LUND UNIVERSITY

Dynamic-Electro Enhanced Chemotherapy brings relief to palliative patients with large tumour burden

Gurusamy, Kalavathy; Gurumurthy, , G.; Kar, Rajesh; Saravanan; Mathew, Asake; Persson, Bertil R

Published in:
Trends in Cancer Research

2018

Link to publication

Citation for published version (APA):
Gurusamy, K., Gurumurthy, , G., Kar, R., Saravanan, Mathew, A., & Persson, B. R. (2018). Dynamic-Electro Enhanced Chemotherapy brings relief to palliative patients with large tumour burden. *Trends in Cancer Research*, *13*, 29-41. http://www.researchtrends.net/tia/title_issue.asp?id=57&in=0&vn=13&type=3

Total number of authors:
6

Creative Commons License:
Unspecified

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Download date: 07. Oct. 2026

Trends in Cancer Research
Vol. 13, 2018

Original Communication

Dynamic-ElectroEnhanced Chemotherapy brings relief to palliative patients with large tumour burden

Kalavathy Gurusamy[1], G. Gurumurthy[2], Rajesh Kar[3], Saravanan[4], Asoke Mathew[5] and Bertil R. R. Persson[6,*]

[1]Pennalam Cancer Centre, Mandaveli, Chennai, India; [2]Patterson Cancer Center, Vadapalani, Chennai, India; [3]CBCC Oncology, Maduravoyul, Chennai, India; [4]International Cancer Centre, Neyoor, Nagercoil, India; [5]Lakshmi Pain Clinic, PH High Road, Chennai, India.
[6]Lund University, Medical Radiation Physics, S-22185 Lund, Sweden.

ABSTRACT

The aim of the present work is to perform a clinical case study evaluating the concept of Dynamic-ElectroEnhanced Chemotherapy™ (D-EECT). Ten patients with squamous cell carcinoma, eight with breast cancer and five patients with each presenting a different type of tumour, were entered in the trials initiated by five different cancer centres. All the patients were given Bleomycin and 2 to 3 treatment sessions with IQWave™ (Scandinavian ChemoTech AB, Sweden) according to the D-EECT protocol, which starts with pulses of amplitude 1000 V that successively reduces to about 400 V with an electrode distance of 12 mm. An average complete response of 26% and an average partial response of 74% add up to 100% objective response for all treated tumours. A new quantity "weighted response" WR = (3 × CR + PR - 3 × PD)/3 was introduced, that considers the cases of progressive disease (PD) as well. For the 10 cases of squamous cell carcinoma in the present study the weighted response was 47%. Considering squamous cell carcinoma (SCC) tumours larger than 3 cm the weighted response of 47% in the present study is about twice the WR of 23% for SCC tumours > 3 cm treated according to the European Standard operating procedures (ESOPE) protocol. The WR results of breast cancer, 43-67%, in the present study are almost equal to the WR averages of 47-80% in treatment of breast cancer nodules of different sizes according to the ESOPE protocol. The WR result of 67% for patients with breast-infiltrated ductal carcinoma with large, 10-15 cm, tumours is however, better than the WR of 47% for tumours larger than 3 cm in breast cancer patients treated according to the ESOPE protocol. In clinical studies of various types of tumours treated according to the ESOPE protocol an average of about 5% progressive disease was recorded, whereas no cases of progressive disease was recorded in the present study.

KEYWORDS: Dynamic-ElectroEnhanced Chemotherapy, D-EECT, squamous cell carcinoma, breast cancer, IQWave, objective response, complete response, partial response, weighted response, ESOPE.

INTRODUCTION

Electro-chemotherapy is the local application of electric pulses to the tumour in order to enhance the transfer of the chemotherapeutic drug (Bleomycin or Cisplatin) from the blood into the tumour cells, where the drug exhibits its cytotoxicity [1-7]. This therapy has been used for tumour treatment for more than 20 years, and nowadays most clinical protocols for electro-chemotherapy follow the European Standard operating procedures (ESOPE) [8]. According to

*Corresponding author: bertil_r.persson@med.lu.se

ESOPE 8 pulses of 1000 V/cm amplitude and 0.1 ms pulse-length are delivered as a pulse train of 8 pulses at a rate of 5 kHz or 1 Hz.

Several electro-chemotherapy studies do indicate that the dying tumour cells trigger the adaptive immune system against surviving tumour cells [9-13]. Despite this indication of an immune effect, electro-chemotherapy according to ESOPE acts as a local therapy, with tumour cells outside the treatment volume unaffected [14, 15].

Dynamic-ElectroEnhanced Chemotherapy (D-EECT) as applied in the present study was developed in order to also modulate the immunological effect. The basis for the development of D-EECT was the observation of tissue conductance in rat muscle after applying electric pulses of various amplitudes. By applying the same amplitude in each pulse as in the ESOPE protocol it was found that the major increase occurred in the first 3 pulses and then there was a minor steady increase [16]. This change in conductivity causes elevating electric currents in the tissue, which may be detrimental to the immunological response. But by decreasing the amplitude of successively applied pulses the electric current in each pulse can be decreased. An example of this is the result of an experiment, shown in Figure 1. The figure is based on data extracted from reference [16]. The upper curve shows the slightly decreasing voltage of the pulses applied in order to achieve the electric current profile shown in the middle curve. The resulting current difference spectrum is shown in the lower curve.

