RECIDIVE DA CARCINOMA DELLA VULVA

Quali indicazioni per l'elettrochemioterapia

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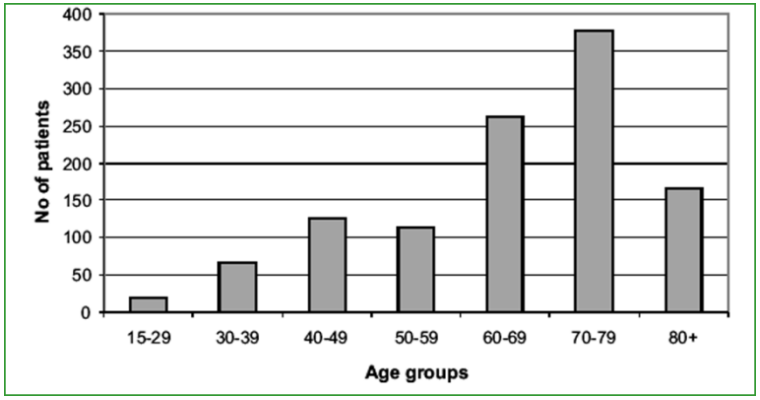
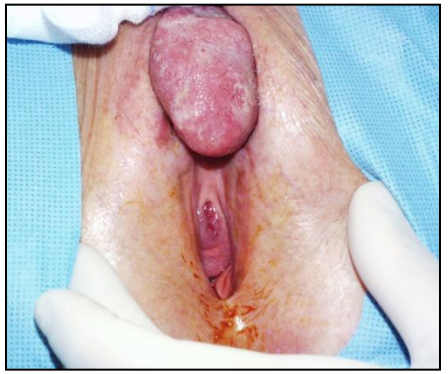
Carcinoma della vulva

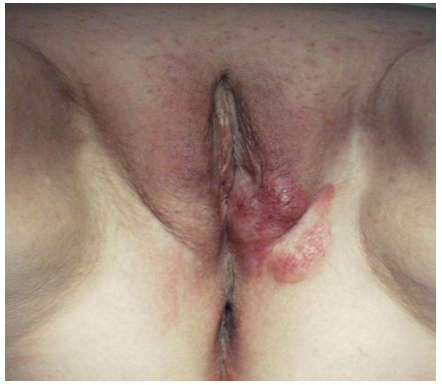
- **Neoplasia rara** (4% di tutte le neoplasie ginecologiche femminili)
- L'istotipo più frequente è il **carcinoma squamocellulare**
- **Neoplasia delle anziane** (frequente sopra i 75 anni di età)



Incidenza correlata all'età

Annual Report, 2005

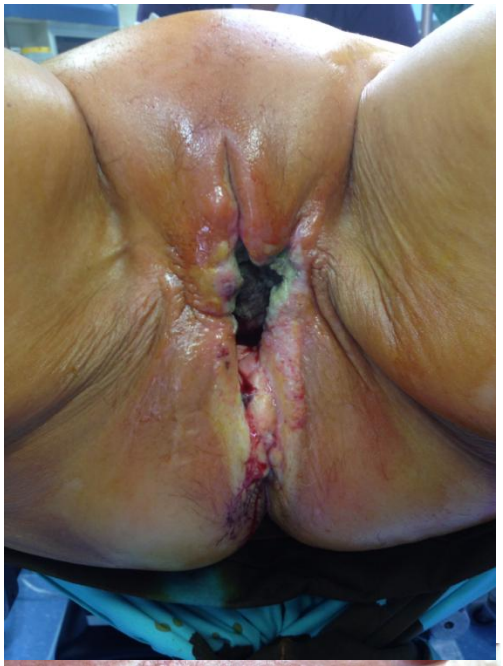


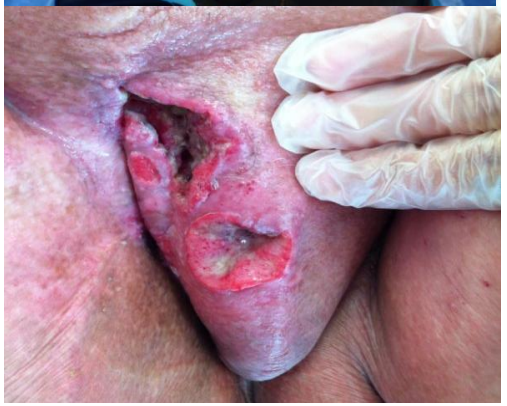


Carcinoma della vulva

- Trattamento è spesso multidisciplinare
  - **Chirurgia +/- Radioterapia +/- Chemioradioterapia neo/adiuvante**
- Nonostante questo "multimodal approach" la recidiva non è rara, soprattutto negli stadi avanzati (33%)

  Crosbie EJ Carcer Treatment Rev 2009
- La terapia della recidiva dopo i molteplici trattamenti multidisciplinare è limitata





Perché **trattare** la recidiva del tumore squamocellulare della vulva?

