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Electrochemotherapy can be used as palliative treatment in patients with repeated loco-regional recurrence of squamous vulvar cancer: a preliminary study

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HIGHLIGHTS

- Patients with recurrence of vulvar cancer were submitted to electrochemotherapy
- The treatment was effective to improve symptoms and easy to perform
- The treatment is able to achieve a local control of disease

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ABSTRACT

Objective. Electrochemotherapy (ECT) is an attractive treatment for solid cutaneous tumours with a good response rate (55–92%). No studies have evaluated ECT performed in vulvar cancer. The aim of our study was to evaluate the safety, local tumour efficacy and relief of symptoms of ECT treatment in patients affected by recurrence of squamocellular vulvar cancer (V-SCC) unsuitable for standard treatments.

Methods. We enrolled nine patients with histological diagnosis of recurrence of V-SCC. Intravenous bleomycin was injected under general sedation after an accurate mapping of all lesions and ECT was performed. Patients were reviewed after one, three and six months. Response to therapy was evaluated using RECIST criteria and quality of life (QoL) was evaluated via questionnaires.

Results. The median age was 84 years (range 80–90 years). The main location of recurrences was the vulva (87.5%). Multiple lesions were present in 25% of cases. No peri-operative complications were observed. Response to therapy was complete in 62.5% of patients, partial in 12.5%, no change was observed in 12.5% and progression of disease in 12.5% of patients respectively. Evaluation of symptoms showed a significant reduction of pain, bleeding, odour ($p < 0.04$) and urinary discomfort ($p < 0.04$). We observed two relapses at four and seven months after treatment. After nine months fifty percent of patients were alive.

Conclusions. Our preliminary study showed that ECT is a suitable procedure in elderly patients with loco-regional vulvar cancer relapses. ECT can be used as palliative therapy and the treatment relieves symptoms and improves QoL.

Introduction

Vulvar cancer represents 5% of all female gynaecologic malignancies and its incidence is 10 times higher in patients over 75 years of age [1]. Treatment and management represent a challenge because of its anatomic location, tendency to spread to the lymph nodes and incidence in the elderly [2].

In the past radical surgery was the primary treatment option in both early and late stages. Nowadays surgery still has an important role but neo/adjuvant chemo and radiotherapy are used to decrease postoperative complications and improve prognosis [3].

Despite this multimodal approach recurrence, especially in advanced stages, is not rare [4]. Loco-regional recurrence is an important risk factor for distant metastatic disease, either synchrone or metachrone with a negative effect on quality of life (QoL) (local pain, vaginal bleeding,

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burning and odour) [5]. Therapy for this pattern of recurrence is limited and options are based on the volume and site of the disease. After multidisciplinary treatment for recurrences surgical resection remains the preferred therapeutic approach [6]. However when surgery cannot be performed with a reasonable cosmetic and functional outcome, other options must be evaluated.

Electrochemotherapy (ECT) is a recent loco-regional therapy that combines low-dose cytotoxic drugs (bleomcyn and cisplatin), administered intravenously or intra-lesionally, and high intensity electric pulses to induce electroporation to improve drug delivery into tumour cells [7].

ECT is used in humans for the treatment of cutaneous neoplasms or the palliation of skin tumour metastases. Since 1995 literature has reported a 92% response rate in patients treated with ECT for disseminated cutaneous and subcutaneous melanoma lesions as a palliative cure [8,9]. In 2006 a multicentre study performed by the European Standard Operating Procedure for Electrochemotherapy (ESOPE) defined the parameters for using ECT. ECT can be proposed in cutaneous metastasis that cannot be excised because of the number and/or site of the tumour and in a palliative setting the procedure offers a good response (85%) and improves patient QoL [10].

In literature, no study has previously evaluated whether ECT could be used for local treatment in cutaneous recurrences of squamous cellular vulvar cancer (V-SCC).

The aim of this preliminary study was to evaluate the safety, local efficacy, acceptability and QoL of ECT with bleomycin in reducing the size of tumours in patients with V-SCC with loco-regional cutaneous recurrence submitted to multiple previous treatments (chemotherapy, radiotherapy and surgery) and unsuitable for standard treatments.

Materials and methods

In our prospective preliminary study we recruited nine women with histological diagnosis of single or multiple loco-regional recurrences of V-SCC. Patients were unsuitable for standard treatments because of tumour characteristics (previous multiple surgeries or previous radiotherapy) and general status and were invited to participate in the study to undergo palliative therapy with ECT.