The principle of successively decreasing the voltage for each pulse is employed in the treatment concept called Dynamic-ElectroEnhanced Chemotherapy™ (D-EECT), which is adopted in the IQWave™ device (Scandinavian ChemoTech AB, Sweden). This device delivers a pulse-train of electrical pulses of gradually decreasing voltage, e.g. pseudo-exponentially decreasing voltage and the electrical current in each pulse is controlled to not exceed an upper pre-set threshold value.

The electrical current level of the pulse depends on the conductivity of the organ or tissue to be treated. In a living human the conductivity values in different tissues vary between 0.02 and 1.5 S/m at a low frequency current of < 1 kHz. After the

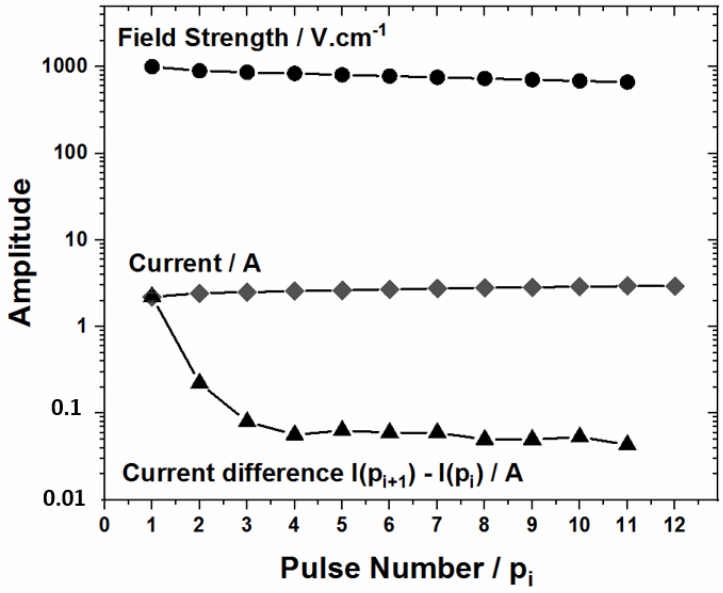

Figure 1. Diagram of current and voltage measurements of 12 consecutive pulses of amplitudes 1000 - 650 V and pulse-length 100 μs applied at 1 s intervals between needle electrodes at a distance of 1 cm inserted in the thigh muscle of 3 rats. The upper curve represents the estimated voltage to achieve constant current in each pulse during the treatment sequence of 12 pulses. The middle curve represents the current and the lower curve represents the current difference of consecutive pulses.

first pulse is delivered by the D-EECT to human tissue the degree of increase in conductance depends on the type of tissue.

The D-EECT protocol is designed to deliver pulse trains with gradually decreasing pulse amplitudes from 1000 V to 400 V for treatment of larger tumours, up to three times, 10-14 days apart.

MATERIALS AND METHODS

Patients

The inclusion criteria were as follows and the number of patients is given in parenthesis:

- Intraductal breast cancer with post-treatment chest-wall recurrence - (4).
- Primary locally advanced inoperable breast cancers.
- Invasive ductal carcinoma (IDC) of high grade with chest-wall deposits - (2).
- IDC of low grade with chest-wall recurrence - (2).
- Adenocarcinoma with chest-wall recurrence after treatment for breast cancer - (3).
- Advanced soft tissue sarcoma of the thigh - (1).
- Fibro-sarcoma of the lumbar region - (1).
- Post-radiation-induced tumour secondary to radiation therapy to pelvis for endometrial carcinoma - (1).
- Unknown primary with painful chest-wall and squamous cell carcinoma in neck nodal metastatic masses - (1).
- Recurrent head and neck squamous cell carcinoma (HNSCC) - (10).
- Vaginal vault recurrence secondary to squamous cell carcinoma of cervix - (1).
- Cutaneous liomyosarcoma - (1).
- Spindle cell carcinoma - (1).

The patients were entered in trials initiated at five different cancer centres. These were located in Chennai (4 centres) and Nagercoil (1 centre). All the patients were in advanced stage of disease, either locally advanced or with metastatic deposits. Patients were put on non-steroidal anti-inflammatory drugs (NSAIDs) or palliative pain killer medicines which include narcotic preparations such as morphine and pethidine. A total of 23 treated patients were evaluated.

All the patients were given a minimum of 2 to 3 D-EECT treatment sessions 7-14 days apart, with low-dose chemotherapy drugs, predominantly Bleomycin 15 USP units. The dose and route of administration were limited to i.v. injections in the initial days, followed by intra-tumoural injections of Bleomycin, which showed promising results observed even from the second session onwards.