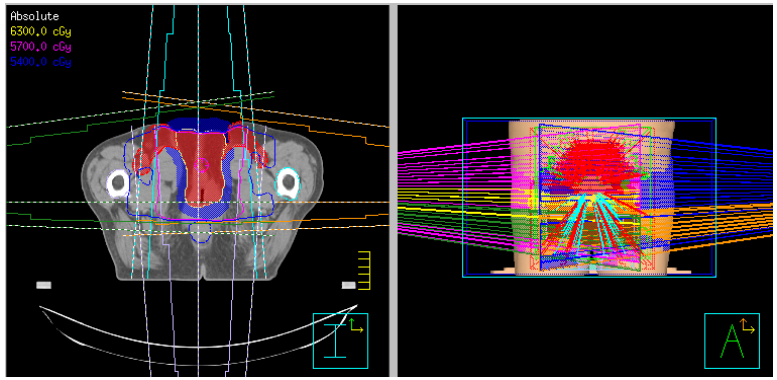
La recidiva loco regionale è un importante fattore di rischio per

- **Metastasi a distanza** (sincrone o metacrone)
- **Sintomi** che hanno effetti negativi sulla qualità di vita
  - Dolore
  - Sanguinamenti vaginali
  - Bruciore
  - Cattivo odore

Chan YM et al. A longitudinal study on quality of life after gynecologic cancer treatment. Gynecol Oncol 2001

La radioterapia nella recidiva del tumore squamocellulare della vulva

- Tumori radiosensibili con buon controllo locale della malattia
- Indicazioni:
  - recidiva in pazienti precedentemente trattati con chirurgia
  - **non può essere ripetuta in pazienti precedentemente irradiate**

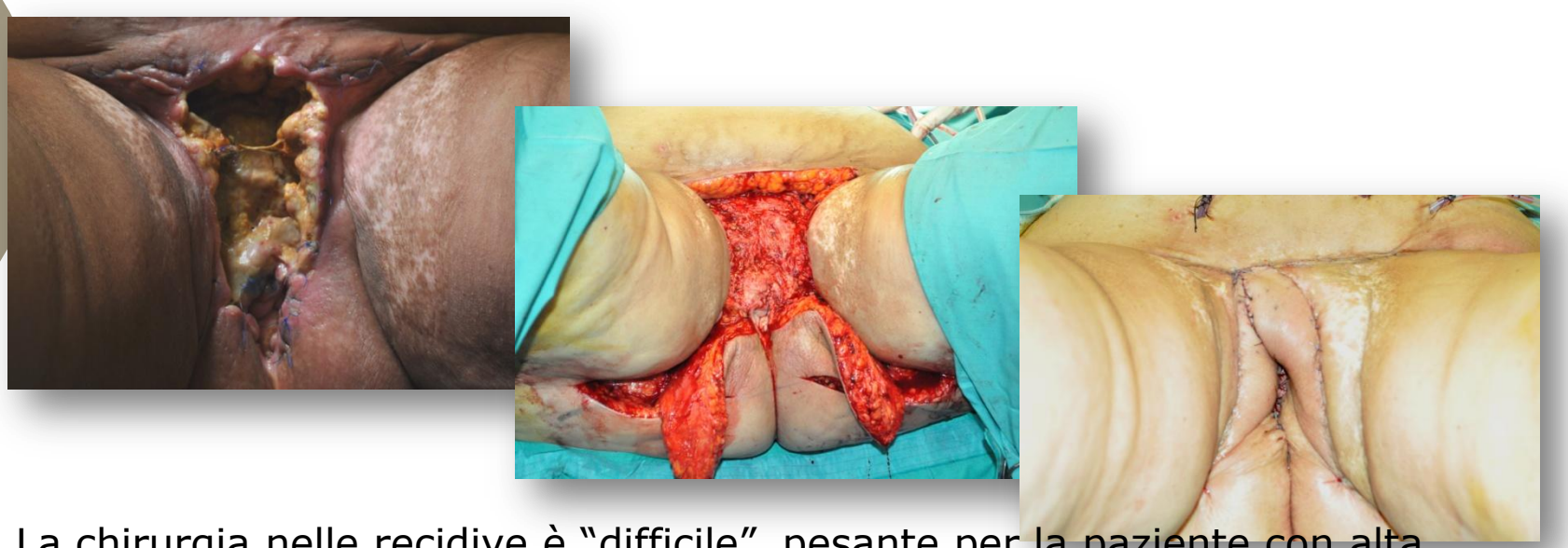


La chemioterapia nella recidiva del tumore squamocellulare della vulva

- Non ci sono schemi prestabiliti per la vulva si ricorre agli stessi trattamenti del carcinoma della cervice
  - (cisplatino/gencitabina-paclitaxel/carboplatino)
- Studi con basso numero di pazienti
- Tossicità

