Electrochemotherapy for Cancers Affecting the Skin: Ten Years of Experience in a Tertiary Referral Hospital

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AIM: Electrochemotherapy (ECT) combines chemotherapy with an electric pulse to directly target tumor cells by increasing cell membrane permeability, facilitating the efficient uptake of chemotherapeutic agents by tumor cells and improving their therapeutic efficacy. It is widely used for treating skin metastatic nodules or metastases of subcutaneous tissue. Therefore, the aim of this study is to report the experience regarding the use of ECT in a tertiary referral hospital and explore its safety and efficacy in treating skin cancer.
METHODS: This study included 97 skin cancer patients treated with ECT at the Surgical Oncological Unit of the University of Perugia, Italy, between 2013 and 2024. ECT was performed using the Cliniporator® device (model EP02, IGEA, Carpi, Italy). The individuals with life expectancy greater than three months and American Society of Anesthesiologists physical status classification of I–III were included in this study, while those with arrhythmia and allergies to bleomycin were excluded.
RESULTS: In this study, melanoma was the most frequently observed malignancy, accounting for 47.4% of all cases. A total of 46 melanoma patients aged between 42 and 93 years underwent ECT treatment. Most of these patients presented with in-transit metastases (67.4%) and often had multiple lesions (71.74%). Furthermore, 21 patients received only one session, while 25 underwent multiple sessions. Almost all procedures were performed with intravenous administration of bleomycin. However, in two cases, intralesional cisplatin was used for a recurrence of melanoma localized in the scalp. Notably, no adverse events were observed during ECT procedure. Moreover, most of the patients (70.45%) were alive one year after the first ECT session. The 5-year probability of survival was 24% after the first ECT session.
CONCLUSIONS: Electrochemotherapy represents a safe and effective therapeutic strategy for various malignancies, with significant potential for future clinical applications.

Keywords: melanoma; skin cancer; electrochemotherapy; Non-Melanoma Skin Cancers

Introduction

Electrochemotherapy (ECT) is an advanced locoregional ablative therapy that combines chemotherapy with electric pulses to directly target tumor cells. This innovative treatment method leverages the phenomenon of electroporation, a process where the application of electric pulses increases cell membrane permeability. This enhanced permeability allows for efficient uptake of the chemotherapeutic agent, improving their therapeutic efficacy [1–3].

ECT is primarily used in treating cutaneous tumors, including melanoma, basal cell carcinoma, and squamous cell carcinoma. However, its application has extended beyond the skin surface to tumors in deeper organs like the pancreas and liver, expanding its therapeutic scope for patients with challenging conditions [4,5].

By combining the physical effect of the electric field with the chemical action of chemotherapy, ECT achieves higher drug concentrations within the tumor while reducing systemic side effects. Furthermore, its ability to control tumor vascularization is crucial for managing bleeding metastases, providing a significant improvement in patients' quality of life. This dual-action therapy represents a significant advancement in tumor treatment, particularly for neoplasms resistant to traditional therapies.

This technique was validated by the European Standard Procedure for ECT (ESOPE) in 2006, and the protocol was updated later in 2018. The original ESOPE study was the first clinical trial to standardize a treatment protocol for lesions smaller than 3 cm, establishing that ECT is both safe and effective under standard parameters. Conducted across four centers, the study evaluated 61 patients with cutaneous

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and subcutaneous metastases of various histological types, including 32 melanomas, 27 carcinomas (breast, skin squamous cell, cervical, colon), and 2 sarcomas. Among the 41 patients assessed, the response rate was 85%, with 73.7% indicating complete responses. Local tumor control after 150 days reached 88% with intravenous bleomycin, 73% with intralesional bleomycin, and 75% with cisplatin [6]. The updated study broadened the protocol to include tumors larger than 3 cm and validated the initial study results [7]. Collectively, these two studies standardized parameters for ECT, including anesthesia choice, chemotherapy dosage, and electrode selection.

Currently, ECT can be performed under general or local anesthesia, depending on the size and number of tumor masses. General anesthesia is advisable for numerous lesions (more than 7) or larger ones (greater than 3 cm). For fewer or smaller lesions, or if the patient is not a candidate for general anesthesia, local anesthesia is preferred [8,9].

The current indications for ECT include (1) symptomatic skin metastases of any histology (presenting with bleeding, ulceration, pain, odor, transudate) [10,11], (2) progressing skin metastases where the development of the symptoms such as those listed above is expected [12,13], (3) primary skin cancers where other therapeutic options, such as surgery, chemotherapy, or immunotherapy, have failed or are impossible [14,15], and (4) patients undergoing systemic therapy who experience progression or insufficient response of skin metastases, despite achieving a good response in internal organs [16,17].

This study presents our clinical experience regarding using ECT in treating skin cancer at the University of Perugia's Oncological Surgery Unit, Perugia, Italy.

Materials and Methods

Study Participants

This study included 97 patients (50 males and 47 females) with a mean age of 74 years, who underwent ECT at the Surgical Oncological Unit of the University of Perugia, Perugia, Italy, between 2013 and 2024. Data for these patients were obtained from the Hospital of Perugia's database. The data included the following parameters: sex (distribution of patients by gender), patient age at the time of treatment, site of the primary neoplasm or metastases, histological type of the neoplasm, electrode used in the procedure, type of anesthesia administered, chemotherapy regimen and route of administration, number of treatment sessions per patient, and survival outcomes.

Inclusion and Exclusion Criteria

The patients with life expectancy greater than three months and American Society of Anesthesiologists (ASA) physical status classification of I–III were included in this study, while those with arrhythmia and allergies to bleomycin were excluded. The study design complied with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from each patient upon hospital admission. The study was approved by the Institutional Bioethical Review Board of the University of Perugia (protocol n. 385797) and the Review Board of the Italian Society of Research in Surgery (n. 0021/2024).