The patient ID No. MT-3 with locally advanced breast cancer, after treatment had no secondary deposits anywhere in the body as proven by positron emission tomography (PET) and computer X-ray tomography (CT). This patient was treated with routine Adriamycin/cyclophosphamide chemotherapy protocol (using the dosage according to body surface area) followed within 24 hrs by D-EECT with i.v. administration of 15 USP units/m^2 of Bleomycin.

The clinical trials were performed after obtaining approval from the institutions where the studies were conducted and getting the written consent from the patients or patient attenders.

Protocols for Bleomycin administration

USP = Units/m^2 according to The United States Pharmacopeial Convention.

IU = International unit according to WHO Expert Committee on Biological Standardization.

1 USP unit corresponds to 1000 IU units which correspond to about 1 mg of Bleomycin potency.

1. 15 USP was injected intravenously (i.v.) as a slow bolus 8 min before electric pulse delivery.
2. 15 USP units/m^2 of Bleomycin dose was injected intravenously (i.v.), and 15 USP units/m^2 (15 mg.m^{-2}) diluted with 10 ml of distilled water was injected intra-tumorally (i.t.) 10 minutes before electrical pulse delivery.
3. Adriamycin and cyclophosphamide were administered i.v. according to body surface area (BSA)-guided dose, and was within 24 hours followed by D-EECT.

Protocols for electric pulse delivery

Data input was provided and the progress of the treatment was monitored visually, directly on the IQWave™ unit (From Scandinavian ChemoTech AB, Sweden). The control device operates on AC main voltage 110 V - 230 V (± 10%) and 50 Hz frequency. Treatment included applying the IQWave™ units' 4 electrodes, directly to tumours

after Bleomycin administration. The electric pulses from the device are delivered in three different directions according to the D-EECT protocol, i.e. it starts with 1000 V and decreases stepwise down to about 400 V. This differs from the ESOPE protocol where a constant value of about 1000 V is applied in the treatment of all kind of tumours. IQWave™ also offers a specific treatment mode for head & neck tumours in the oral cavity. This mode generates a maximum of 500-400 V/cm which is advisable for use in the intraoral cavity and is without any observed complications. It was designed to take into account the much higher conductivity of the oral cavity. Studies of repeated sessions of electro chemotherapy report increased therapeutic response [17, 18]. Thus in this study, patients with resistant tumours were treated in several sessions as presented in the Tables 1-5 reporting the results.

Electrodes & probe

The electrodes should be inserted in the holes provided on the probe, to select the distance between electrodes. If the tumour is less than 40 mm in diameter, a distance of 8 mm between the electrodes should be selected. If the tumour is larger than 40 mm in diameter, a distance of 12 mm between the electrodes should be selected.

The four electrodes with an active length of 30 mm, and 0.6 mm in diameter are made of stainless steel, and approved for high voltage application. A specific ergonomic hand-probe (IQWave Probe™) was used to maintain a fixed distance between the four electrodes. Electric pulses were delivered by the IQWave™ device using the D-EECT protocol, in which the directions of the electric field alternate between opposite and diagonally positioned electrodes in order to minimize the risk of coldspots.

Follow-up

During D-EECT and some hours later, patients were carefully monitored for treatment side-effects. The procedure was performed on an outpatient basis. All of them were examined as outpatients at regular intervals after D-EECT. Tumour measurements were made using measuring tape, radiological measurement and documented with photographs. Response rates were based on the tumour volume which was estimated by measuring the longest diameter (a) and the next longest diameter (b) perpendicular to (a). The tumour volume (TV) was calculated by using the ellipsoid formula: TV = thickness × width × length × $\pi/6$. When the results were analysed on a per treated nodule basis, the number of objective responses (OR) was determined by adding the number of complete responses (CR, no palpable or measurable tumour detected for at least 30 days after treatment) and partial responses (PR, greater than 50% decrease in tumour volume for at least 30 days after treatment). Stable disease (SD) was defined as no tumour growth, but less than 50% reduction in tumour volume. Progressive disease (PD) was defined as continued tumour growth. To determine the response rate per patient, the poorest response on per treated nodule basis was taken into account.

The treatment result of each patient is reported in terms of the following quantities where the fractional response f is defined as:

f = (No. of tumours with an actual response divided by the total no. of tumours).

CR = Complete response
PR = Partial response
SD = Stable disease
PD = Progressive disease
OR = Objective response
f_{CR} = Fractional complete response
f_{PR} = Fractional partial response
f_{SD} = Fractional stable disease
f_{PD} = Fractional progressive disease
f_{OR} = Fractional objective response

Usually without considering the responses of stable and progressive disease the sum of complete and partial responses, called objective response (OR = CR + PR) is used as a general quantity for evaluating the response of the treatment in question.

A new quantity named “fractional weighting response”, f_{WR} that also considers the cases of stable disease SD and progressive disease PD was introduced, and is used as a measure of the total response. This quantity f_{WR} is defined as follows:

$$f_{WR} = (3 \cdot f_{CR} + 1 \cdot f_{PR} + 0 \cdot f_{SD} - 3 \cdot f_{PD})/3;$$

The results of the present study were compared with the averages of all responses of the clinical electro-chemotherapy for each specific type of tumour, derived from the data of published reports [19].