Inclusion criteria and technical procedures followed the European Standard Operating Procedures of ECT Study (ESOPE) [11]. The study was approved by the local ethical committee and all patients signed an informed consent form before enrolment.

Before initiating the procedure accurate digital mapping of all lesions was performed and the area involved was sketched. All nodules were measured and the tumour area was calculated [11]. If multiple nodules were present the area was the sum of the area of each lesion. A full clinical history, clinical examination, routine blood biochemistry, computer tomography scan (CT) and 18 F-FDG-PET/CT to evaluate distant metastasis were required.

The procedure required a hospital stay of 24 h and general sedation.

Intravenous Bleomycin (Bleomicina Nippon K fl) was injected in an i.v. bolus (30 s) at a dose of 15000 UI/m2. Electrical pulses started eight minutes after bolus and treatment was completed 28 min after the end of infusion [11]. ECT electroporation was performed using a Cliniporator device with type III electrodes placed into the lesion (Igea S.p.A. Carpi Italy). Pulse delivery frequency was 5 kHz at a duration of 100 μs. Electrodes were gently inserted into the skin of the area affected at a depth of one centimeter; the procedure was repeated progressively covering all of the area to be treated.

Patients were seen again four weeks after the procedure and then every four months. During follow-up treatment efficacy was determined by careful inspection of genitalia and the pelvic region and all new suspected lesions were mapped and a histological sample was taken. ECT response criteria was defined according to the WHO Handbook for Reporting Results of Cancer Treatment [12]: complete response (CR) when the tumour nodule was not palpable; partial response (PR) when the tumour size decreased by more than 50% in the products of the largest perpendicular diameters of the measurable lesions; no change (NC) when the lesion had a reduction <50% and an increase of up to 25%; progressive disease (PD) when the tumour size had increased by more than 25%.

To evaluate an improvement in QoL following ECT treatment we administered visual analogue score (VAS) for pain and vulvar cancer subscale (VCS) part of functional assessment of vulvar cancer therapy (FACT-V) for QoL [13], before and four weeks after the procedure. Willingness to undergo further ECT treatment, if necessary, was asked to patients.

Statistical analysis

All continuous data are expressed in terms of mean and standard deviation of the mean and range. Unpaired T test was performed to investigate response to VCS before and after ECT. $p < 0.05$ was considered significant. Statistical analysis was carried out by means of the Statistical Package for the Social Sciences (SPSS) software version 9.0 (SPSS Inc., Chicago, USA).

Results

Between 2009 and 2012, nine women were eligible for the study according to the inclusion criteria and were enrolled in the study. Patient age was 84 ± 3.9 years (mean ± SD) at time of enrolment.

Diagnosis stage of primary tumours, according to the FIGO system, was: one patient at stage IA, (11%), one patient at stage IB (11%), three

Table 1
Patients characteristics.

Patients	NR[a]	Type R[b]	Location[c]	*ab* before ECT(cm^2)[d]	Response	Δab After ECT (cm^2)[e] (%)	Time R after ECT (days)	Location [f]
1	1	S	1r	1.4	PD	−0.8 (57)	–	–
2	0	M	2r–2l	2.5–2	CR	0 (100)	230	1
3	2	S	3	0.32	CR	0 (100)	–	–
4	4	S	5	10	PR	8.9 (89)	–	–
5	3	S	4	2.5	CR	0 (100)	–	–
6	1	S	1l	1.5	CR	0 (100)	124	1
7	1	S	6r	2.6	SD	2.3 (11)	–	–
8	1	M	3	3	CR	0 (100)	–	–

NR = number of recurrence before ECT.
R = Recurrence.
[b] S = singular recurrence or lesion, M = multiple recurrence or lesion.
[c] 1 = labium mayus, 2 = labium minus, 3 = posterior commissure, 4 = paraurethral region, 5 = emivulva, 6 = inguinal region, l = left, r = right.
[d] *a* = largest diameter of the tumour nodule, *b* = diameter of the tumour nodule perpendicular to *a*.
[e] Δ *ab* = *ab* before ECT – *ab* after ECT.
[f] 1 = same site treated, 2 = other site.

Table 2
Descriptive statistics for the vulvar cancer specific subscale items.

