Seminars in Oncology 46 (2019) 173–191

Contents lists available at ScienceDirect

Seminars in Oncology

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

Electrochemotherapy of superficial tumors – Current status: Basic principles, operating procedures, shared indications, and emerging applications

Luca G. Campana[a,b,*], Damijan Miklavčič[c], Giulia Bertino[d], Roberto Marconato[e], Sara Valpione[f], Ilaria Imarisio[g], Maria Vittoria Dieci[b,h], Elisa Granziera[i], Maja Cemazar[j], Mauro Alaibac[k], Gregor Sersa[j]

[a] Department of Surgery Oncology and Gastroenterology (DISCOG), University of Padua, Italy
[b] Surgical Oncology, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy
[c] University of Ljubljana, Faculty of Electrical Engineering, Ljubljana, Slovenia
[d] Department of Otolaryngology Head Neck Surgery, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy
[e] University of Padua School of Surgery, Padua, Italy
[f] Christie NHS Foundation Trust, Manchester, UK
[g] Medical Oncology Unit, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy
[h] Medical Oncology-2, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy
[i] Anesthesiology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy
[j] Department of Experimental Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[k] Dermatology, Department of Medicine, University of Padua, Padua, Italy

ARTICLE INFO

Article history:
Received 7 October 2018
Revised 19 April 2019
Accepted 24 April 2019

Keywords:
Electrochemotherapy
Bleomycin
Melanoma
Breast cancer
Skin cancer
Head and neck cancer

ABSTRACT

Treatment of superficial tumors with electrochemotherapy (ECT) has shown a steep rise over the past decade and indications range from skin cancers to locally advanced or metastatic neoplasms. Based on reversible electroporation, which is a physical method to achieve transient tumor cell membrane permeabilization by means of short electric pulses, ECT increases cellular uptake of bleomycin and cisplatin and their cytotoxicity by 8,000- and 80-fold, respectively. Standard operating procedures were established in 2006 and updated in 2018. Ease of administration, patient tolerability, efficacy across histotypes, and repeatability are peculiar advantages, which make *standard* ECT (ie, ECT using fixed-geometry electrodes) a reliable option for controlling superficial tumor growth locally and preventing their morbidity. Consolidated indications include superficial metastatic melanoma, breast cancer, head and neck skin tumors, nonmelanoma skin cancers, and Kaposi sarcoma. In well-selected patients with oropharyngeal cancers, ECT ensures appreciable symptom control. Emerging applications include skin metastases from visceral or hematological malignancies, vulvar cancer, and some noncancerous skin lesions (keloids and capillary vascular malformations). Repeatability and integration with other oncologic therapies allow for consolidation of response and sustained tumor control. In this review, we present the basic principles of ECT, recently updated operating procedures, anesthesiological management, and provide a synthesis of the efficacy of *standard* ECT across histotypes.

Introduction

Solid tumors present several barriers to targeted delivery of drugs [1,2]. Reversible electroporation (EP) has been developed to achieve transient permeabilization of the cell membrane by means of short electric pulses, thus increasing intracellular uptake of some chemotherapeutics [3]. Using reversible EP, electrochemotherapy (ECT) has been adopted in surgical oncology to treat superficial tumors not amenable to resection [4-7]. After extensive development, the procedure entered the clinic in 2006, when the European Standard Operating Procedures of ECT (ESOPE)

Abbreviations: BCC, basal cell carcinoma; BLM, bleomycin; CDDP, cisplatin; CR, complete response; ECT, electrochemotherapy; EP, electroporation; ESOPE, European Standard Operating Procedures of Electrochemotherapy; GET, gene electro transfer; HR, hormone receptor; IRE, irreversible electroporation; i.t., intratumoral; i.v., intravenous; LDFS, local disease-free survival; LPFS, local progression-free survival; MDT, multidisciplinary team; OR, overall response; PR, partial response; ROS, reactive oxygen species; SCC, squamous cell carcinoma; Standard ECT, fixed electrode-geometry electrochemotherapy; VG-ECT, (long-needle) variable electrode-geometry electrochemotherapy.

* Corresponding author. Surgery Oncology and Gastroenterology University of Padova 83–85 Old Lansdowne Road, Manchester M202NZ, UK.
E-mail address: luca.giovanni.campana@gmail.com (L.G. Campana).

https://doi.org/10.1053/j.seminoncol.2019.04.002
0093-7754/

were released [8]. Based on ESOPE, ECT application has shown a steep rise, mainly in Europe, and large multicenter studies have demonstrated its efficacy, tolerability, and high levels of patient satisfaction [9-12]. Key aspects favoring its broad acceptance are the simplicity and versatility of the procedure. In fact, *standard* ECT (ie, ECT applied by means of fixed-geometry electrodes) represents an easy-to-master procedure, and is based on a flexible technology, which allows treating a variety of cancers. Interestingly, recent technological advances are opening new avenues for ECT application. For instance, the development of long, freely placeable needle electrodes has enabled targeting deep-seated malignancies (*long-needle variable electrode-geometry* ECT) [13], while *endoscopic* ECT is gleaming into the clinic to palliate gastrointestinal tumors [14]. Herein, we provide an update on *standard* ECT for superficial tumors, which includes the basic principles, recently updated operating procedures, along with expert-based recommendations on patient management. Finally, we synthetize the results of published studies and discuss the role of ECT within cancer-specific algorithms.

Electroporation

EP is a phenomenon occurring at the cell membrane, due to its exposure to high electric fields. Although the underlying physical and chemical processes are not yet completely elucidated, the phenomenon is general and reproducible [3,15–21]. High electric fields leads to a reorientation of water molecules at the water-lipid interface and induces the formation of aqueous pores, that is, short-lived conductive pathways for water, ions, and molecules, which otherwise are deprived of transport mechanisms [3]. Recently, it was demonstrated that also lipid peroxidation contributes to membrane permeabilization [22,23]. EP was devised in the early 1980s as a DNA delivery system and was then translated in the clinic as the basis of ECT [15,24,25].

Reversible EP

The goal of reversible EP in ECT is to provide voltage pulses of sufficient strength and duration to create transient membrane permeabilization, thus allowing the passage and accumulation of chemotherapy, while preserving cell viability [26]. Electric pulses usually include 8 squared-waved pulses of 100 µs duration, with amplitude of 100–1000 Volts (V), depending on the distance between the electrodes and their shape (voltage-to-distance ratio 1,300 V/cm), and a pulse repetition frequency of 5,000 Hz (the high frequency allows delivering the 8 pulses in just 1.5 ms, thus producing a single twitch). Reversible EP is also used in gene electro transfer [15,26,27]. Contrary to ECT, gene electro transfer is still investigational [28–32], the most promising strategies being EP-based DNA vaccination and cytokine therapy [33–36].

Irreversible EP

Irreversible EP (IRE), involves solely the administration of high-voltage electric pulses (no coadministration of chemotherapy) to induce cell death by irrecoverable disruption of the cell membrane and lethal biochemical imbalance [37,38]. In IRE, higher number of pulses (at least 80–100) and amplitude (up to 3,000 V, currents up to 50 A) are used, thus invariably requiring general anesthesia and neuromuscular block. IRE holds promise for ablation of intra-abdominal malignancies [39–42], and cardiac catheter ablation [43,44].

ECT mechanisms of action

Three mechanisms of action appear biologically important in determining the antitumor effect of ECT (Fig. 1). The first mechanism is a direct cytotoxic effect exerted by enhancing the delivery of chemotherapy to the tumor cells. This implies that for ECT to be effective, there must be a sufficient drug concentration in the tumor interstitium as well as the simultaneous coverage of the target lesion with electric fields [45,46]. The second mechanism is a multifaceted antivascular effect [47], which includes an immediate local vasoconstrictive response (“vascular lock effect”), due to a stimulation of the sympathetic nervous system and precapillary sphincters [48], and a delayed antivascular effect (“vascular disrupting action”), which is produced by the selective killing of tumor vasculature [48,49]. Lasting several hours, the “vascular lock effect” effect is much more durable in neoplastic than in normal tissues, and, by reducing blood washout, increases tumor exposure to chemotherapy. The antivascular effect has been observed on vessels smaller than 5 mm [49,50], and can be exploited to palliate bleeding tumors [51,52]. The third mechanism involves immune stimulation. In fact, ECT with either bleomycin (BLM) or cisplatin (CDDP), leads to an immunogenic cell death and the release of damage-associated molecular patterns molecules [53–56], which in turn can induce a strong priming of cancer immunity locally [33,57,58] and counteract tumor escape mechanisms [59,60]. On this basis, ECT may convert the tumor into an “in situ” vaccine, and the combination with appropriate stimulating agents awaits investigation. [61,62]. Preliminary immunohistochemical studies on melanoma metastases treated by ECT observed a rich inflammatory infiltrate including activated dendritic and T-cytotoxic CD3/CD8-positive cells [63–65]. Developing clinical experience suggests a combination of ECT with checkpoint inhibitors is feasible and safe of [66–69].

Chemotherapy

Based on extensive preclinical screening, BLM and CDDP are the most active agents with EP [70–78].