RESULTS

Head & neck squamous cell carcinoma

In 8 patients with head & neck squamous cell carcinoma, a Bleomycin dose of 15 USP units/m^2 was administrated intra-tumorally i.t., or intravenously i.v., and in 2 patients a Cisplatin dose of 10 mg/m^2 was administrated i.v. Patients were treated at a field strength of 800 $V.cm^{-1}$ in 2 to 8 sessions with the total number of pulses as shown in Table 1. The therapeutic results are given as fractional complete response (f_{CR}), fractional partial response (f_{PR}), fractional objective response ($f_{OR} = f_{CR} + f_{PR}$), and fractional weighting response (f_{WR}) based on evaluated tumours.

The result of the only previously reported squamous cell carcinoma case treated with Cisplatin and ECT is not quite comparable with that of the present study due to the former case´s pre-treatment with radiotherapy and extensive ECT treatment [20].

Breast adenocarcinoma

In 3 patients with breast adenocarcinoma a Bleomycin dose of 15-30 USP units was administrated intravenously i.v. The patients were treated at field strengths of 800-400 $V.cm^{-1}$ in 5 sessions with the total number of pulses as given in Table 3.

Breast cancer-infiltrated ductal carcinoma

In 4 patients with breast cancer-infiltrated ductal carcinoma a Bleomycin dose of 15-30 USP units

Table 1. Responses of head & neck squamous cell carcinoma tumours treated with Bleomycin D-EECT.

Patient ID	Bleo IU	No. of pulses	No. of sessions	No. of tumours	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
CT3	15000	6	1	1	0	1	0	0	1	0.33
MT3	15000	20	3	1	0	1	0	0	1	0.33
TT4	15000	14	2	3	0.67	0.33	0	0	1	0.78
ST4	15000	58	8	2	0.5	0.5	0	0	1	0.67
ST4	15000	24	4	1	0	1	0	0	1	0.33
GT4	15000	37	7	1	0	1	0	0	1	0.33
TT4	15000	26	3	2	0	1	0	0	1	0.33
ZT 4	15000	20	3	1	0	1	0	0	1	0.33
Average	15000	26	4	2	0.15	0.85	0	0	1	0.43
Sd	0	16	2	0.8	0.27	0.27	0	0	0	0.18
se		6	1	0.3	0.10	0.10	0	0	0	0.06

Table 2. Responses of head & neck squamous cell carcinoma tumours treated with Cisplatin D-EECT.

Patient ID	Cisplatin	No. of pulses	No. of sessions	No. of tumours	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
QT4	10 units	12	1	1	0	1	0	0	1	0.33
RT4	10 units	12	1	1	0	1	0	0	1	0.33
From ref. [20]	3.5-8.5 mg	3	90 - 432	1	1	0	0	0	1	1

Table 3. Responses of breast cancer adenocarcinoma treated with D-EECT.

ID No.	Bleo IU	E-pulses	No. of sessions	No. of tumours	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
ST4	30000	23	4	3	0.33	0.67	0	0	1	0.56
KT3	15000	20	3	4	0.25	0.75	0	0	1	0.50
ST4-2	30000	10	3	7	0	1	0	0	1	0.33
Average	25000	18	3	5	0.19	0.81	0	0	1	0.46
Sd	8660	7	1	2	0.17	0.17	0	0	0	0.12
se	5000	4	0	1	0.10	0.10	0	0	0	0.07

Table 4. Responses of breast cancer-infiltrated ductal carcinoma treated with D-EECT.

ID No.	Bleo IU	E-pulses	No. of sessions	No. of tumours	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
ID4	30000	85	10	1	0	1	0	0	1	0.33
MU4-4	120000	218	10	3	1	0	0	0	1	1.00
V4-2	60000	70	10	4	0	1	0	0	1	0.33
TA-4-3	90000	38	10	2	1	0	0	0	1	1.00
Average	75000	103	10	3	0.50	0.50	0	0	1	0.67
Sd	38730	79	0	1	0.58	0.58	0	0	0	0.38
se	22361	46	0	1	0.33	0.33	0	0	0	0.22

Table 5. Responses of various types of cancer treated with D-EECT.

ID No.	Bleo IU	No. of E-pulses	No. of sessions	No. of tumours	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
Breast cancer (poorly differentiated carcinoma)										
GT4	30000	34	1	1	0	1.00	0	0	1	0.33
Rectal cancer adenocarcinoma										
SVT4	30000	16	1	1	0	1.00	0	0	1	0.33
Vaginal vault squamous cancer										
JT4	15000	44	1	1	0	1.00	0	0	1	0.33
Soft tissue sarcoma										
DT4-3	90000	150	3	20	0	1.00	0	0	1	0.33
Fibrosarcoma										
RT4-5	150000	370	5	3	0.67	0.33	0	0	1	0.78

Table 5 continued..