Patient Treatment Protocol

ECT was performed using the Cliniporator® device (model EP02, IGEA, Carpi, Italy). This device consists of a console with a command-and-control section that is used to enter patient data, select the electrode, and perform the treatment. The device has a power unit for pulse generation and a radio-frequency section for automatic electrode recognition. The system utilizes disposable electrodes, which connect to the console via a sterilized handpiece, and delivers electrical impulses synchronized with the heart's absolute refractory period using an R-wave detector. During electroporation, the Cliniporator offers real-time voltage and current waveforms, signaling correct current delivery both visually and audibly.

All patients were treated in the outpatient surgical unit. The principal endpoint of the study was to evaluate the safety profile and survival outcomes of ECT.

Results

Among the total patients (n = 97), melanoma was the most frequently observed malignancy, accounting for 47.4% of the cases, followed by Non-Melanoma Skin Cancer (NMSC, 34.02%). Fig. 1 shows the distribution of different malignancies across our study cohort. The data collected for each subgroup of patients are presented in detail, classified according to the type of neoplasm. Each section provides a description of the demographic, clinical, and therapeutic characteristics of the patients, analyzing the relevant variables and the results obtained.

Table 1. Characteristics of patients with melanoma.

Patient characteristics	N
Male/female	24/22
Age (years)	42–93
Location of melanoma	
- Limbs	27
-Trunk	12
- Head	4
- Vulva	1
- Scrotum	1
- Anus	1
Type of skin pathology	
- Transit metastases	31
- Multiple lesions	33
- Local disease recurrence	15
Regional lymphadenectomy	13

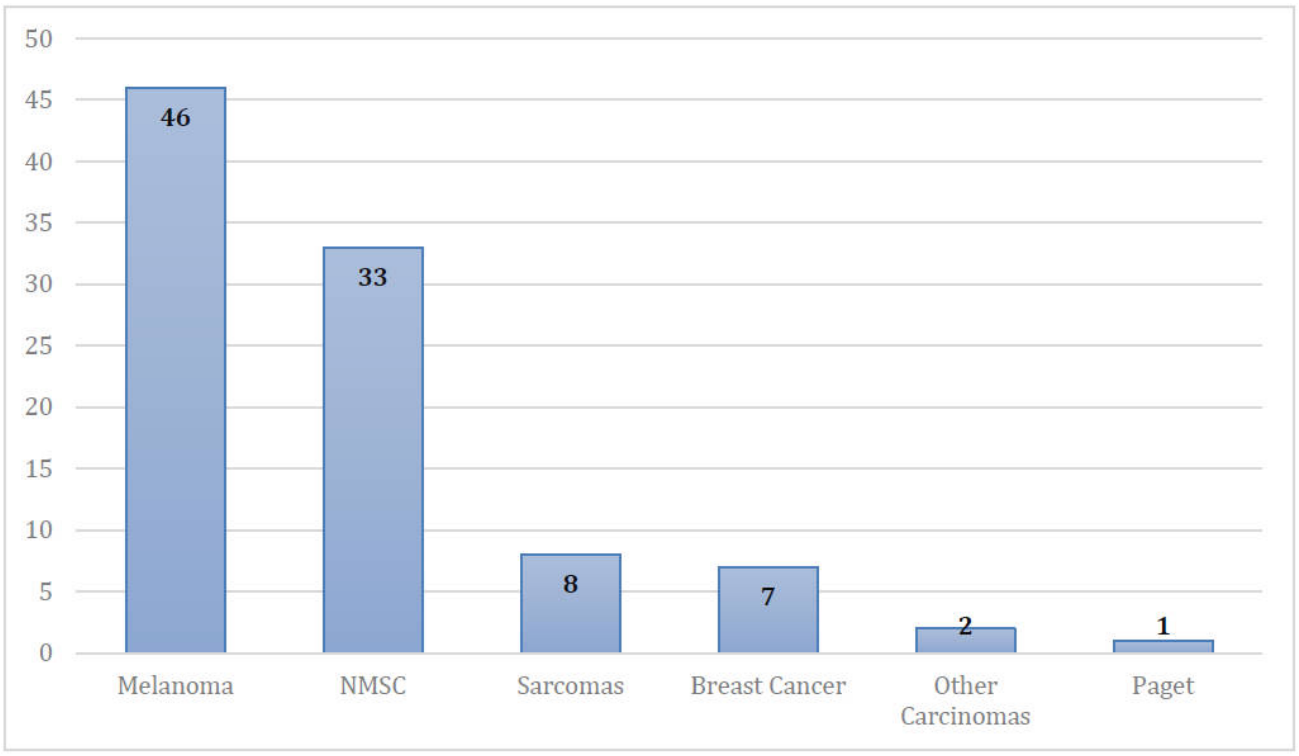

Fig. 1. Distribution of malignancies across the study cohort presented with skin cancer (horizontal axe: type of skin cancer; vertical axe: number of patients). NMSC, Non-Melanoma Skin Cancer.

Table 2. Characteristics of ECT in patients with melanoma.

ECT sessions	
1	21
2	14
3	9
4	2
Type of anestesia	
General	53
Local + sedation	18
Sedation	7
Peripheral block	4
Peripheral block + sedation	2
Type of chemotherapy	
Bleomycin	82
Cisplatin	2
Route of administration	
IV	82
Intralesional	2

ECT, electrochemotherapy; IV, intravenous.

In patients underwent ECT, after analgesia and sedation, bleomycin was administered intravenously (15.000 IU/m^2 in 30/60 min).

Characteristics of Melanoma Skin Cancer Patients

A total of 46 melanoma patients, aged between 42 and 93 years, underwent ECT treatment. The majority of these patients presented with in-transit metastases (67.4%) and often had multiple lesions (71.74%). In cases with locally advanced lesions, treatment focused on hemostatic and palliative purposes to improve patients' quality of life and manage bleeding (Table 1).

