Project Title:

Gentle Electrotherapy to Inhibit a Pivotal Enzyme - Ribonucleotide Reductase (GEIPE-RR) -- A Low-cost & Effective Cancer Treatment

NOTE: This project does not offer to provide 'an efficient solution in particle detection targeted to early cancer diagnosis'. However, the proposed cancer therapy meets your greater goal of having 'higher impact on premature cancer death reduction' – and at very low cost.

1. Scientific Basis of Therapy & Evidence of Effectiveness

Cancer is uncontrolled cell growth. For a cell to divide, it must replicate its DNA strand. An enzyme called ribonucleotide reductase (RR) converts building blocks of RNA into those of DNA in a critical step for DNA synthesis (1). Due to its pivotal role in cell division, the activity of RR is tightly linked, *much more than that of any other enzyme*, to cancerous growth (2). See table below:

Weber, G. (1983) Biochemical strategy of cancer cells and the design of chemotherapy. *Cancer Research.* **43,** 3466-3492.

Table 1

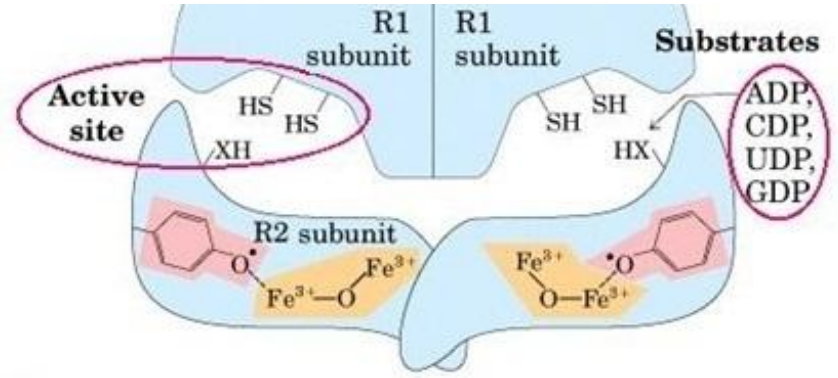
Comparison of activities of pyrimidine- and DNA-synthetic and -catabolic enzymes in liver and in rapidly growing hepatoma

Data are expressed as specific activity and as percentages of the normal liver values. In calculations, the values 200 mg of protein per g, wet weight, of tissue for homogenates and 80 mg of protein per g for supernatant fluids were used. Enzymic activities were those determined in this laboratory and in other centers.

Enzymes	EC no.	Normal liver (pmol/hr/mg protein)	Rapidly growing hepatoma 3683F (% of liver)
Anabolic enzymes			
Ribonucleotide reductase	1.17.4.1	23	18,348
DNA polymerase	2.7.7.7	56	5,806
dTMP synthase	2.1.1.b	180	2,860
dTMP kinase	2.7.4.9	420	7,000
Deoxycytidine kinase	2.7.1.74	800	1,400
Thymidine kinase	2.7.1.21	900	3,920
CTP synthetase	6.3.4.2	5,500	1,122
Carbamoyl-phosphate synthetase II	2.7.2.9	10,000	950
dCMP deaminase		12,000	750
Uracil phosphoribosyltransferase	2.4.2.9	19,000	760
Ornithine-5'-monophosphate decarboxylase	4.1.1.23	34,000	889
Orotate phosphoribosyltransferase	2.4.2.10	47,000	599
Uridine phosphorylase	2.4.2.3	164,000	671
Uridine-cytidine kinase	2.7.1.48	156,000	694
Dihydroorotase	3.5.2.3	246,000	418
Aspartate carbamoyltransferase	2.1.3.2	448,000	706
UDP kinase	2.7.4.6	444,000,000	298
Catabolic enzymes			
Dihydrouracil dehydrogenase	1.3.1.2	26,000	9
β-Ureidopropionase	3.5.1.6	144,000	
Thymidine phosphorylase	2.4.2.4	234,000	31
Dihydropyrimidinase	3.5.2.2	276,000	

An entire family of anti-cancer drugs is known as “ribonucleotide reductase inhibitors” (3), of which hydroxyurea is best known. However, utility of such chemotherapeutic drugs is limited since inhibition of the enzymatic activity is only partial and undesirable side-effects are many.

A novel way of arresting the activity of this pivotal enzyme in cell growth, is suggested by the fact that the active-site of RR contains a free-radical which is essential for its activity (1).



Since such free-radicals or unpaired electrons can be neutralized/destroyed by free-floating electrons, low-level direct electric current should have an inhibitory effect on RR and, thus, on uncontrolled cell proliferation. This hypothesis is strongly supported by the results of several cancer electrotherapy studies reported over the years. An article about this bio-physical approach to treat cancer was published in a peer-reviewed scientific journal in 1997 (4) **(Enclosure #1)**.