ID No.	Bleo IU	No. of E-pulses	No. of sessions	No. of tumours	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
Spindle cell carcinoma										
RE4	15000	42	1	2	0	1.00	0	0	1	0.33
Average	55000	109	2	5	0.11	0.89	0	0	1	0.41
Sd	54222	136	2	8	0.27	0.27	0	0	0	0.18
se	22136	56	1	3	0.11	0.11	0	0	0	0.07

was administrated intravenously i.v. The patients were treated at field strengths of 800-400 $V.cm^{-1}$ in 10 sessions with the total number of pulses as given in Table 4.

Other tumours

In 6 patients with various types of cancer Bleomycin in doses of 15-150 USP units was administrated intra-tumorally i.t., or intravenously i.v. The patients were treated at field strengths of 800-400 $V.cm^{-1}$ in 1-5 sessions with the total number of pulses as given in Table 5.

DISCUSSION

Summary of treatment results

In Table 6 a summary of the treatment results of all type of cancers is given.

Multivariate analyses and modelling

The quality and structure of data in the tables were analysed by using principal component analyses (PCA) and clustering. In Figure 2 the results of PCA analyses and data of the clusters of different types of tumours responding differently to the D-EECT treatment and the descriptors involved are shown.

Squamous cell carcinoma (SCC), breast cancer (BCA), and rectal cancer (RC) are in the group surrounded by a solid line in the figure. Vaginal vault cancer (VC) and spindle cell carcinoma (SC) are in the group surrounded by a dotted line in the figure.

Details of the use of projection to latent structure regression (PLSR) modelling are given in the references [21-23].

By applying the PLSR model to the data from the tables in the present publication, equations are derived to predict the dependent variables OR and PR from the following descriptors: patient age, tumour diameter (cm), number of pulses and Bleomycin dosage (USP units).

R^2 is the mean of the squares of the correlation coefficients between the variables and the latent components. This value is a measure of redundancies between the dependent variables and descriptors.

From the redundancies, the variables of importance for the projection (VIPs) that measure the importance of the various descriptors for the building of latent components is deduced, and is shown in Figure 3 [24].

Equations of the model:

$$CR\% = 7.04 - 0.168 \times Age + 0.077 \times No.\ pulses + 0.185 \times BleoU + 0.398 \times diam$$

$$PR\% = 93.0 + 0.168 \times Age - 0.077 \times No.\ pulses - 0.185 \times BleoU - 0.398 \times diam$$

Goodness of fit statistics $R^2 = 0.53$.

The model indicates that the fraction of complete remissions increases with larger number of pulses and units of Bleomycin dose.

Tolerance during and after the treatment

No significant modification of haemodynamic or cardiological parameters was noticed during D-EECT. A contraction of the muscles located beneath the site of treatment was observed. The contractions were instantaneous, disappearing immediately after the end of each electric pulse train. Several procedures, either local or systemic,

Table 6. Patient information and the number of tumours that responded to D-EECT treatment, with CR and PR. Objective response OR = CR + PR.

Histological type	Patient age	Tumour diameter	No. of responders to D-EECT		
	(range)	(cm) (range)	CR	PR	OR
Squamous cell carcinoma					
10 patients, 14 tumours	(40-70)	5-6	3	11	14
Adenocarcinoma-breast					
3 patients, 14 tumours	(40-65)	7-8	2	12	14
Breast-infiltrated ductal carcinoma					
4 patients, 10 tumours	(50-60)	10-15	5	5	10
Poorly differentiated breast carcinoma					
1 patient, 1 tumour	(31)	8-10	0	1	1
Adenocarcinoma-rectum					
1 patient, 1 tumour	(56)	7-8	0	1	1
Squamous vaginal-vault carcinoma					
1 patient, 1 tumour	(78)	6	0	1	1
Spindle cell carcinoma					
1 patient, 2 tumours	(72)	4-5	0	1	1
Soft tissue sarcoma					
1 patient, 20 tumours	(62)	15-20	20	0	20
Fibrosarcoma					
1 patient, 3 tumours	(53)	8-10	2	1	3

OR- objective response; CR – complete response, PR-partial response, based on evaluated tumours.

as described above, were used for relief of the sensations that accompanied the contractions. General anaesthesia seems more appropriate when large and/or multiple nodules are treated, whereas local anaesthesia would be sufficient for the treatment of a few small tumours.

Erythema and slight oedema at the site of the treated areas were the only noticeable side-effects observed transiently and remained for less than 24 h. Transient marks from electrodes were also often visible after D-EECT. Superficial leuco-necrosis was observed in the case of large tumours because of which the skin was already altered before D-EECT. For patients receiving only sedatives or local anaesthesia some pain was involved during the procedure, which subsided immediately after the last pulse was delivered. All patients agreed that it was tolerable and they would undergo the procedure again. As a matter of fact, several patients returned for the treatment of additional lesions. In addition, no delayed pain was reported by the patients. In several cases, the pain associated with the tumour was attenuated after D-EECT. No enhanced systemic Bleomycin toxicity was observed.

