Abstract
Electrochemotherapy (ECT) is a therapeutical procedure based on the induction of cell membrane electroporation, by cell exposure to electric fields lasting a few microseconds, combined with the local or systemic administration of cytotoxic drugs, with an intracellular target and high intrinsic efficacy, but poor cell membrane permeability. ECT is an effective local therapy for any histological tumour that has been used clinically since 2005 and is currently in use in 83 centres all over Europe. In the literature, ECT as a local oncological treatment shows an objective response between 70 and 90% in mucocutaneous primary and metastatic lesions, is cost effective and has few local and systemic side effects. In this manuscript, we present an overview of the European experience in ECT, as well as our own experience in a specialised Spanish oncological centre and in a basic oncological unit in Nicaragua. The purpose is to reflect on the role that this procedure could have in the treatment of skin and mucosal cancer as part of a multidisciplinary approach.

Keywords
Electroporation · Electrochemotherapy · Skin cancer · Skin metastasis · Breast cancer · Local relapse

Background
Electroporation is a physical phenomenon induced by application of electric fields to the cell membrane lasting a few microseconds. Above threshold values of transmembrane potential, the biological structures of the cell membrane experience temporary alteration allowing a bidirectional exchange of materials. Cell membrane exposure to protracted and very intense electric pulses can lead to cell death (necrosis) due to irreversible conformational changes in the membrane. The application of intense but short electric pulses will induce reversible electroporation, maintaining cell membrane viability [1]. In 1972, Neumann and Rosenheck demonstrated that electric pulses between 18 and 24 Kv/cm with a duration of 150 microseconds induced a reversible permeabilisation on medullar bovine cell granules [2]. In 1977 Kirosita and Tseng suggested that this transient permeation is due to formation of pores with a diameter in the range of Angstroms (Å) [3].

Electrochemotherapy (ECT) is a therapeutical procedure based on the electroporation of tissues combined with the local or systemic administration of cytotoxic drugs, with an intracellular target and high intrinsic efficacy, but poor cell membrane permeability [4]. Preclinical studies, mainly led by the Vectorology Department at the Institut Gustave Roussy (Villejuif, France) demonstrated ECT efficacy in clones of tumoral cell cultures, showing that survival of tumoral cells was almost null with low doses of bleomycin associated to cell electroporation while higher bleomycin doses, between 1000 and 10,000-fold, were
needed to achieve a similar response without electroporation [5].

In 1986 Mir and collaborators from Institut Gustave Roussy (Villejuif, France) described how cells in culture or tissue exposed to determined and controlled electric pulses could go through a transient permeation state, remaining viable and undamaged [6]. Lack of simple diffusion of bleomycin across the cell membrane has been explained by its molecular size and physicochemical properties; bleomycin molecules need to bind to specific carrier proteins to be internalised by an endocytic mechanism. Therefore, bleomycin diffusion capacity is limited by the amount of membrane carrier protein and by the turnover of binding carriers [7, 8]. However, after cell electroporation, bleomycin can freely diffuse into cell cytoplasm and subsequently remains trapped inside the cells due to the pores resealing. Bleomycin induces cell death, hence damaging DNA double helix during cell division; it will cause tumour cell death independently of the histology and remaining quiescent peritumoral cells. The amount of drug needed to achieve therapeutic effects is minimal, as are secondary effects. In summary, in vitro and animal experimental models have provided a new tool for safe, selective and inexpensive pharmacological treatment for local tumour care. Researchers from Villejuif named it electrochemotherapy.

During initial Phase I and Phase II trials for progressing cutaneous diseases of various histologies refractory to standard treatments, classified as melanoma and non-melanoma, an objective response rate of 85% was found with a prolonged response in 65% of the cases. Response was evaluated with individualisation of every single tumoral nodule treated [9]. ECT using intratumoral cisplatin (mainly) or systemic treatment showed a 77% prolonged objective response for single nodules in comparison to 17% for nodules treated only with cisplatin [10].

ECT has been validated and its administration procedures standardised by means of two projects sponsored by the European Commission within the Fifth Framework Program. The first, an engineering project called CLINIPORA-TOR (GSI), with registry code QLK3-1999-00484, developed the technology to release electric pulses according to European Safety Standards. Within the second project, called ESOPE (European Standard Operating Procedures in Electrochemotherapy), registry code QLK3-2002-02003, a prospective multicentre clinical trial led by a group of researchers from Institut Gustave Roussy of Villejuif France, was conducted in collaboration with the Institute of Oncology Ljubljana (OI), Ljubljana, Slovenia; University of Copenhagen at Herlev Hospital (HH), Herlev, Denmark; and Cork Cancer Research Center Bio-Sciences Institute and Mercy University Hospital, National University of Ireland (CCRC), Cork, Ireland [9, 11]. ESOPE defined the main indications, drug dosages and routes of administration, electrode configurations, etc.

Indications can be summarised in three cases: standard treatment failures controlling local disease, organ sparing if appropriate surgery resection includes amputation or mutilation, and finally the palliative use in those lesions in which large extensions do not allow eradication, therefore requiring symptomatic treatment, mainly to control lesion bleeding and compressive or infiltrating pain [9].

Since 2005 ECT has been used as a standardised clinical procedure all over Europe. In 2006 it was introduced in Spain by Luis Mir and ourselves through some workshops and clinical courses. In the same year ECT was initiated in the Republic of Nicaragua as part of a cooperation project for the treatment of advanced, relapsed and metastasised skin and mucosal cancer [12]. After 5 years of clinical use of ECT we would like to briefly present our overall experience considering its role as an efficient local tumour treatment underlying the multiple benefits of its use, especially in areas where funds and resources are limited.

Experience

The first clinical study related to ECT administration was published in 1991 by Mir et al. from the Institut Gustave Roussy (Villejuif, France) [13]. Patients affected by squamous cell carcinoma in head and neck areas were treated, showing good tolerance to treatment, without any major adverse reactions and with significant antitumoral effect. Since then, several clinical studies has been published and finally in 2006 the ESOPE project results were published [9] in a prospective multicentre study including 41 patients, with a total of 171 tumoral nodules treated following the standardised protocol. Overall response was 85% (73.7% complete response).

Up-to-date results of published studies are analogous regarding efficacy in local control of cutaneous and subcutaneous tumours independent of the histology, with a complete response rate of almost 75% and 10% partial response of treated nodules [14].

Clinical trials published before ESOPE

Between 1995 and 2005, 15 studies were published including 94 patients affected by melanoma. Up to 642 cutaneous and subcutaneous nodules were treated, with an 85% overall response (67% complete response) (Table 1). Response rates were 88% and 90% for bleomycin administration (IV and IT) respectively and 83% for cisplatin IT administration. In non-melanoma tumours results are analogous. In 17 studies published up to 2005, 153 patients were gathered and 367 nodules were treated. The tumours histologies most frequently treated were head and neck squamous cell carcinoma, basal cell carcinoma and breast cancer (101, 32 and 10 patients respectively). Overall response rate (OR) was 79% with a 58% complete response (CR) and 21% no response or progressive disease (PD-NC) [29].