Han SN, Vergote I, Amant F.1. Int J Gynecol Cancer. 2012

Terapia chirurgica della recidiva dopo ripetuti trattamenti



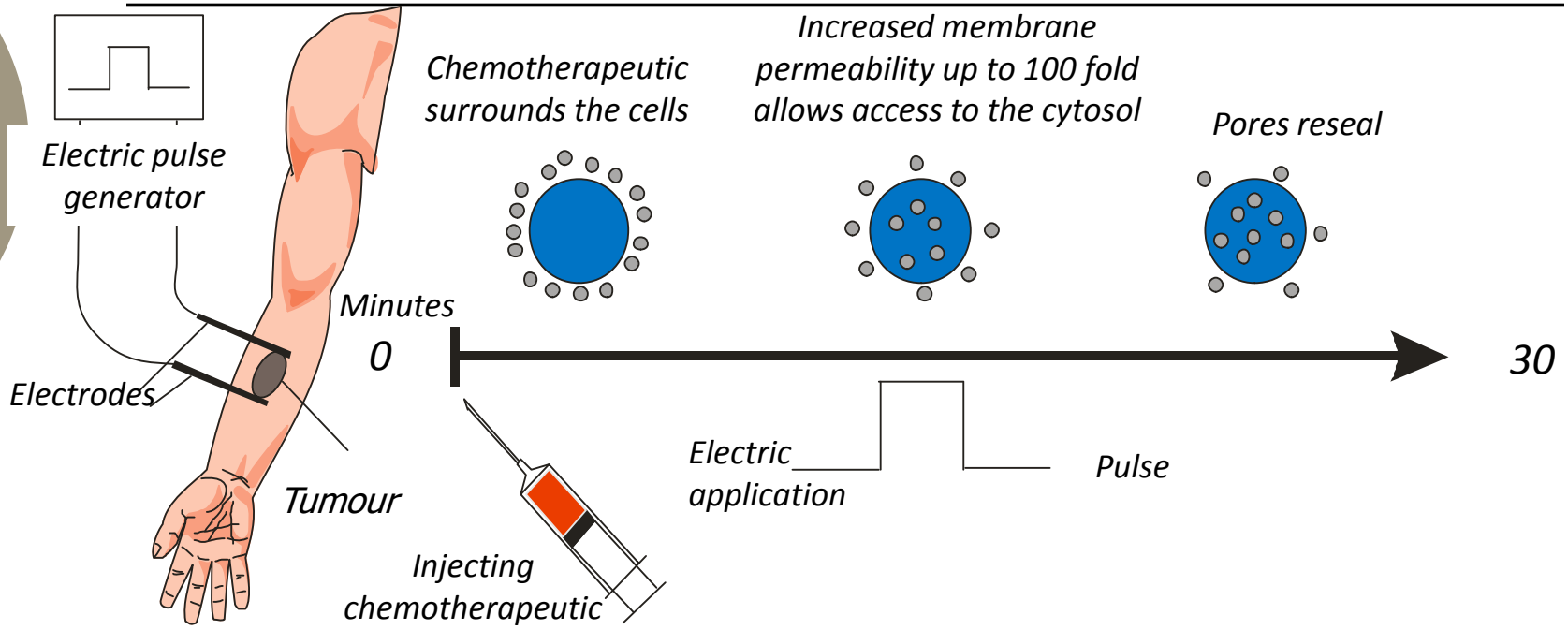
- La chirurgia nelle recidive è “difficile”, pesante per la paziente con alta incidenza di morbilità
- É difficilmente proponibile alle pazienti “vecchie”perchè spesso demolitiva
- Quando la terapia chirurgica non può essere eseguita con soddisfacenti risultati cosmetici e funzionali altre opzioni devono essere valutate

De Melo Ferreira AP et al. Quality of life in women with vulvar cancer submitted to surgical treatment: a comparative study. Eur J Obstet Gynecol Reprod Biol 2012

Trattamento palliativo

- Funzioni (spt sui sintomi)
- Poche complicanze
- Riduzione degli accessi in ospedale

WHAT IS **ELECTROCHEMOTHERAPY**?



Delivering, either systemically or locally, non-permeant cytotoxic drugs (e.g. **bleomycin**) or low-permeant drugs (e.g. **cisplatin**) and applying electric pulses to the area to be treated when the concentration of the drug in the tumor is at its peak. With the delivery of the electric pulses, cells are subjected to an electric field that causes the formation of nanoscale defects on the cell membrane, which alter the permeability of the membrane.

