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Submission date: 12-Feb-2024 02:26PM (UTC+0700)
Submission ID: 2292666523
File name: The_Specificity_and_Efficacy_of_Alternating_EF.pdf (687.35K)
Word count: 7715
Character count: 43105

ASM Sc. J., 18, 2023

https://doi.org/10.32802/asmscj.2023.1588

The Specificity and Efficacy of Alternating Electric Fields as a Prospective Cancer Treatment

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An external electric field is still debatable for cancer treatment, although many study results proved its capacity. Cancer involves complex mechanisms, including how the cancer cells arise and grow. Thus, this disease is known to have many hallmarks. This condition complicates precise and accurate treatment. The study proved that an external electric field has prospects to become an effective cancer treatment, demonstrated by its ability to inhibit cancer growth through anti-proliferative and pro-apoptotic capacities. Several devices generating electric fields for cancer treatment were Tumour Treating Fields (TTFields), nanosecond Pulsed Electric Fields (nsPEF), picosecond Pulsed Electric Fields (psPEF), and Electro-Capacitive Cancer Therapy (ECCT). This article will compare those devices' efficacy, safety, treatment methods, and research progress, including the advantages and disadvantages of static electric field devices and future research prospects. More attention will be focused on ECCT, which has been closely and profoundly investigated in breast cancer treatment.

Keywords: AC source; anti-cancer; anti-mitotic; electric fields; pro-apoptotic

I. INTRODUCTION

The electric field in organisms is essential in biological systems (Levin, 2014). The proof for this is the membrane potential produced on cells and the cell membrane permeability responding to the external electric field (Bhavsar *et al.,* 2020). In cancer cells, membrane potential will affect the cell cycle, ultimately impacting their proliferation (Yang & Brackenbury, 2013; Bhavsar *et al.,* 2020).

Cancer is a disease that involves uncontrollable cell proliferation and metastases for cancer progression (Hanahan & Weinberg, 2000). More than 19 million new cancer cases emerged in 2020, which will increase significantly by about 47% during the next 19 years. There are many types of cancer, but breast cancer is the most common type in women, while lung cancer is in men (Sung *et al.,* 2021). These facts impact the increase in the number of medical, pharmaceutical, biotechnology, and biomedical science studies to obtain the exact cancer treatment and minimise the side effects of treatment.

Scientific development has bridged the utilisation of electric fields to control cell proliferation. This concept could be applied in medicine. One of the findings is the invention of an

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electric field device used in cancer treatment, namely TTFields (Kirson *et al.*, 2004). It initiated further research by utilising the electric fields for cancer treatment, and nsPEF (Ren *et al.*, 2013), psPEF (Chen *et al.*, 2013; Wu *et al.*, 2019), and ECCT (Alamsyah *et al.*, 2015) were developed electric fields devices. The last one to mention is the electric field device designed by Dr. Warsito P. Taruno, an Indonesian. However, its use for this purpose is still debated by many circles.

Electric field devices for cancer treatment usually share similar aspects. Thus, the TTFields, nsPEF, psPEF, and ECCT utilise A.C. sources but have distinct specificity. Those four devices have been proven capable of cancer treatment, but only TTFields has been approved by the U.S. Food and Drug Administration (FDA) (Fabian *et al.*, 2019). However, research is still being conducted to obtain the most suitable electric field therapy for each cancer type since it is characteristically different. Therefore, all those electric field devices used in cancer treatment will be described and compared for several criteria as a background for further research. This paper particularly confirms the effectiveness of A.C. electric fields in cancer treatment, mainly ECCT.

II. AN ELECTRIC FIELD IN THE BIOLOGICAL SYSTEM

A cell is the smallest structural and functional unit in carrying out the biological system (Mescher & Junqueira, 2016). Cell bioelectricity plays an important role in this mechanism. Principally, the cell can produce and respond to electricity. As a functional unit, a cell has its electricity, called endogenous bioelectricity (Levin, 2014), while exogenous electricity comes from outside the cell (Bhavsar *et al.*, 2020). The membrane potential is an example of endogenous bioelectricity (Levin, 2014), whereas the electric field therapy outside the cell is exogenous electricity (Bhavsar *et al.*, 2020). Both sources of electricity affect the physiological system, particularly the effect of exogenous electricity on cancer growth (Nuccitelli, 2019).

The membrane potential is crucial to utilising the electric field in cancer treatment. The membrane potential of a cell varies for each cell type, affecting distinct cell cycles. The depolarised membrane induces mitosis (Figure 1a), ultimately affecting cell proliferation capability (Yang & Brackenbury, 2013). Therefore, actively dividing cells tend to be depolarised (Figure 1b) (Bhavsar *et al.*, 2020).