GEIPE-RR (Gentle Electrotherapy to Inhibit Pivotal Enzyme – Ribonucleotide Reductase) selectively targets the malignant cells – where concentration of enzyme RR is exponentially higher, and its free-radical seemingly exposed – and thus has no toxic side effects.

*

The very first study of gentle electrotherapy published in journal Science in 1959 reported “total regression” or disappearance of tumor in 60% of test animals (5)**(Enclosure #2)**.

In 1985, a study published in the prominent journal Cancer Research reported up to 98% shrinkage of tumor -- virtual cure – of subject animals on being treated for only 5 hours over 5 days with gentle electrotherapy (6)**(Enclosure #3)**.

Angiogenesis-based tumor therapy was hailed as a major advance some years ago and got a lot of press coverage. Initial Electrotherapy studies have shown much more promise but have been ignored. There seems to be only one reason: the procedure is non-patentable and very inexpensive.

This non-toxic, low-cost and highly effective cancer therapy may be called “the most scientific” since enzymes control what takes place in biological tissues, and this therapy blocks the most critical enzyme for cell growth. Yet, it is not being explored and established.

The **top cancer institutions** like National Cancer Institute (NCI) and M.D. Anderson Cancer Center, Houston, USA have called this approach to treat cancer “very interesting” and deserving of further investigation, but they have refused to take initiative to study and establish this protocol.

The letter of MD Anderson Cancer Center acknowledging the validity of this approach to treat cancer is shown on the next page. Additional letters and other documentation about this therapy can be seen on the website www.cancer-treatment.net.

An article was published in a scientific journal in 2010 showing effectiveness of this therapy on a human patient (7). A recently-built solid-state electrotherapy device has proven effective on multiple human patients. **Further exploration of such an inexpensive and effective therapy is very desirable.**

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

June 7, 1994

Jay Kulsh
1333 N. Sweetzer Ave. #2F
Los Angeles, California 90069

Dear Mr. Kulsh,

Your letter to Dr. Charles A. LeMaistre, President of the M.D. Anderson Cancer Center, was forwarded to me for review and reply. We appreciate your interest in our institution as well as your interest in studying therapeutic approaches to the treatment of cancer. I found your correspondence and the enclosed reprints dealing with the effect of low-level direct current on the growth of tumors very interesting. There is a reasonable body of research to support the concept that electrical fields are important in determining the growth and healing patterns of tissue. Likewise, it is documented that electrochemical processes occurring at electrodes connected to any voltage in excess of 1.2 volts produces free radical products that are converted to reactive oxygen intermediates in living tissues. These latter intermediates are believed to account for the activity of some of the chemotherapeutic agents currently in clinical use. Conversely, they are also believed to be the species implicated in the cardiotoxicity of Adriamycin, for example. Thus, the information you forwarded, independent of the mode of action, are interesting and deserving of further investigation. Unfortunately, our institution is not currently in a position to pursue such studies which we feel would require an extensive commitment of resources. Since research is largely an investigator-initiated endeavor, the administration of M.D. Anderson Cancer Center does not direct the research efforts of our research staff. Although there are many areas of research interest, among our faculty, no-one is investigating the effects of low level direct currents on tumor growth. However, I have shared your materials with individuals working in related areas. If they are so inclined, they are free to pursue this area of research as an independent project.

We will keep the material on file should opportunities arise to study the effects of electrical currents on the regression of tumors. In the meantime we wish you success in pursuing this topic. Again, thank you for sharing this material with us and for your interest in the research activities of the M.D. Anderson Cancer Center.

Sincerely yours,

A. Mastromarino

Anthony J. Mastromarino, Ph.D.
Associate Vice President for Research

AJM/dm

cc: Charles A. LeMaistre, M.D.
Frederick F. Becker, M.D.

JayKulsh

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A Comprehensive Cancer Center Designated by the National Cancer Institute

2. Objective

We aim to optimize treatment parameters of GEIPE (Gentle Electrotherapy to Inhibit Pivotal Enzyme – RR) for near-surface tumors.

Animal Studies (5,6) as well as documented treatment of four human patients (7 & References A-D) have shown that this inexpensive non-toxic therapy holds great promise to provide a humane and more effective alternative for cancer patients.

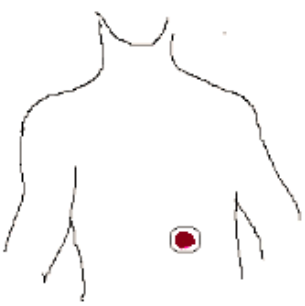
Approximate treatment parameters of GEIPE therapy for patients are already known. We need to refine these parameters so that the therapy can be standardized.