Sizes available:
1–3 cm
For small lesions

Sizes available:
1–3 cm
For large lesions
and disseminated
lesion sections

Symmetries available:
Linear, hexagonal

Variable length:
0.5–3 cm

Sizes available:
0.5 and 1 cm
Finger electrodes for
orifices and locations
which are difficult
to access

Igea, Carpi Italy

Elettrochemioterapia (ECT)

ECT is a new local treatment of solid tumours

- Cutaneous neoplasms
- Liver metastasis
- Breast
- Head
- Neck

ESOPE

European Journal of Cancer Supplements

Volume 4, Issue 11, November 2006, Pages 3–13

Electrochemotherapy

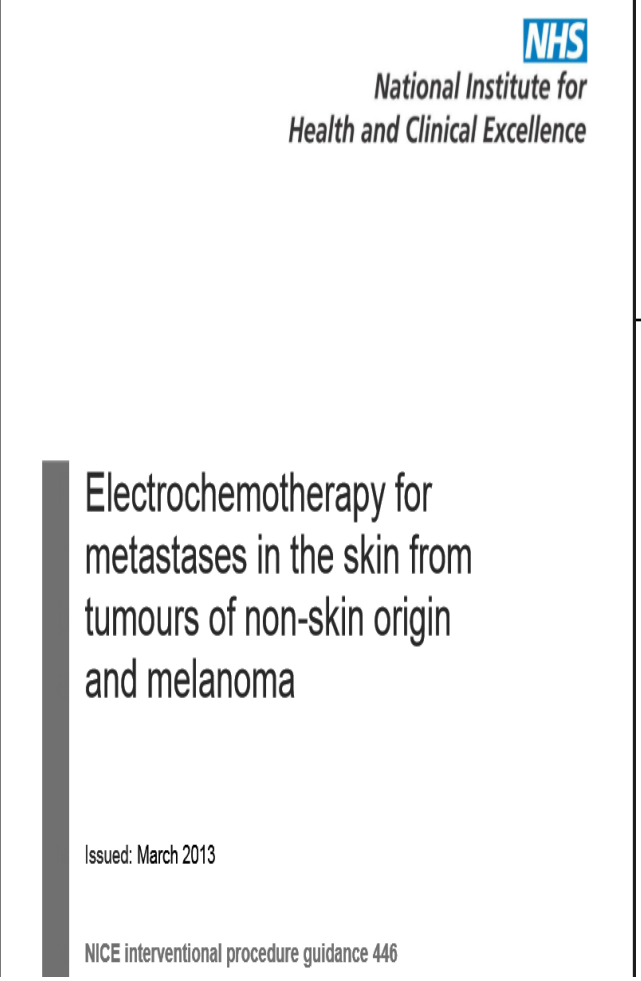
Electrochemotherapy – An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study

Michel Marty[a,1], Gregor Sersa[b,1], Jean Rémi Garbay[a], Julie Gehl[c], Christopher G. Collins[d], Marko Snoj[b], Valérie Billard[a], Poul F. Geertsen[c], John O. Larkin[d], Damijan Miklavcic[e], Ivan Pavlovic[e], Snezna M. Paulin-Kosir[b], Maja Cemazar[b], Nassim Morsli[a], Declan M. Soden[d], Zvonimir Rudolf[b], Caroline Robert[a], Gerald C. O'Sullivan[d], Lluis M. Mir[a,f,g,]

102 pts with cutaneous and subcutaneous metastases of any histologically proven cancer, 41 pts evaluable for response to treatment and 61 evaluable for toxicity.

At 150 days after the treatment local tumour control rate for ECT was 88% with bleomycin given intravenously, 73% with bleomycin given intratumourally and 75% with cisplatin given intratumourally. Side-effects of ECT were minor and acceptable, as reported by the patients.

SIZE → no difference in response
Nodules in previously irradiate areas → no difference in OR rate



THERE IS SUFFICIENT EVIDENCE OF EFFICACY OF ELECTROCHEMOTHERAPY FOR TREATING METASTASES IN THE SKIN FROM TUMORS OF NON-SKIN ORIGIN AND MELANOMA TO SUPPORT ITS USE AS A PALLIATIVE TREATMENT

There are no major safety concerns. Therefore, in the context of palliative treatment the procedure can be used with normal arrangements for clinical governance, consent and audit. Electrochemotherapy aims to enhance the effects of chemotherapy and can be performed as an outpatient procedure.

It can be used for local control of cancers that are unsuitable for surgery and resistant to radiotherapy or chemotherapy.

USE OF **ELECTROCHEMOTHERAPY** IN VULVAR CANCER ? WHY NOT?