Furthermore, 31 melanoma patients underwent treatment specifically for in-transit metastases, represented as clinically evident dermal and/or subcutaneous metastases located at a distance >2 cm from the primary melanoma, within the region between the primary tumor and the first local-regional lymph node basin. These patients benefited from treatments designed to reduce disease progression and decrease associated symptoms. The remaining 15 patients were treated for local disease recurrence, characterized by lesions confined to or near the original site. In these cases, the treatment aimed to remove or shrink the primary tumor and its satellite lesions, thereby reducing the risk of further spread.

This case series highlights the diverse clinical presentations of melanoma and the significance of adopting diversified therapeutic approaches to alleviate its complexity. Fig. 2 illustrates the clinical presentation of in-transit metastases in melanoma patients.

A total of 84 ECT procedures were conducted. Twenty-one patients received only one session, while 25 out of 46 patients underwent multiple sessions. Particularly, 14 patients underwent 2 sessions, 9 patients underwent 3 sessions, and 2 patients underwent 4 sessions of ECT.

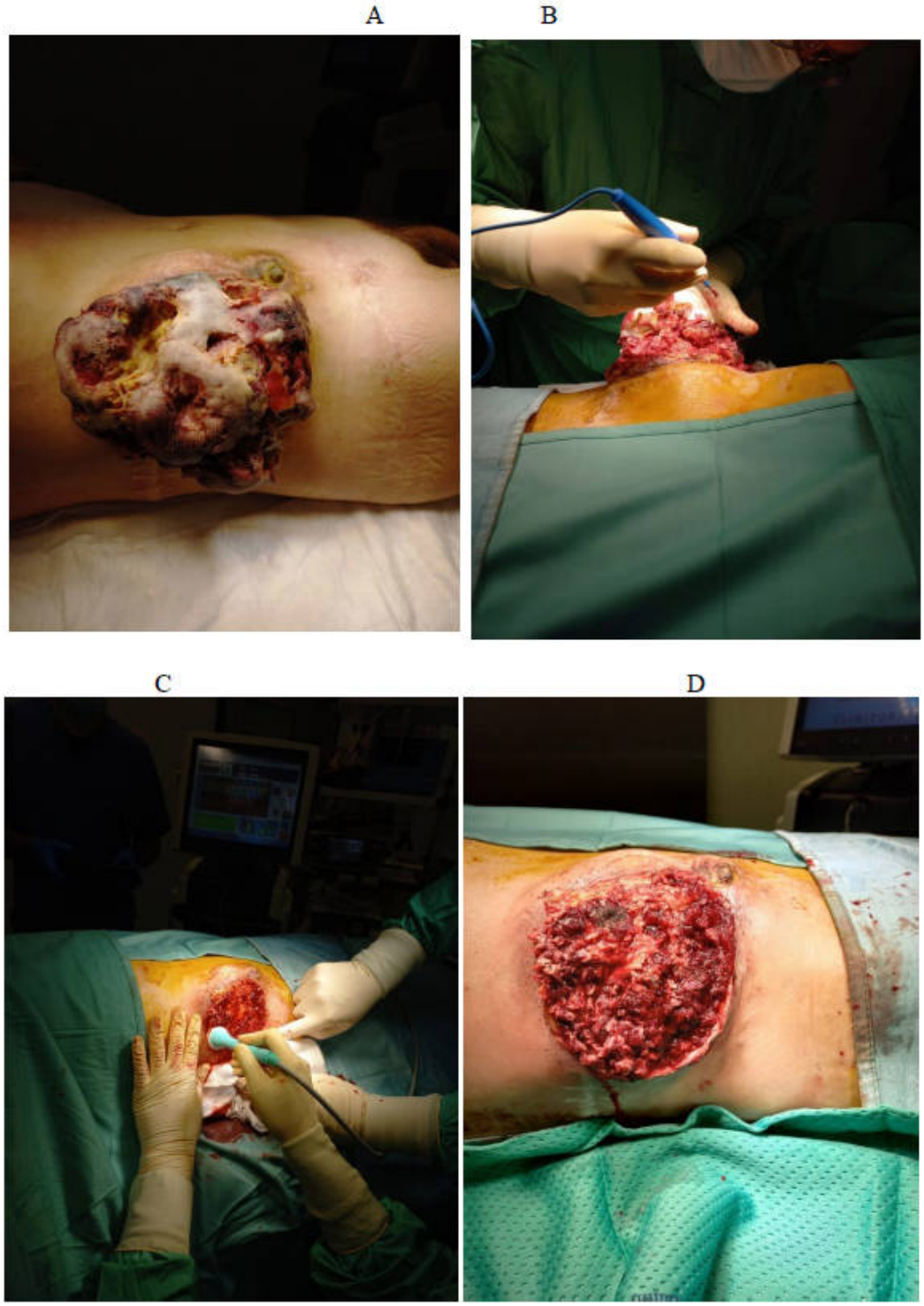

Fig. 2. Clinical presentations of in-transit metastases observed in melanoma patients. A 47-year-old male patient presented with a large melanoma metastasis on the left side of thorax. (A) The lesion was ulcerated and bleeding, resulting in recurrent anemia. (B) Excision of the exophytic neoplastic mass was conducted using an electric scalpel. (C) Electrochemotherapy was applied to the entire area using a Hexagon electrode (model N-20-HG). (D) The final appearance after performing electrochemotherapy.

Most procedures employed intravenous administration of bleomycin; however, intralesional cisplatin was used in two cases involving recurrent melanoma localized to the scalp (Table 2). During ECT, we did not observe any adverse events.

