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Electrochemotherapy in Cancer Patients: First Clinical Trial in Greece

IOANNIS SKARLATOS[1], GEORGE KYRGIAS[2], EYTYXIA MOSA[1], XENI PROVATOPOULOU[3], MARIA SPYROU[4], KYRIAKI THEODOROU[2], ANTONIOS LEPOURAS[4], ANTONIA GOUNARIS[3] and MICHAEL KOUKOURAKIS[5]

[1]*First Department of Radiation Oncology, St. Savvas Anticancer Hospital of Athens, Athens, Greece;*
[2]*Radiation Oncology Department, University Hospital of Thessaly, Larissa, Greece;*
[3]*Research Center, Hellenic Anticancer Institute, Athens, Greece;*
[4]*Department of Internal Medicine/Diabetology, Athens Medical Center, Clinic of Psychikon, Athens, Greece;*
[5]*Radiation Oncology Department, Democritus University of Thrace, Alexandroupolis, Greece*

Abstract. *Electrochemotherapy is currently undergoing intensive investigation in the field of local control of cancer. In Greece, five medical centers have co-operated to perform ECT for the efficient management of growing, recurrent or newly emerging cutaneous and subcutaneous tumor nodules. ECT was applied alone or in combination with external beam radiation therapy, brachytherapy and surgery in 52 cancer patients, using bleomycin according to standard protocols. The treatment response for various tumors was 63.83% complete, 31.91% partial, and 95.74% overall of the treated nodules. Patients exerted neither systemic nor local side-effects. The results of ECT performance in Greece provided evidence that this new treatment strategy is safe and permits the effective control of tumors of various origins and histological types.*

Electrochemotherapy (ECT) is a new treatment modality for tumor ablation, suitable for the local control of various types of solid tumors. The efficacy of ECT is based on the local application of short and intense electric pulses that increase the permeability of cell membranes, allowing non-permeant or low-permeant anticancer drugs (typically bleomycin or cisplatin) to enter the cells (1). The application of electric pulses to tumors significantly increases the antitumor effectiveness of the anticancer agents (2-5). Typically, a single treatment is sufficient for efficient local control, however, it can be repeated on growing, recurrent or newly emerging tumors with equal effectiveness (6). The treatment is safe, well-tolerated and presents high efficacy on treated nodules, while it allows the immediate return of patients to daily life since it is typically performed on an out-patient basis. Moreover, it is an easy to apply, quick and cost-efficient treatment approach.

Correspondence to: I. Skarlatos, First Department of Radiation Oncology, St. Savvas Anticancer Hospital of Athens, 171 Alexandras Ave., 11522, Athens, Greece. E-mail: skarl@ath.forthnet.gr

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Principles of ECT. Electrochemotherapy is effective when sufficient drug concentration is obtained inside the tumor nodules and the whole tumor volume is adequately covered by the electric pulses, so that most of the cells become electroporated (7, 8). Nevertheless, the selective death of tumor cells and the vascular effects imposed on normal and cancerous tissues are also key concepts of this therapeutic modality (9). In ECT, the electric pulses are solely used in order to increase the permeability of the cell membranes, enabling the efficient delivery of the chemotherapeutic drugs inside the cells. More specifically, the presence of an external electric field generates a change in the transmembrane potential difference of the cells that superimposes upon the resting one. As a result, the plasma membranes undergo structural changes that render the cells permeable to otherwise non-permeant molecules (9-12).

The application of electric pulses to tissues also causes changes in blood flow, more specifically, a transient hypoperfusion of the area between and distally from the electrodes due to reflexory vasoconstriction of afferent arterioles, known as the vascular effect (13, 14). Basically this means that when the cells become permeabilized, the drug is held within the electroporated area due to vascular lock. Normal blood flow is subsequently restored but the process may last for hours, and in fact it takes longer in tumors than in normal tissues. These vascular effects contribute significantly to the efficacy of ECT with anticancer drugs, as well as in the treatment of hemorrhaging nodules (15, 16).