3. Methods

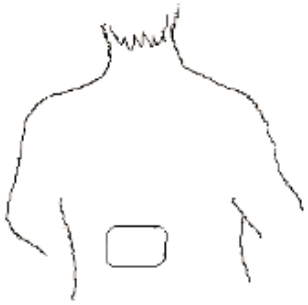
GEIPE treatment can be offered in 2 modalities:

1. Non-invasive GEIPE therapy

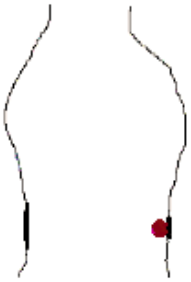
In this protocol, an active (small) electrode is placed on or near the tumor area and a passive (large) electrode is placed away so that the cancerous tissue falls in the path ("sandwiched") between them. Low-level current (1 to 20 mA) is then passed for many hours using the GEIPE device.



Small (active) electrode near the tumor, in the front here



Large (passive) electrode away from the tumor, on the back, here



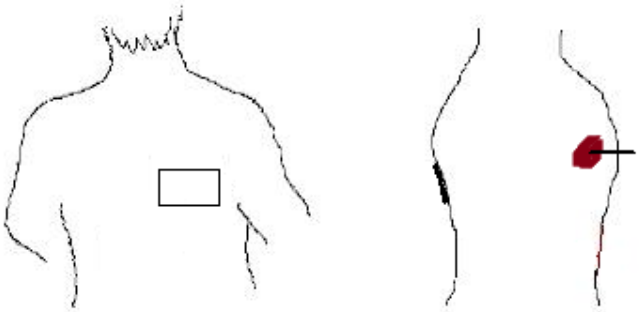
Side view

Before placing patch electrodes, skin is prepped by removing top layer of dead skin cells using strokes of very fine sandpaper, followed by putting a layer of electrode gel.

The findings so far suggest that current should be passed, on average, 4 to 8 hours per day for 10 to 20 weeks. These parameters will be varied to arrive at a range which is most beneficial in the least amount of time.

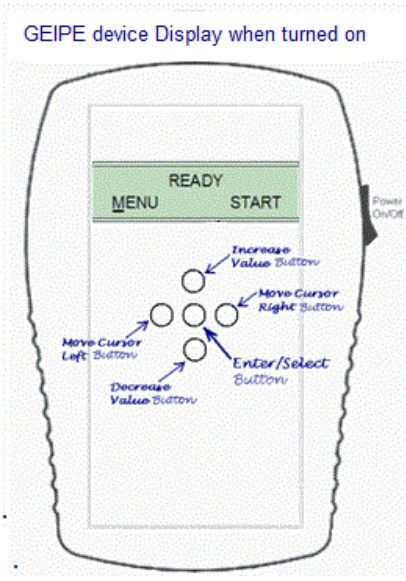
2. Semi-invasive GEIPE therapy

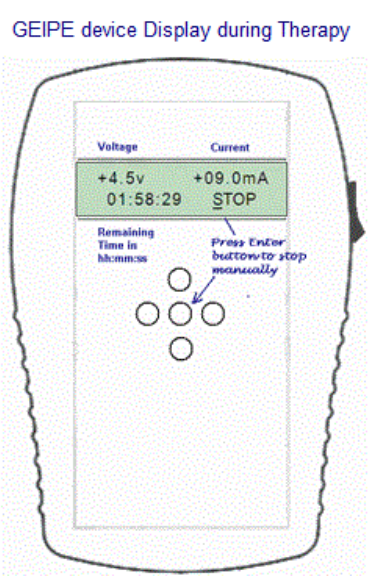
The semi-invasive method is used when the tumor is a bit inside and/or there is no flat surface area near the tumor where a patch electrode can be placed.
In this protocol, we pass similar low-level current from the GEIPE device -- after placing a surface (passive) electrode away from the tumor and inserting the exposed tip of a needle (active) electrode in the tumor.



Duration of this treatment – in weeks – is usually a little shorter than that of non-invasive method.

About GEIPE device and its operations:





The latest GEIPE device, built in early 2010, is based on solid-state electronics and can provide DC electricity for the GEIPE therapy in either constant current or constant voltage mode. It runs on four AA batteries – preferably rechargeable.

Using buttons in the front, the four values are set in the menu, before starting the therapy.