Among the 44 patients assessed, 70.45% (n = 31) were alive one year after their first ECT session. Most deaths occurred within the first 18 months, followed by a brief period of relative survival stabilization, which gradually declined starting in the second year. Another stabilization in survival

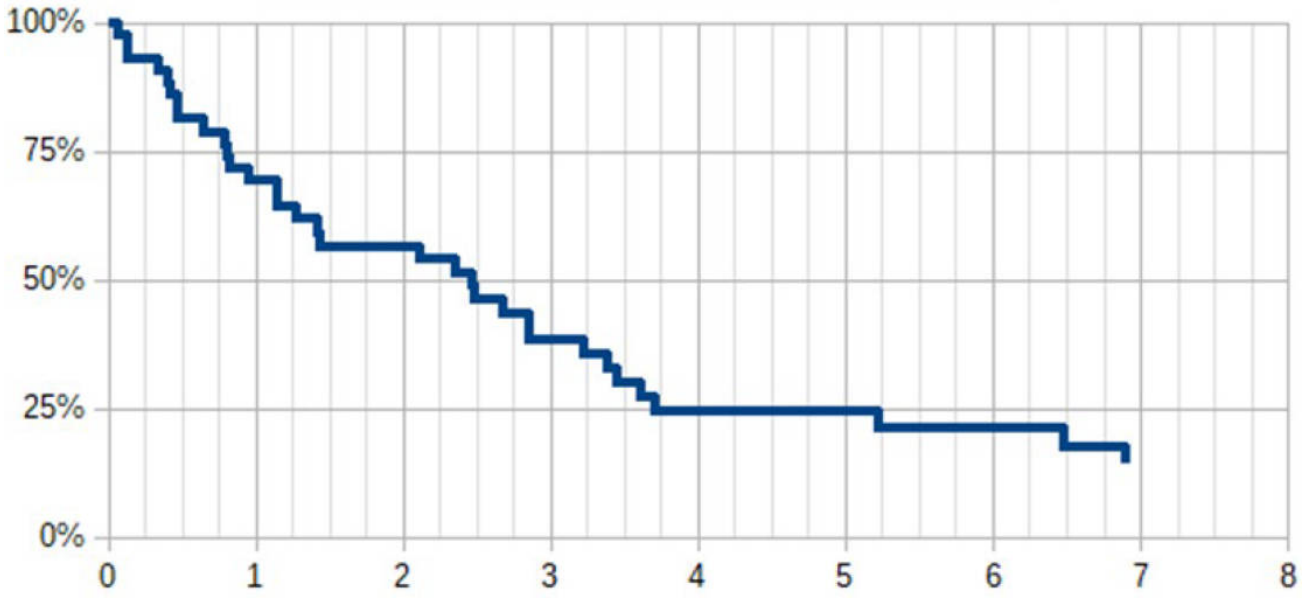

Fig. 3. Survival rate in melanoma: years from first electrochemotherapy session (horizontal axe: years of follow-up; vertical axe: rate of survival).

Table 3. Characteristics of patients with NMSC.

Patient characteristics	N
Male/female	21/12
Age (years)	42–96
Type of NMSC	
- Basal cell carcinoma	19
- Squamous cell carcinoma	10
- Actinic keratosis	1
- Meta-typical basal cell carcinoma	1
- Keratoacanthoma	1
- Merkel carcinoma	1
Location	
- Left/right ear	2/2
- Left/right temporal region	1/0
- Trunk	2
- Vertex head	5
- Face	2
- Left frontoparietal region	1
- Vulva	2
- Axillary region	1
- Neck	2
- Frontal region	1
- Hand	1
- Left frontotemporal region	2
- Left preauricular region	1
- Behind-the-ear region	2
- Left thigh	1
- Right parietal region	3
- Left cheek	2

NMSC, Non-Melanoma Skin Cancer.

Table 4. Characteristics of ECT in patients with NMSC.

ECT sessions	
1	23
2	8
3	2
Type of anaesthesia	
General	11
Local	4
Local + sedation	25
Sedation	5
Type of chemotherapy	
Bleomycin	31
Cisplatin	12
Route of administration	
IV	31
Intralesional	12

rates was observed from the fourth year onwards. The 5-year survival probability after the first ECT session was 24% (Fig. 3).

Characteristics of Non-Melanoma Skin Cancer (NMSC) Patients

Over the course of this study, we treated 33 patients, aged between 42 to 96 years, with skin carcinomas predominantly located in the head and neck area (Table 3). The most common type of NMSC treated were 19 cases of basal cell carcinoma (Fig. 4) and 10 squamous cell carcinomas.

A total of 45 ECT procedures were conducted. Among them, 23 patients underwent a single session, 8 underwent 2 sessions, and 2 underwent 3 sessions. Compared to melanoma, intralesional cisplatin was significantly used,