Bleomycin

BLM’s mechanism of action depends on its intracellular concentration [77,79]. When only a few 100 molecules are internalized, cells display G2-M arrest (*slow mitotic cell death*), making tissues with high cell turnover much more vulnerable than normal tissues [80,81]. Conversely, at higher concentrations (ie, millions of molecules), BLM acts as an endonuclease and leads to cellular *apoptosis* [82,83]. Additionally, it produces reactive oxygen species, which damage DNA [84–86]. BLM elimination takes place by renal excretion (45–70% in the first 24 hours), while a minor fraction is metabolized by BLM hydrolase, which is deficient in lung and skin [87–89]. Following a bolus injection, the mean plasma terminal half-life in subjects with normal creatinine is 3–4 hours [87]. In ECT, BLM can be administered intravenously or intratumorally [8,90]. Patients with few, small tumors can receive intratumoral (i.t.) injections [5,90,91] (Table 1); other patients require intravenous (i.v.) bolus infusion of 15,000 IU/m^2. Recent pharmacokinetic studies indicate a slow elimination rate in elderly patients and support a reduction of dosages or, alternatively, an extension of the therapeutic window for pulse application, while preserving treatment efficacy [92–94]. BLM is the preferred drug in ECT because of its favorable toxicity profile. However, clinicians should be cognizant of possible side effects, which are not specific to ECT, to inform patients and manage toxicity promptly. Allergic reactions with fever, hypotension, and wheezing occur in less than 1% of cases, after the first or the second administration. Common constitutional symptoms include chills and mild febrile reactions, which can be easily prevented by steroids or antipyretics [11,95–97]. Delayed toxicity includes cutaneous, mucosal, and pulmonary side effects. While skin toxicity is common – occurring in up to

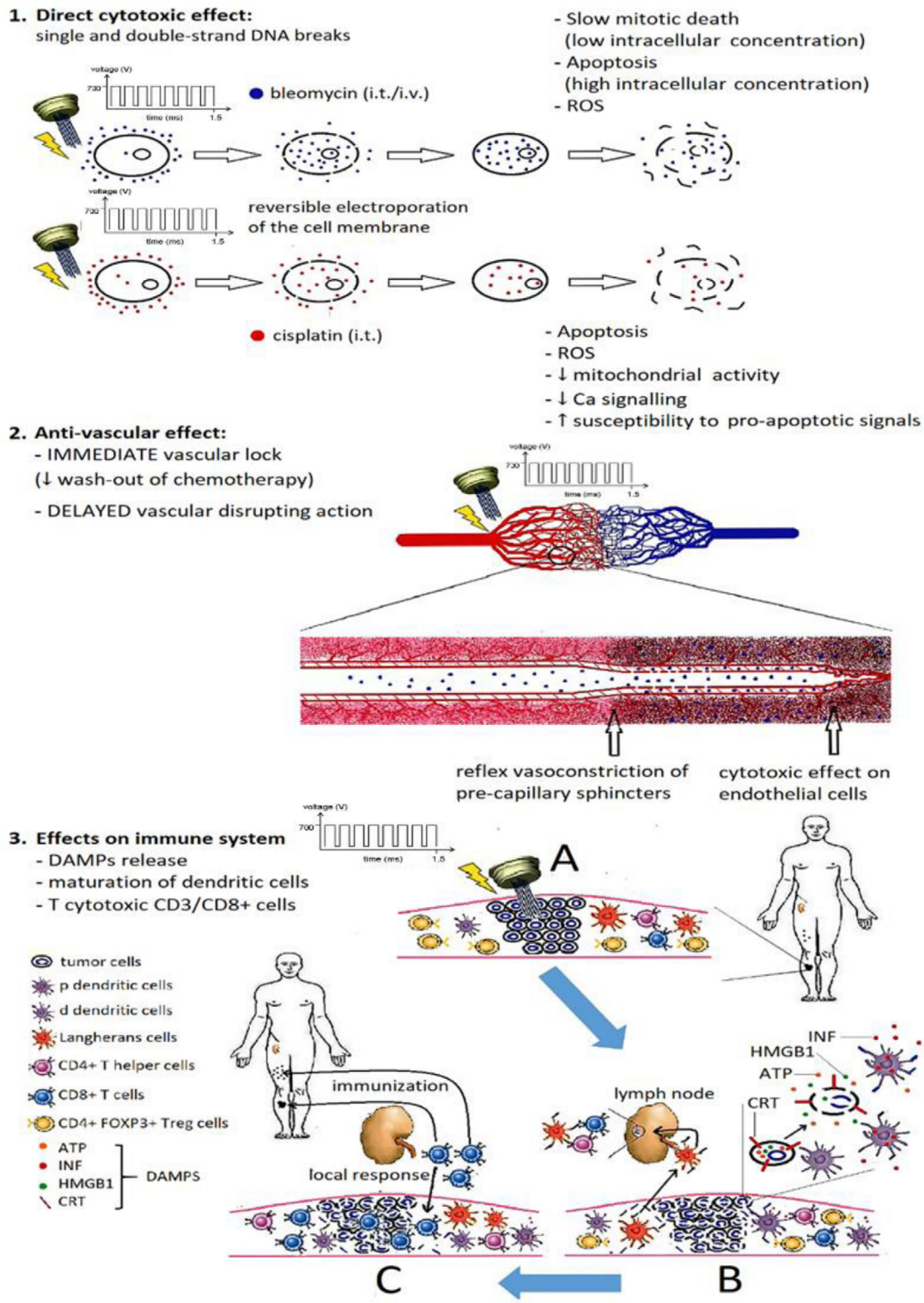

Fig. 1. Mechanisms of action of electrochemotherapy. (1) Direct cytotoxic effect exerted by drug molecules accumulated into cells. (2) Antivascular action. It includes an immediate vasoconstrictive effect and a delayed cytotoxic effect on endothelial cells. (3) Effect on tumor microenvironment (based on immunohistochemical studies in melanoma patients) with activation of the antigen presenting cells and T lymphocytes. (3a) The immune system is locally downregulated due to tumor-derived immunosuppressive cytokines (TGF-β, IL-10), which recruit Treg lymphocytes [60,272]. Langerhans cells are quiescent, but well represented in the epidermis and partially intermingled with tumor cells; dermal dendritic cells are low [63]. (3b) Electrochemotherapy produces cell death partly through necrosis and partly through immunogenic cell death, a peculiar type of apoptosis characterized by release of ATP, translocation of calreticulin (CRT) on the cell membrane, and release of highly mobility group box 1 (HMGB1) protein [33,57,65]. ATP molecules act as a "find me" signal for dendritic cells, leading to their maturation and secretion of IL-1β [54]. CRT represents an "eat me" signal [55], while HMGB1 protein promotes the release of proinflammatory cytokines (IL-1, IL-6, and IL-8) and the process of antigen presentation [53,56]. Both dermal and plasmacytoid dendritic cells increase during the first 2 weeks after treatment [63]. Plasmacytoid dendritic cells have a controversial role in cancer immunology, producing both inflammatory cytokines (type I IFN), which inhibit Tregs, and tolerogenic molecules (indoleamine 2-3 dioxygenase, IDO) [59]. Shortly after ECT application, Langerhans cells become CD83+ (marker of dendritic cells maturation) and CCR7+ (marker of migration to the lymph nodes) and migrate to the lymph nodes where they activate CD8+ T cells. (3c) Two weeks after ECT, Treg cells are still low, while CD8+ T cells are significantly increased in the dermis around tumor. At the same time, CRT expression on cell surface becomes gradually weaker and Langerhans cells start repopulating the epidermal surface, while dermal and plasmacytoid dendritic cells are still represented [63,65].

Table 1
Treatment modalities of *standard* ECT (adapted from Mir et al, Eur J Cancer Suppl. 2016, and Gehl et al Acta Oncol 2018 [8,90]).

Treatment modality	Type of anaesthesia	Route of chemotherapy administration[1]
"A"	local[2]	Intratumoral[3]
"B"		intravenous[4]
"C"	sedation[5]	Intratumoral[3]
"D"		intravenous[4]

[1] The route of administration depends on the number and size of tumors as well as on patient's features (lung and kidney function) and previous administration of systemic bleomycin (the maximum cumulative dose of bleomycin in patients under 60 is 400 x 10^3 IU)

[2] Lidocaine 2% with epinephrine 0.5%

[3] Patients with ≤7 tumors, each <3 cm in size can be managed by intratumoral injection of either bleomycin or cisplatin. Drug dose depends on tumor volume, calculated with the formula $V = ab^2\pi/6$ (where "a" is the largest tumor diameter and "b" the diameter perpendicular to "a").