1. Constant (current or voltage)

CONSTANT	
CURRENT	VOLTAGE

2. Current Limit (in mA)

CURRENT LIMIT	
05mA	NEXT

3. Invertion Time

INVERTION TIME	
401Min	NEXT

4. Duration (in Hr & Min)

DURATION	
01h 00min	SET

4. Data Collection

For each patient:

- Ultrasound, MRI or PET scan images, as appropriate and available, will be taken before the treatment and then after every 4 weeks. (Treated patients will also be asked to come every month or every other month so as to monitor recurrence, if any, of malignancy.)
- Colored photos of tumor area will be taken before the treatment commences, and then after each week.
- For each session of treatment, the following data will be recorded:

Date	Start Time (S_T)	Current (in mA)	Avg. Voltage (in V)	End Time (E_T)	Duration (E_T -S_T)	Remarks

In 'Remarks', observations such as inability to pass adequate current (due to a bad electrode or lack of muscles on patient's body, or poor skin preparation) and presence of skin-burns, etc. will be recorded.
NOTE: Skin-burns are usually caused by (i) lack of gel between skin and electrodes, or (ii) poorly-prepped skin, or (iii) bony area under electrodes. They are not painful and heal in 1to 2 weeks.

5. Study Design

In the initial phase, GEIPE therapy would be offered to patients with near-surface tumors:

- whose tumors have stopped responding to chemo and radiotherapies.
- who are too old to endure chemo or radiotherapies.
- whose tumors, because of their location, are unsuited to be treated by any of the conventional treatments.

If in the 1st phase, GEIPE therapy is shown to be of considerable benefit to the vast majority of patients (80% or more), in the second phase it may be offered as an option to near-surface-tumor patients who have not yet gone thru chemo or radiations.

6. Ethical Considerations

In the initial phase, GEIPE treatment will be offered only to those cancer patients who are no longer getting any benefit from conventional treatments. It will be humane to offer a new inexpensive, promising, non-toxic cancer therapy to these 'terminal' patients.

Direct Current electricity at the low-levels of GEIPE therapy is deemed to be safe. For example, major manufacturers of electrotherapy electrodes include an advisory with their electrodes that patients should not exceed 0.1 watts/cm^2. Current and voltage levels employed with GEIPE treatment will generate less than one-hundredths (1/100th) of this limit.

7. Publications

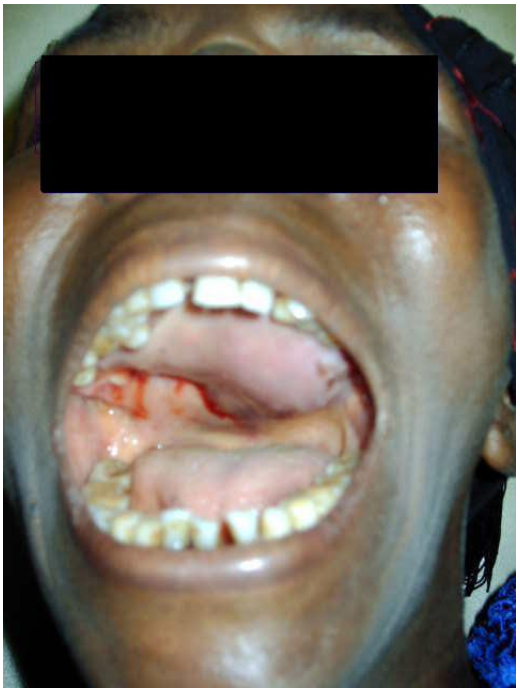
1. Nordlund P, Reichard P (2006). "Ribonucleotide reductases". *Annu. Rev. Biochem.* **75**: 681-706.
2. Weber, G. (1983) Biochemical strategy of cancer cells and the design of chemotherapy. *Cancer Res.* **43,** 3466-3492.
3. Cerqueira NM, Pereira S, Fernandes PA, Ramos MJ (2005). "Overview of ribonucleotide reductase inhibitors: an appealing target in anti-tumour therapy". *Curr. Med. Chem.* **12** (11): 1283–94.
4. Kulsh, J. (1997) Targeting a key enzyme in cell growth: a novel therapy for cancer. *Medical Hypotheses* **49**, 297-300.
5. Humphrey, C.E., and Seal, E.H. (1959) Biophysical approach toward tumor regression in mice. *Science* **130,** 388-390.
6. David, S.L., Absolom, D.R., Smith, C.R., Gams, J., and Herbert, M.A. (1985) Effect of low level direct current on in vivo tumor growth in hamsters. *Cancer Res.* **45,** 5625-5631.
7. Chima Oji and John Ani (2010) Destruction of an advanced malignant tumour by direct electrical current - case report. *Health* **2**(9), 1049-1053.