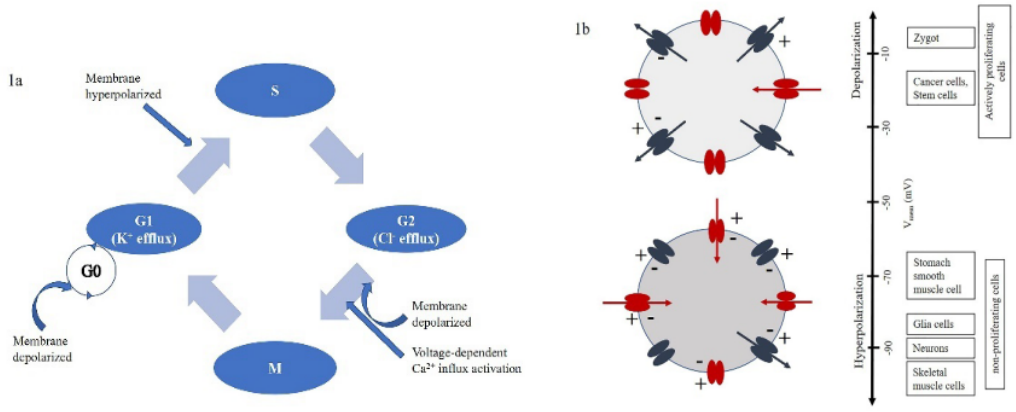

Figure 1. The cell bioelectricity. 1a) The changing of membrane potential in a cell cycle. Membrane depolarisation of cells in the G2 phase induces the cells to enter a mitotic phase (image modified from Yang & Brackenbury, 2013). 1b) The membrane potential of several cell types. The actively proliferating cells tend to undergo membrane depolarisation, contrasting with differentiated cells (image modified from Bhavsar *et al.*, 2020; Yang & Brackenbury, 2013).

Based on cell bioelectricity, an external electric field (exogenous electricity) can be utilised in biomedical areas such as cancer treatment. Many research publications show the anti-cancer capacity of these external electric fields. Even though the devices are slightly different, they aim to inhibit cancer growth.

Using an external electric field for cancer growth inhibition is based on anti-mitotic and pro-apoptotic capacities through several mechanisms. First, exogenous electricity may influence cell bioelectricity, particularly regarding membrane potential. A depolarised cell membrane is more affected by an external electric field (Yang & Brackenbury, 2013). Furthermore, polymerised tubule polarity in the actively proliferating cancer cells causes the cells to become more sensitive to the external electric fields; thus, the disruption of tubule polymerisation will inhibit cell mitosis (Giladi *et al.,* 2015). In addition, an external electric field may affect cell proliferation by regulating ion channels because external electric fields induce membrane potential change (Yang & Brackenbury, 2013). Moreover, membrane electroporation from an external electric field may facilitate drug delivery for cancer patients (Dev *et al.*, 2000).

The A.C. source is the general characteristic of those external electric fields for cancer treatment. It is different from the direct current (D.C.) source because there is a change in the electric field direction of the A.C. source. Furthermore, the external electric field for cancer treatment devices utilises static electric fields with low to intermediate frequencies. Details are described in the sections below.

III. EXTERNAL ELECTRIC FIELDS CAPABILITY FOR CANCER TREATMENT

The complexity of cancer is the reason for the difficulties of treatment. Several characteristics of cancer hallmarks were sustaining proliferative signalling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death (Hanahan & Weinberg, 2000). In addition, genome instability and inflammation are the enabling hallmarks, besides reprogramming energy metabolism and evading immune destruction (Hanahan & Weinberg, 2011). Furthermore, some studies demonstrated the role of cancer stem cells (CSCs) in cancer growth and metastasis (Yu *et al.,* 2012). In some cases, CSCs are believed to be the primary target for anti-cancer discovery because the symmetric division of CSCs induces cancer growth and sustainability (Liu *et al.,* 2005). In addition, the immune system also plays a crucial role during cancer growth, particularly for inflammatory immune cells (Gonzalez *et al.*, 2018). It may be an essential aspect of future research utilising external electric fields for cancer treatment since external electric field exposure may increase the activity of immune cells against cancer development (Alamsyah *et al.,* 2021).

For those reasons, many treatments and therapies have been researched and developed for the different targets of cancer. One of those is minimising side effects and supporting applied treatments and therapies. The prospective invention from the last two decades has used external electric fields for cancer treatment. The research on electric fields' capacity for cancer treatment has been initiated by Kirson *et al.* (2004) using TTFields to disturb cancer cell line proliferation (Kirson *et al.,* 2004). Afterward, much research has been carried out.

The research of external electric fields for cancer treatment has been conducted to obtain the exact specifications and determine the level of efficacy, especially for the most common cancer. TTFields is a device that generates external electric fields for cancer treatment, applied for glioblastoma and other cancers, resulting in good progress (Fabian *et al.*, 2019). Other devices, nsPEF, psPEF, and ECCT, have been studied, both *in vivo* and *in vitro*, and have the potential for cancer treatment in the future (Table 1). Principally, the general character of those devices is similar, except for specific parameters of the device for each cancer type.

