■ Review

ECCT: Physical Therapy for Cancer -clinical report-

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Abstract

Electro Capacitive Cancer Therapy (ECCT) is one of the Electrical Field (EF) therapy that play to evoke depolarization of microtubules at mitosis phase of cell cycle. Over the last decade, EF therapy has been implicated as major therapeutic determinants that confer resistance to conventional anti-cancer modalities including chemotherapy, radiotherapy, immunotherapy, targeted therapy, and anti-angiogeneic therapy. Here, we present an integrative medical approach to the pleiotropic indication of ECCT and discuss their emerging roles in relation to ECCT response and Electrical capacitance volume tomography (ECVT) index. Taken together, these findings suggest that ECCT may increase not only clinical efficacy but long-term survival benefit in anti-cancer strategies.

Key words ECCT, Electrical Field, cancer treatment, glioblastoma multiforme, microtubule

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Introduction

Cancer is the comprehensive term utilized to demonstrate a heterogenous group of various disorders characterized by rapid, uncontrolled growth of abnormal cells that can affect any part of the body. Cancer can change its genetic profile and go to other organs if not detected at an early stage, making it a difficult disease to conquer, resulting in still leading cause of death globally (1). The World Health Organization's International Agency for Research (WHO IARC) https://gco.iarc.fr/today/online-analysis-pie estimated 19.3 million cancer diagnosis with more than 50% mortality in 2020. And 49.2% of cancer death was occurred in Asia. Despite continuous efforts in cancer treatment strategies, cancers including lung, colorectal, prostate and stomach cancers still demonstrate deplorable five-year survival rate (2) especially with the global COVID-19 pandemic retarding diagnosis and obscuring to receive cancer treatment (3, 4). Recent progress in understanding the molecular based cancer biology have allowed swift action and approval of breakthrough drug including highly selective pharmacologic product as well as aim driving fundamental characteristic of cancer. Now that we're in an age of uncommon scientific advance against cancer. Notwithstanding this positive momentum, number of cancer related death has been steadily rising. Up-to-date developments in cancer research, especially in immunotherapy and targeted therapy, have initiated a reform. Electrical Field (EF) is the fourth modality in cancer therapy and is one of the most competitive emerging sphere in global biotechnology. Brain health, a Chinese company developing tumor treating fields, has made headlines when it raised about 100 million US dollar in 2021. We've been incorporating Electro Capacitive Cancer Therapy (ECCT) in Japan and overseas, which have a cooperative relationship centering on ECCT with conventional therapy, so that synergistic effects can be expected.

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Basic principle of EF is to collapse cell division by interrupting mitosis. There are two types of attractive machines until now. One is tumor-treating Fields (TTFields), the other is ECCT. TTFields are low intensity, medium-frequency, alternating EF through noninvasive transducer arrays setting up around the tumor. Because TTFields have found survival benefit in glioblastoma multiforme (GBM) patients, it led to its approval by FDA for recurrent and afresh diagnosed GBM after surgery and radiotherapy with adjuvant temozolomide (5-9).

ECCT, which employs exposure to alternating current (AC) electric fields, is an emerging alternative approach to cancer therapy. Preliminary study shows that treatment involving low-voltage (18Vpp) medium-frequency (100 kHz) electric field exposure in vitro can inhibit MCF-7 growth by 28-39% and cause carcinoma cell shrinkage in mice after 2 weeks of EF exposure (10). ECCT can also have an anti-proliferative effect on breast tumor, in terms of the down-regulation of IL-18 and CCL-2 whose roles in the development of breast tumor (11). Omat RH, et al proved that non-contact EF exposure induces apoptosis of osteosarcoma cell line (MG-63 Cell Lines) through p53-independent p21 pathway (12). Until now, in vivo studies on effects of alternating EFs condition, have been studied diligently (11,13-17). These studies demonstrated that anticancer effects were achieved at specific modulation frequencies, that is cancer cell type, and clarified proliferative inhibition and mitotic spindle disruption following exposure to alternating electric fields (14,18,19). Delving a novel therapy that specifically recognize and kills cancer cells without affecting normal cells, has been a recent objective in theranostics (18).