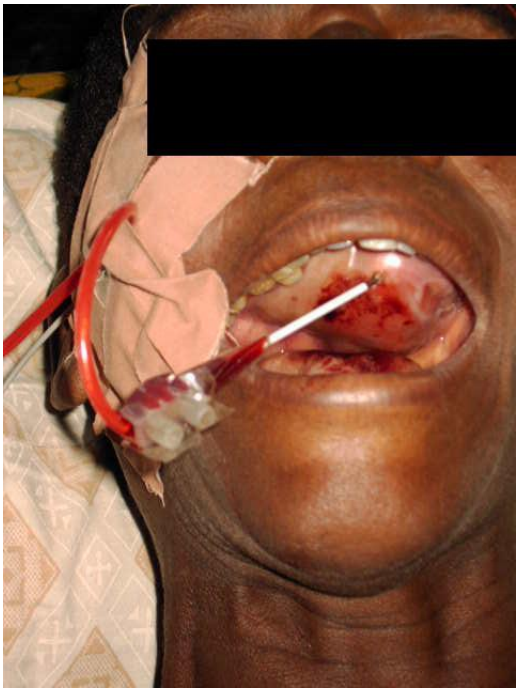
8. References

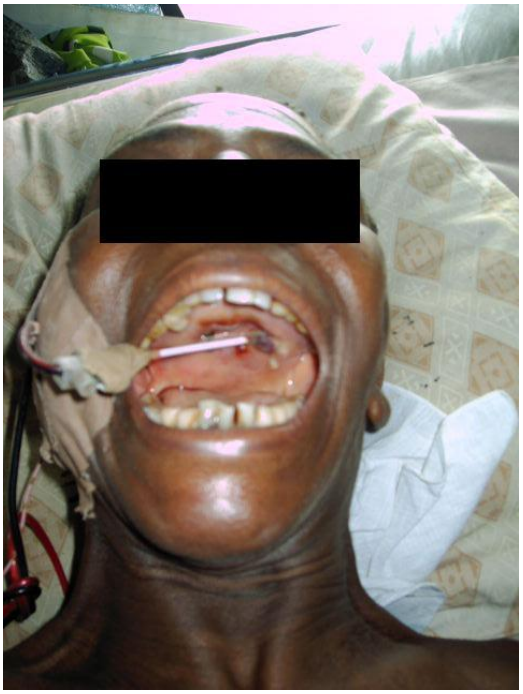
Next 4 pages have details about 4 treated patients.

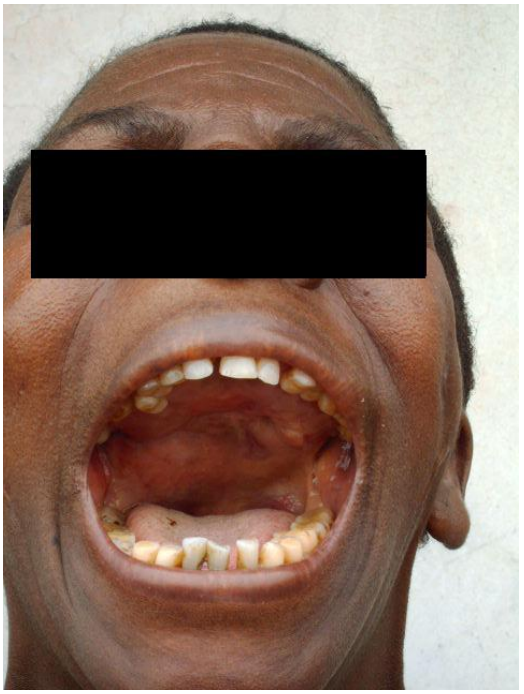
(A) A Patient Treated with Gentle Electrotherapy in Nigeria

Semi-invasive Gentle Electrotherapy treatment was applied to squamous cell carcinoma of the palate of a 50-year old woman, over 16 weeks, in 2007. Details of this study were recently published in a scientific journal (7).









The patient was “feeling great” one year after the treatment as the tumor had not come back.