BLEOMYCIN [BLM]: The concentration of bleomycin solution is 1,000 IU/ml and the dose ranges according to the estimated tumor volume:

- 1 ml (1,000 IU)/cm^3 for tumors <0.5 cm^3
- 0.5 ml (500 IU)/cm^3 for tumors >0.5 cm^3 and <1 cm^3
- 0.25 ml (250 IU)/cm^3 for tumors >1 cm^3

CISPLATIN [CDDP]: The concentration of cisplatin solution is 2 mg/ml and the dose varies according to the estimated tumor volume:

- 1 ml (2 mg)/cm^3 for tumors <0.5 cm^3
- 0.5 ml (1 mg) /cm^3 for tumors >0.5 cm^3 and <1 cm^3
- 0.25 ml (0.5 mg)/cm^3 for tumors >1 cm^3

[4] According to the Standard Operating Procedures, the intravenous route has been codified only for bleomycin (the standard dose is 15,000 IU/m^2 of body surface area)

[5] Sedation and analgesia

- Sedation: (a) propofol (bolus, 0.5 mg/kg, followed by 2-4 mg/kg/h); (b) midazolam (1-3 mg ev over 2-3 minutes; starting dose 0.03 mg/kg to a maximum total dose of up to 0.05 mg/kg when used with opioid; the dose can be elevated up to 0.1 mg/kg when used alone)
- Analgesia: (a) remifentanil (bolus, 0.5 μg/kg, followed by 0.1-0.15 μg/kg/min adjusted to patient response, or target controlled infusion (target, 2-4 ng/ml); (b) fentanyl (bolus 50-100 μg, followed by 0.7-1.4 μg/kg); weight-based dose: 0.7-1.4 μg/kg (c) a combination of an opioid and a non-opioid drugs i.e. fentanyl (b) + ketamine at sub-hypnotic doses (<1 mg/kg)

50% of patients even after a single i.t. administration – lung toxicity is associated with i.v. infusion and high cumulative dosages. Hyperpigmentation is the most salient skin finding (Suppl. Figure 1), followed by pruritus, hyperkeratosis, rash, vesicles, nail dystrophy, and transient alopecia, which are mild to moderate [98]. "Flagellate" erythema, Raynaud's phenomenon, eccrine hidradenitis, and exanthematous pustulosis have been occasionally reported [89,98]. Mucosal side effects include stomatitis, mucositis, and ulceration, generally following the administration of 150,000–200,000 IU. In very rare cases, patients may develop, sometimes unpredictably, interstitial pneumonia, which ultimately can evolve to lung fibrosis. Cough, dyspnea, and inspiratory dry rales can be the only clinical clues of this life-threatening condition, usually associated with parenchymal infiltrates on radiographic examinations [98,99]. BLM should be administered with caution in elderly patients with compromised pulmonary or renal function, previous chest irradiation, or when the maximum cumulative dose (400,000 IU in patients <60 years; 200,000–300,000 in patients of 60–69 years; 150,000–200,000 in patients 70–79 years; 100,000 in patients older than 80 years) has been reached [99,100]. Lung fibrosis may be caused by an overexpression of transforming growth factor-beta and other fibrogenic cytokines by alveolar macrophages, fibroblasts, and endothelial cells [98,99].

Cisplatin

The mechanism of action of CDDP is multifaceted [101,102]. Besides forming intra- and interstrand cross-links within DNA, which prevent repair mechanisms and lead to *apoptosis* [103–105], additional mechanisms include generation of reactive oxygen species, increased susceptibility to pro-apoptotic signals, and interference with mitochondrial activity and calcium signaling [106]. CDDP is cleared by glomerular filtration and tubular secretion [107]. According to ESOPE, CDDP is administered only intratumorally (Table 1) [8,87], and its activity is increased 80-fold when combined with EP [108,109]. Literature regarding CDDP toxicity mainly refers to standard chemotherapy regimens, with kidney, nervous system, gastrointestinal tract, and bone marrow as the principal organs affected [110]. However, i.t. administration makes these toxicities negligible in ECT patients. At standard systemic doses, dermal

exposure (due to extravasation) can result in skin irritation, allergic reactions, and burns [111]. However, in previous ECT studies where CDDP was administered intratumorally, the patients reported only transient local pain, erythema, and edema, and no other toxicities were observed using doses up to 2 mg per tumor nodule [109,112].

The ESOPE study

The ESOPE project, which was funded by the European Commission (Project ID: QLK3-2002-02003), led to several major advances in ECT, including the development of an EU-certified pulse generator, the introduction of a standardized EP protocol, and the conduction of the first multicenter trial [12,113]. The latter enrolled patients (n = 61) with cutaneous metastases smaller than 3 cm of various histotypes. All were included in the toxicity analysis, but only 41 (171 tumors) were evaluable for efficacy. Overall response (OR) rate was 84.8%, with a complete response (CR) rate of 73.7%. Local disease control at 150 days was equally high, irrespective of drug and route of administration (88.2%, 75.4%, and 73.1% with i.v. BLM, i.t. CDDP, and i.t. BLM, respectively, $P = 0.09$). In tumors larger than 0.5 cm^3, i.v. BLM was more effective than i.t. BLM. The treatment was well tolerated, and 93% of patients stated that they would undergo another ECT session, if required.

Standard operating procedures

Standardization of the procedure represented a landmark in clinical ECT and allowed for confirmation of the results of the ESOPE study on a large scale. The standard operating procedures have been recently updated and offer general guidelines concerning patient selection, chemotherapy administration, anesthesia, electrode selection, and post-treatment care [8,90]. Briefly, ECT can be delivered according to 4 *treatment modalities*, based on type of anesthesia and route of chemotherapy administration (Tables 1 and 2). In the most frequently applied modality (ie, general anesthesia/sedation and i.v. BLM), when the patient is properly anesthetized, a bolus of BLM is followed, after 8 minutes, by the application of electric pulses over a 40-minute interval [92–94]. At present, there is no supporting information as to the optimal number of ECT sessions and interval between them. It is not rare that patients with locally advanced tumors undergo up to 6–7 treatment sessions during their disease course [95,97,114,115]. However, given their heterogeneity, treatment strategy should be individualized and guided by response to the first ECT, patient tolerance, and optimal combination with other therapies [116]. Since the resolution of treated tumors is generally slow (ie, 1–2 months, depending on tumor size and histotype), an interval of at least 4 weeks between ECT applications is advisable.

Anesthesiology management

The role of the anesthesiologist is key to ensuring patient safety and quality of life. In fact, over the last decade, ECT has been progressively applied to larger and more widespread tumors than in early investigational studies (Suppl. Figure 2) [117]. Moreover, real-world patients may present with comorbidities, chronic pain, and toxicities from previous therapies [12,118,119]. Decisions regarding the use of ECT should begin with discussions in a multidisciplinary team (MDT) meeting. Then, procedural risk should be quantified, and preoperative investigations should be focused on airways, lung, heart, and kidney function [90]. The presence of a cardiac pacemaker does not necessarily preclude treatment [90,120]. Collective experience has led to the recognition that achievement of optimal pain control before ECT is crucial [117]. The intraoperative management depends on disease extent and anatomical location, along with electrode type. Options include local anesthesia, analgosedation, or general anesthesia. The latter is best suited for some tumors of the face, scalp and oropharynx to ensure patient comfort and maintain airway control [121,122]. To avoid BLM-induced lung injury, FiO_2 should be maintained lower than 30%, and oxygen administration should not exceed 2L/min [90]. ECT can be safely performed under Monitored Anesthesia Care in most cases [11,95,114,115,119,123]. In this management protocol, spontaneous ventilation is maintained throughout the procedure and the level of sedation is continuously adapted according to patient feedback; analgesia is provided through neuroaxial (e.g. spinal) or regional (e.g. peripheral block) anesthesia, and a drug with amnestic properties (propofol or midazolam) is also administered (Table 1). More robust analgesia can be provided with remifentanil or fentanyl, or a combination of an opioid and a non-opioid drug. In particular, ketamine at sub-hypnotic doses (<1 mg/kg, to avoid the risk of postoperative delirium) may reduce opioid requirement and postoperative nausea and vomiting [124]. A promising management modality is tumescent local anesthesia, which implies the infiltration of a large volume of diluted anesthetics in the subcutaneous tissue [125]. In a proof-of-principle study, the mean extension of treated skin was 126 cm^2 and the patients reported adequate pain control up to 24 hours after ECT. Postoperatively, multimodal analgesia may occasionally be required.

Management of local toxicity

According to a recent meta-analysis, ECT is associated with a 6% incidence of G3 toxicity, which is in line with other skin-directed therapies [9]. In the largest clinical study (n = 376 patients), the incidence of G3 skin toxicity (ie, erythema, ulceration, and hyperpigmentation) was 7.8% [11]. In other major series, relevant dermatological toxicity ranged from 0% to 18%, and was manageable on an outpatient basis [95,96,122,126]. In case of skin ulceration, tissue healing takes place by secondary intention over 6–10 weeks, depending on tumor size, tumor response, and concomitant oncologic therapies [127]. In these cases, superinfection may occur [128]. When treating ulcerated or fungating neoplastic wounds, the involvement of a dedicated nurse team is advisable, together with a cancer pain service [129]. Generally, during the inflammatory phase, treated skin should be covered with nonadherent, comfortable dressings, whereas ulcerated lesions are best managed by means of advanced wound dressings including alginates, charcoal, and silver. Tissue necrosis can be managed by enzymatic and/or surgical debridement to avoid superinfection and promote healing [90].

Shared indications

ECT has been recognized as a safe and effective option by several cancer-specific guidelines (Table 3) [130-141]. Nonetheless, timing of their use and positioning within management algorithms remain elusive, due to heterogeneity of published series [11,128] and lack of randomized trials. However, recent studies are focusing on more homogeneous populations, while investigating ECT in a real-world context (ie, as a complementary therapy), and, importantly, are also evaluating patient-reported outcomes [66,68,69,116,128,142]. An effort to increase the quality of the ECT literature has been made through specific recommendations and a dedicated checklist designed to assist investigators [143].

Melanoma

Recognition of the varied manifestations of superficially recurrent melanoma may aid in early treatment application [144]. In-transit limb disease represents a common indication for ECT. With

Table 2
Fixed-geometry electrodes used in *standard* electrochemotherapy.