CONCLUSIONS

In the present study a total of 23 patients were treated in 38 D-EECT sessions at five different cancer centres. The treatment responses for a total

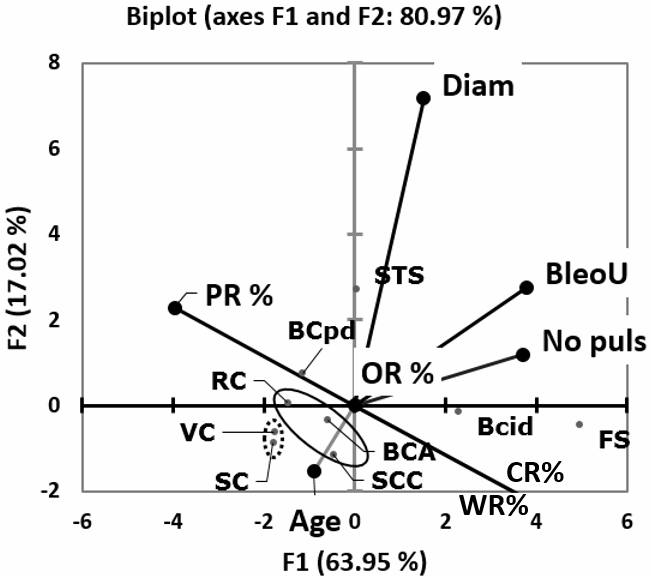

Figure 2. Biplot of PCA factor scores F1 versus F2 for the different predictors and types of tumours in the various clusters.

id	Tumour type	Histology
SCC	Squamous cell carcinoma	HN SCC
BCA	Breast cancer	Adeno ca.
BCid	Breast cancer	Infiltrated ductal
BCpd	Breast cancer	poorly differentiated
RC	Rectal cancer	Adenocarcinoma
VC	Vaginal vault cancer	Squamous
STS	Soft tissue sarcoma	
FS	Fibrosarcoma	
SC	Spindle cell carcinoma	

of 66 tumours of various sizes and histological types are given in Table 7. In all of the evaluable tumours the objective responses were found to be 100%, with complete remissions at 18%, and partial remissions at 82%. No progressive disease was recorded, and the average weighted response became 45 ± 17%.

The 100% objective response of squamous cell carcinoma cases in the present study is better than the overall average of 74% for objective response in all reported clinical studies of SCC [19]. The weighted response of 47% in the current study is about the same as the overall average of 40 ± 7 (s.e.)% for the weighted response in all reported clinical studies of SCC [19]. The overall average of progressive disease was 12 ± 4 (s.e.)% in all reported clinical studies of SCC while no progressive disease was observed in the present study, which might indicate a better immune response [19].

The results of a recent report on the electro-chemotherapy treatment of 43 patients with recurrent mucosal head and neck tumours, according to the ESOPE protocol are summarized in Table 8, which is based on data extracted from the Tables 1 and 3 of reference [25]. Of the

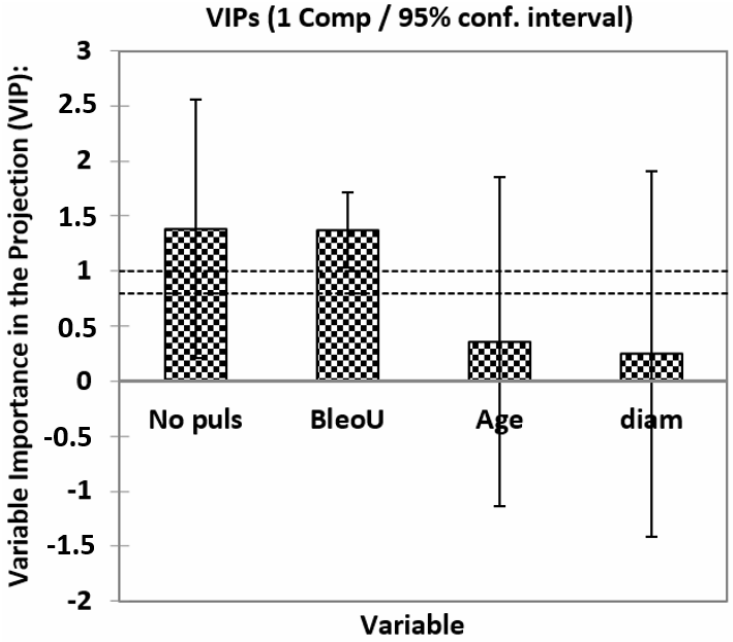

Figure 3. The importance of the various descriptor variables for building the model.

Table 7. Type of tumour and the percentage of tumour response to D-EECT treatment.