VCS questions	Pre-treatment (mean + SD)	Post-treatment (mean + SD)	$p < 0.05$
I am bothered by discharge or bleeding from my vulva	2.2 + 1.2	3.0 + 1.1	0.04
I am bothered by odor coming from my vulva	1.5 + 0.8	2.2 + 1.2	0.02
I am afraid to have sex	–	–	–
I am bothered by swelling/fluid in my legs	3.7 + 0.5	3.8 + 0.4	ns
My vagina feels too narrow or short	2.2 + 0.8	2.5 + 0.5	ns
I am bothered by discomfort in my groin or legs	3.5 + 0.8	3.7 + 0.5	ns
I am afraid the treatment may harm my body	2.0 + 0.6	2.7 + 1.0	0.03
I am interested in sex	–	–	–
I like the appearance of my body	1.8 + 0.4	2–0 + 0.1	ns
I am bothered by constipation	2.8 + 1.2	3.0 + 1.1	ns
I have a good appetite	3.2 + 0.8	3.3 + 0.5	ns
I have trouble controlling my urine	1.7 + 0.5	2.0 + 0.9	ns
I am bothered by itching/burning in my vulva area	1.0 + 0.1	1.3 + 0.5	ns
I have discomfort when I urinate	0.8 + 0.8	1.3 + 0.8	0.04
I am bothered by pain or numbness in my vulva area	1.2 + 0.4	1.3 + 0.5	ns
I have trouble bending	2.5 + 1.0	2.8 + 0.8	ns
I have discomfort when I am sitting	1.8 + 1.2	2.0 + 1.1	ns
I am bothered by wearing compression stockings	3.3 + 0.5	3.5 + 0.5	ns
I am able to eat the foods that I like	3.2 + 0.8	3.3 + 0.5	ns
Higher score represent better quality of life.			

patients at stage II (33%), three patients at stage IIIA (33%), one patient at stage IIIB (11%). Eight patients were previously submitted to surgery and/or radio-chemotherapy and the mean time to relapse after last treatment was 52 ± 49 months (mean ± SD). One patient was submitted to ECT without any previous treatment because of age (89 years) and recent gluteal abscess following hip replacement surgery. One patient was excluded from the study as they were lost during follow-up. Mapping of the lesions showed that disease was present in the vulva in seven of eight patients (87.5%) and in the upper thigh region in one patient (12.5%). Multiple lesions were present in two patients (25%). Lesion characteristics are shown in Table 1.

All patients received treatment under general anaesthesia as described in the protocol, with no adverse events observed. Procedure time was 20 ± 4 min (range 15–28 min). During the procedure there was minimal blood loss from the application site resulting in an oedema which disappeared after 24–72 h.

Postoperatively patients did not experience local pain, fever or nausea; no antibiotic or anti-thrombotic prophylaxis was performed; patients received oral fluids and a solid diet 3 h after anaesthesia. Postoperative hospital stay was 24 h for all patients.

We evaluated the response to the therapy after one month and we observed: CR in five patients (62.5%), PR in one patient (12.5%), NC in one patient (12.5%), and PD in one patient (12.5%). In patients with CR the nodule disappeared and the residual skin was pale and soft and regular.

After a follow-up of 9.1 ± 3.5 months (mean ± SD) four patients (50%) were alive. Two patients with CR relapsed after four and seven months and were candidates for further treatment with ECT. One patient with PD for age and poor performance status was not submitted to other treatments and was supported by palliative cure. One patient was free from disease at the time of follow-up.

All patients responded to VAS and VCS questionnaires pre-treatment, one month after and six months after the procedure. Evaluation of VAS and VCS performed one month after treatment showed a significant reduction in pain ($p < 0.03$) and a significant reduction in bleeding, odour and urinary discomfort (Table 2). The total VCS score showed a significantly better QoL after treatment ($p < 0.001$). All patients were sexually inactive and did not respond to sexual questions. All patients confirmed that the procedure could be repeated.

Discussion

Our preliminary study showed that ECT can be performed in loco-regional vulvar cancer recurrence as palliative therapy as the treatment relieves symptoms and improves patient QoL (Fig. 1).

