor status was seen in over half of the patients (20 of 33, 55.2%). Since 21 (63.6%) patients had a distant metastases along with several other affected organ systems, it was ensured that the systemic therapy interval could be freely set as short as possible, ECT could be conducted on all patients without procedure related complications. For follow up the patient came 2 weeks after ECT therapy for local control. If patients were under treatment in our department they were seen regularly. In case of treatment of patients referred to our institution by other hospitals, disease progression was reported to us by the referring centre and the patients evaluated for further treatment proposal including additional ECT if appropriate. In case of local tumour progression, generally in the border area of the original recurrence, additional ECT took place within the following 6 months, but was in dependency of tumour biology and aggressiveness. For patients under chemotherapy, the best time for planning ECT was one week before the next chemotherapy administration, but a specific timeline was not determined *a priori*. The primary aim was to avoid the so-called nadir, this means the peak period with risk of neutropenia. In rare cases of extended ECT, the following chemotherapy was delayed for one to two weeks until patient's performance status was considered adequate. Since all except 4 patients generally received fractionated monochemotherapy treatments, the appointment for treatment could be easily selected without any major shift in the interval, at which point it was ensured there was no grade 3 or 4 neutropenia.

Discussion

Despite operative intervention and radiotherapy, loco-regional relapses can occur repeatedly, persist, or exhibit therapy-resistance, often in a highly disseminated form. In these cases, additional local treatments can be proposed, and may be applied simultaneously or parallel to systemic therapy. In our study, ECT was offered as an additional treatment to systemic anticancer therapy with the objective of preventing local (skin) disease progression in patients with a highly extended local finding and/or disseminated tumours and to treat the symptoms of ulceration or lymphangitic tumour areas. Repeated therapy (ECT) was deemed necessary if the lesion was too extensive for complete treatment in one session or if the tumour progression was observed at follow-up.

In our institution, breast cancer metastases to the skin and subcutaneous tissue are the most frequent lesions treated with ECT. In the past clinical experiences, ECT has been applied to patients in different disease stages, *i.e.* locoregional disease such as chest wall recurrence after mastectomy or visceral disease with concomitant skin tumour involvement.^{9,12} In most cases, the treatment has been reserved to very advanced cases with large ulcerated bleeding metastatic nodules.¹³ It has been observed that early patient treatment would not require multiple treatment session, save the patient discomfort and improve quality of life, while achieving higher local tumour control rates and longer local progression-free survivals.^{8,13-17} ECT represents an attractive locoregional therapy for unresectable chest wall recurrence (CWR) from breast cancer. In the study of Campana *et al.*⁸ thirty-five consecutive patients with refractory CWR were enrolled from December 2006 through September 2011 and were administered with bleomycin-based ECT. Although only approximately

one third of patients (12 out of 35) achieved an effective chest wall control, the authors observed that if ECT would be applied earlier in the clinical course of chest wall recurrence, patients with fewer and less scattered skin metastases are less likely to develop new lesions. In a multicentre retrospective cohort study, 125 patients with breast cancer skin metastases underwent ECT between 2010 and 2013. The overall response rate after 2 months was 90.2%, while the complete response (CR) rate was 58.4%. Small tumour size, absence of visceral metastases, estrogen receptor positivity, and low Ki-67 index were predictors of CR after ECT. Patients who experienced CR had durable local control.¹⁶ In a prospective observational study performed by Benevento *et al.*¹⁸, twelve consecutive elderly (median age of 76 years) with regional or distant skin or subcutaneous metastases from breast cancer, with or without visceral disease, were treated with ECT. A CR was observed in 75.3%, partial response in 17% no change in 7.7% patients. No serious ECT-related adverse events were reported. According to the authors, ECT could be suggested as a primary local therapy in patients not suitable for surgical removal of the primary tumour, and clinicians should not hesitate to use it even in the elderly.¹⁸ Campana *et al.* confirmed that elderly breast cancer patients are highly responsive to ECT and achieved durable local tumour control.¹⁹