Drug administration of ECT. ECT is most commonly performed in combination with the administration of bleomycin. Bleomycin is a non-permeant molecule that can neither diffuse through the plasma membrane nor be actively transported (17). Cell electropermeabilization facilitates the free diffusion of molecules of bleomycin inside the cells. It is interesting that drug diffusion may last for much longer periods of time than the pulse duration (18, 19). It was found that the combination of bleomycin with cell electropermeabilization *in vitro* substantially increases the toxicity of the drug (20). Bleomycin has significant intrinsic cytotoxicity since it causes single-stranded and double-stranded DNA breaks. Cells bearing unrepaired double-stranded DNA breaks are killed during the mitotic phase. Mitotic cell death enables the selective killing of the dividing tumor cells, sparing the non-dividing normal cells surrounding the tumor (9). Bleomycin can be delivered intravenously or intratumorally (9). In intravenous delivery, bleomycin enters the interstitial fluids of the tumor and subsequently the cells, provoking mitotic cell death as described above. In intratumoral administration, there is an increased local concentration of the drug that, in combination with its uptake by the cells and its toxicity after the application of the electric pulses, causes necrosis of the cells exposed to the electric field.

ECT with intravenous administration of bleomycin requires relatively small amounts of the agent, however it is important that the drug is administered in a bolus in order to reach the tissue at an appropriate concentration. When bleomycin is administered intratumorally, less of the drug is required, in an amount which is proportional to the tumor volume. Systemic injection is suitable for the treatment of several nodules simultaneously or of large nodules (9).

ECT can also be performed using cisplatin (21, 22). Unlike bleomycin, cisplatin is a low-permeant drug that is active on many tumor types, even when delivered as a single agent. ECT causes a much lower increase in cisplatin efficacy, compared to bleomycin, however, it is satisfactory since it directly corresponds to an increase in its antitumor effects (23). Because of the small increase in its efficacy, cisplatin is administered intratumorally when combined with ECT and is considered suitable for the treatment of a few small nodules (9). Several other common chemotherapeutic agents have been tested in combination with cell permeabilization, but none showed a significant increase in toxicity. Nevertheless, the combination of ECT with oligonucleotides, as well as other molecules such as interleukins and chemokines, is currently under investigation (9, 24-27).

Clinical studies. Many clinical studies have demonstrated that ECT using bleomycin or cisplatin is an effective treatment for local tumor control, with few side-effects (28, 29). Treatment of cutaneous and subcutaneous tumor nodules in patients with progressive disease of various malignancies with ECT using bleomycin showed 85% objective response and 56% complete response (30). Similarly, ECT with cisplatin presented 77% complete response of melanoma tumor nodules, compared to 19% response when cisplatin was administered alone (21). More recently, the European Standard Operating Procedures of Electrochemotherapy (ESOPE) multicenter non-randomized study confirmed that ECT using bleomycin or cisplatin is an easy, highly effective and safe treatment approach for cutaneous and subcutaneous tumor nodules of various malignancies, offering immediate clinical benefit in patients (31). More specifically, ECT with administration of bleomycin locally or systemically and administration of cisplatin locally resulted in 88.2%, 73.1% and 75.4% local tumor control respectively, suggesting that all three approaches are similarly effective. Moreover, ECT was shown to be equally effective irrespective of the histological type of tumor and of the size of tumor nodules.

Table I. *European cancer centers performing electrochemotherapy.*

Country	Medical centers (N)
Italy	29
Germany	12
Austria	2
Portugal	1
Spain	3
Sweden	3
Greece	5
United Kingdom	4
Hungary	1
ESOPE	4
Laboratory/Veterinary	12
Total	76

Clinical application. ECT is typically applied in patients with progressive and metastatic disease involving cutaneous and subcutaneous tumor nodules with palliative intent (21, 30). Several studies suggest that it can also be used as a neoadjuvant cytoreductive treatment before conventional surgical resection and as an organ-sparing and function-saving treatment in areas where surgery or radiation therapy cannot be performed (32-34). Clinical data indicate that ECT is also suitable for the treatment of hemorrhagic and painful tumor nodules since it prevents bleeding and alleviates pain (15, 16, 35, 36). Moreover, it can be used in areas heavily pre-treated either by surgery or radiotherapy (31). Finally, ECT is considered a suitable approach for the treatment of elderly patients and patients with poor physical condition, where surgery is contraindicated (31). Several studies suggest that ECT can be used as a first-line treatment (*e.g.* in the treatment of non-operable primary or recurrent melanoma) (7).