In literature, no study had evaluated ECT

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journal homepage: www.elsevier.com/locate/ygyno

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

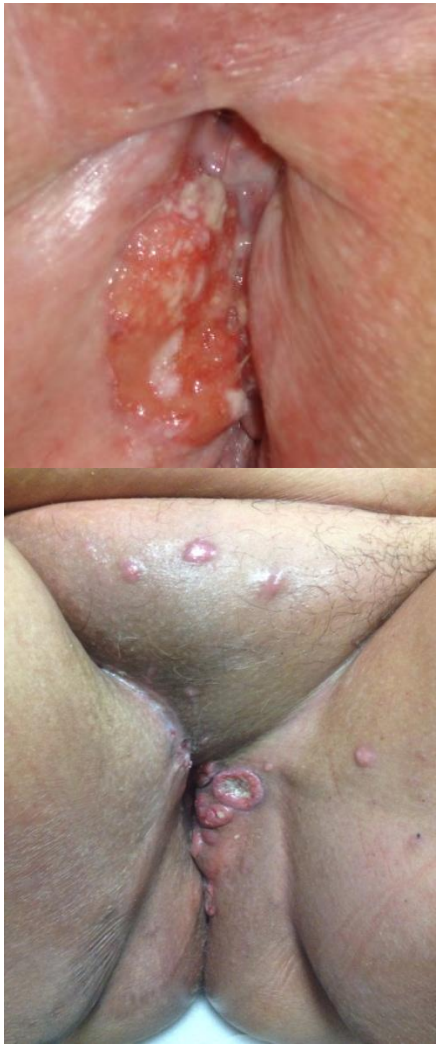
Anna Myriam Perrone [a,*], Andrea Galuppi [b], Simona Cima [b], Federica Pozzati [a], Alessandra Arcelli [b], Annalisa Cortesi [b], Martina Procaccini [a], Alice Pellegrini [a], Claudio Zamagni [c], Pierandrea De Iaco [a]

[a] Oncologic Gynecology Unit, Sant'Orsola-Malpighi hospital, Bologna, Italy
[b] Radiotherapy Unit, Sant'Orsola-Malpighi hospital, Bologna, Italy
[c] Medical Oncology Unit, Sant'Orsola-Malpighi hospital, Bologna, Italy

Materials and Methods

Inclusion criteria

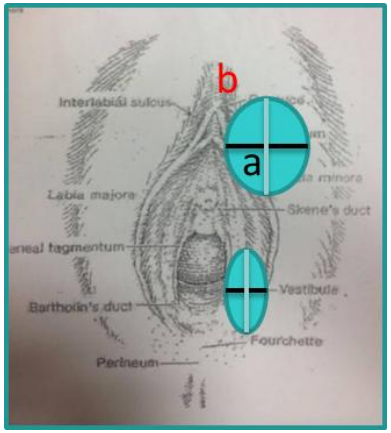
- Patients with histological diagnosis of single or multiple loco-regional recurrences of V-SCC
- Unsuitable for standard treatments because of tumour characteristics and general status



Materials and Methods

Before the procedure

- mapping of all lesions
- clinical history, clinical examination, routine blood biochemistry, computer tomography scan (CT) and 18 F-FDG-PET/CT to evaluate distant metastasis
- validate questionnaires: VAS and VCS



Tumour's area was calculated

If multiple nodules are present the area is the sum of all area of each lesion

Materials and Methods

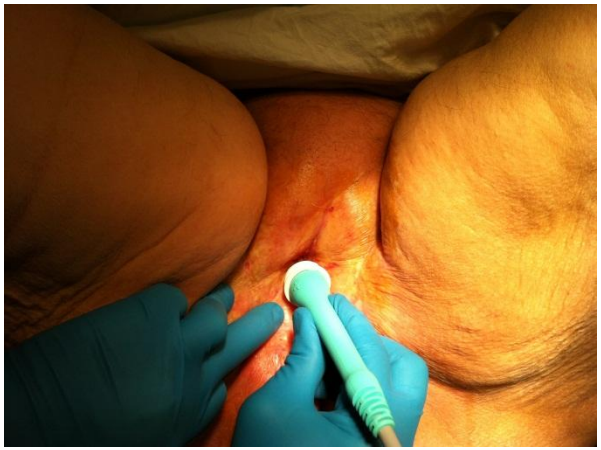
ECT Procedure:

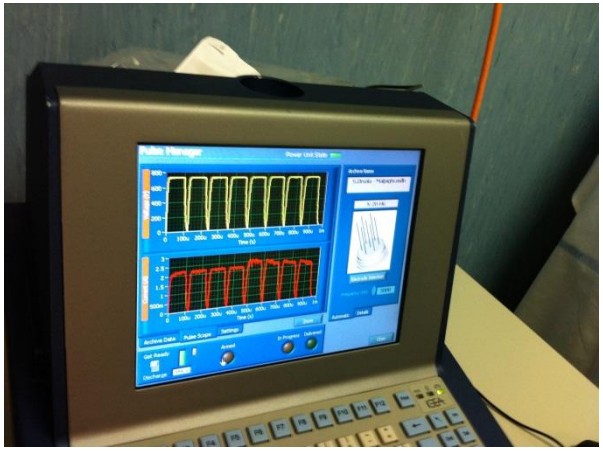
- The procedures was performed in day surgery with an hospital stay of 24 hours
- General sedation
- Application of electrical pulse to each tumor nodule within 8 min after intravenous bleomicin administration (dose 15000 UI/m2)