Contact electrodes		
Plate electrodes[a]		**Indications:** Treatment of superficial, exophytic (epidermal) tumors
		Limitations / drawbacks: Requires a conductive gel applied to the electrodes/skin beneath the electrodes to improve the electrical contact and facilitate pulse delivery
Needle electrodes		
Finger electrodes[b]		**Indications:** Treatment of tumors very small in size or difficult to access with standard electrodes due to peculiar anatomical location (i.e. oropharynx, vagina, anal canal)
		Limitations / drawbacks: Limited needle length; not always optimal maneuverability and visibility when used in narrow spaces
Linear needle electrodes[c]		**Indications:** Treatment of small tumors, cutaneous or subcutaneous
		Limitations / drawbacks: Limited treatment area per application. Stiffness decreases with increasing needle length.
Hexagonal needle electrodes[d]		**Indications:** Safe and targeted treatment of patients with heterogeneous metastases (as to thickness and depth)
		Limitations / drawbacks: Delivers high voltage pulses and requires deeper patient sedation. Stiffness decreases with increasing needle length.
Adjustable length hexagonal needle electrodes[e]		**Indications:** Treatment of widespread, deep-seated or large tumors
		Limitations / drawbacks: More expensive than other electrodes

[a] Spacing between plaques: 8 mm.
[b] available needle length: 0.5 cm; 1 cm.
[c] available needle length: 1, 2 and 3 cm.
[d] available needle length: 1, 2 and 3 cm.
[e] available both in linear and hexagonal configuration. Adjustable needle length in 5 mm increments from 0.5 to 3 cm active part. Also available with maximum needle length of 4 cm with distal 2 cm active part.

- The electrodes used in *standard* ECT have different configurations and sizes, but are characterized by a fixed geometry. The applied pulses have specific-to-electrode, fixed parameters (i.e., number, duration, voltage, and pulse repetition frequency). There are two kind of fixed-geometry electrodes, i.e. contact (plate) and needle electrodes. All the electrodes used in *standard* ECT have an array of fixed size and geometry, while the length of the needles can range between 5 and 30 mm.
- The plate electrodes are placed just over the tumor so that the tumor itself is contained between the two plates. When treating tumors larger than the distance between electrode plates, the tumor has to be covered by means of multiple, juxtaposed electrode placements. As a consequence, the plate electrodes are best suited for superficial, exophytic tumors, and the operator should have care to achieve a close contact between the electrode plates and the tumor/skin by means of a conductive gel. Conversely, the needle electrodes, instead, are inserted percutaneously (although they can be used also in other settings, e.g. intraoperatively, during a laparotomy procedure, to treat intra-abdominal tumors [271], or to treat oropharyngeal cancers.
- In order to achieve effective drug delivery into tumor cell and for ECT to be effective, it is crucial to cover the whole target volume with sufficiently high electric fields. This can be obtained when the tumor is covered by a sufficiently high electric field and current, as can be checked on the display of the pulse generator during the procedure [45]. During the procedure, after each pulse delivery, the operator has the unique opportunity to control the actual electric field and current. When these parameters are excessively low, another pulse application can be delivered or the electrode can be replaced and, when feasible, inserted more deeply into tumor tissue [8] (Mir 2006).
- The choice of electrode type is an important aspect of the procedure, since it may have an influence on anesthesiology management. In fact, while patients treated by means of the finger or linear array electrodes can be easily managed under local anesthesia or mild sedation; those treated with hexagonal array electrodes more often require stronger analgosedation or general anesthesia. Additionally, in patients with scattered superficial metastases, also the extension of the involved skin can impact on anesthesiology management. For instance, in selected patients with widespread tissue infiltration (e.g. those with chest wall recurrence from breast cancer or head and neck tumors), general anesthesia may be required in order to achieve optimal pain control.

Ref. [271] cited in this table.

the advent of targeted and novel immune therapies, prolonged survival is being achieved and new patterns of disease have emerged [145]. Thus, ECT is increasingly applied not only as a locoregional, but also as a complementary therapy, to precisely target superficial metastases, that can often be resistant to systemic treatment [95–97,146]. Historically, several ECT studies included melanoma patients [75,147], and since the publication of the 2006 ESOPE guidelines 9 case series have been published [11,95–97,122,148–151] (Table 4). CR rates range between 20% and 50%. In well-selected cases, ECT has allowed for the management of metastases in challenging anatomical locations such as the face [152], oral cavity [114], and perianal region [146], thus sparing patients from mutilating surgery. Interestingly, ECT can be combined with surgical resection, with either a neoadjuvant or adjuvant intent [152], and the 2018 ESOPE guidelines introduced the option of debulking surgery followed by ECT within the same procedure [90]. Patient-reported outcomes were preliminarily investigated in 36 patients who reported a positive impact on wound healing, bleeding, aesthetics, activities of daily living, social relations, or pain in the short term [114]. These findings were subsequently confirmed in 211 patients by the EORTC QLQ-C30 questionnaire [11].

Breast cncer

Breast cancer metastases have an exceptional propensity to localize to the skin (relative incidence, 24%), and this can result in

Table 3
Clinical guidelines supporting the use of electrochemotherapy.

Tumor	Guideline	Reference
Melanoma	ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Dummer, 2015 [132]
	Revised U.K. guidelines for the management of cutaneous melanoma 2010	Marsden, 2010 [138]
	Electrochemotherapy for metastases in the skin from tumors of non-skin origin and melanoma	NICE Interventional procedures guidance [IPG] 446, March 2013 https://www.nice.org.uk/guidance/ipg446
	Malignant Melanoma S3-Guideline "diagnosis, therapy and follow-up of melanoma"	Pflugfelder, 2013 [140]
	Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – update 2012	Garbe, 2016 [133]
	Melanoma guidelines of the Italian Society of Medical Oncology	http://www.aiom.it/professionisti/documenti%2Dscientifici/linee%2dguida/1,413,1,
Squamous cell carcinoma	Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline.	Stratigos, 2015 [141]
	Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines	Mellerio, 2015 [139]
	Electrochemotherapy for primary squamous cell carcinoma	NICE Interventional procedures guidance [IPG] 478, February 2014 https://www.nice.org.uk/guidance/ipg478
Breast cancer	AGO recommendations for diagnosis and treatment of patients with advanced and metastatic breast cancer: update 2013	Harbeck, 2013 [136]
Merkel cell carcinoma	Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline.	Lebbe, 2015 [137]
Basal cell carcinoma	Electrochemotherapy for primary basal cell carcinoma	NICE Interventional procedures guidance [IPG] 478, February 2014 https://www.nice.org.uk/guidance/ipg478
Soft tissue sarcomas	UK guidelines for the management of soft tissue sarcomas	Dangoor, 2016 [131]
Bone metastases	Algoritmo terapeutico per il trattamento delle metastasi del sacro. Raccomandazioni del Gruppo di Studio SIOT sulle metastasi ossee (article in Italian)	Capanna, 2016 [130]
	Management of patients with metastasis to the vertebrae: recommendations from the Italian Orthopaedic Society (SIOT) Bone Metastasis Study Group	Gasbarrini, 2014 [135]

Table 4
Efficacy and safety of electrochemotherapy in metastatic melanoma.

Author (year)	No of pts	Follow-up (mo)	Response (first ECT)	Additional ECT cycles (% of pts)	Tumor control (LPFS)	Toxicity (CTCAE)
Kunte (2017)	151	4	CR: 48%[1] PR: 25%	18	6-mo: 86%	- Pain, various grades: 39% - G3 skin ulceration: 1.3% - G1/2 lymphedema: 3%
Campana (2016)	211	13.9	CR: 54%[1] PR: 30%	24	1-yr: 70% 3-yr: 39%	- Skin toxicity G2-4: 25% - Axillary neuropathy: n = 1[2]
Bertino (2016)	10	12	CR: 55%[1,3] PR: 22% SD: 11% PD: 11%	18	1-yr: 56%	Not reported
Mir-Bonafè (2015)	31	12	CR: 23% PR+SD: 49% PD: 28%	77	1-yr: 55%	- Pain, edema, mild erythema (<48 h): 100% - Ulceration: 26% - Nausea and vomiting - One patient dead for respiratory failure[4]
Ricotti (2014)	30	20	CR: 20% PR: 80%	Not reported	2-yr: 72%	Not reported
Caracò (2013)	60	27.5	CR: 48.4% PR: 38.3%	43	2-yr:21%	- Mild pain: 36.6% - Myalgia: 13.3%
Campana (2012)	85	26	CR: 48%[1] PR: 46% SD: 4% PD: 2%	75	2-yr: 87%	- Pain G1-2: 92% - G3 Cutaneous toxicity: 18% - G1/2 Nausea/vomiting: 13% - G2 Bradycardia: 1 patient - G1/2 Fever: 4.7%
Kis (2011)	9	6.5	CR: 23%[5] PR: 39% SD: 30% PD: 8%	Not reported	Not reported	Pain, erythema, mild edema (lasting <48 h)
Quaglino (2008)	14	21	CR 50% PR 43%	100	2-yr: 74.5%	Mild erythema and edema (<72 h): 21%

Abbreviations: LPFS = local progression free-survival; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; LDFI = local disease-free interval.

[1] Response assessed with RECIST criteria.

[2] The patient reported paresthesia and pain in her upper extremity and weakness of shoulder abduction, which lasted 6 mo and required treatment with opioids, pregabalin and tricyclic antidepressants.

[3] Per-tumor response in 9 metastases.

[4] Patient with previous pulmonary fibrosis, treated with intravenous bleomycin.

[5] Per-tumor response in 158 metastases.

Table 5
Efficacy and safety of electrochemotherapy in superficially recurrent breast cancer.