Historical Background of ECCT

ECCT has been developed for the first time by Dr. Warsito P. Taruno in 2010 to help his sister, Mrs. Suwarni, to fight breast cancer which was already in stage 4 when diagnosed in late 2009 and having mastectomy in early 2010 but refusing to have chemotherapy and getting no other treatment. After developing the first ECCT system and doing cell study which showed a promising result, Dr. Warsito developed ECCT bra powered with batteries for her sister as alternative to chemo. Her sister got remission after 2 months of wearing ECCT device, having recurrences 3 times within 5 years, but getting remissions again every time with ECCT, and now achieved 14 years of survival, free of cancer and in normal condition. 1 year after successfully helped her sister fighting with final stage breast cancer, Dr. Warsito helped a 21-year-old boy who was diagnosed with malignant brain cancer astrocytoma. The boy, who was already in paralyzed condition before treatment, has recovered to normal only after 2 months of ECCT treatment. He survived for more than 9 years but died for viral infection in June 2020. The boy is the first case of brain cancer treated with ECCT.

Mechanism of Action

Electric charges distribution during cell mitosis

During cell split under normal condition (A), replicated chromosomes are directed evenly to both sides of the cell poles to create two identical nuclei by the roles of microtubule spindles. The cell during split is highly electrically polarized, negatively charged on the center of both poles, and positively charged in the middle of the splitting cell where the replicated chromosomes are lined up (B). In the present of external EF, the charge distribution inside the splitting cell may be interfered, disrupting spindles arrangement and hence the process of chromosomes separation, resulting in an uneven chromosomes division that yields eventual cell death (self-destruction) (C). Different mechanisms of the cell death may exist dependent on the type of the cell, the mitosis speed (the grade of the cancer), and the modulation of the external EF (intensity and frequency). (Fig.1)

The roles of microtubules and charge distribution during cell split (mitosis)

Microtubules has a crucial role during cell split (mitosis). The spindle shape macromolecule is constructed by electrostatic (van der Waals) forces from small molecules called tubulin dimers, with negatively charged end on both poles, and positively charged end in the middle of the splitting cell. By an electrostatic interaction, the microtubule spindles direct the chromosomes towards both poles, and evenly separate the replicated chromosomes to create two identical nuclei, and hence cells. EF disrupt the normal polymerization-depolymerization process of microtubules during mitosis. During mitosis phase, microtubules are made up by assembling α- and β-Tubulin. EF induces depolymerization of microtubules,