Table 1. The comparison of several external electric field devices for cancer treatment.

Electric Field Devices	Device specifications in research/treatment	Research/Treatment method	Effectiveness	Research progress	References
TTFields	- 1 – 1.4 V/cm, 100 kHz	- *In vitro*, research using animal and human cell line. - *In vivo* using C57BL/6 mouse and BALB/c mouse, inoculated with malignant melanoma and adenocarcinoma cells, respectively.	- Anti-proliferative effect on mitotic cells after 24-h TTFields exposure. - TTFields-exposed tumour size was decreased by about 47% and 73% to control tumour size for malignant melanoma and adenocarcinoma cells, respectively, within 3 – 6 days. - No side effects, including no histopathological injuries.	- Pre-clinical study - These results promoted further studies.	Kirson *et al.*, 2004
	- 2 V/cm with a frequency of 100, 150, 200 kHz for 24 h exposure	- *In vitro* research (mouse melanoma, human breast carcinoma, rat and human glioma with optimum frequency in "specification," respectively).	- Anti-proliferative effect on various cancer cell line.	- Pre-clinical study.	Kirson & Dbaly´, 2007
	- 2 V/cm, 200 kHz for six days exposure	- *In vivo* (mice intradermal melanoma and *Fischer rats* for malignant melanoma and glioma cells, respectively). - Clinical trial on GBM patients.	- Treated tumour volume 19.8% smaller than sham control tumours; n= 26; P= 0.19. - TTP= 26.1 weeks; PFS at six months is 50%; O.S. is 62.2 weeks. It was > 2 times that of historical control patients.	- Pre-clinical study. - Clinically study with non-invasive but contact device.	Kirson & Dbaly´, 2007
	- 0.9 V/cm, 150 kHz for 48 h exposure	- *In vitro* using human glioblastoma cell.	- Metastatic inhibition. - Anti-angiogenesis by downregulating VEGF, HIF1α, MMP2, and MMP9.	- Pre-clinical study. - Supports TTFields as anti-invasive and anti-angiogenic therapy.	Kim *et al.*, 2016
	- Low intensity, 200 kHz	- Clinical research on 91 patients who suffered ndGBM, therapied with TMZ.	- One and 3-year O.S was 80% and 18%, respectively, during 26.5 months of median follow-up for surviving patients. - Higher average usage, longer O.S.	- Clinically study with non-invasive but contact device.	Ballo *et al.*, 2022
	- 2 V/cm, 200 kHz	- Clinical research (delivered by non-invasive insulated electrodes) on newly diagnosed and recurrent GBM.	- Adjuvant chemotherapy for ndGBM with STR. - TTFields was more effective for ndGBM treatment than rGBM.	- Clinical study with non-invasive but contact device.	She *et al.*, 2023
	- 40 kV/cm, five ns rise time, 300 ns duration, 0.5 Hz, 100 pulses in total	- *In vivo* using SKH-1 mice injected with melanoma cells.	- Anti-angiogenic effect by downregulating VEGF and PD-ECGF, thus decreasing microvascular density.	- Pre-clinical study.	Chen *et al.*, 2007
	- 30 kV/cm, 100 ns, 4 Hz, 720 pulses in total	- *In vivo* on Balb-C mice using human breast cancer.	- Inhibit tumour growth up to 79%. - Pro-apoptotic, decreased blood vessel density, suppressed VEGF and VEGFR. - Pro-apoptotic and anti-mitotic (anti-proliferative).	- Non-thermal approach. - Pre-clinical study.	Wu *et al.*, 2014