Table II. *Recruitment of patients in the five medical centers that perform ECT in Greece.*

HeGECT Centers	Departments	Patients (N)	Applications (N)
St. Savvas Anticancer Hospital of Athens	Radiation Oncology Surgery	35	55
University Hospital of Thessaly	Radiation Oncology Medical Physics and Informatics Dermatology Head and Neck Surgery	9	11
Attikon University Hospital of Athens	Dermatology	1	1
Doctors' Hospital Athens	Oncology and Surgery	4	4
Athens Medical Center, Clinic of Psychikon	Internal Medicine/Diabetology	3	3

The potential clinical applications of ECT render it an approach of intense scientific interest. Clinical data indicate that ECT is effective, well-tolerated and can provide a suitable approach for therapeutically challenging situations. ECT is currently being used in 76 cancer centers in Europe (Table I) and several hundred patients have been successfully treated. In Greece, five medical centers co-operated to form the Hellenic Group of Electrochemotherapy (HeGECT) for the performance of ECT across the country. Since 2007, electrochemotherapy has been applied in 52 patients, not only in the standardized way but also in combination with other therapeutic treatments in selected cases of increased difficulty.

Patients and Methods

Patients. Between November 2007 and the time of writing, 52 patients were eligible according to the inclusion criteria and were included in the study. The patients were recruited from the five medical centers participating in the Hellenic Group of Electrochemotherapy (HeGECT), as follows: 35 patients from St. Savvas Anticancer Hospital of Athens, 9 patients from the University Hospital of Thessaly, 1 patient from the Attikon University Hospital of Athens, 4 patients from the Doctors' Hospital Athens and 3 patients from the Athens Medical Center, Clinic of Psychikon (Table II).

ECT was considered only for patients with progressive and metastatic disease, for whom standard therapeutic treatments had been exhausted. The following exclusion criteria were applied: progressive visceral disease, allergic reactions to bleomycin or previous administration at an excessive dose, peripheral neuropathy, chronic renal dysfunction, abnormal hemostasis (platelet count of $<70{,}000/mm^3$), arrhythmia, epilepsy, pregnancy and lactation. Moreover, patients with a pacemaker were eligible for treatment by ECT only for nodules located in sites other than the anterior chest wall. Patients taking anticoagulants or with an international normalized ratio (INR) >1.5 were excluded from treatment with needle insertion.

Study design. This prospective non-randomized study was conducted in accordance to the standard operating procedures for ECT, as previously validated during the ESOPE project. The patients were treated by ECT using bleomycin, followed by application of electric pulses to the tumors by the electric pulse generator Cliniporator (IGEA S.r.l., Carpi, Italy). Bleomycin was administered either intravenously (systematic administration), after calculation of the surface area for each patient, at a dose of 15,000 IU/m^2 in a bolus lasting between 30 and 60 seconds, or intratumorally at a dose quantified based on the number and size of tumor nodules; specifically, the dose of bleomycin was 1000 IU/cm^3 of tumor for nodules smaller than 0.5 cm^3, 500 IU/cm^3 for nodules ranging between 0.5 and 1.0 cm^3, and 250 IU/cm^3 for nodules bigger than 1.0 cm^3.

In intravenous administration of bleomycin, the electric pulses were applied to the tumor nodules at least 8 minutes after drug injection and within the next 20 minutes. In intratumoral administration, the electric pulses were applied within 10 minutes after injection. Electric pulses were applied by needle electrodes with linear configuration (N-20-4B), needle electrodes with hexagonal configuration (N-20-HG and N-30-HG) or plate electrodes (P-30-8B) (IGEA S.r.l., Carpi, Italy), depending on the location and size of the tumors. In general, plate electrodes were used for the treatment of superficial tumor nodules and needle electrodes for the treatment of nodules that were either deeply located or superficially located but large and thick. Linear needle electrodes were used for small nodules, whereas hexagonal ones were used for large nodules. The amplitude of the electric pulses was 400 V, 730 V or 960 V depending on the type of electrodes used.

Patients underwent local or general anesthesia for alleviation of pain associated with the procedure. General anesthesia was performed by general sedation, whereas local anesthesia by injection of 2% lidocaine around the area of the tumor nodule. General anesthesia was used in patients with multiple or very large tumor nodules, with nodules located in particularly sensitive areas of the body, as well as in those with poor physical condition. ECT treatment was typically performed on an out-patient basis in a one-day clinic (ODC). When hospitalization was regarded necessary, patients remained for 1-2 days.