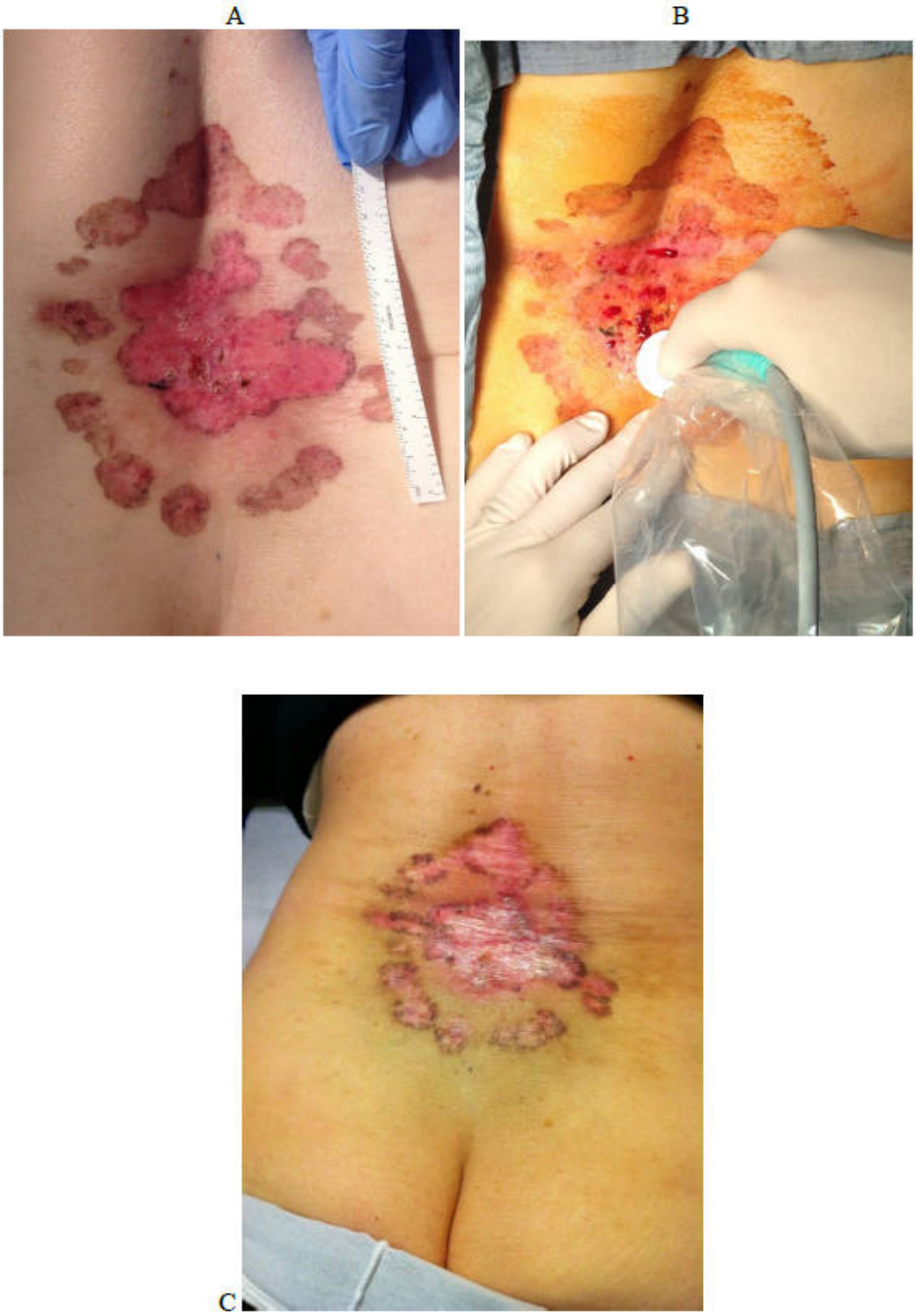

Fig. 4. Clinical presentations of Non-Melanoma Skin Cancer (NMSC). (A) A 79-year-old woman with Gorlin Goltz syndrome (a rare autosomal dominant genetic disorder characterized by a predisposition to the development of numerous basal cell carcinomas, as well as various bone, neurological, ocular abnormalities and other systemic manifestations) with giant basal cell carcinoma of the back. (B) The basal carcinoma underwent ECT using a Hexagon electrode (model N-20-HG, https://www.igeamedical.com/design/igea/pdf/terapie-geniche/prodotti/Mod_EPS02m_Rev.1.0_scheda_tecnica_IT.pdf). (C) In remote control, the reduction of the lesion is highlighted.

primarily because the lesions were generally smaller, single, and often located in areas such as the auricle, earlobe, or nasal wing and tip (Table 4). Notabaly, no adverse reactions were observed during the ECT procedure. However, survival outcomes were better than those of melanoma patients. Of the 33 patients, 19 remain alive, yielding an over-

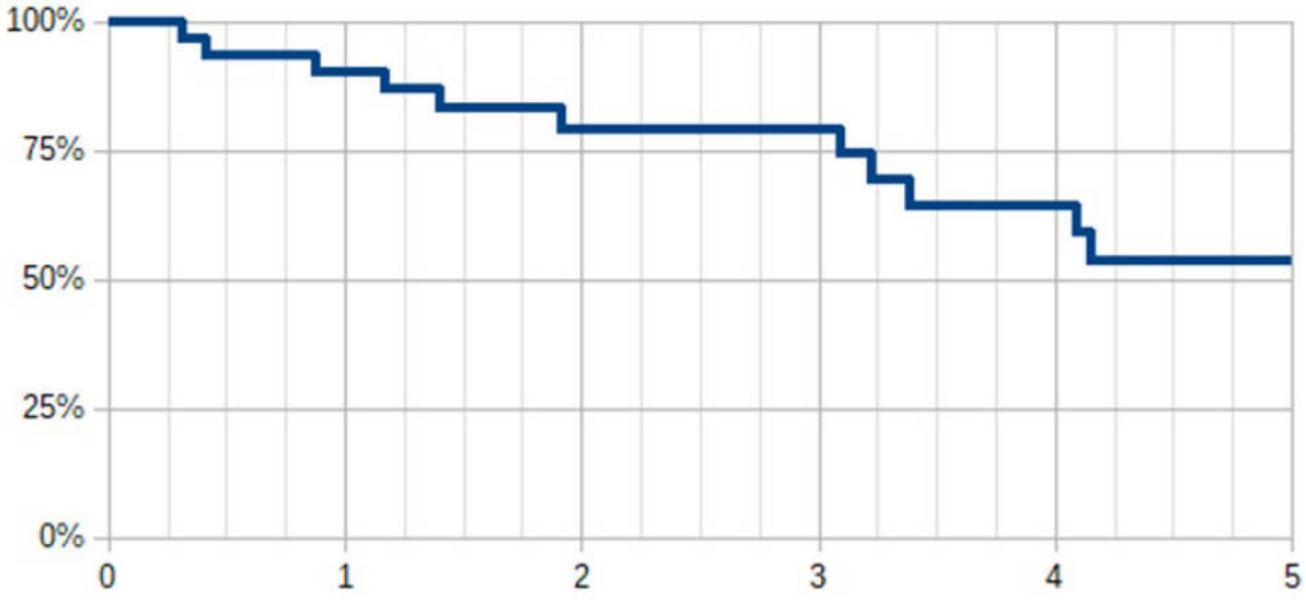

Fig. 5. Rate of survival in NMSC: years from first electrochemotherapy session (horizontal axe: years of follow-up vertical axe: rate of survival).