nsPEF	- 20 kV/cm – 60 kV/cm, 100 ns, 100 pulses	- *In vitro* using human pancreatic carcinoma cell line. - *In vivo* using mice, induced by HCC cell line.	- Pro-apoptotic. - Anti-proliferative. - Metastasis inactivation. - Anti-angiogenesis by inhibiting VEGF and MMP expression.	- Pre-clinical study.	Ren *et al.*, 2013
	- 15 kV/cm – 25 kV/cm, 65 ns, 250 pulses + 0.38 µM gemcitabine (GEM)	- *In vitro* (breast cancer cell line).	- A combination of GEM and nsPEFs has more benefits for breast cancer ablation. - Cytotoxicity on breast cancer cell line. - Pro-apoptotic.	- Pre-clinical study.	Wu *et al.*, 2014
	- 40 kV/cm of intensity, 30 pulses for 24 h post nsPEF treatment	- *In vitro* using human osteosarcoma cell line.	- Pro-apoptotic and anti-mitotic (anti-proliferative). - Induce adaptive immune response.	- Pre-clinical study. - Minimal invasive. - Non-thermal ablation.	Miao *et al.*, 2015
	- 24 – 30 kV/cm, 300 ns, 200 – 400 pulses	- *In vivo* with xenograft model (from human pancreatic cell line and fresh tumour). - Non-invasive treatment on subcutaneous mice.	- CD8+ was increased. - Decreasing of immune suppressive cells. - TNFα, IL1β were increased, while IL6 was decreased. - Trigger immune response.	- Pre-clinical study. - Minimal invasive. - Non-surgical.	Zhao *et al.*, 2021
	- 15 kV, 300 ns, 50 pulse/electrode	- *In vivo* on mice using hepatocellular carcinoma/HCC cell line.	- There was a correlation between gut microbiome and HCC prognosis after ablation.	- Pre-clinical study. - Minimally invasive tumour ablation with needle electrodes implanting tumour.	Zou *et al.*, 2023
psPEF	- 2000 pulses, 800 ps duration, 0 – 600 kV/cm	- *In vitro* using HeLa cell line.	- Pro-apoptotic. - Cell cycle arrest at the G2/M phase.	- Pre-clinical study. - Minimally invasive.	Chen *et al.*, 2013
	- 120 – 140 kV/cm, 3 Hz, 800 ps duration, 2000 pulses	- *In vivo* with xenograft models using mice injected with HeLa cell line.	- Pro-apoptotic. - Disrupt potential membrane. - Caspase activation. - Inhibitory effect was 9.11 % at day 7.	- Pre-clinical study. - Non-invasive device.	Jia *et al.*, 2015
	- 0 – 70 kV/cm, 3 Hz, 800 ps duration, 2000 pulses, exposure time 11 minutes	- *In vivo* with Xenograph models in Balb/c mice that were injected with HeLa cell line.	- Anti-tumour in cervical cancer. - Necrosis of cervical cancer. - Increasing intensity, decreasing microvascular density. - Anti-angiogenic by downregulating HIF1α, HIF2α, VEGF.	- Pre-clinical study. - Non-invasive device.	Wu *et al.*, 2016
	- 200 – 600 kV/cm, 3 Hz, 800 ps duration, 2000 pulses	- *In vitro* using HeLa and HUVECs cell line.	- Anti-angiogenic effect by downregulating angiogenesis-associated factors secreted by cancer cells.	- Pre-clinical study. - Minimally invasive, non-thermal treatment.	Wu *et al.*, 2019
	- 100 kHz, 18 Vpp	- *In vitro* using MCF-7 cell line. - *In vivo* using C3H mice.	- Growth inhibition of 28 – 39 % of *in vitro*. - Tumour size decreased by 67% *in vivo*.	- Pre-clinical study. - Non-invasive device.	Alamsyah *et al.*, 2015
	- 100 kHz, 18 Vpp	- *In vivo* using rats.	- Lowering growth rate of rat breast tumour of 0.01 cm^2/day than 0.121 cm^2/day without exposure.	- Pre-clinical study. - Non-invasive device.	Alamsyah *et al.*, 2018

ECCT	- 150 kHz, 18 Vpp	- *In vivo* using rats.	- Downregulation of PCNA and ErbB2 protein, upregulation of Caspase-3 and macrophage CD68. - Downregulation of CCL2 and IL-18 mRNA expression. - Lowering of the mitotic figure.	- Pre-clinical study. - Non-invasive device.	Pratiwi *et al.*, 2019
	- 100 kHz, 18 Vpp	- *In vivo* using rats.	- Downregulation of PCNA, Caspase-3, CD-68 protein expression. - Upregulation of CD8+ cells. - Decreasing of CD4/CD8 ratio.	- Pre-clinical study. - Non-invasive device.	Alamsyah *et al.*, 2021
	- 150 kHz, 18 Vpp	- *In vivo* using rats.	- An ECCT was safe for the liver and kidney of a rat.	- Pre-clinical study. - Non-invasive device.	Nurhidayat *et al.*, 2022
	- 150 kHz, 18 Vpp	- *In vivo* using rats.	- Upregulation of HMGB1 and PD-L. - An ECCT was safe for brain and liver.	- Pre-clinical study. - Non-invasive device.	Fathurrohmah *et al.*, 2022
	- 100 kHz, 18 Vpp	- *In vivo* using rats.	- An ECCT was safe for kidney and liver structure. - An ECCT may increase normal renal function.	- Pre-clinical study. - Non-invasive device.	Alamsyah *et al.*, 2023

A. Tumour Treating Fields

TTFields has been investigated and developed for cancer treatment for about two decades. Its anti-cancer capacity has been proven by inhibiting tumour cell line proliferation *in vitro* and malignant cell proliferation *in vivo* in mice (Kirson *et al.,* 2004). Furthermore, many studies have confirmed similar results. TTFields can inhibit tumour growth, as demonstrated in human breast carcinoma cell line (MDA-MB-231), non-small-cell lung carcinoma (H1299), and animal tumour models (B16F1 melanoma and intracranial F-98 glioma), as well as human glioblastoma (Kirson & Dbaly´, 2007), the most common human brain cancer (Fabian *et al.,* 2019). Based on those results, TTFields has been approved by the FDA for glioblastoma multiform (GBM), both for recurrent and newly diagnosed GBM (Zhu & Zhu, 2017; Fabian *et al.,* 2019).