Author (year)	No of pts	Follow-up (mo)	Response (first ECT)	Additional ECT cycles (% of pts)	Tumor control (LPFS)	Toxicity (CTCAE)
Matthiessen (2018)	119	Not reported	CR: 50%[1] PR: 21%	26	Median LPFS not reached	G1 skin hyperpigmentation: 34.6[2] G1 temporary ulceration: 12.5 severe pain (NRS 5–10): 8.6
Grieschke (2017)	33	36	OR: 90%	27.3	Not reported	G1/2 Injection site reaction: (frequency not reported)
Bourke (2017)	24		CR: 12.5 PR: 33.3	54.2	Not reported	Not reported
Campana (2016)	31	13.9	CR: 37 PR: 52	23.7	Not reported	G1 skin toxicity: 48.4%; G2/3 skin toxicity: 51.6%
Cabula (2015)	125 (113 evaluable)	5.9	CR 58.4 PR 31.8 SD 7.1 PD 1.8 NE 0.9	Not reported	1-yr, 86.2%	- G3 local pain (<48 h): 10.4% - G3 skin ulceration: 8% - G3 skin infection: 0.8 - G2 hyperpigmentation: 8.8%
Campana (2014)	27 (<70 yr) 28 (>70 yr)	32	CR 40 PR 47.3 SD 12.7	Median, 3 cycles Median, 2 cycles	2-yr, 93% 67% (2 yr)	- Pain ≥3[3] (<2 mo): 28% - G3 skin ulceration: 14%
Benevento (2012)	12	7	CR 75.3[4] PR 17 SD 7.7	33	Not reported	- Pain (within 48 h): 8.3% - Ulceration: 8.3%
Campana (2012)	35	32	CR 54.3 PR 37.1 SD 8.6	60	81% (3 yr)	- G2 pain after 1 mo: 6% - G3 skin ulceration: 6% - G2 hyperpigmentation after 2 Months: 20% - G1 urticaria: 3% - G1 alopecia: 8.5% - G1/2 fever: 17% - G1/2 nausea/vomiting: 11%
Matthiessen (2012)	12	2.5	CR 8 PR 8 SD 76 PD 8	42.6	Not reported	- G3 pain: 44% - G2 ulceration: 6% - G1 hyperpigmentation: 19% - G2 nausea: 31%

Abbreviations: ECT = electrochemotherapy; LPFS = local progression-free survival; CTAE = common terminology criteria for adverse events; OR = overall response; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; LPFS = local progression free survival; VAS = visual analogue scale.

*Response "*per tumor*" in 142 nodules.

[1] Tumor response was assessed on 90 evaluable patients.

[2] Toxicity rates are calculated on 104 evaluable patients, based on toxicity data indicated within 45 d after ECT.

[3] Based on a VAS scale ranging from 1 to 10.

[4] Per-tumor response (evaluation of 142 tumor nodules treated at first ECT cycle).

both physical and psychological distress [153]. This can presents a therapeutic dilemma, particularly in women who have been heavily pretreated because surgical resection is rarely indicated, and reirradiation is often not feasible. Aside from the variety of clinical presentations [154], 2 main patterns of disease can be identified. On the one hand, skin involvement can be the hallmark of diffuse metastatic disease [153,155]. In these women, treatment is focused on visceral metastases, nonetheless multimodal strategies should be considered as an opportunity to increase symptom control. In fact, thanks to the increasing pool of effective systemic treatments, survival can now exceed 5 years from the diagnosis of metastatic disease, at least in women whose tumors are either hormone receptor positive or human epidermal growth factor receptor-2 (HER2) positive. The occurrence of such long-term survival introduces the opportunity to integrate locoregional treatments to improve response at critical sites, such as the skin, and these interventions can have an impact on a patient's quality of life. Conversely, cutaneous metastases may appear in the absence of visceral disease. Locoregional recurrence develops in 10–20% of women who underwent breast conserving surgery and radiotherapy [156], and in 3–27% of women after mastectomy [157,158]. Skin recurrences represent 13% of locoregional relapses after breast conserving surgery, and 71% of locoregional relapses after mastectomy [158]. In these patients, local treatment has as its goal tumor eradication.

The published experiences indicates it is possible to achieve high response rates and prolonged local control with ECT (Table 5) [11,115,116,119,142,159-162], and tumor size represents the most reliable predictive parameter [142,160,161,163]. Waiting for future studies, actionable recommendations include the following: the procedure is tolerable by elderly patients [119]; the chance to obtain an effective chest wall control inversely correlates with the scattering of skin metastases [115]; ECT is active in previously irradiated fields, although retreatment may be associated with increased pain and skin toxicity [115]; in this setting, BLM should be used with caution given its known ability to induce radiation recall toxicity, even though this has not emerged as a problem at present. Finally, ECT can be safely combined with systemic chemotherapy [116].

In the multicenter cohort study (n = 125 patients) by the Italian Senologic Group for ECT, the most frequent side effects were pain (G3, 10%) and mild dermatologic reactions (G3 ulceration, 8%) [142]. Perpatient CR rate was 58.4%, with higher rates in women with small (<3 cm), hormone receptor-positive, low-proliferating tumors, which identify the "luminal A-like" subtype according to the St. Gallen classification [164]. Sustained response was observed also in patients with nonulcerated tumors, and no visceral disease. Interestingly, triple-negative and HER2-positive tumors also proved responsive with CR rates of 57.1% and 54.5 %, respectively. Overall, 1-year local progression-free survival (LPFS) was 86.2%. Comparable results were observed in 90 patients from the International network for sharing practices of ECT database [162]. A prospective registry has been activated (ISRCTN study ID: ISRCTN56719146) aiming to identify reliable patient selection criteria. Future

studies will have to clarify whether skin-directed treatment provides a clinically meaningful benefit [165,166].

Head and neck cancer

This group includes malignancies of the upper aero-digestive tract, salivary glands, and skin. The clinical experience with ECT is presented in Table 6 [7,25,75,92,121-123,167-185]. Historically, ECT was initially investigated in patients with skin metastases or skin tumor infiltration from underlying neoplasms ("permeation tumors") [25,75], and subsequently pioneered in mucosal cancers [178]. Approximately, two-thirds of patients with head and neck cancer present with advanced disease and standard treatment has included concurrent chemoradiotherapy with CDDP or immunoradiotherapy with cetuximab [186]. Unfortunately, these regimens often affect a patient's quality of life by altering body appearance, speech, and swallowing. Moreover, local recurrence develops in 10–30% of cases and second primary tumors develop at a rate of 2–3% per annum. In these patients, ECT may represent a low-invasive option with unique advantages in terms of hospitalization, tissue preservation, and costs [170,180,187]. Some have proposed administering ECT with neoadjuvant and/or curative intent in patients with small size cancers of the lower lip, tongue, and palate [173,188]. Treatment of these tumors is challenging, due to anatomic constraints, and possible side effects. For these reasons, concerns about the reproducibility of results and actual clinical benefit were raised [183,189]. However, the most recent experiences confirm the feasibility of the ECT in these patients [123,173,176,185], and prompted the conduct of multi-institutional studies [121,174,175]. It is now evident that careful patient selection, thoughtful treatment application and meticulous anesthesiological management are crucial. A European multicenter study on 43 patients with recurrent mucosal cancers, indicated a 56% OR rate (CR, 19%), with transient mild pain and tissue swelling [121]. Another European collaborative study enrolled 105 patients with cutaneous malignancies of various histotypes and reported a 62% CR rate, with significant improvement of quality of life scores according to the EQ-5D, EORTC-QLQC30, and EORTC QLQ-H&N35 questionnaires [122]. The authors argued that multifocal or locally advanced basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) of the lower lip can be suitable ECT indications when surgery is deemed to not be practical.

Peristomal tumor recurrences represent an investigational indication [180,190]. Although experience is still limited, ECT proved to be effective in maintaining airway patency at the ostomy site [190]. Finally, it was successful in palliating selected patients with skin tumor infiltration from underlying tumors of the parotid [173,176] and thyroid gland [191]. In 3 of 4 patients with metastatic papillary thyroid cancer who were resistant to radioiodine and sorafenib, ECT led to stabilization of local disease until death.

Nonmelanoma skin cancer

Positive treatment results with BCC [11,118,122,192–200] and SCC [122,172,187,201–203] have been reported in several case series (Table 7), while clinical experience in Merkel cell carcinoma [204–206], sebaceous carcinoma [207], and keratoacanthoma is still patchy [11,92,118,122,123,127,177,196,197,208,209]. ECT can be advantageous in patients with multifocal BCC (eg, in Gorlin-Goltz syndrome or Xeroderma Pigmentosum) to reduce the morbidity associated with repetitive surgical excisions [109,197], and several creditable reports are available [109,47,192,193,199,210]. According to a monoinstitutional retrospective experience on 84 frail patients with multifocal, recurrent, or locally advanced BCC, the clearance rate after the first application was 50%, and G3 dermatological toxicity was 6% [118]. In patients with local BCC, the clearance rate was 72.5% and 85% after the first and the second ECT cycle, respectively. Primary tumor presentation, size <3 cm, well-defined borders, absence of ulceration, and nonaggressive histology were significantly associated with tumor clearance. With a median 49.2-month follow-up, local failure was documented in 20.2% of patients. A randomized trial (EudraCT Number: 2010-019260-37) is evaluating treatment durability of surgical excision versus ECT in primary BCC. An interim analysis, based on 86 patients at 3-year follow-up, indicates comparable efficacy (local disease-free survival, 97 and 92%, respectively, P= 0.37) [211].