During the study, 15 patients received ECT in combination with another treatment. More specifically, eight patients with large or relapsed tumors received ECT combined with external beam radiation therapy, whereas one patient underwent concominant ECT and brachytherapy. In addition, six patients underwent ECT during surgery, four of whom received ECT after tumor resection, while the remaining two patients received ECT to the whole tumor mass due to the presence of inoperable disease.

Table III. *Patients treated with electrochemotherapy at the five medical centers of the Hellenic Group of Electrochemotherapy since November 2007.*

Cases	Malignancy	No. of patients	No. of applications
Skin tumors	Melanoma	5	7
	Kaposi's sarcoma	4	5
	Dermatoinosarcoma	2	3
	Hydroadenocarcinoma	1	1
Head and neck tumors	Skin of the nose	5	8
	Scalp	4	6
	Orbital	1	1
	Eyelid	1	1
	Lip	1	1
	Skin of the frontal region	1	1
	Skin of the lower neck	1	1
Solid tumors	Lower extremity liposarcoma	1	1
	Neck nodal metastasis	1	1
	Buccal mucosa	3	6
	Parotid gland	4	8
	Mandibular	1	1
	Breast	9	13
	Anal	3	5
	Vulvar	1	1
	Uterine cervix	1	1
	Renal	1	1
	Pancreatic	1	1
Total		52	74

Patient monitoring and response evaluation. Prior to treatment, all patients were subjected to physical examination, standard laboratory tests, ECG and imaging studies. A complete medical history of chronic, malignant and non-malignant disease was also taken. Patients were clinically monitored during follow-up. Their first examination was conducted one month after treatment. In certain cases of partial response, an additional session of ECT was applied. The evaluation of overall response was conducted after a follow-up period of 2 months.

Complete response was determined when the tumor nodule was no longer palpable, whereas a partial response was defined as a more than 50% decrease in tumor nodule size or number. A decrease of less than 50% was considered as no response. Tumor nodules were measured and photographed both before and after treatment. Five patients were excluded from the evaluation of response due to less than 60 days' follow-up.

Results

During the study, 52 patients were treated in 74 applications of ECT at the five Greek medical centers (Table II). More specifically, 34 patients underwent one application of ECT, 14 patients underwent 2 applications and 4 patients received 3 applications. Among patients, 34/52 (65.4%) were female and 18/52 (34.6%) were male. The mean age of the patients was 69.8 years.

Patients were categorized into three groups according to the type and location of tumor nodules: 12/52 (23.1%) patients with skin tumors, 14/52 (26.9%) patients with skin tumors of the head and neck region, and 26/52 (50.0%) with solid superficial or deep-seated tumors. Tumor characteristics of the patients treated with ECT are presented in Table III.

Intratumoral administration of bleomycin was used in 20/52 (38.5%) patients and intravenous administration in 28/52 (53.8%), whereas 4/52 (7.7%) patients received a combination of both methods. Patients experienced neither systemic nor local side-effects at the administered doses. ECT was performed under local anesthesia in 42/52 (81%) patients and under general anesthesia in 9/52 (17%) patients, while one patient (2%) received epidural anesthesia. Needle electrodes with linear configuration (N-20-4B) were used in 18/52 (34.62%) of patients, with hexagonal configuration (N-20-HG and N-30-HG) in 27/52 (51.92%) of patients, and plate electrodes (P-30-8B) were used in 1/52 (1.92%). Moreover, 6/52 (11.54%) patients underwent repeated sessions of ECT with both types of needle electrodes.

Treatment response. Among patients, 47/52 (92.38%) were eligible for clinical response evaluation. The five patients that could not be assessed due to the recent application of ECT were two patients with dermatoinosarcoma, one patient with hydroadenocarcinoma, one patient with breast cancer and one patient with anal cancer.

Out of a total of 47 patients, 45 (95.74%) responded to treatment. Complete treatment response was achieved in 30/47 (63.83%) of patients, whereas a partial response occurred in 15/47 (31.91%). Two patients (4.26%) showed no response. No patients exhibited progression of disease. Figure 1 presents one case of efficient application of ECT for a patient with a head and neck tumor, who is still in complete response. Independently of their response, 13/52 (25.0%) patients died no sooner than six months after their last ECT application.