TTFields, a non-invasive cancer treatment device, utilises intermediate frequency (100–300 kHz) and low intensity (1–3 V/cm) generated by alternating electric fields (Kirson *et al.,* 2004). The biological effect of TTFields in cancer cells is disruption of microtubule spindles (Giladi *et al.,* 2015; Zhu & Zhu, 2017), lowering of the polymerised tubulin and total tubulin ratio, and inhibiting of mitotic spindle assembling (Giladi *et al.,* 2015). Moreover, TTFields effectively disrupts several mitotic processes, particularly metaphase, anaphase, and telophase (Kirson & Dbaly´, 2007; Zhu & Zhu, 2017). Furthermore, it causes an anti-proliferative effect during metaphase, while during telophase, it induces cell death due to cytokinesis disruption (Zhu & Zhu, 2017). Principally, those biological effects of TTFields leads to asymmetric chromosome segregation, mitotic arrest, and delaying mitosis. Those effects ultimately inhibit cancer growth (Zhu & Zhu, 2017). In addition, mitotic disruption leads to stress signal production that mediates immune activation (Zhu & Zhu, 2017).

However, TTFields, approved by the FDA for treating patients with GBM, have limitations. It is a contact device used on the patient's scalp to deliver electric fields of specific specification by four transducer arrays consisting of nine insulated electrodes each (Kirson *et al.,* 2004). It may lead to skin toxicity in direct contact with the transducers, particularly on the scalp. Skin reactions range from mild (14%) to moderate (2%) (Stupp *et al.,* 2012), and dermatitis is a common side effect on the scalp (Kirson *et al.,* 2004). The longer duration of TTFields application could impact more severe side effects, such as dermatitis, allergies, ulcers, skin infections, or pustules (Zhang *et al.,* 2020). In addition, TTFields is a complicated device due to rechargeable batteries and caregiver intervention for the first use; thus, it is pretty heavy to carry and will be difficult for elderly or disabled patients to guarantee the application of the device for more than 18 hours/day (Zhang *et al.,* 2020).

B. Nanosecond Pulsed Electric Field

nsPEF is a type of pulsed electric field (PEF) based on the duration and shows effectiveness in cancer treatment due to its pro-apoptotic and anti-proliferative effects (Miao *et al.,* 2015; Zhao *et al.,* 2021). This device facilitates cell membrane electroporation for drug delivery (Dev *et al.,* 2000). Thus, electrochemotherapy (ECT) is the main target of utilising nsPEF. nsPEF uses the range duration of PEF and the intensity (kV/cm) from tens to hundreds of ns (Miao *et al.,* 2015).

The nsPEF capacity for cancer treatment was demonstrated by several studies in inhibiting cancer growth. Its ability was pro-apoptotic (Ren *et al.,* 2013; Miao *et al.,* 2015), anti-proliferative (Miao *et al.,* 2015), anti-angiogenic (Ren *et al.,* 2013; Wu *et al.,* 2014), and immune surveillance enhancing (Chen *et al.,* 2014). Each researcher has specific characteristics of nsPEF for the research but a similar duration range.

The pro-apoptotic capacity of nsPEF has been proven by inducing cell apoptosis of the human pancreatic carcinoma cell line (PANC-1) and human hepatocellular carcinoma cell line (Hep-3b) *in vitro*. These results indicate that the 100 ns duration and electric field intensity from 0 kV/cm to 60 kV/cm induced cell apoptosis by unequal of Bcl2-family protein. Thus, the pro-apoptotic effect is through the dependent-mitochondria intrinsic apoptotic pathway (Ren *et al.,* 2013). Zhao *et al.* (2021) supported this result by using a mouse model, injected with a pancreatic tumour fragment, and treated with a single treatment of nsPEF with the 24 kV/cm amplitude, 400 pulses, and 300 ns duration. Caspase-3 protein was higher in the early nsPEF therapy, in contrast with Ki-67 protein expression, thus indicating that nsPEF was adequate in inducing cell apoptosis (Zhao *et al.,* 2021).

Another result showed the pro-apoptotic effect of nsPEF, which, as the specification, has 30 pulses, 40 kV/cm at 24 h post nsPEF therapy on osteosarcoma cell line (MG-63) (Miao *et al.,* 2015). Furthermore, the nsPEF capacity as an anti-proliferative has been proven by lowering NF-kB and cyclin protein expression in a dose-dependent manner (intensity range from 0 kV/cm to 60 kV/cm). It indicated that the NF-kB signalling pathway inhibits cell proliferation (Ren *et al.,* 2013).