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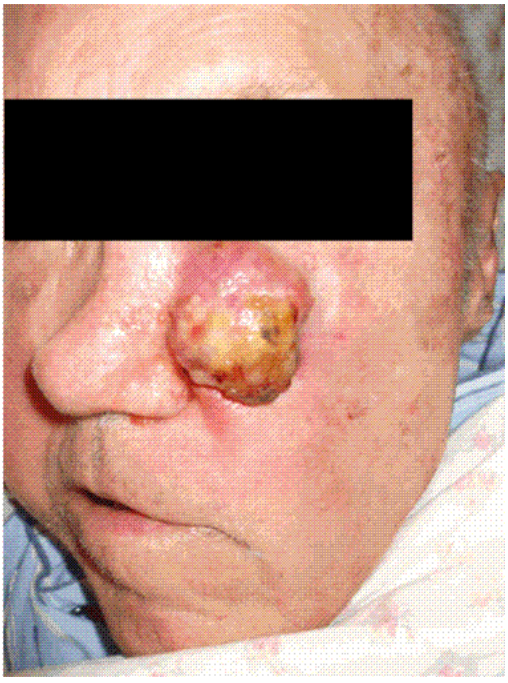
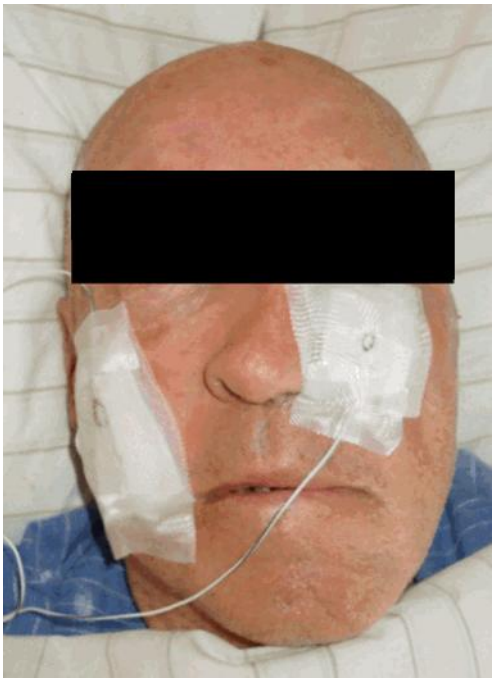
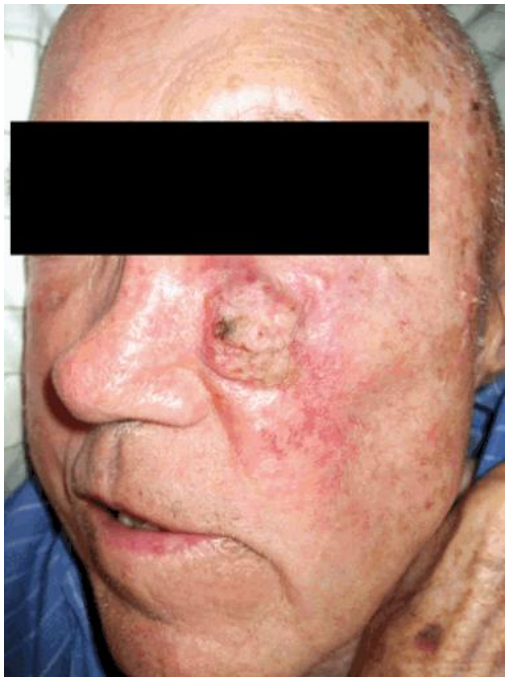
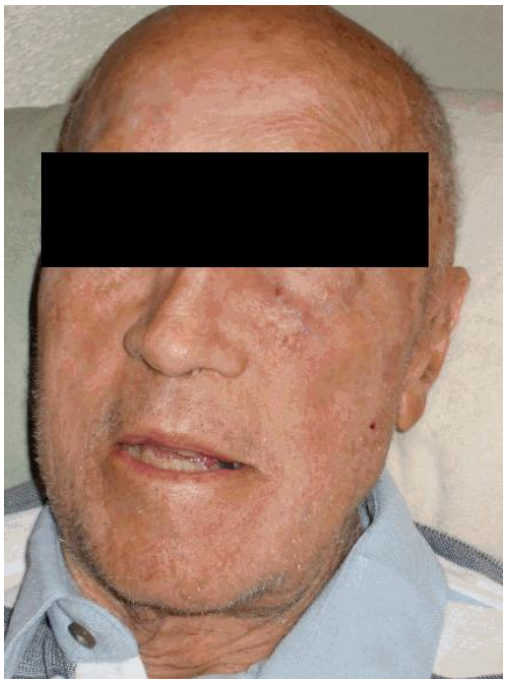
(B) A Patient Treated with Gentle Electrotherapy in USA

Non-invasive Gentle Electrotherapy was applied to protruding carcinoma on the face of a 93-year old man in June-August 2008 resulting in total disappearance of the tumor, as shown below:









The patient also took Low-Dose Naltrexone (LDN), an apparent immune booster, though its contribution is uncertain.