Table IV presents treatment responses according to tumor type and location. Amongst 9 patients with skin tumors that were assessed for treatment response, 6 had a complete response, 2 had a partial response and 1 showed no response. Among 14 patients with skin tumors of the head and neck, 9 had a complete response, 4 had a partial response and 1 had no response. Finally, among 24 patients with solid tumors assessed for treatment response, 15 had a complete response and 9 had a partial response.

Discussion

ECT has emerged as a promising new therapeutic modality for efficient local control of cancer disease. Recently, an increasing number of centers in Europe have incorporated the performance of ECT in their therapeutic armentarium,

Table IV. *Responses of patients who underwent electrochemotherapy at the five medical centers of the Hellenic Group of Electrochemotherapy.*

Tumor	No. pts	CR	PR	NR	NA
Melanoma	5	3	2	-	-
Kaposi's sarcoma	4	3	-	1	-
Dermatoinosarcoma	2	-	-	-	2
Hydroadenocarcinoma	1	-	-	-	1
Skin tumors (Total)	9/12	6	2	1	3
Skin of the nose	5	3	1	1	-
Scalp	4	3	1		-
Orbital	1	-	1	-	-
Eyelid	1	1	-	-	-
Lip	1	1	-	-	-
Skin of the frontal region	1	-	1	-	-
Skin of the lower neck	1	1	-	-	-
Head and neck tumors (Total)	14/14	9	4	1	0
Lower extremity liposarcoma	1	1	-	-	-
Neck nodal metastasis	1	1	-	-	-
Buccal mucosa	3	2	1	-	-
Parotid gland	4	2	2	-	-
Mandibular	1	1	-	-	-
Breast	9	2	6	-	1
Anal	3	2	-	-	1
Vulvar	1	1	-	-	-
Uterine cervix	1	1	-	-	-
Renal	1	1	-	-	-
Pancreatic	1	1	-	-	-
Solid tumors	24/26	15	9	0	2
Total	47/52	30/47 (63.83%)	15/47 (31.91%)	2/47 (4.26%)	

CR: Complete response, PR: partial response, NR: no response, NA: not assessed.

indicating its significance in the treatment of challenging cases. Performance of ECT in Greece began in 2007, with the co-operation of the five medical centers of the Hellenic Group of Electrochemotherapy (HeGECT), according to the European Standard Operating Procedures as previously validated during the ESOPE project. To date, ECT has been performed in 52 patients with superficial and deeply-located tumors of various types after all standard therapeutic approaches had been exhausted. ECT was performed in combination with systemic or intratumoral administration of bleomycin and it was well tolerated since none of the patients developed side-effects. Our data suggest that ECT offers immediate clinical benefit to patients as indicated by their responses to treatment. An overall response of 95.74% was achieved, while 63.83% of patients had a complete response. These results are in agreement with previously published data on patients with progressive disease of various malignancies (30). In the present study, ECT was applied to tumors of variable origin, histological type and location. Nevertheless, a significant number of patients with skin or solid tumors of the head and neck region were included.

Management of head and neck cancer. Head and neck cancer encompasses various diseases that despite sharing similar location and histology actually appear to be quite heterogeneous regarding pathogenesis, tumor biology, sublocation within the head and neck region, diagnosis, prognosis and treatment, as well as effect on quality of life. As a result, the clinical management of head and neck cancer is exceptionally complicated and requires a co-operative approach, including surgery, chemotherapy, radiation therapy and treatment with biological agents (37).

Intratumoral chemotherapy is considered an effective approach for the treatment of head and neck tumors (36). Its main advantage arises from the fact that the injected agents limit their action on cancer cells and do not affect the healthy ones. However, certain aspects of intratumoral chemotherapy, including the type of drug used, the injection technique and the treatment periodicity, need to be further explored. The combination of intratumoral chemotherapy with concurrent application of electric pulses has recently attracted scientific interest.