In addition, nsPEF also affects the formation of new blood vessels (angiogenesis). A nsPEF of 40 kV/cm, 5 ns rise time, and 30 ns duration downregulated the VEGF and PD-ECGF protein expression, lowered the CD31, CD34, and CD105 expression in B16-F10 melanoma-injected mice (Chen *et al.,* 2007). The nsPEF capacity to inhibit angiogenesis and prevent metastasis has been proven by inhibiting the Wnt/β-Catenin signalling pathway, impacting the downregulation of VEGF and MMPs protein expression (Ren *et al.,* 2013). During angiogenesis, the VEGF is the primary growth factor (Hicklin & Ellis, 2005), while MMPs are a digestive enzyme to promote basement membrane degradation (Quintero-Fabián *et al.,* 2019). Furthermore, nsPEF could induce an immunological effect. The death of cancer cells may be advantageous for antigen-presenting (Zhao *et al.,* 2021). Another immunological evidence showed macrophage infiltration in hepatocellular carcinoma (HCC) *in vitro* and *in vivo* treated by nsPEF (Chen *et al.,* 2014).

C. *Picosecond Pulsed Electric Field*

According to the pulse durations, PEF is classified into milliseconds (ms), microseconds (µs), nanoseconds (ns), and picoseconds (ps) (Nuccitelli, 2019). PEF induces membrane electroporation, and some research results showed that the electroporation effects of the cell membrane caused an increase in cell membrane permeability, thus facilitating the transport of drug molecules (drug delivery) (Dev *et al.,* 2000). The cancer treatment combines chemotherapy and electrical therapy, termed electrical chemotherapy/electrochemotherapy (ECT) (Dev *et al.,* 2000). This method was effectively proven for cutaneous tumours (Nuccitelli, 2019). In addition, ECT stimulates danger-associate molecular patterns (DAMPs), attracting dendritic cells to treat tumour cells by regulating the immune system (Nuccitelli, 2019). Several European countries have approved this method for human cancer treatment, whereas the United States has not (Nuccitelli, 2019).

psPEF indicated an anti-tumour effect in some studies. The psPEF therapy (2,000 pulsed for 800 ps with various electric field amplitudes) induced apoptosis of HeLa cells and promoted cell cycle arrest at the G2/M phase. It also affected the phosphorylation level of endoplasmic reticulum sensors, upregulated GRP78, GRP94, and C/EBP homologous protein, and increased intracellular Ca2+ concentration. These results indicated the pro-apoptotic effect of psPEF through endoplasmic reticulum stress. Other results supported that effect through the caspase-dependent signalling pathway, marked by the Caspase-12, -9, and -3 activation followed by the downregulation of Bcl-2 and upregulation of Bax (Chen *et al.,* 2013). Furthermore, the latest research indicated the capacity of the anti-angiogenic effect of psPEF, shown by inhibiting tube formation and proliferation, inducing HUVECs apoptosis and necrosis. The psPEF specification was the 3 Hz frequency, 800 ps duration, 2,000 pulse number, and intensity of 0, 200, 400, and 600 kV/cm *in vitro*. Moreover, VEGF and HIF1α downregulation in HeLa cells supported the anti-angiogenic effect of psPEF (Wu *et al.,* 2019). Those studies expressed the efficacy of psPEF to inhibit tumour growth in a dose-dependent manner.

D. *Electro-capacitive Cancer Therapy*

The ECCT is a non-contact device for cancer treatment that employs a low to intermediate frequency (<300 kHz) and low intensity (<30 Vpp). Dr. Warsito P. Taruno invented and developed this device from CTech Labs Edwar Technology Company (IDN Patent REG P00201200011, 2012). Since its invention, much research has been conducted to prove the ECCT's effectiveness in cancer treatment. The results have proven that ECCT has anti-cancer capabilities with no effects on normal cells because normal and actively proliferating cells have different conditions. Principally, the polymerisation of polarised microtubules during mitosis impacts differences in cell sensitivity to external electric fields (Giladi *et al.,* 2015).

The ECCT capacity to treat cancer cells has been studied *in vitro* and *in vivo*, using a frequency of 100 kHz and 150 kHz.

An ECCT of 100 kHz and 18 Vpp has been applied on human breast cancer MCF-7 cell line and C3H strain mice. These mice were injected with mammary tumour cells from a C3H donor to induce breast tumours in the animal tumour model. The results indicated the MCF-7 inhibition of 28%–39%, whereas tumour size reduction was up to 67% with no side effects in the surrounding area (Alamsyah *et al.,* 2015). Furthermore, an ECCT of 100 kHz and 18 Vpp was safe for the kidney and liver in a rat-bearing tumour. Instead, it may positively impact normal rats, particularly renal function (Alamsyah *et al.,* 2023). Besides that, ECCT therapy may induce immune cells to infiltrate breast tumours. At the exact ECCT specification, but in different cancer types, the ECCT caused cancer cell death (oral cancer cells and HeLa cell lines of 18.39% and 6.60%, respectively) (Mujib *et al.,* 2017). In addition, the ECCT efficacy as adjuvant therapy was potential for nasopharyngeal carcinoma after 50 days of ECCT 5–500 kHz and 6–20 Volt from an A.C. source (Chusnu *et al.,* 2019). Another result for those ECCT characteristics (100 kHz and 18 Vpp) using the DMBA-induced rat breast tumour model showed decreased PCNA, Caspase-3, and CD68 expression after the ECCT therapy. Moreover, ECCT induced CD8+ expression and caused the lowering of the CD4/CD8 ratio, which gave a good prognosis in cancer treatment. It may be potential for wound healing during electric field therapy (Alamsyah *et al.,* 2021).