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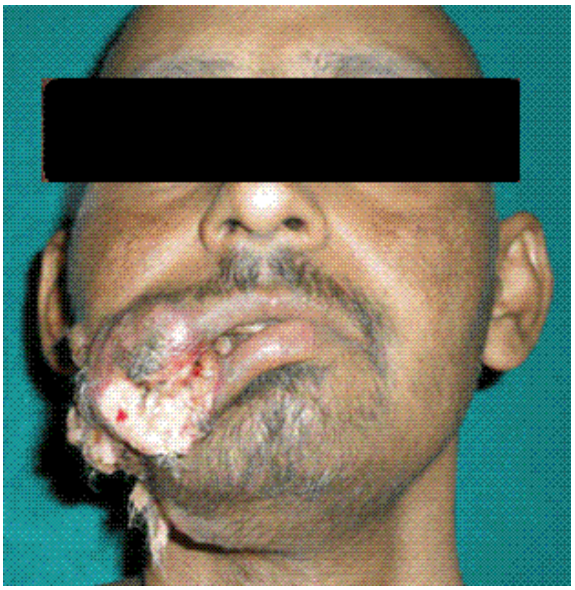
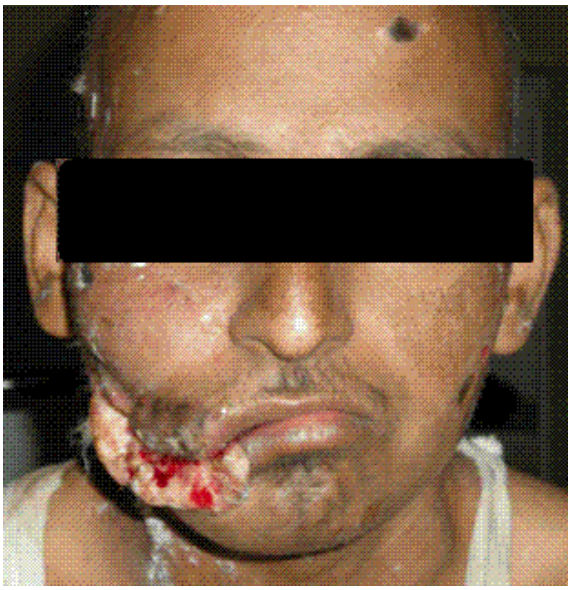
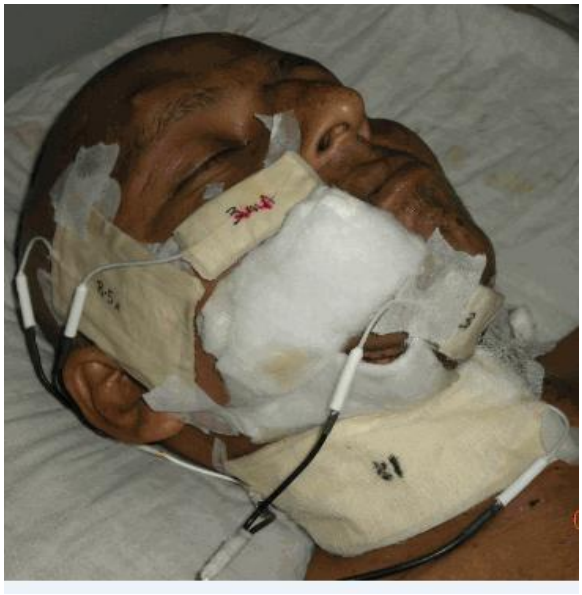
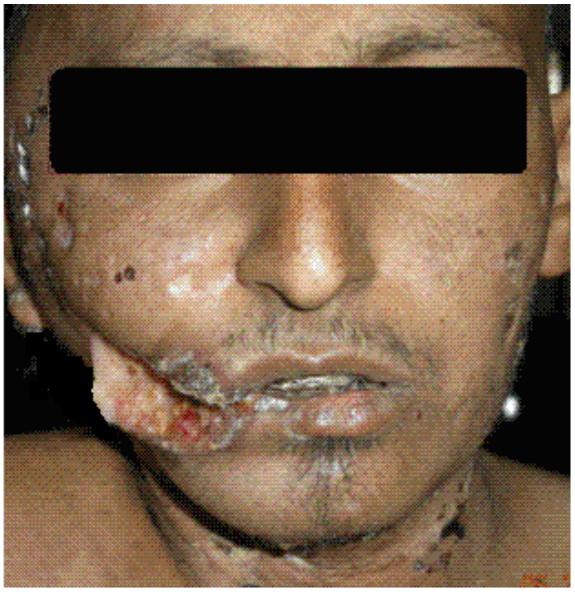
(C) A 32-year old Patient Treated with GEIPE in India

Non-invasive Gentle Electrotherapy was applied to the tumor of cheek and lips (caused by tobacco chewing) of this patient over a period of 5 weeks in April-May of 2010.