Soft tissues sarcomas

Clinical experience is sparse [212–222]. However, small tumor size, superficial location, and prominent vascularization make Kaposi's sarcoma an ideal target for ECT, by allowing its antivascular effect to be exploited [47]. A 60%–100% CR rate is invariably reported following a single course of treatment, with mild side effects and prolonged local control (Table 8). These findings prompted researchers to investigate ECT also in angiosarcoma. According to a multicenter retrospective study on 19 patients with locally advanced or metastatic disease (median size of the target lesions, 2 cm), CR was observed in 8 patients and 1-year LPFS was 68%, with a beneficial effect on tumor bleeding [219]. Isolated case reports, where ECT was applied alone or in combination with locoregional chemotherapy, support further investigations [220,223]. A phase II study enrolled 34 patients with recurrent sarcomas of various histotypes (median tumor size, 4 cm) unsuitable for conventional treatments [213]. The OR rate was 92.2% (CR, 32.3%), with no improvement by additional ECT sessions. Two-year LPFS, in patients whose tumors achieved a response was 72.5%. Notably, treatment delivery proved to be critical as indicated by the low (<50%) accuracy of electrode placement and suboptimal electric current in tumor tissue (15% of patients). These findings are likely explained by the large size and inhomogeneity of these neoplasms. Isolated reports highlight the value of ECT as a tissue-sparing option in patients with soft tissue (and bone) sarcomas [212,216,224]. de Bree et al treated a 5-cm subcutaneous recurrence from a malignant peripheral nerve sheath tumor of the scalp with ECT plus i.t. BLM and reported tumor necrosis and a CR by week 10. The patient was tumor free at 17 months. Bonadies et al treated a 2-cm recurrent dermatofibrosarcoma protuberans of the eyebrow. PR was observed at 2 months, followed by further tumor shrinkage and no evidence of recurrence after 3 years.

Emerging applications

Skin metastases from visceral malignancies

Several solid organ and hematologic neoplasms can metastasize to the skin, with an overall incidence of 0.7–10% [225–227]. ECT has been occasionally investigated to palliate patients with lung, gastric, bladder, and kidney cancer [11,191,200,228,229]. However, because the evidence relies on isolated reports, any possible clinical benefit must be carefully evaluated on an individual basis. ECT has been proposed for the management of skin tumor infiltration around an ostomy site, which can occur either in head and neck cancer patients or in those with metastatic abdominal malignancies, posing a palliation challenge [190,228]. In these cases, ECT aims at maintaining airway patency or reducing the adherence of the flange around the ostomy.

Table 6
Clinical experiences with electrochemotherapy in head and neck cancers.

Author (year)	No of pts	Follow-up (mo)	Tumor location (number)	Presentation	Size (mm or T)	Tumor response (first ECT)	Additional ECT cycles (% of pts)	Local control	Toxicity (CTCAE) (number of pts or % of patients)
Pichi (2018)	24[1]	7.6	Skin, Mucosal LN	Recurrent	Not reported	CR: 8% PR: 92%	42	Not reported	Mild pain: 23 Severe pain: 1
Plaschke (2018)	36	2.3	Mucosal	Recurrent	29	CR: 19% PR: 39%	0	Not reported	G4 bleeding: 1 G3 dysphagia: 7[2]
Montuori (2018)	15	1.5	Skin	Primary or recurrent	Not reported	CR: 100%	13	With median follow-up of 12 mo, one "in-field" recurrence	Transient pain, eyelid edema
Groselj (2018)	28	2	Skin	Primary (42 tumors) Recurrent (10 tumors)	17–21[5]	CR: 94–100%	0	Not reported	G3 infection: 1 G3 ulceration: 1[6]
Plaschke (2017)	43	12	Mucosal[3]	recurrent	35[4]	CR: 19% PR: 37% (37/43 evaluable)	0	1-yr, 54%	G1/2 ulceration: 9% G3/4 ulceration: 9%
Bertino (2016)	105	6	Skin	Primary, 53 Recurrent, 52	20	CR rate BCC: 91% SCC: 55% MM: 55% Other: 0%	6	1-yr, 89%	G5 sepsis, G5: 1 G3 ulceration, 5
Rotunno (2016)	55	13	Skin	Primary (20) Recurrent (35)	30	CR: 60%	23	13-mo, 87%	G3 skin pain: 3
Domanico (2015)	4	2	Mucosal	Primary	T3–T4	PR: 3 pts SD: 1 pt.	0	Not reported	Severe local pain 2–12 h after ECT[7]
Landström (2015)	19	58	Mucosal[8]	Primary (19)	T1–T2	Not reported	0	5-yr, 100%[9]	G3 aspiration: 1
Landström (2015)	4	20	Mucosal	Primary	T2	CR: 100%[10]	0	2-yr, 100%	4 SAEs (1.5–8 mo after ECT): Osteoradionecrosis (2), fistula (1), bleeding (1)
Campana (2014)	39	14	Skin (27) Mucosal (12)	Primary (13) Recurrent (26)	35	CR: 38% PR: 21%	39	1-yr, 51% (skin) 1-yr, 59% (mucosal)	G1/2 facial edema:: 5 Prolonged (>2 mo) pain: 2 G3 mucositis: 1 G2 mucosal ulceration: 1
Seccia (2014)	9	8	Skin (6) Mucosal (3)	Persistent (6) Recurrent (3)	58	CR: 4/14 tumors PR: 6/14 tumors	11	2 pts LDF after 5 and 12 mo	Slow healing: >8 weeks in all pts; tissue loss / fistula: 3
Mevio (2012)	15	9	Skin (2) Mucosal (13)	Primary (2) Recurrent (13)	Not reported	CR: 19/31 tumors (61.5%)	40	9-mo LDFS, 29%	Not reported
Gargiulo (2012)	25	18	Skin (17) Mucosal (8[11])	Primary (22) Recurrent (3)	T1-2: 19 T3-4: 6	CR: 72% PR: 28%	20	18-mo LPFS, 100%	Local necrosis and delayed healing: 2 (parotid tumors)
Skarlatos (2011)	17	2	Skin (14) Mucosal (3)	Not reported	Not reported	Skin, CR: 9 Skin PR: 4 Mucosal CR: 2 Mucosal PR: 1	Not reported	4 pts with LA skin tumors had 2-yr LDF interval[12]	Not reported
Larkin (2007)	3	2-12	Skin	Recurrent	<3 cm: 1 ≥3 cm: 2	CR: 2 pts NC: 1 pt.	Not reported	Not reported	Not reported
Tijink (2006)	6	13	Skin (4) Mucosal (2)	Recurrent or metastatic	Not reported	ORR: 100%	Not reported	1-yr per-tumor control, 82.4%	Mild pain: 2 Mild hair loss: 1
Bloom (2005)	54	3	Mucosal	Not reported	Not reported	CR: 17/69 tumors (25%) PR: 22/69 tumors (32%)	Not reported	Not reported	G2 bleeding: 3; G3 bleeding: 1 G5 bleeding: 1 G3 infection: 6 G2 swelling: 1
Burian (2003)	12	10.6	Mucosal	Primary	T1: 3 pts T2: 9 pts	CR: 10 pts[13] PR: 2 pts	0	All pts were LDF at after months	G2 pain: 5 G3 pain:: 2
Allegretti (2001)	14	31.5	Mucosal	Persistent/ recurrent (13)	T1-2: 5 pts T4: 9 pts Tx: 1pt	CR: 6 pts PR: 6 pts	71	Not reported	Poor wound healing, dysphagia and osteomyelitis in pts with LA disease

(*continued on next page*)

Table 6 (*continued*)

Author (year)	No of pts	Follow-up (mo)	Tumor location (number)	Presentation	Size (mm or T)	Tumor response (first ECT)	Additional ECT cycles (% of pts)	Local control	Toxicity (CTCAE) (number of pts or % of patients)
Panje (2000)	2	12- 20	Mucosal	Primary, persistent	20, n.r.	CR: 1 pt. PR. 1 pt.	50	20 and 12 mo	Nasal septum perforation (at the site of septal tumor infiltration): 1
Mir (1998)	17	1	Skin	Recurrent	17.5 (3–125)	CR: 2 pts PR: 4 pts	29	Not reported	Erythema, slight edema. Several patients accepted retreatment for additional lesions
Panje (1998)	10	10	mucosal	Recurrent	T1–T4 Largest tumor, 25 cm^3	CR: 2 pts PR: 3 pts SD: 2 pts	60	Not reported	Nasal septal perforation: 1 Bone exposure: 1
Domenge (1996)	5	Not reported	Skin	Recurrent	22–65	CR: 1 pt. PR: 1 pt. NC: 1 pt. PD: 2 pts	0	Not reported	Sporadic erythema, phlyctenes, epidermal erosions, skin ulceration, leukocytosis
Belehradek (1993)	8	Not reported	Skin	Recurrent	3–55	CR: 4 pts PR: 1 pt. NC. 3 pts	37	The 4 pts with CR were LDF after 26–250 d	Transient erythema and slight edema, 6 pts; skin ulceration, 2 pts

Abbreviations: BCC = basal cell carcinoma; CR = complete response; LA = locally advanced; LDF = local disease-free; LPFS = local progression-free survival; LDFS = local disease-free survival; LN = lymph nodes; MM = malignant melanoma; NC = no change; n.r. = not reported; PD = progressive disease; PR = partial response; SAE = serious adverse event; SCC = squamous cell carcinoma;

[1] Twenty out of 24 patients had SCC.

[2] These patients had baseline G2 dysphagia before ECT.