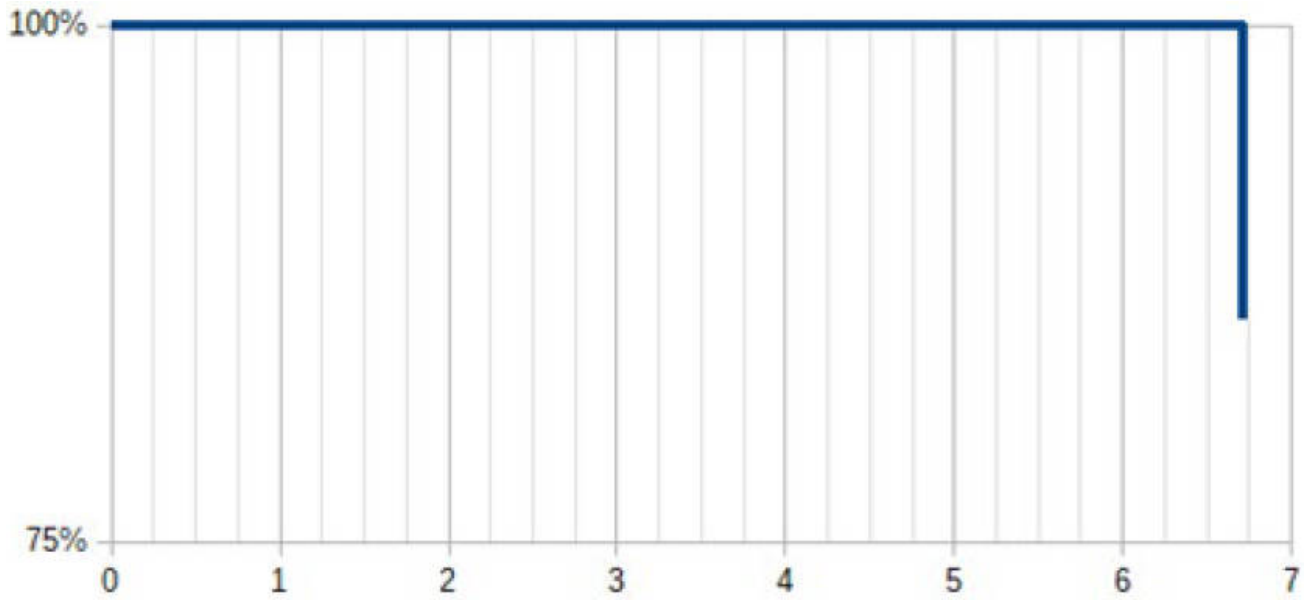

Fig. 6. Rate of survival in sarcomas: years from first electrochemotherapy session (horizontal axe: years of follow-up vertical axe: rate of survival).

all survival rate of 57.58% (Fig. 5). We observed a moderate and progressive decline in survival during the first two years and after the third year, with a period of relative stabilization observed between the second and third years.

Characteristics of Sarcomas

A total of 8 patients underwent ECT, including 7 with Kaposi's sarcoma lesions and 1 patient with multirelapsed sarcoma. All patients received intravenous bleomycin. The outcomes were highly favorable, with 7 out of 8 patients still alive, resulting in an overall survival rate of 87.5%. Only one patient died approximately 6 years and 8 months after the first ECT session. Furthermore, no adverse reactions were noted during the procedure (Fig. 6).

Characteristics of Breast Carcinomas

A total of 7 women, aged between 35 to 81 years, presented with skin metastases of breast cancer underwent ECT treatment (Fig. 7A–D). Intravenous bleomycin was administered in nearly all cases, except for one patient who received intralesional cisplatin. Furthermore, no adverse events were observed during the ECT. Furthermore, only