Note: Just before Gentle Electrotherapy was started, the patient had gone thru 12th round of chemotherapy. As a result, his immune system was very weak. On a trip to his village in the 4th week, he caught an infection which made his health progressively worse. The treatment had to be discontinued after the 5th week.

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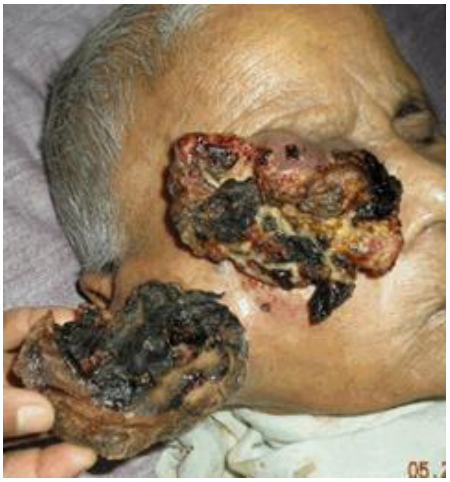
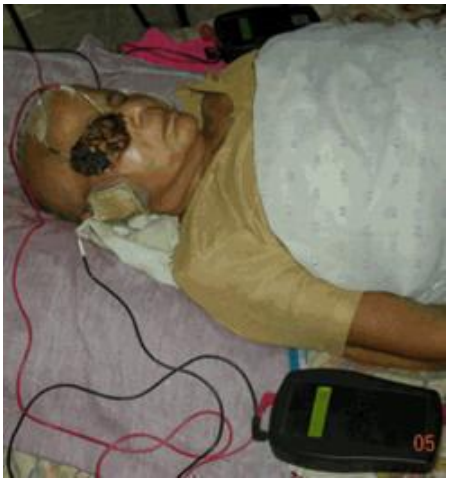
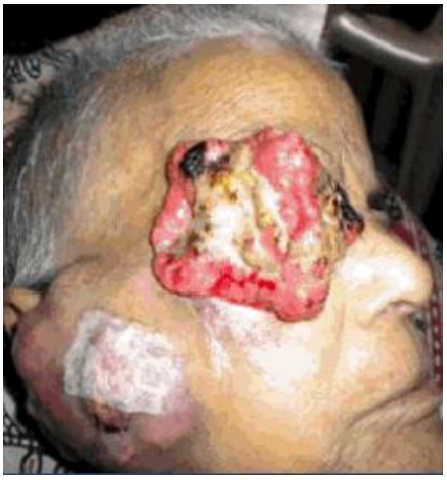
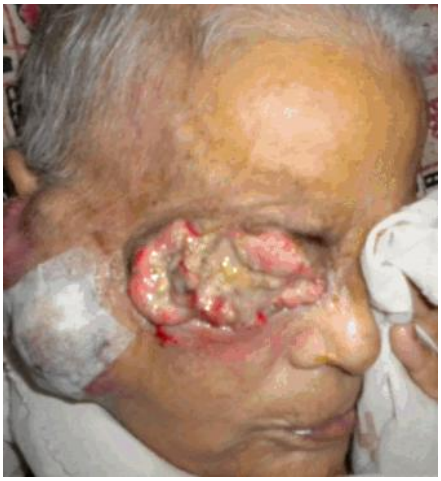
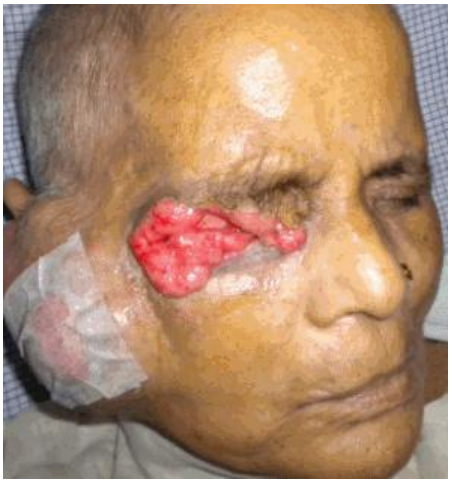
(D) An 80-year old Patient Treated with Gentle Electrotherapy in India

Semi-invasive Gentle Electrotherapy was applied to the tumor on top of the right eyelid of an 80-year old lady in April-June of 2010. It stopped further growth of the tumor and caused necrosis of cancer cells.

The therapy was suspended after 14 weeks since it was no longer safe to use needle electrodes near the eye and custom surface electrodes could not be made as primary therapy-giver had gone back to USA.

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