Another ECCT specification, a frequency of 150 kHz and an intensity of 18 Vpp, has been applied for DMBA-induced rat breast tumours. The results indicated that ECCT has anti-proliferative and pro-apoptotic effects. The ECCT exposure in the DMBA-induced treatment group has significantly downregulated PCNA and ErbB2 expression while upregulating Caspase-3 and CD68 protein. Furthermore, ECCT therapy in rat breast tumours induced the significant downregulating of CCl2 and IL18 but did not affect IL23α and TNFα. The lowering of CCl2 and IL18 may correlate with an anti-proliferative effect of ECCT (Pratiwi *et al.,* 2019).

The differences in the electric field frequency may result in a distinct therapeutic effect. ECCT of 100 kHz of frequency serves caspase-independent apoptosis due to Caspase-3 downregulation. Moreover, a lower level of CD68 in ECCT-treated rat breast tumours than in those without ECCT exposure may inhibit M2 macrophage amplification (Alamsyah *et al.,* 2021). Conversely, Pratiwi *et al.* (2019) have proven that ECCT with a 150 kHz frequency provides caspase-dependent apoptosis, following significant upregulation of caspase-3 in rat breast tumours after ECCT exposure. Besides that, the increase of CD68 in that group shows the role of phagocytic cells, such as macrophages, to finalise the end of the apoptosis step, removing the apoptotic' cell debris (Pratiwi *et al.,* 2019). In addition, ECCT 100 kHz frequency (Alamsyah *et al.,* 2021) and 150 kHz (unpublished data) have increased CD8+ expression in rat breast tumours. Those results provide cytotoxic T cells against cancer cells. It suggests that ECCT may support immunotherapy effects. Instead, anti-proliferative and pro-apoptotic effects only.

The ECCT's effectiveness and efficacy have become more powerful in supporting its safety and affordable cost. The ECCT of 100 kHz and 18 Vpp does not affect normal mice, as proven by the normal skin layer surrounding the breast and breast tissue (Alamsyah *et al.,* 2015). Another specification, an ECCT of 150 kHz and 18 Vpp, did not affect breast tissue morphology (Pratiwi *et al.,* 2019). In addition, ECCT has been proven to be safe for the liver and kidneys of ECCT-treated rats bearing breast tumours. That electric field exposure has no significant effects on the histopathological injury of both organs (Nurhidayat *et al.,* 2022), as well as ECCT of 100 kHz frequency (Alamsyah *et al.,* 2023). Moreover, the creatinine, AST, and ALT levels of blood plasma were not significantly affected by the ECCT exposure (Nurhidayat *et al.,* 2022). Based on the pre-clinical research, ECCT has complied with the safety requirement but not yet on the total cost due to unfinished clinical trials. However, the data from a typically similar device, TTFields for GBM, has high treatment costs (Bernard-Arnoux *et al.,* 2016). Besides that, this device is not covered by any insurance companies. Therefore, the total costs exceed conventional treatments (Fabian *et al.,* 2019). Regarding this, there may be scepticism for further development since one of the reasons for complementary and alternative medicines (CAM) choosing is the affordable cost (Basry *et al.,* 2022). Furthermore, Basry *et al.* (2022) stated that the total cost of CAM (and other CAMs) for the long-term duration is higher than surgery (Basry *et al.,* 2022). Therefore, price regulation by health authorities is a crucial aspect of ECCT device continuity for breast cancer patients in the future.

However, ECCT has an additional value to offset the price issue. It may have the capability to trigger the immunotherapy effect. Therefore, ECCT is worth developing to treat breast cancer patients. An ECCT of 100 kHz and 18 Vpp has significantly increased CD8 in ECCT-treated rat breast tumours, indicating a good prognosis since it increases the immune system against tumour cells (Alamsyah *et al.,* 2021). Besides, an ECCT 150 kHz and 18 Vpp has upregulated CD68 in rat breast tumours after ECCT exposure (Pratiwi *et al.,* 2019). Furthermore, this specification of ECCT caused the over-expression of CD8+ in the same group (Unpublished data). It seems an ECCT, both 100 and 150 kHz, may induce and support the immunotherapy effect. Considering the previous data, the immunotherapy effect of using a combination of TTFields and chemotherapy for GBM patients may positively impact patients. It supports and enhances immune system activation by expressing HMGB1, a cellular stress signal secreted by dead cells (Zhu & Zhu, 2017). A similar result was obtained from ECCT-treated rat breast tumours, in which ECCT of 150 kHz increased HMGB1 expression (Fathurrohmah *et al.,* 2022).