Although ETC is routinely used with palliative intent in treatment of cutaneous and subcutaneous tumours of different histological types no data is available on vulvar squamous cellular cancer. In a recent systematic review and meta-analysis Marty et al. [10] evaluated 548 patients affected by melanoma, cutaneous sarcoma, Kaposi's sarcoma and breast cancer relapses treated with bleomycin or cisplatin and ECT. The data showed CR in 59.4% of cases and PR in 24.7% of cases. Treatment was ineffective in only 15.9% of cases. In the ESOPE study of 62 patients with skin neoplasia Marty et al. [10] observed a local tumour control rate of 88% with bleomycin given intravenously, 73% with bleomycin given intra-tumourally and 75% with cisplatin given intra-tumourally. These data are comparable to the present study where local control of tumour was achieved in 75% of the patients and CR in 62.5%. The

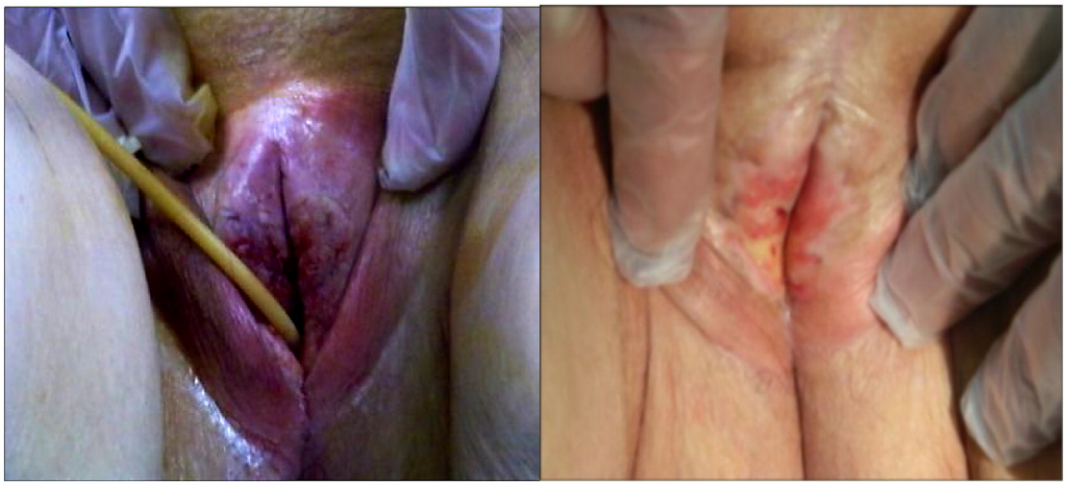

Fig. 1. Pre and post treatment vulvar recurrence. The pictures showed tumour recurrence in left and right minor labia before treatment. After one month the lesion disappeared and the residual skin was pale and soft and regular.

treatment was ineffective in 12.5% (one of eight) of patients. The patient who demonstrated PD could probably have been treated effectively with an intra-tumoural drug injection due to fibrosis and the low perfusion of pre-irradiated tissues.

Marty et al. [10] reported higher efficacy of ECT with intravenous injection of bleomycin for large tumours compared to intra-tumour injection which they explained was the result of more uniform distribution of the drug within the tumour. We therefore used i.v. bleomycin instead of local injection and the treatment was effective in small and large lesions with a 90% reduction observed in a 10 cm^2 relapse.

Current treatments of local vulvar cancer relapses are surgery, external radiotherapy, brachy-therapy and their combination. Radiotherapy achieves local control of the tumour but it is not repeatable and cannot be offered in previously irradiated patients. Surgery is frequently associated with delayed healing, lymphedema, local infections and poor cosmetic results with a decrease in the QoL [14]. ECT was safe with good cosmetic results obtained in patients who had previously been treated with surgery and radiotherapy.

In our study the procedure was performed in patients with a short life-expectancy and the impact on survival was not the main endpoint; nevertheless patients experienced an improvement in local pain, discharge, odour and burning with significant improvement in QoL.

Our study showed that ECT was very acceptable even in elderly patients. In fact our group had an average age of 84 years (range 80–90 years) and all patients tolerated the treatment well. This was confirmed by the willingness to repeat the procedure in all patients.

An advantage of the ECT procedure is also that it is easy and quick to perform with an average treatment time of 25 min together with a short hospital stay.

Local or general anaesthesia for ECT has been proposed to relieve the pain associated with drug injection and electric pulse application. In our experience general anaesthesia was necessary because of the sensibility of the vulvar area and to avoid the discomfort of muscle contraction at the time of pulse delivery.

A limit of our study was the small series of patients treated and the short follow-up period, a larger scale study is needed to confirm our data.

ECT for local vulvar cancer relapses is to be proposed in a selective group of heavily pre-treated patients. Local control of the disease is frequently obtained during the early follow-up period. The procedure is safe, quick, easily performed and well tolerated.

Longer follow-up is necessary to confirm long term efficacy.

Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

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