In 1991, Mir and co workers performed the first clinical trial using ECT combined with intravenous administration of bleomycin for the treatment of head and neck squamous carcinomas (38). Several studies have been carried out since then, with some of them reporting very high rates of complete response, with few or no recurrences. According to

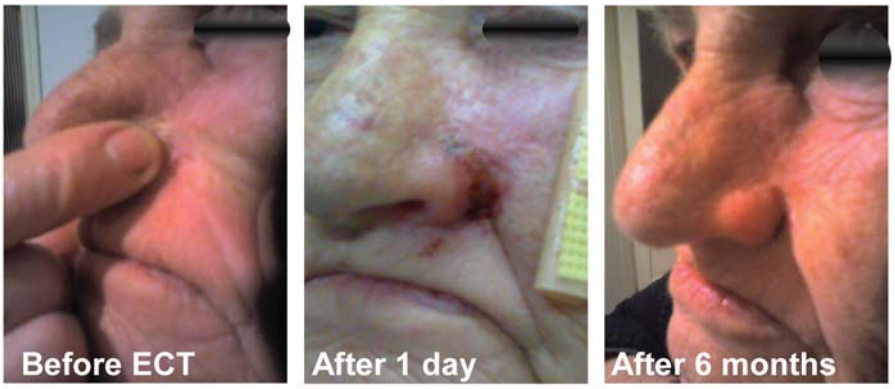

Figure 1. *Response of nasal carcinoma to a single application of electrochemotherapy using bleomycin. A 76-year-old female patient with basal cell nasal carcinoma. The patient had previously been treated by surgery for tumor resection, but healthy tissue margins were not achieved. Subsequently the patient received standard treatment by radiation therapy. After tumor recurrence, the patient received a single application of electrochemotherapy using N-20-4B needle electrodes with linear configuration, with intratumoral administration of bleomycin under local anaesthesia. The patient is still in complete response, more than two years after the performance of the procedure (St. Savvas Anticancer Hospital of Athens, February 2008).*

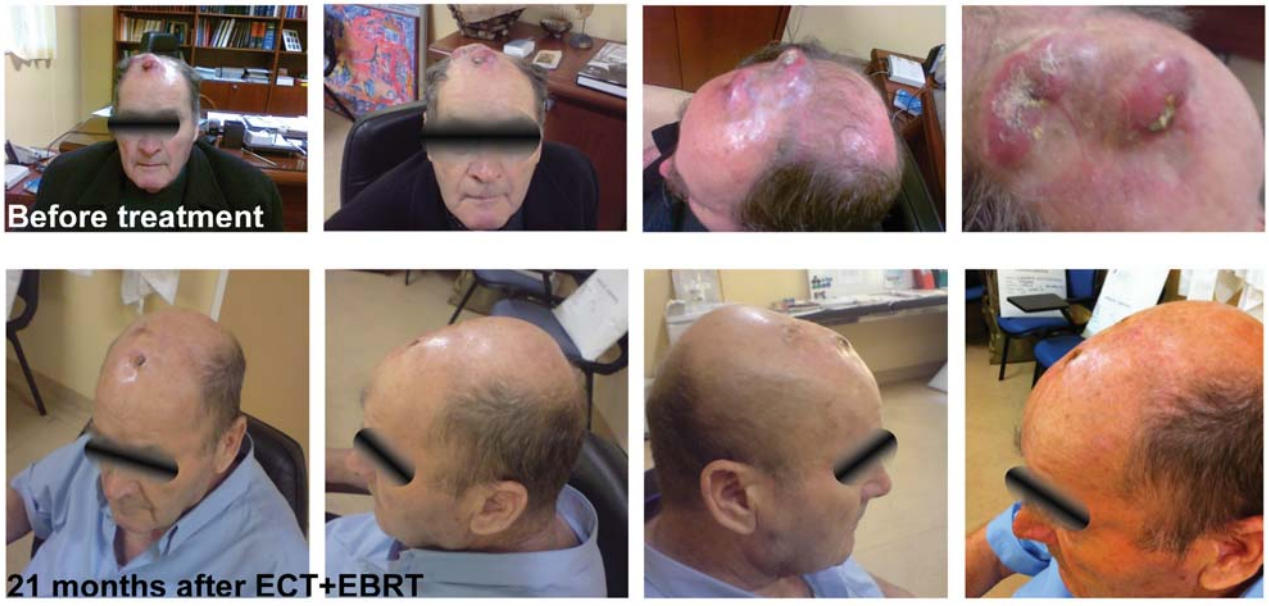

Figure 2. *Response of cutaneous tumor of the scalp after combined treatment with electrochemotherapy and external beam radiation therapy. A 75-year-old male patient with recurrent tumor of the scalp. The patient had been previously treated by surgery many times but tumor always recurred. The patient received a single application of electrochemotherapy using N-20-4B needle electrodes with linear configuration, with intravenous administration of bleomycin under general sedation. Subsequently one session of external beam radiation therapy was applied. The patient is still in complete response, two years after the therapeutic approach (University Hospital of Thessaly, June 2008).*