Mir Lmet al. Eur J Cancer Suppl 2006

- ECT electroporation was performed by a Clinoporator device with a type III electrodes placed into the lesion (frequency 5 kHz and the pulse duration 100 µs)

Mir Lmet al. Eur J Cancer Suppl 2006





Patients characteristics

- median age **84** yrs (range 80-89)
- stage at diagnosis of the primary tumours
  - 1 patient in stage IA (11%)
  - 1 patient in stage IB (11%)
  - 3 patients in stage II (33%)
  - 3 patients in stage IIIA (33%)
  - 1 patient in stage IIIB (11%)
- Eight patients were previously submitted to surgery and/or radiochemotherapy
- Time to relapse after last treatment was 52±49 months (mean±SD)

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

Anna Myriam Perrone[a], Andrea Galuppi[b], Simona Cima[b], Federica Pozzati[a], Alessandra Arcelli[b], Annalisa Cortesi[b], Martina Procaccini[a], Alice Pellegrini[a], Claudio Zamagni[c], Pierandrea De Iaco[a]

Table 1
Patients characteristics.

Patients	NR[a]	Type R[b]	Location[c]	*ab* before ECT(cm^2)[d]
1	1	S	1r	1.4
2	0	M	2r–2l	2.5–2
3	2	S	3	0.32
4	4	S	5	10
5	3	S	4	2.5
6	1	S	1l	1.5
7	1	S	6r	2.6
8	1	M	3	3

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 = paraureth
[d] *a* = largest diameter of the tumour nodule, *b* = diameter of the tumour nodule p
[e] Δ *ab* = *ab* before ECT – *ab* after ECT.
[f] 1 = same site treated, 2 = other site.

Topography:

- in the vulva in 7 patients (87.5%)
- in the upper thigh region in 1 patient (12.5%)

Type of relapse:

- Single in 6 patients (75%)
- Multiple in 2 patients (25%)

LOCAL RESPONSE AFTER ONE MONTH

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.

- **response criteria** according to the WHO
- subscale **VCS** part of functional assessment of vulvar cancer therapy (FACT-V) and **VAS** for **QoL**

- **CR 5 pts** ***62.5%***
- PR 1 pt *12.5%*
- SD 1 pt *12.5%*
- PD 1 pt *12.5%*

QoL: QUALITY OF LIFE

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.			

VAS: significant reduction in pain ($p < 0.03$)

Palliative electro-chemotherapy in elderly patients with vulvar cancer: a phase II trial.

Anna Myriam Perrone MD, PhD[1], Simona Cima MD[2], Federica Pozzati MD[1], Rezarta Frakulli MD[2], Fotios Labropoulos MD[2], Marco Tesei MD[1], Giuseppe Gasparre PhD[3], Andrea Galuppi MD[2], Alessio G. Morganti[2], Pierandrea De Iaco MD[1].

..... 2014

- January 2009-July 2014
- **25** women
- Age **84** ± 6.7 years (mean ± SD)

Follow-up 6.7 ± 3.9 months
OS 6 months 76%

- **CR** 5 pts *62.5%*
- PR 1 pt *12.5%*
- SD 1 pt *12.5%*
- PD 1 pt *12.5%*

- **CR** 12 pts *48%*
- PR 8 pts *32%*
- SD 3 pt *12%*
- PD 2 pt *8%*

SECOND SESSION OF ECT

PATIENTS	RESPONSE TO FIRST ECT	TIME R AFTER ECT (MONTHS)[A]	LOCATION OF R [B]	RESPONSE TO SECOND ECT[C]	STATUS TO LAST FOLLOW-UP
II	CR	8	1	CR	Alive
VI	CR	4	2	na	DOD
IX	CR	8	1	CR	Alive
X	CR	6	1	PD	Alive
XI	PR	-	1	CR	Alive
XIII	PR	-	1	PD	DOD
XXIII	PR	-	1	PR	Alive

a Time R = time to relapse after first treatment b 1 = same site treated, 2 = other site c na = not available