In our study, the data were collected over a period of three years. Of the 33 patients, 21 also had distant metastases and underwent appropriate cytotoxic systemic therapy. An indication for ECT followed either none or limited response of the loco-regional tumour to previous or current systemic therapy. Patients enrolled in this study not only received treatment for the systemic character of the disease, but also received ECT to control the tumour locally. In considering the risk factors arising from each additional intervention during ongoing chemotherapy, the patients showed no increased local toxicity, especially no higher dermal toxicity with formation of local necrosis. Patients with pulmonary metastases were given a preoperative pulmonary function test, depending on the extent of the metastases and clinical limitations. The extra bleomycin dosage of 15 mg/m² of body surface area did not result in any higher dermal or non-dermal toxicity, compared with prior toxicities.

The literature research showed that none of the studies noted the clinical response of primary systemic chemotherapy (neo-adjuvant chemotherapy) applied as a part of primary treatment of the breast carcinoma. In our study, almost half of the patients,

i.e. 15 of 33, underwent primary systemic therapy, whereby 13 of these patients still had a ypT2 to ypT4 stage tumour after successful application of the systemic therapy. These characteristics mean that the group included exclusively high-risk patients. Moreover, 25% of the patients, or 8 of 33, had a triple negative tumour. In comparison, the literature listed a maximum of 5 from 35 such patients or 14.3% that fell into this category.^{16,17}

In our experience, ECT proved to be an effective supplement to a cytotoxic systemic therapy, especially for high-risk patients who did not respond well to systemic therapy of loco-regional metastases, without creating any greater systemic or loco-regional toxicities (grades 3 & 4 dermal toxicity). Tolerance and response of ECT did not differ between patients undergoing any systemic therapy and those receiving only endocrinal treatments, especially from the standpoint of the most common known side effects such as pain, muscle soreness, and local paraesthesia.

Furthermore, even the presence of distant metastases was not contraindicated for ECT, and did not hamper the local therapeutic effect. It is important to select the proper time for application and to monitor it. No evidence was seen of any possible occurrence of myelotoxicity resulting from the cytotoxic systemic therapy.

An analysis of the primary tumour data (prognosis factors) and the phenomenon of an overly high rate of failure of primary chemotherapy of large remaining tumours showed that this study treated a group of patients with an extremely high-risk of recurrence, especially at the loco-regional level. Particularly in these cases, ECT was found to be a key supplementary therapy that should be applied as early as possible during the course of the disease. The data clearly rule out any higher levels of local or systemic toxicity.

References

1. Gerber B, Freund M, Reimer T. Recurrent breast cancer: treatment strategies for maintaining and prolonging good quality of life. [German]. *Dtsch Arztl Int* 2010; **107**: 85-91. doi:10.3238/arztebl.2010.0085
2. Bruce J, Carter DC, Fraser J. Patterns of recurrent disease in breast cancer. *Lancet* 1970; **1**: 433-5. doi:http://dx.doi.org/10.1016/S0140-6736(70)90829-9
3. Kurtz JM, Amalric R, Brandone H., Aymes Y, Jacquemier J, Pietra JC et al. Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. *Cancer* 1989; **63**: 1912-7. doi:10.1016/j.ijrobp.2014.04.039
4. Grischke, E-M. Wallwiener D, Souchon R, Fehm T, Loehberg CR, Jud SM, et al. Isolated loco-regional recurrence of breast cancer – established and innovative therapy concepts. *Geburtsh Frauenheilk* 2013; **73**: 1-12. doi:10.1055/s-0032-1328660