a review of summarized clinical results, 17 patients with a total of 77 head and neck squamous cell tumors were treated with ECT with intravenous administration of bleomycin (29). The overall response was 62%, while complete response was 43%. Similarly, among 14 patients with an equal number of head and neck nodules who received bleomycin intratumorally, the overall and complete responses were 86% and 50%, respectively. A recent study of ECT with intratumoral injection of bleomycin in patients with basal cell and squamous skin carcinomas of the head and neck further supports ECT as a promising new treatment that could be potentially applied as an alternative to surgery in skin cancer (39). In the present study, ECT was performed on 23 patients with head and neck tumors, 14 of whom had skin nodules and 9 had solid ones. Application of ECT exhibited equal effectiveness, independently of tumor type.

Figure 3. *Response of hemorrhagic tumor in the nose after combined treatment with electrochemotherapy and external beam radiation therapy. An 84-year-old female patient with a huge hemorrhagic nasal tumor. The patient was treated with one application of electrochemotherapy using N-20-HG needle electrodes with hexagonal configuration, with intravenous administration of bleomycin under local anesthesia, subsequently followed by external beam radiation therapy of a total dose of 45 Gy (3 Gy/15 sessions). Three months after treatment with electrochemotherapy and radiation therapy, the size of the tumor was reduced by approximately 50%. Two additional applications of electrochemotherapy were subsequently performed with a one-month interval, resulting in the complete response of the tumor (St. Savvas Anticancer Hospital of Athens, January 2008).*

Figure 4. *Response of tumor in the cheek after combined treatment with electrochemotherapy and external beam radiation therapy. A 78-year-old female patient with a huge tumor in the right cheek. The patient was treated with one application of electrochemotherapy using N-20-HG needle electrodes with hexagonal configuration, with intravenous administration of bleomycin under local anesthesia, subsequently followed by a single dose of radiation therapy (10 Gy). After three months, two additional applications of electrochemotherapy were performed with a one-month interval. The patient was in complete response for two years, until her death due to disease (St. Savvas Anticancer Hospital of Athens, March 2008).*

Cases of exceptional interest. Of the 52 patients treated with ECT, the majority had malignancies of high severity which were multi-treated. Amongst these, some were exceptionally challenging cases that required immediate and efficient management through combination of treatments. ECT was applied in combination with external beam radiation therapy in eight patients with very large tumors, which were either multi-treated or at an advanced stage (Figures 2-4). The rationale underlying this therapeutic approach is that ECT in combination with radiation therapy is expected to exert significantly enhanced efficiency. Preclinical studies have showed that ECT acts synergistically with radiotherapy, exerting a radiosensitizing effect on different types of tumors, which results in toxicity enhancement (40). Similar observations have also been reported for the combined application of ECT with classical chemotherapy (doxorubicin), as well as with radiation therapy and chemotherapy (41). The presented results also support the application of ECT prior to radiation therapy as inducing a radiosensitizing effect and significantly enhancing antitumor effectiveness.

Furthermore, for the first time worldwide, in this study ECT was applied during surgery for tumor excision in six patients. A single application of ECT was performed immediately after the surgical removal of the tumor in four of the patients (Figure