CR 3 pts 42.8 % **PR** 1 pts 14.3 % **PD** 2 pts 28.5 %

Long term results

After six months

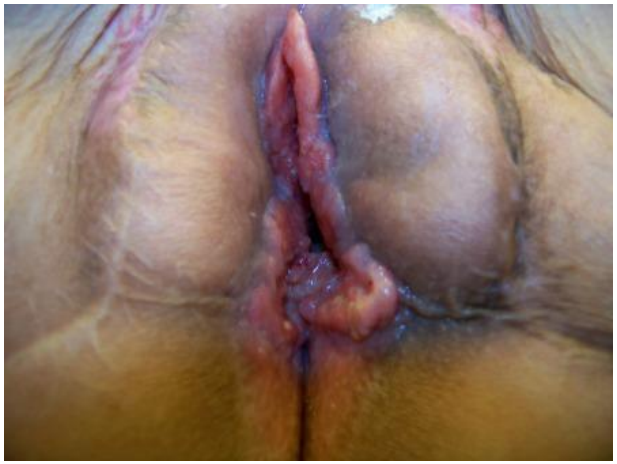
- all the patients were alive
- one relapse was observed 4 months after the procedure
- no serious adverse events were observed
- no local adjunctive therapies were required
- no other distal metastases were observed

Quality of life

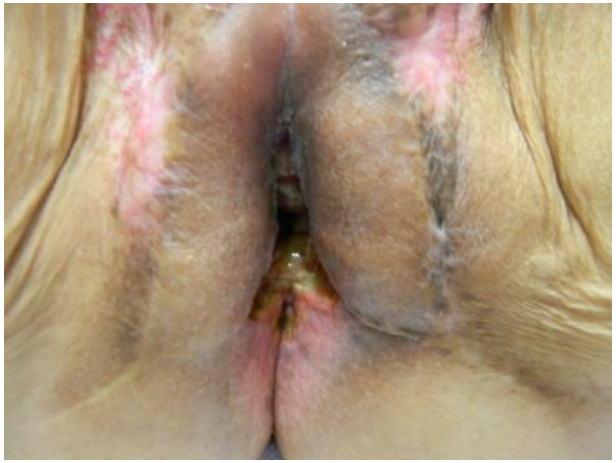
One month after treatment:

- significant reduction of pain ($p<0.03$)
- significant reduction of bleeding, odour and urinary discomfort ($p<0.03$)
- better quality of life (VCS score 49.0 vs 46.0)
- all patients affirmed that a repeated procedure was acceptable