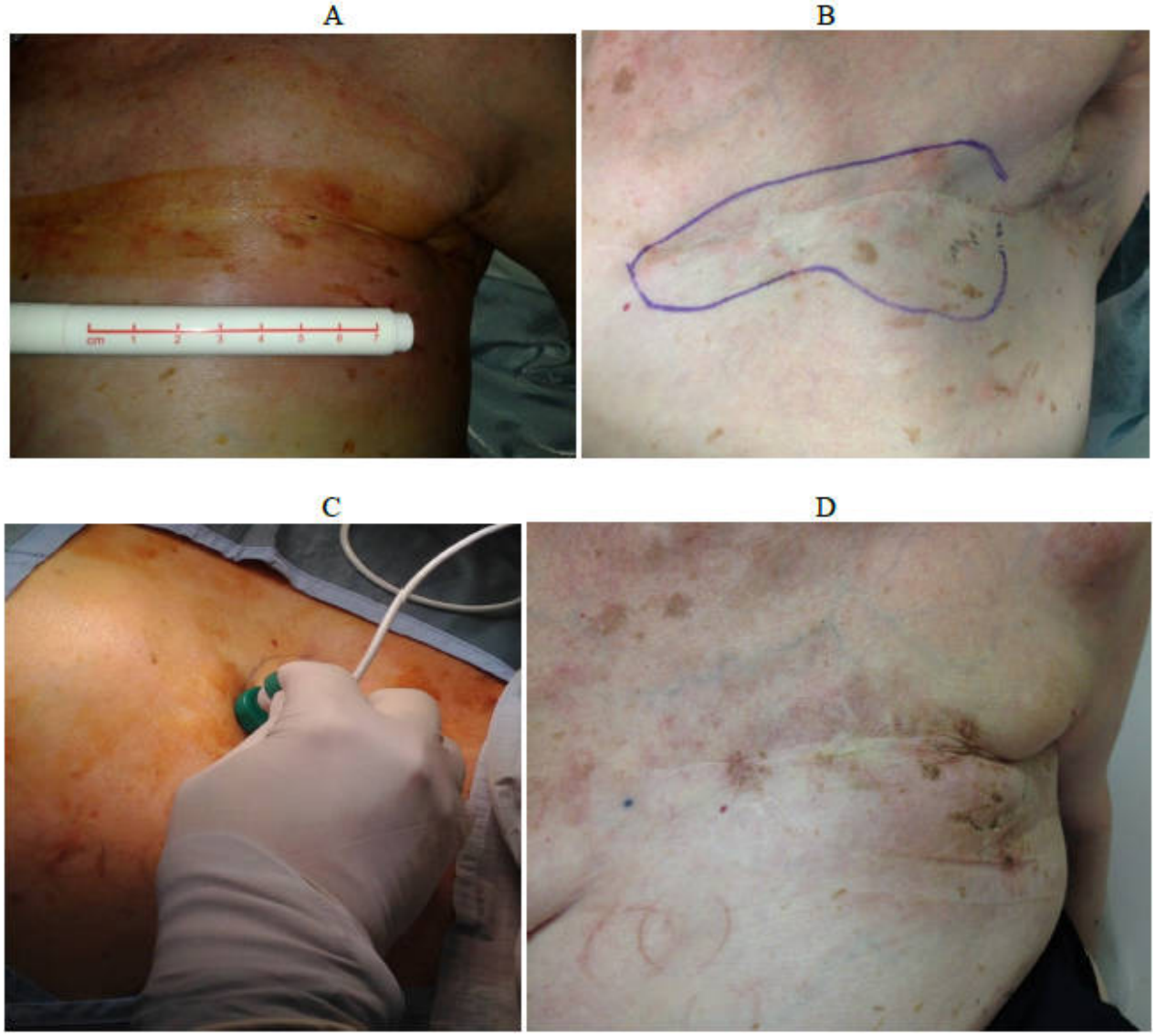

Fig. 7. Clinical presentation of breast carcinomas. (A) Subcutaneous recurrences in mastectomized patients. (B) Lesions marked with a dermographic pen in the preoperative phase. (C) Lesion treatment with finger electrode. (D) Follow-up one month later.

2 patients were still alive. Analyzing the survival curve demonstrated a reduction in survival in the first year, continued reduction, and significant declines until the fifth year. After about 5 years, the survival curve stabilizes at around 40% (Fig. 8).

Other Cancers

A case of vulvar Paget's carcinoma, oral carcinoma, and pharyngeal carcinoma presented with lymph node metastases in the right laterocervical site also received ECT treatment. Each patient underwent only one session of ECT. However, no adverse events were observed during ECT treatment.

Discussion

This study explores the safety and advantages of ECT based on our experience in treating skin cancer patients. The procedure is well tolerated, even by older patients, and is easy to perform. Its tolerability, along with the absence of severe adverse events, makes it a safe and accessible treatment approach for a wide range of patients. Furthermore, the simplicity of the technique allows it to be performed in various clinical settings, thus increasing its availability.

The chemotherapeutic agents used in ECT are bleomycin and cisplatin. Bleomycin can be administered intratumorally or intravenously, while cisplatin is exclusively given intratumorally [18]. One of the most common indications for ECT is the progression of skin metastases. In melanoma patients, the incidence of cutaneous metastases varies from 5% to 10% for satellite or in-transit metastases and can reach up to 50% for distant metastases [19]. The primary therapeutic options for melanoma metastases are surgery, systemic therapies, limb perfusion, radiotherapy, and ECT. Numerous studies have demonstrated the effec-

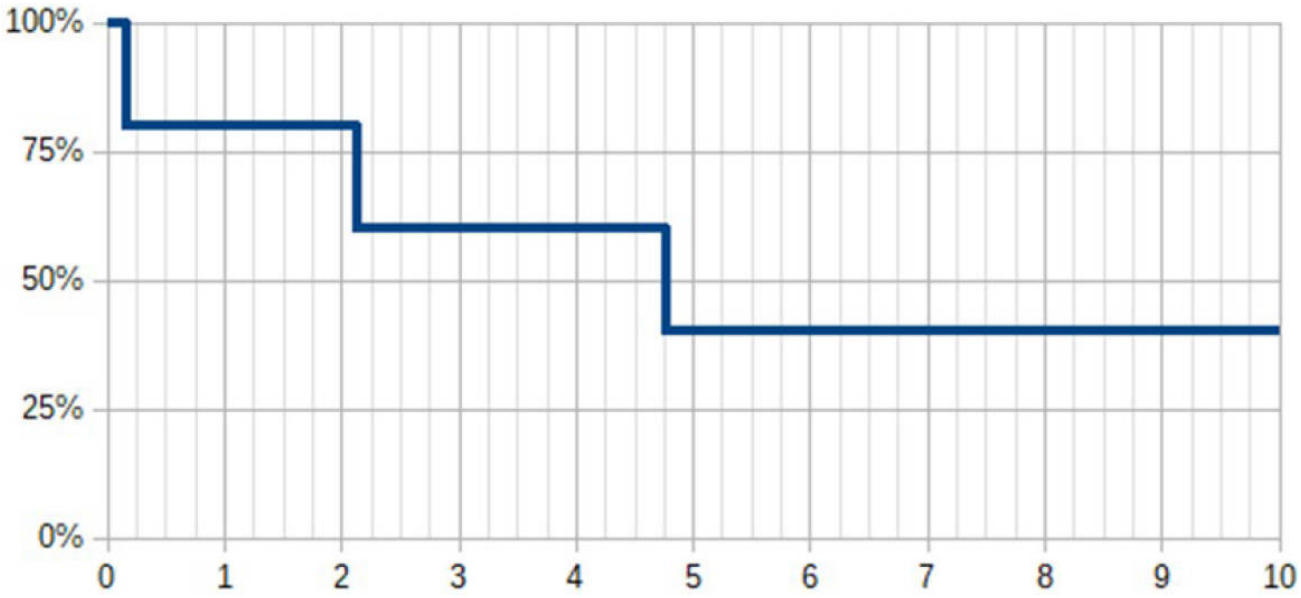

Fig. 8. Rate of survival during breast cancer carcinoma: years from first electrochemotherapy session (horizontal axe: years of follow-up vertical axe: rate of survival).