Tumour type	Histology	CR%	PR%	OR%	WR%
Squamous cell carcinoma	HN SCC	21	79	100	47
Breast cancer	Adenocarcinoma	14	86	100	43
Breast cancer	Infiltrated ductal	50	50	100	67
Breast cancer	poorly differentiated	0	100	100	33
Rectal cancer	Adenocarcinoma	0	100	100	33
Vaginal vault cancer	Squamous	0	100	100	33
Soft tissue sarcoma		0	100	100	33
Fibrosarcoma		67	33	100	78
Spindle cell carcinoma		0	100	100	33
Average		18	82	100	45
SD		25	25		17

total cohort, 34 patients had evaluable SCC tumours and 3 patients were adenocarcinoma patients. The evaluable SCC patients were split into two groups, one group with nodule diameter less than 3 cm, and another group with nodules larger than 3 cm, and the average treatment results are given in Table 8.

There was no remarkable variation of responses in the various groups of patients, except that the weighted response was 31% in the group with small tumours and 23% in the group with large tumours. In the present work the size of the SCC nodules were in the range of 5-6 cm (Table 6) with 47% weighted response which is twice the

corresponding value of 23% for tumours larger than 3 cm treated according to the ESOPE protocol [25].

The objective responses of 100% for breast cancer in the present study are better than the overall average of 80 ± 6 (s.e.)% for the objective response in all reported clinical studies of breast cancer [19]. But the ratio of complete to partial remissions is 0.25 in the present study, which is much smaller than the ratio of 2 for corresponding averages in all reported clinical studies of breast cancer [19].

The results of a recent report on electro-chemotherapy treatment of 90 patients with cutaneous recurrence of breast tumours, according to the ESOPE protocol at 10 European cancer centres are summarized in Table 9. The table was generated by using data given in Table 5: "*Response at 2 months after electrochemotherapy according to size*" of reference [26]. Fractional response values for breast tumour electro-chemotherapy are given in the Table 9, according to size of nodules: less than 3 cm, or larger than 3 cm. The fractional response of all 198 evaluable tumours are presented at bottom of the table.

There is a variation in complete responses among the various groups of patients, with about half the responses being in the group of patients with tumours larger than 3 cm. But the objective response is almost of the same order of magnitude due to the increased partial response in the group of patients with tumours larger than 3 cm. The weighted response, however, was 80% in the group with small tumours and 47% in the group with large tumours.

In the present study of breast cancer patients with nodules in the range of 7-8 cm, the weighted response is 43% which is about the same as that for tumours larger than 3 cm in the ESOPE study. D-EECT treatment of patients with breast-infiltrated ductal carcinoma with even larger, 10-15 cm, tumours resulted in a weighted response of

Table 8. Summary of the results of electro-chemotherapy in the treatment of head and neck cancer according to the ESOPE protocol.

Type of patients	No. of patients	No. of patients evaluable	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
All	43	37	0.22	0.43	0.27	0.08	0.65	0.28
All SCC 91%		34	0.21	0.44	0.26	0.09	0.65	0.26
SCC < 3 cm		14	0.21	0.50	0.21	0.07	0.71	0.31
SCC > 3 cm		20	0.20	0.40	0.30	0.10	0.60	0.23
Tot AD 9 %	4	3	0.2	0.4	0.3	0.1	0.6	0.3

Only evaluable patients are included in the evaluation of fractional response.

Table 9. Tumour response to electro-chemotherapy according to size of nodules (< 3 cm, and > 3cm), and the total number of evaluable nodules at 2 months after treatment according the ESOPE protocol.

	Total no. of nodules	No. of evaluable nodules	f_{CR}	f_{PR}	f_{SD}	f_{PD}	f_{OR}	f_{WR}
Nodules < 3cm	113	107	0.76	0.15	0.08	0.01	0.91	0.80
Nodules > 3cm	94	91	0.44	0.29	0.21	0.07	0.73	0.47
All evaluable nodules	207	198	0.61	0.21	0.14	0.04	0.82	0.65

Only evaluable patients are included in the evaluation of fractional response.

67% which is much better than the 47% weighted response for tumours larger than 3 cm in the ESOPE study [26]. Thus for breast cancer tumours of comparable sizes in the range 3-8 cm the weighted response of the treatments performed according to the D-EECT protocol in the present study seem to be equal to the results of the treatments performed according to the ESOPE protocol. But for even larger breast tumours the weighted response in tumours treated according to the D-EECT protocol in the present study is better than the weighted response for tumours larger than 3 cm treated according to the ESOPE protocol.

Thus in the present study Dynamic-ElectroEnhanced Chemotherapy (D-EECT), was shown to be a safe, simple and effective treatment protocol aimed towards managing large inoperable tumour masses. It opens up a new trend of treatment for inoperable, chemo-resistant and radio-resistant tumours.

ACKNOWLEDGEMENTS

The clinical work was performed by Kalavathy Gurusamy, Gurumurthy G, Rajesh Kar, Saravanan, and Asoke Mathew. Kalavathy Gurusamy summarized the clinical data and Professor Emeritus Bertil R. R. Persson PhD MDh.c. analysed the data, and configured the manuscript. We gratefully acknowledge the support from Mohan Frick (Scandinavian ChemoTech AB, Malmoe, Sweden).