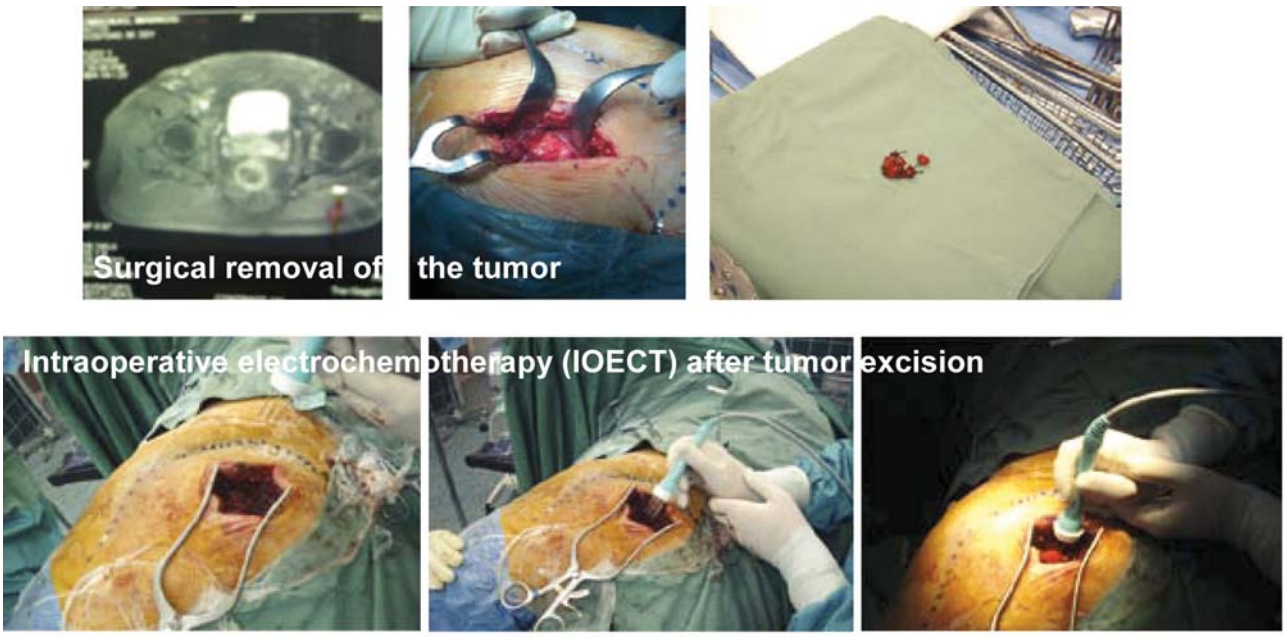

Figure 5. *First worldwide application of intraoperative electrochemotherapy. A 59-year-old patient with recurrent gluteal liposarcoma. The patient had previously been treated with surgery followed by standard radiation therapy and chemotherapy. After tumor recurrence, the patient received one application of intraoperative electrochemotherapy immediately after tumor excision. Electrochemotherapy was performed using N-30-HG needle electrodes with hexagonal configuration, with intravenous administration of bleomycin and under general sedation. The patient is in complete response (St. Savvas Anticancer Hospital of Athens, April 2008).*

Figure 6. First worldwide application of intravaginal electrochemotherapy and brachytherapy for a 29-year-old female patient with recurrence of inoperable endometrial cancer. The patient had previously received external beam radiation therapy (54 Gy) followed by brachytherapy (7.5 Gy×3). After 3 months, the disease remained stable. Subsequently, one application of electrochemotherapy was performed in combination with brachytherapy (8 Gy) to the surface area. Electrochemotherapy was performed using N-20-HG needle electrodes with hexagonal configuration, with intravenous administration of bleomycin under general sedation. Complete response was histologically evident after two months, while the recurrence-free survival period was 9 months (St. Savvas Anticancer Hospital of Athens, March 2009).

5). The concept behind this application is that ECT can be used after tumor excision with the intent of eradicating residual tumor cells. In the other two cases, the tumor was determined to be inoperable. As a result, ECT was applied to the whole volume of the tumor for the purpose of reducing the tumor mass. The application of ECT during surgery has yielded very promising results since all treated patients are still in complete response. Nevertheless, further monitoring of the patients is required for the evaluation of treatment efficiency. The efficacy of intraoperative and postoperative ECT has been evaluated on feline animal models with spontaneous sarcoma (42). According to the results of this, as well as other preclinical studies, adjuvant ECT offers a significant advantage regarding local control and overall survival, compared to surgery alone (43).

In addition, the first worldwide application of ECT in combination with brachytherapy is reported. Concurrent intravaginal ECT and brachytherapy was applied in one

patient with recurrence of inoperable endometrial cancer (Figure 6). Complete response was observed two months after treatment, without signs of side-effects. Nevertheless, the tumor recurred nine months later.

Conclusion

Although ECT is a new therapeutic modality, plenty of clinical evidence supports its increased efficiency in local cancer control. Thus, ECT appears to be a highly promising approach in the management of cancer. The results of ECT performance in Greece, whether in the standardized way or in combination with other treatments, verify its potential medical applications. In the future, the combined application of ECT with other treatment modalities may provide an additional tool for the treatment of tumor nodules since their combination is expected to exert an amplified effect regarding the efficient control of cancer.

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