tiveness of ECT in treating cutaneous melanoma metastases. In the review by Ferioli *et al*. [5], eighteen studies were included, reporting clinical response rates in terms of local response per lesion or patient. The analysis revealed overall response rates ranging from 33.3% to 100%, with complete responses ranging between 9% and 92% in studies evaluating response 'per lesion'. In studies analyzing response 'per patient', the overall response rate varied from 66.7% to 100%, with complete responses ranging from 15.2% to 50%. Moreover, three studies reported 1-year survival rates of 67% and 15-month survival rates of 86.2% in patients treated with ECT and immunotherapy [20–22].

A systematic review conducted by Petrelli *et al*. [23] included 27 studies, reporting an overall response rate of 77.6% and a complete response rate of 48%. Both reviews indicated pain and erythema as the most common adverse events, with less common occurrences of infections, ulcerations, muscle spasms, and nausea. Furthermore, Gasbarrini *et al*. [24] conducted a study on the efficacy of ECT in spinal melanoma metastases in a 51-year-old patient with metastases at the L5 level. After a laminectomy to expose the vertebral pedicle, four-needle electrodes were placed under fluoroscopic control and neuronavigation. Following bleomycin injection, electrical discharges were applied according to the ESOPE protocol. At three months of follow-up, a percutaneous biopsy revealed >95% necrosis. Six months later, a Positron Emission Tomography/Computed Tomography (PET-CT) scan showed a lesion that had stabilized after radiotherapy, and overall, there was a significant reduction in pain. They reported that there is a scientific rationale for using ECT in spinal metastases, though randomized, controlled, long-term studies are needed to validate this hypothesis [24]. Lastly, ECT has been proposed as an approach to reduce tumor size before surgery, helping to preserve organ function, as reported for anal melanomas [25,26].

However, there are many other possible therapeutic applications of ECT, such as in Non-Melanoma Skin Cancers and sarcomas. Basal cell carcinoma (BCC) is the most common form of skin cancer worldwide. Although its metastatic spread is rare, it often occurs in functional areas or in locally advanced or recurrent BCCs, for which surgery may not be feasible. In such cases, ECT could be a promising treatment approach [27–31].

This study has several limitations. First, the retrospective nature of the analysis, combined with missing data, prevents us from sweeping statements or drawing robust conclusions. Second, while the study reports on the experience of using ECT at a tertiary referral hospital, the findings cannot be generalized. In the future, we aim to create a regional network for collaboration with other health care facilities, which could help develop a regional registry and offer a more comprehensive representation of this procedure. Lastly, we included all patients hospitalized for ECT in the registry; however, a prospective enrollment model, based on selection criteria outlined in a multidisciplinary protocol, might have been a more promising option.

The literature review clearly indicates that ECT should also be considered a viable option for treating advanced cutaneous sarcoma [29,32,33]. Based on the observations from our study and the results from existing literature, it can be confirmed that ECT is an effective therapy, especially for Non-Melanoma Skin Cancers and sarcomas.

The future of ECT foresees an increasingly widespread application, especially in combination with immunotherapy.

The integration could enhance treatment efficacy by using the synergy between the direct tumor cell destruction by ECT and the stimulation of the immune system, leading to a more robust and long-lasting response against the neoplasm. It may also enable the treatment of lesions not directly targeted by ECT.

ECT has demonstrated therapeutic benefits in both curative and palliative treatments. Its hemostatic effect, which helps control bleeding in patients with advanced cancers, significantly improves the quality of life for these patients. Additionally, this study highlights the technical simplicity of the ECT procedure. This feature is particularly relevant, as it makes the procedure accessible to less experienced surgeons, thereby expanding its potential use in various clinical settings. The ease of execution, combined with its therapeutic and palliative benefits, underscores the importance of ECT as a valid and versatile treatment option in cancer therapy.

Conclusions

In conclusion, ECT represents a valuable and versatile therapeutic strategy for different malignancies, with significant potential for future clinical applications, especially when combined with other therapeutic modalities such as immunotherapy. Further research and technological innovation will continue to refine and expand the use of ECT, offering new opportunities for effectively treating cancers in patients with limited treatment options.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the corresponding author if needed.

Author Contributions

Conceptualization, PC, VG, GP and RC; methodology, PC, MarM, FB; data analysis, PC, RC, MatM, GT, CB; investigation, PC, GT and CB; writing—original draft preparation, RC and MatM; writing—review and editing, RC, MarM, FB, GT, MatM, GP and PC. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study design complied with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from each patient upon hospital admission. The study was approved by the Institutional Bioethical Review Board of the University of Perugia (protocol n. 385797) and the Review Board of the Italian Society of Research in Surgery (n. 0021/2024).

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Conflict of Interest

The authors declare no conflict of interest. Piero Covarelli and Roberto Cirocchi are serving as the Guest editor of this journal. Roberto Cirocchi is serving as one of the Editorial Board of this journal. We declare that Piero Covarelli and Roberto Cirocchi had no involvement in the peer review of this article and have no access to information regarding its peer review.

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