[3] Oral cavity, n = 32 patients; pharynx/larynx (n = 11 patients).

[4] Tumor margins were adequately covered in 13 out of 43 patients due to anatomical constraints.

[5] This study compared 2 groups of patients: those treated with standard (15,000 IU/m^2) BLM dose (n = 16, median tumor size 17 mm) with those treated with a reduced (10,000 IU/m^2) BLM dose (n = 12, median tumor size 21 mm).

[6] Skin toxicity (≤G3) was observed only in the group who received the standard dose of BLM (15,000 IU7m^2).

[7] Postoperative pain was measured by means of a visual analog scale (VAS) ranging from 0 to 100 and a verbal rating scale (VRS) ranging from 0 to 5.

[8] Oral cavity, n=18 patients; pharynx, n = 1 patient.

[9] Twelve out of 19 patients received adjuvant radiation therapy after ECT.

[10] The patients were treated with i.t. BLM (1,000 IU/cm^3) and tumors were electroporated with a hexagonal array needle electrode with 1-cm tumor-free margin; the applicator was connected to the MedPulser generator which delivered pulses of 0.1 ms and 1,100 V/cm. Three out 4 treated patients received accelerated hyper fractionated radiotherapy after ECT (1.7 Gy twice a day up to a total dose of 57.8 Gy).

[11] Mucosal tumor included the following anatomical locations: lower lip (n = 6), tongue (n = 1), and soft palate (n = 1).

[12] In these four patients, ECT was followed by radiation therapy and further ECT cycles.

[13] Response to treatment was pathologically confirmed in all patients on post-ECT surgical specimens.

Cutaneous metastases from hematologic cancers

Sporadic primary cutaneous T- or B-cell lymphomas (eg, mycosis fungoides and marginal zone lymphoma) have been managed by ECT, with extended disease-free follow-up [190,202,228,230]. More studies will be necessary, however, to draw conclusions. Although interferon-α is not part of the ECT protocol, a single study explored its injection followed by EP in patients with mycosis fungoides with favorable results [231].

Vulvar carcinoma

Vulvar cancer comprises 5% of gynecologic malignancies, and its incidence increases with age [232]. Approximately, one-third of patients presents with locally advanced disease and debilitating symptoms [233], and even following multimodal treatment, recurrence develops in one-third of cases [232,234,235]. Attempts to fully excise the tumor are often difficult given the important surrounding anatomical structures and if surgery cannot provide reasonable functional and cosmetic outcomes, alternative options should be pursued. Despite positive preclinical results [236], ECT has been investigated in humans only recently. Perrone et al initially treated 9 elderly women with recurrent squamous cell vulvar carcinoma with no relevant side effects [237]. One-month CR rate was 62.5%, with significant reduction of pain, bleeding, odor, and urinary discomfort. In a phase II study, the same investigators used i.v. BLM and a fixed-geometry hexagonal needle electrode to treat 25 women with a median tumor size of 4.5 cm^2 [238]. Only minimal blood loss and transient tissue edema were noticed, and all patients were discharged within 24 hours. Thirteen patients (52%) achieved a CR, and 6-month LPFS and symptom-free survival (assessed by the Functional Assessment of Vulvar Cancer Therapy questionnaire) were 53% and 40%, respectively. Another Italian study investigated ECT on 10 highly elderly patients with recurrent disease all of whom had received multiple prior therapies [239]. A CR was achieved in 20%, a PR, in 40, and further ECT cycles led to an objective regression in 8 of 10 patients. After a median 12-month follow-up, there was a single local recurrence. The patients indicated a significant improvement in pain, discharges, and urinary discomfort. Recently, ECT has been investigated also in the neoadjuvant setting. Nine patients with primary vulvar carcinoma underwent ECT followed by surgical resection, after a median of 50 days. A response was observed in 7 patients and allowed for more conservative surgery in 6 of 9 cases, with no detrimental effects on surgical outcomes [240].

Noncancerous skin lesions

Keloid scars are benign fibroproliferative lesions with a propensity for the earlobe, and the presternal and deltoid regions, which are notoriously difficult to treat despite the availability of several treatments (5-year recurrence rate 8%–50%) [241]. Because i.t. BLM is a well-documented agent in keloid treatment, its use with EP awaits investigation [242]. In 2010, Sainsbury et al treated a male patient with a 5×4 cm earlobe scar who previously underwent surgery, steroid therapy, and radiation [243]. Four ECT cycles

Table 7
Efficacy and safety of electrochemotherapy in basal cell carcinoma.

Author (year)	No of pts	Follow-up (mo)	Tumor presentation (number of patients)	Tumor size (median, mm)	Response (first ECT)	Additional ECT cycles (% of pts)	Tumor control (LPFS)	Toxicity (CTCAE)
Montuori (2018)	11	12.2	Not reported	Not reported	CR:100%	9[1]	1-yr, 100%	Transient pain, eyelid edema
Campana (2017)	84	49.2	Primary multifocal or recurrent[2]	20	CR: 50%[3]	29	5-yr, 70%	G3 skin: 6%
Groselj (2018)	17	2	Primary	17–21 mm	CR: 96–100%[4]	0	Not reported	G3 skin infection: 1 G3 ulceration: 1
Bertino (2016)	34		Primary (20) Recurrent (14)	31/33 tumors ≤ 3 cm	CR: 91%	3	4 local recurrences at 1-yr	Not reported
Campana (2016)	24	Not reported	Primary or Recurrent	15	CR: 66.7%	Not reported	Not reported	Skin toxicity: G ≤1 in all cases
Campana (2014)	9	14	Primary or Recurrent	Not reported	CR: 78%	Not reported	1-yr, 86%	
Kis (2012)	3[5]		Not reported	9.4	CR: 87%	33	Not reported	Mild erythema, skin marks, skin necrosis
Rodriguez-Cuevas (2001)	9	8.6	Primary (8) Recurrent (1)	16	CR: 77.7%	33	Not reported	None
Heller (1998)	20	20	Recurrent/Persistent[6]	8.1	CR: 94%[7]	10	100%	Erythema, transient skin ulceration
Glass (1997)	20 (54 tumors)	18	Primary	9	CR:94%	2/54 tumors completely responded after 2nd ECT	18 mo, 100%	Painless erythema, ulceration, healing by second intention in 4-6 weeks; one patient developed skin infection and responded to oral antibiotics

Abbreviations: BLM = bleomycin; CR = complete response; ECT = electrochemotherapy; PR = partial response; SD = stable disease; PD = progressive disease; LDFI = local disease-free interval.
[1] A single patient underwent a second ECT cycle due to a newly occurred BCC, outside the previous treatment field.
[2] In this study, treated patients had local (n = 40), locally advanced (n = 41), or metastatic (n = 3) BCC.
[3] The following parameters were associated with CR achievement: younger (≤69 yr) age, primary tumor presentation, local disease extent, small (≤3 cm) tumor size, well-defined borders, non-aggressive histology, and no tumor ulceration. After a second ECT cycle, the CR rate increased from 50% (42/84 patients) to 63% (53/84 patients).
[4] The patients were treated with two doses of systemic bleomycin.
[5] 99 tumors (this study presents a series of three patients with Gorlin-Goltz syndrome).
[6] All treated BCC were of nodular subtype.
[7] The patients enrolled in this study underwent ECT with intralesional BLM.

Table 8
Clinical experiences with electrochemotherapy in soft tissue sarcomas.

Author (year)	Histotype	No of pts	Follow-up (mo)	Response (first ECT)	Additional ECT cycles (% of pts)	Local control (LPFS)	Toxicity
Starita (2017)	Kaposi[1]	27	24-68	CR: 74.1%	25.9	Not reported	Not reported
Guida (2017)	Angiosarcoma	1	17	PR[2]	100	LDF at last f-up	Not reported
Guida (2016)	Angiosarcoma	19	12	CR: 42%	21	1-yr, 68%	G3 skin ulceration: 11%
Bonadies (2015)	DFSP	1	36	CR	0	LDF	G1 edema, skin necrosis, and palpebral bruise
Di Monta (2014)	Kaposi[1]	19	16	CR: 73.6%[3]	26.2	LDFS: 100%	Not reported
Campana (2014)	Various[4]	34	19.3	OR: 92.2% CR: 32.3%	44.1	2-yr LPFS: 72.5%	G3 skin ulceration: 35% G3 soft tissue necrosis: 23%
Latini (2012)	Kaposi[1]	18	22	CR: 100%	50	LDF: 89%	G3 skin ulceration: 5.5% G3 pain: 5.5%
Curatolo (2012)	Kaposi[1]	23	18	CR: 60.9%	21.7	2-yr LPFS:76.2%	G2 skin infection: 8.7% G1 pain: 8.7%
Gualdi (2010)	Kaposi[1]	1	2	CR	0	LDF	G1 skin ulceration
Curatolo (2008)	Kaposi[1]	1	14	CR	0	LDF	G1 erythema G1 edema
De Bree (2006)	MPNST	1	17	CR	0	LDF	G3 skin ulceration with delayed wound healing (12 mo)

Abbreviations: CR = complete response; DFSP = dermatofibrosarcoma protuberans; LDF = local disease free; LDFS = local disease-free survival; LPFS = local progression-free survival; MPNST = malignant peripheral nerve sheet tumor; PR = partial response.
[1] Classic type form.
[2] CR was achieved by means of a second ECT cycle with no other oncological treatments.
[3] CR was achieved in all patients through additional ECT cycles (2 ECTs in 3 patients and three ECTs in 2 patients).
[4] Tumor distribution according to sarcoma histotype: leiomyosarcoma (n = 9), pleomorphic sarcoma (n = 8), liposarcoma (n = 3), epithelioid sarcoma (n = 3), malignant peripheral nerve sheath tumor (n = 2), rhabdomyosarcoma (n = 2), desmoplastic round cell tumor (n = 1), spindle cell sarcoma (n = 1), Kaposi's sarcoma (n = 1), extra-skeletal chondrosarcoma (n = 1), and fibromatosis (n = 1).

under local anesthesia appreciably reduced tumor size and after 14 months there was no evidence of recurrence. Manca et al treated 20 patients with keloids or hypertrophic scars [244]. ECT produced a median 87% reduction of keloid size, with significant improvement in pain and itching. A single patient had a local recurrence after 18 months.