CONFLICT OF INTEREST STATEMENT

Professor Emeritus Bertil R. R. Persson acts as Scientific Advisor and is Shareholder of Scandinavian ChemoTech AB, Malmoe, Sweden.

REFERENCES

1. Belehradek, J., Orlowski, S., Poddevin, B., Paoletti, C. and Mir, L. M. 1991, European Journal of Cancer, 27, 73-76.
2. Belehradek, J., Orlowski, S., Ramirez, L. H., Pron, G., Poddevin, B. and Mir, L. M. 1994, Biochimica Et Biophysica Acta-Biomembranes, 1190, 155-163.
3. Belehradek, J. J., Orlowski, S., Poddevin, B. and Mir, L. M. 1990, Journal of Cancer Research and Clinical Oncology, 116, 620-620.
4. Belehradek, M., Domenge, C., Luboinski, B., Orlowski, S., Belehradek, J. and Mir, L. M. 1993, Cancer, 72, 3694-3700.
5. Mir, L. M., Banoun, H. and Paoletti, C. 1988, Experimental Cell Research, 175, 15-25.
6. Mir, L. M., Orlowski, S., Belehradek, J. and Paoletti, C. 1991, European Journal of Cancer, 27, 68-72.
7. Mir, L. M., Tounekti, O. and Orlowski, S. 1996, General Pharmacology, 27, 745-748.
8. Marty, M., Sersa, G., Garbay, J. R., Gehl, J., Collins, C. G., Snoj, M., Billard, V., Geertsen, P. F., Larkin, J. O., Miklavcic, D., Pavlovic, I., Paulin-Kosir, S. M., Cemazar, M., Morsli, N., Rudolf, Z., Robert, C., O'sullivan, G. C. and Mir, L. M. 2006, Ejc Supplements, 4, 3-13.
9. Calvet, C. Y. and Mir, L. M. 2016, Cancer and Metastasis Reviews, 35, 165-177.
10. Mir, L. M. 2006, Ejc Supplements, 4, 38-44.
11. Mir, L. M. and Orlowski, S. 1999, Advanced Drug Delivery Reviews, 35, 107-118.
12. Sadadcharam, M., Soden, D. M. and O'sullivan, G. C. 2008, International Journal of Hyperthermia, 24, 263-273.
13. Calvet, C. Y., Famin, D., Andre, F. M. and Mir, L. M. 2014, Oncoimmunology, 3.
14. Pinkawa, M., Djukic, V., Klotz, J., Petz, D., Piroth, M. D., Holy, R. and Eble, M. J. 2014, Future Oncology, 10, 835-843.
15. Queirolo, P., Marincola, F. and Spagnolo, F. 2014, Archives of Dermatological Research, 306, 521-526.
16. Persson, B. R. R. 2016, Acta Scientiarum Lundensia, ISSN 1651-5013, 2016, 1-16.
17. Jaroszeski, M. J., Gilbert, R., Perrott, R. and Heller, R. 1996, Melanoma Research, 6, 427-433.
18. Hyacinthe, M., Jaroszeski, M. J., Dang, V. V., Coppola, D., Karl, R. C., Gilbert, R. A. and Heller, R. 1999, Cancer, 85, 409-417.
19. Persson, B. R. R. 2018, Acta Scientiarum Lundensia, ISSN 1651-5013, 2018, 1-62.
20. Sersa, G., Stabuc, B., Cemazar, M., Jancar, B., Miklavcic, D. and Rudolf, Z. 1998, European Journal of Cancer, 34, 1213-1218.

21. Tenenhaus, M., Pages, J., Ambroisine, L. and Guinot, C. 2005, Food Quality and Preference, 16, 315-325.
22. Wold, S., Kettaneh, N. and Tjessem, K. 1996, Journal of Chemometrics, 10, 463-482.
23. Wold, S., Sjostrom, M. and Eriksson, L. 2001, Chemometrics and Intelligent Laboratory Systems, 58, 109-130.
24. Xlstat, 2015, Data analysis and statistics with MS Excel®, Web: www.xlstat.com, Addinsoft,, 40 rue Damrémont 75018, Paris, France.
25. Plaschke, C. C., Bertino, G., Mccaul, J. A., Grau, J. J., De Bree, R., Sersa, G., Occhini, A., Groselj, A., Langdon, C., Heuveling, D. A., Cemazar, M., Strojan, P., Leemans, C. R., Benazzo, M., De Terlizzi, F., Wessel, I. and Gehl, J. 2017, European Journal of Cancer, 87, 172-181.
26. Matthiessen, L. W., Keshtgar, M., Curatolo, P., Kunte, C., Grischke, E.-M., Odili, J., Muir, T., Mowatt, D., Clover, J. P., Liew, S. H., Dahlstroem, K., Newby, J., Letulé, V., Stauss, E., Humphreys, A., Banerjee, S., Klein, A., Rotunno, R., De Terlizzi, F. and Gehl, J. 2018, Clinical Breast Cancer, 19, 1-9.