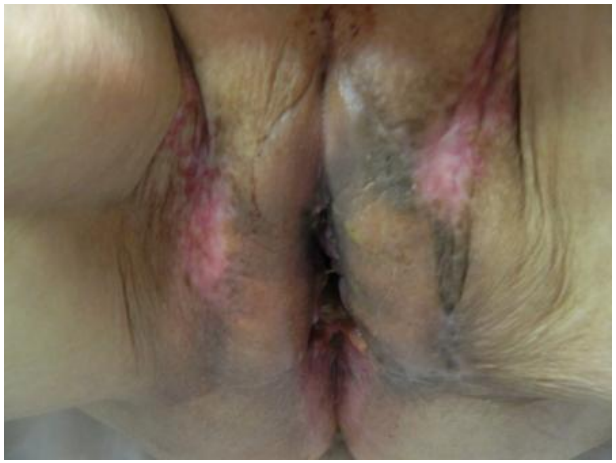
USE OF **ELECTROCHEMOTHERAPY** IN RECURRENCE OF SQUAMOUS VULVAR CANCER



- 11/6/12 Emivulvectomy
- Adiuvant radiochemotherapy
- 1/6/13 Recurrence → ECT

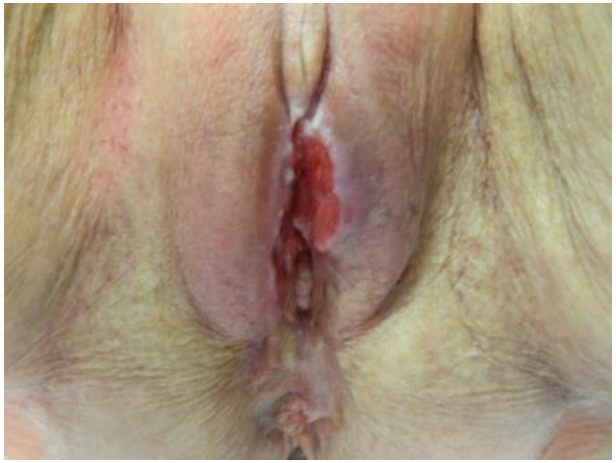


1 month after ECT

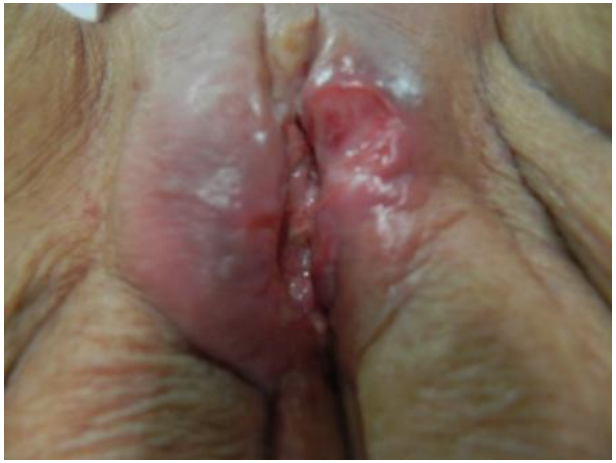


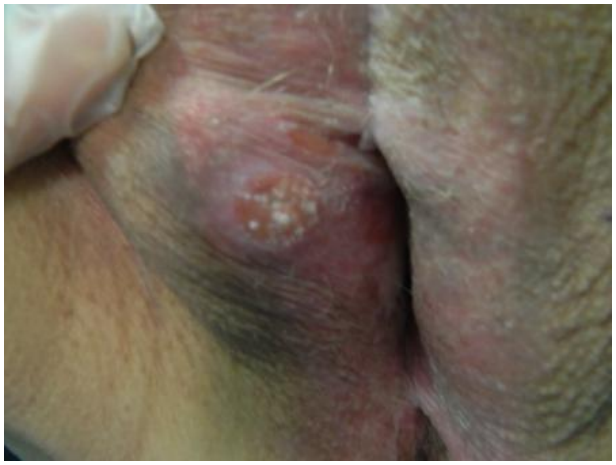
2 months after ECT

USE OF **ELECTROCHEMOTHERAPY** IN RECURRENCE OF SQUAMOUS VULVAR CANCER

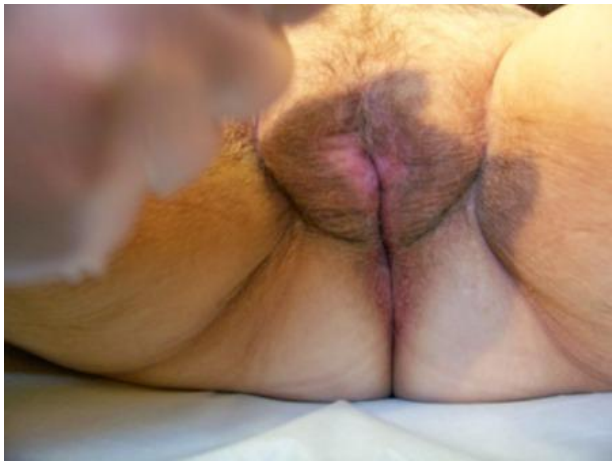


1 months





4 months



CONCLUSIONS

- Outpatient procedure
- Easy
- Highly effective
- Safe treatment
- Minimal side effects
- Cost effective favorable

Thanks!!!

Materials and Methods

Follow up

- The patients were evaluated at 4 weeks, three and six months after procedure
- The criteria to response to the ECT was defined in according to WHO Handbook for Reporting Result of Cancer Treatment

World Health Organization. WHOhandbook for reporting results of cancer treatment. Geneva, Switzerland: World Health Organization; 1979

complete response (CR): when the tumour nodule was not palpable;

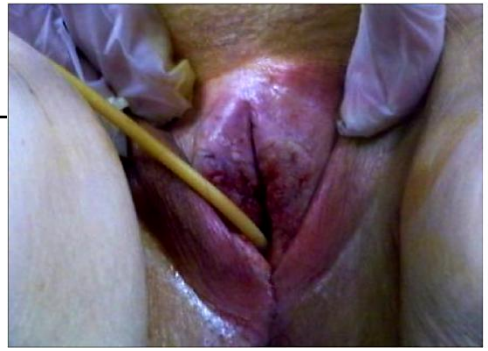
partial response (PR): when the tumour size decreased more than 50% in the products of the largest perpendicular diameters of the measurable lesions;

no change (NC): when the lesion had a reduction <50% and an increase up to 25%;

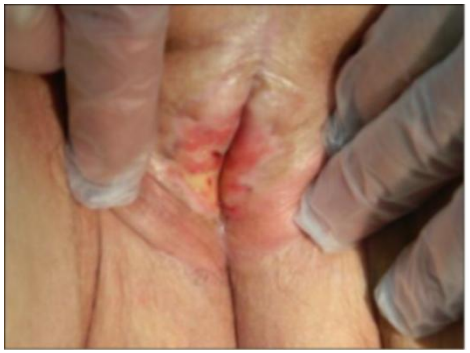
progressive disease (PD): when the tumour size increased more than 25%

Local efficacy of ECT after one month

- CR in 5 patients 62.5%
- PR in one patient 12.5%
- NC in one patient 12.5%
- PD in one patient 12.5%



Before treatment



After treatment

In the patients with CR the nodule disappeared and the residual skin was pale and soft and regular

Conclusions

Our preliminary study showed that ECT was a suitable procedure in elderly patients with single or multiple and repeated loco-regional vulvar cancer relapses.

ECT can be used as palliative therapy and the treatment relieves symptoms and improves quality of life