5. Spratt D, Spratt E A, Wu S, DeRosa A, Lee NY, Lacouture ME, Barker CA. Efficacy of skin-directed therapy for cutaneous metastases from advanced cancer: A meta-analysis. *J Clin Oncol* 2014; **55**, 4634. doi:10.1200/JCO.2014.55.4634
6. Banerjee SM, Keshtgar MRS. Electrochemotherapy for treatment of cutaneous breast cancer metastases: A Review *Arch Breast Cancer* 2016; **3**: 108-17. doi:http://dx.doi.org/10.19187/abc.201634108-117
7. Bourke MG, Salwa SP, Sadacharam M, Whelan MC, Forde PF, Larkin JO, et al: Effective treatment of intractable cutaneous metastases of breast cancer with electrochemotherapy: Ten-year audit of single centre experience. *Breast Cancer Res Treat* 2017; **161**: 289-97. doi:10.1007/s10549-016-4046-y
8. Campana L, Valpione S, Falci C, Mocellin S, Basso M, Corti L, et al. The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. *Breast Cancer Res Treat* 2012; **7**: e39484. doi:10.1007/s10549-012-2095-4
9. Marty M, Sersa G, Garbay JR Gehl J, Christopher G, Collins CG, Snoj M, et al. Electrochemotherapy – an easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. *Eur J Cancer Suppl* 2006; **4**: 3-13. doi:http://dx.doi.org/10.1016/j.ejcsup.2006.08.002
10. Mali B, Jarm T, Snoj M, Sersa G, Miklavcic D. Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis. *Eur J Surg Oncol* 2012; **39**: 4-16. doi:http://dx.doi.org/10.1016/j.ejcsup.2006.08.002
11. Mir, L, Gehl, J, Sersa G, Collins CG Garbay JR, Billard V, et al. Standard operating procedures of the electrochemotherapy: Instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the Cliniporator by means of invasive or non-invasive electrodes. *Eur J Cancer Suppl* 2006; **4**: 14-25. doi:http://dx.doi.org/10.1016/j.ejcsup.2006.08.003
12. Larkin JO, Collins CG, Aarons S, Tangney M, Whelan M, O'Reilly S, et al: Electrochemotherapy aspects of preclinical development and early clinical experience. *Ann Surg* 2007; **3**: 469-79. doi:10.1097/01.sla.0000250419.36053.33
13. Matthiessen LW, Chalmers RL, Sainsbury DC, Veeramani S, Kessel G, Humphreys AC, et al. Management of cutaneous metastases using electrochemotherapy. *Acta Oncol* 2011; **50**: 621-5. doi:10.3109/0284186X.2011.573626
14. Sersa G, Cufer T, Paulin SM, Cemazar M, Snoj M. Electrochemotherapy of chest wall breast cancer recurrence. *Cancer Treat Rev* 2012; **38**: 379-86. doi:10.1016/j.ctrv.2011.07.006
15. Quaglini P, Matthiessen L, Curatolo P, Muir T, Bertino G, Kunte C, et al. Predicting patients at risk for pain associated with electrochemotherapy. *Acta Oncol* 2015; **54**: 298-306. doi:10.3109/0284186X.2014.992546
16. Cabula C, Campana LG, Grilz G, Galuppo S, Bussone R, De Meo L, et al. Electrochemotherapy in the treatment of cutaneous metastases from breast cancer: A multicenter cohort analysis. *Ann Surg Oncol*, 2015; **22**: S442-50. doi:10.1245/s10434-015-4779-6
17. Matthiessen L, Johannesen HH, Skougard K, Gehl J, Hendel HW, et al. Dual time point imaging fluorine-18 flourodeoxyglucose positron emission tomography for evaluation of large loco-regional recurrences of breast cancer treated with electrochemotherapy. *Radiol Oncol* 2013; **47**: 358-65. doi:10.2478/raon-2013-0054
18. Benevento R, Santoriello A, Perna, G, Canonico S. Electrochemotherapy of cutaneous metastases from breast cancer in elderly patients: a preliminary report. *BMC Surgery* 2012; **12**: S6. doi:10.1186/1471-2482-12-S1-S6
19. Campana L, Galuppo S, Valpione S, Brunello A, Ghiotto C, Ongaro A, Rossi CR. Bleomycin electrochemotherapy in elderly metastatic breast cancer patients: clinical outcome and management considerations. *J Cancer Res Clin Oncol* 2014; **140**: 1557-65. doi:10.1007/s00432-014-1691-6