Based on the ECCT brochure and publication, it is clear that ECCT was explicitly developed for breast cancer and has potency for its treatment. This invention is advantageous because this type of cancer is the most dominant in women (Sung *et al.,* 2021). The ECCT vest is easy to use for daily activities without assistance; thus, it may be an ECCT strength if the patients use it according to the procedures. Ignoring the data is incomplete (particularly clinical trials), it is clear that an ECCT treatment becomes valuable, prospective, and futuristic for breast cancer treatment. Further research will complete the puzzle.

Four described alternating electric field devices generating distinct specifications. However, those devices have a primary mechanism against cancer (Table 2). Similar characteristics of TTFields and ECCT provide both devices to inhibit cancer growth through anti-mitotic and pro-apoptotic capacities. While nsPEF and psPEF enhance the chemotherapy effect through electroporation and cell membrane modification.

Table 2. Action mechanism, advantages, and disadvantages among alternating electric field devices.

No.	Electric Fields device	Advantages	Disadvantages	Action mechanism
1	TTFields	- Non-invasive device. - Effective on ndGBM.	- Contact device, thus, induce mild to moderate skin problems, e.g., dermatitis. - Heavy battery. - Needs caregiver for the first time using. - Difficult to use for elderly and disabled patients. - Not covered by insurance.	- Anti-mitotic by spindle disruption and polymerisation microtubules inhibition (Giladi *et al.,* 2015). - Pro-apoptotic by Caspase-dependent pathway (Giladi *et al.,* 2015). - Anti-angiogenic (limited data) by inhibiting angiogenic factors (Kim *et al.,* 2016).
2	nsPEF	- Minimal invasive. - Support chemotherapy, drug-free and non-thermal therapy could be combined with immunotherapy (Iyer *et al.,* 2022).	- Mild uncomfort. - Needs standard therapy accompanying nsPEF treatment.	- Inducing electrochemotherapy, modification of cell membrane permeability, and electroporation effect (Iyer *et al.,* 2022). - Pro-apoptotic, disrupts tumour microenvironment, cytotoxicity effect, anti-angiogenic effect (Ren *et al.,* 2013) - Induce cell differentiation (Miao *et al.,* 2015).
3	psPEF	- Minimal invasive. - Support chemotherapy.	- Mild uncomfort. - Needs standard therapy accompanying psPEF treatment.	- Electrochemotherapy effect by modification of cell membrane permeability, electroporation effect (Iyer *et al.,* 2022). - Pro-apoptotic through Caspase-dependent signalling pathway and endoplasmic reticulum stress (Chen *et al.,* 2013).

				- Anti-angiogenic effect (Wu *et al.*, 2016; Wu *et al.*, 2019).
4	ECCT	- Non-invasive. - Non-contact device. - Light and easy to use.	- Daily and long-term using.	- Anti-mitotic through PCNA inhibition, pro-apoptotic through Caspase-dependent signalling pathway, and induce immune response (Pratiwi *et al.*, 2019; Alamsyah *et al.*, 2021).

IV. CONCLUSION

The specific character of external electric field devices correlates to the cancer types and their heterogeneity and complexity. In pro-apoptotic and anti-mitotic, the TTFields and ECCT induce cellular effects, whereas nsPEF and psPEF enhance chemotherapy by plasma membrane electroporation. Considering cancer hallmarks, it is crucial to investigate the impact of alternating electric fields on other aspects, e.g., angiogenesis, the presence of CSCs, and cancer cells' ability to evade the immune system. Therefore, it provides an overview to involve those aspects in further research. The immune system's involvement in the body in cancer treatment will make the treatment more natural and expressive. Related to this, ECCT is a prospectus for cancer therapy due to the research results and waiting for the clinical study to complete the data.

V. ACKNOWLEDGEMENT

This study was supported by the Indonesian Endowment Fund for Education (LPDP) through Beasiswa Unggulan Dosen Indonesia-Dalam Negeri 2019 (BUDI-DN 2019 scholarship), 2020022130196. We sincerely thank Anita Restu Puji R. for providing advice on language and proofreading.

VI. CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

VII. ABBREVIATIONS

This review includes several abbreviations for types of electric field devices and related terminologies:

CSC(s): Cancer stem cell(s)

CAM: complementary and alternative medicines

ECCT: Electro-Capacitive Cancer Therapy

ECT: electrochemotherapy

GEM: gemcitabine

HCC: hepatocellular carcinoma

ndGBM: newly diagnosed GBM

ns: nanosecond

nsPEF: nanosecond Pulse Electric Fields

O.S.: overall survival

PEF: Pulse Electric Fields

PSF: progression-free survival

ps: picosecond

psPEF: picosecond Pulsed Electric Fields

rGBM: recurrent GBM

STR: subtotal resection

TTFields: Tumour Treating Fields

TTP: the median time to disease progression

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