Capillary vascular malformations consist of abnormal blood vessels, which may vary greatly in size. Laser therapy is the mainstay of treatment, but the outcome is suboptimal in 50% of cases. "Sclerotherapy" with intralesional BLM is known to be highly effective in malformations with large vessels, whereas its efficacy in capillary malformation is lower due to the small diameter of the blood vessels, which prevents intralesional injection [242]. In this disease, EP may promote BLM uptake. A Dutch trial is currently investigating "BLM electrosclerotherapy" in patients with hypertrophic capillary malformations [245].

Discussion

Given the new era of targeted and immune-based therapeutics which can prolong patient survival and the awareness of morbidity associated with cutaneous metastases, the interest in skin-directed therapies has surged [9]. Moreover, the synergistic partnership between modern immunotherapies and local treatment modalities has made skin metastases a focus for increasing local response and, possibly, as a means to augment the efficacy of immunotherapy [246,247]. ECT represents a valuable alternative/complementary option for patients with superficial tumors and compares very favorably with other skin-directed therapies [9]. Moreover, by often resulting in prolonged tumor control and symptom palliation, it represents a versatile adjunct in the management of several cancer types. Delivering high-quality ECT treatment entails some challenges, including difficulties with care (ie, need for advanced wound dressing and pain management) and treatment coordination with other specialists. In this review, we provide a succinct, but comprehensive update on ECT and provide a summary of its efficacy across histotypes. As such, it is intended not only for ECT users, but also for all members of the MDT in the hopes of promoting the integration of different treatments. Finally, this report may assist health care providers and stakeholders who plan to introduce ECT platforms at their centers as they attempt to reach informed decisions.

Currently, *standard* ECT is a codified procedure and a substantial body of evidence supports its use at the level of care [8,9,90]. The majority of patients can be managed by tailored anesthesiology protocols, thus ensuring rapid functional recovery. Noteworthy, the 2018 ESOPE guidelines have extended the maximum duration of the procedure, thus allowing for the treatment of patients with more widespread tumors. Conversely, the BLM dose can be safely de-escalated without affecting treatment efficacy [92-94]. In this regard, clinicians should be acquainted with use of chemotherapy, and cognizant of its possible, although rare, side effects.

Current indications include a range of superficial tumors. Historically, ablation therapies have shown results similar to surgical resection in oligometastatic melanoma [248]. Likewise, ECT has proved highly active [95-97] and a valuable adjunct to locoregional therapies (isolated limb infusion/perfusion and oncolytic virus therapy) for in-transit disease [146,249,250]. Notably, modern breakthroughs in immunotherapy and target therapy are opening new avenues for combining ECT with cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [68,69,251], programmed death 1 (PD-1) [66], or BRAF/MEK inhibitors [145].

In *breast cancer*, the treatment landscape is an evolving scenario [252], with immunotherapy showing some efficacy in some subsets [253,254]. However, the combination of immune-drugs with locoregional treatments with the potential for boosting antigen presentation remains to be explored [254–257]. Despite improvements, metastatic breast cancer is still an incurable disease, with skin or soft tissue metastases frequently accompanied by morbidity and an impact on quality of life [258]. Indications for ECT should be guided by molecular subtype [142], extent of cutaneous metastases [115], and associated symptoms.

In the *head and neck region*, ECT indications include patients with either cutaneous malignancies or mucosal cancers of the oral cavity and oropharynx. A large proportion of cutaneous malignancies occurs in this region due to high exposure to ultraviolet radiation and poses a significant problem in terms of resection and reconstruction [259]. Achieving satisfactory cosmetic outcomes with ECT largely depend on tumor size and location, prior surgeries, and judicious treatment application. Conversely, treatment of mucosal cancers can be challenging due to anatomical constraints, which may impair electrode placement, and possible side effects (eg, swelling, infection, bleeding, or tissue loss), which may be clinically relevant. Nevertheless, the accumulating evidence supports the feasibility, safety, and efficacy of ECT at referral centers [121,122]. In the near future, long-needle *variable electrode-geometry* ECT (VG-ECT) will make these cancers more easily accessible through navigation-based insertion of dedicated electrodes [260].

ECT holds promise in the treatment of nonmelanoma skin cancer, particularly locally advanced SCC [201] and multifocal BCC [118]. However, the availability of several effective options (eg, Mohs surgery, radiotherapy, topical immunotherapy, photodynamic therapy, and targeted agents) makes it imperative that comparative trials be conducted in this field.

The majority of soft tissue sarcomas are found deep, nevertheless a small group, such as Kaposi's sarcoma**,** arise in skin [261]. Interestingly, also in patients with superficial, small size angiosarcoma, *standard* ECT was effective in halting local progression and controlling tumor bleeding [219,220,223]. Multi-institutional studies are needed to establish treatment safety margins, and to optimize combinations with systemic treatment. Conversely, treatment of other histotypes is challenging, and *variable electrode-geometry* ECT has been developed to overcome technical limitations and improve treatment delivery in these large and deep-seated malignancies [13,262,263].

Finally, in women with recurrent *vulvar carcinoma* ECT seems tolerable and appears able to effect appreciable tumor control along with symptomatic relief.

Irrespective of histotype, tumor size has been consistently reported as a predictor of response [11,114,115,118,122,123,161,163]. With the use of ECT for a broader range of tumors, [96,100,116], new histotypes are being investigated [238,240]. Additionally, other compelling uses of ECT may yet emerge from noncancerous lesions.

It is important that prior to the use of ECT, there occur a MDT discussion and that the patient undergo meticulous evaluation by an anesthesiologist as these are key to ensure optimal patient outcome. ECT exerts a cytotoxic, vascular, and immune action, which produce a vasoconstrictive and inflammatory reaction, and, sometimes, also tissue necrosis [51,52,63-65,119,264]. Users should be cognizant of these effects not only to prevent toxicity, but also to capitalize on them. In fact, the effect of ECT on the tumor microenvironment could be exploited in the frame of new combined strategies with immunotherapy [66,68,69,251,254]. This is of particular interest since the majority of patients experience disease progression outside treatment fields, and response at distant untreated tumors (ie, abscopal effect) has been observed only rarely [265]. Thus combined administration with checkpoint inhibitors is under investigation [66,68,69,266] and its use in combination with immunotherapies is not endorsed as we await the results of ongoing trials. In order to maximize the potential of ECT, collaborative strategies need to be adopted and this effort will require the adop-

tion of shared clinical outcomes as well high quality standards for reporting [143,267]. Since BLM is a low-cost drug included in the World Health Organization list of essential medicines [268], it is conceivable that ECT might be adopted also in low-/middle-income countries. However, since health care expenditures are constantly increasing and often must confront pressing budget restrictions, evidence of its cost efficacy will be necessary through the collection of standardized data and quality of life outcomes [269,270]. In this context, this review only provides a qualitative analysis of the ECT literature. A more rigorous synthesis would be difficult at present due to the heterogeneity of published studies, as shown in 2 previous meta-analyses [9,10].

Conclusions

ECT is a credible, low-demand skin-directed therapy, which leverages a multifaceted mechanism of action. The procedure is flexible and can be applied to a range of superficial cancers, where it has a profound impact in halting local disease progression, and preserving a patients' quality of life. Since low tumor burden and limited disease spread are invariably associated with better results, moving ECT treatment earlier in the course of disease may prove helpful to improving patient outcomes. The conduct of multicenter, histotype-oriented studies should further clarify the clinical benefit of ECT and delineate its role within cancer-specific algorithms. Based on available evidence, it is conceivable that thoughtful incorporation of ECT into standard healthcare settings will improve the treatment of various patients with cancer. For ECT to be further consolidated at the level of care, specific training of clinical staff and continuous improvement of research evidence are warranted.

Conflict of interest statement

All authors take full responsibility for the content of the present publication; they confirm that the article reflects their view point and medical experience. The content of the manuscript is not influenced by any pharmaceutical or medical device company. Authors did not receive any compensation for authoring the manuscript. No writing assistance was provided. DM holds patents which are licensed to ECT device manufacturer IGEA S.p.A.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Acknowledgments

Prof. Paolo Caliceti, University of Padova, for providing insightful comments on chemotherapy. Dr. Sara Galuppo and the Anesthesiology Team of Veneto Institute of Oncology of Padova, for their valuable support with patients' care. Dr. Luigi Corti and Prof. Carlo Riccardo Rossi for logistic support. This work was in part supported by the Slovenian Research Agency (ARRS) - research core funding nos. P2-0249 and P3-0003. The research was conducted within the scope of the electroporation in Biology and Medicine (EBAM) European Associated Laboratory (LEA).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminoncol.2019.04.002.

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