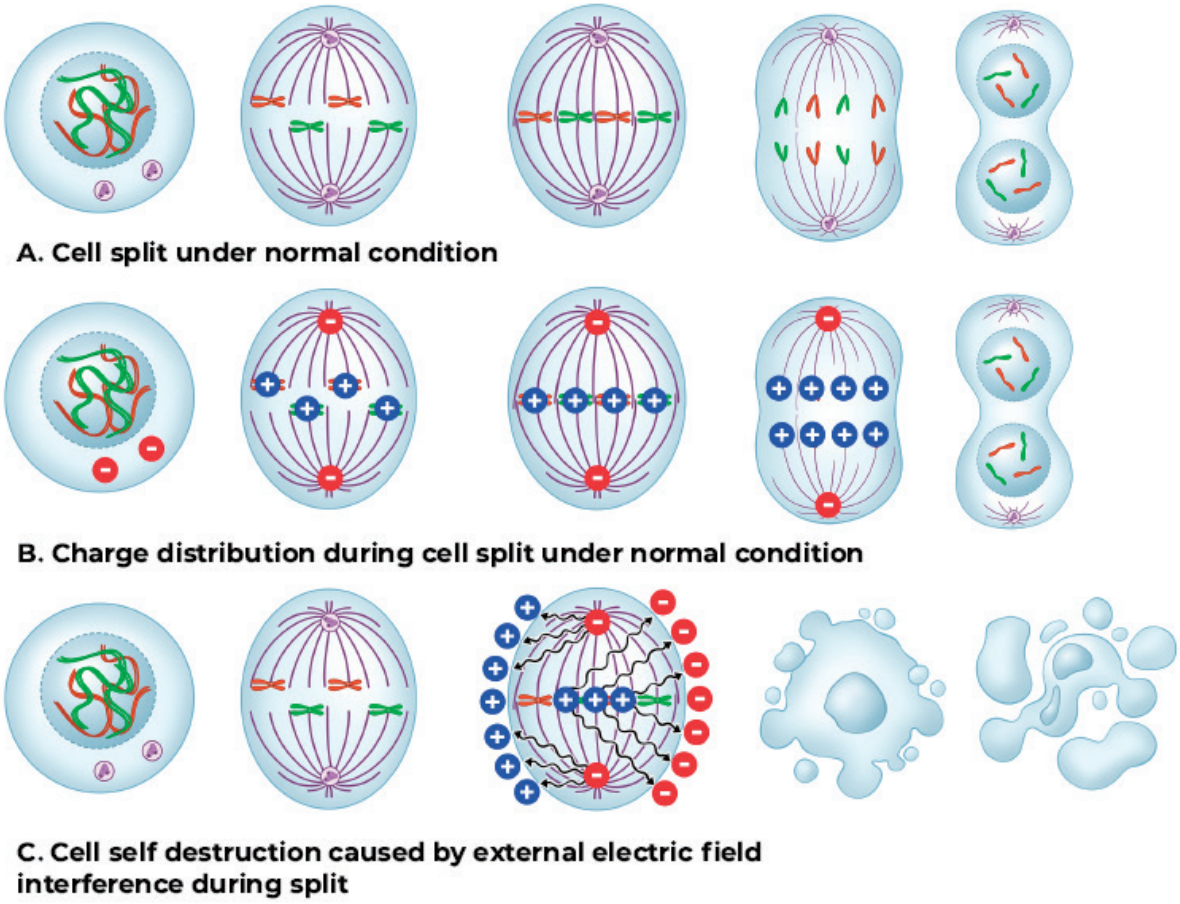


Fig. 1 Electric charges distribution during cell mitosis

that is, unwinds microtubules. Another mechanism, which interferes with cell division and is most likely to play an important role in cell destruction, becomes dominant during cleavage (13).

Patients and Methods

ECCT equipment

ECCT equipment comprises apparel and oscillation, is a method for treating and low frequency (<100kHz and intensity of <30Upp) of electro-static wave by capacitive electrodes embedded in apparels to wear (Fig. 2).

The battery is stored in the right pocket. This device contains thin metal, so do not lie down while wearing it. Also, keep it away from water such as rain. The size can be adjusted according to one's body shape. This suit is also available in longer and shorter versions.

Eligibility criteria

Patients 4 years of age or older were eligible if they had histologically or cytologically confirmed solid tumor malignancy that was metastatic or unresectable, and for whom either standard curative or palliative measures did not exist, were no longer effective, or for whom ECCT was an appropriate treatment strategy. In addition, Eastern Cooperative Oncology Group (ECOG) performance status 0-4, adequate organ and pulmonary function (oxygen saturation 86% when ambulating and not requiring supplemental oxygen). Measurable or evaluable/non-measurable disease per RECIST version 1.1 (RECIST 1.1) was required, as well as an accessible non-bone tumor lesion from which serial core biopsy specimens could be obtained.

Exclusion criteria, active disease or history of autoimmune disease that autoimmune might recur and affect vital organ function or require immune-suppressive treatment, and corticosteroid use (>10 mg daily prednisone equivalent) within 30 days of enrollment. The study was approved by the Institutional Review Boards of participating institutions, and participants signed a written informed consent prior to enrollment. The trial was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki.

This manuscript confers the mechanism of action of

Fig. 2 The cord at the back connects to the battery along with the cord at the torso. This device is easy to put on and take off.
A. Helmet type of ECCT device
B. Truncal type of ECCT device
C. ECCT oscillator

ECCT, currently progressing treatments in solid cancers and pivotal phase II trial in GBM.

Toxicity and Adverse Effect

All 5,195 enrolled patients showed no high-grade systemic and local toxicity related to ECCT treatment.

Local pain occurred in the three patients of lung carcinoma, etc. Grade 0-1 of hematological disorder was observed. But recovered after ECCT treatment. Multiple clinical trials conducted to date have reported no other significant ECCT related adverse effects for several years.

Clinical Responses

Electrical capacitance volume tomography (ECVT), developed from the two-dimensional electrical capacitance tomography (ECT), is a promising non-intrusive imaging technology that can provide real-time three-dimensional images of the sensing domain (20). ECVT technology is based on utilizing nonlinear distributions of electric field lines to reconstruct a volume image of different materials in the imaging domain (21). The 3D ECVT sensor design variability coupled with a robust image reconstruction algorithm render it possible to obtain, in good quality, the real-time, 3D images of multi-phase flows in the sensing domain from capacitance measurements.

(21, 22). Our group classified ECCT response and ECVT index into 5 types (Fig.3).

Case 1. Female (36 y.o.), Breast cancer, invasive ductal carcinoma, metastasized to bone, lung, liver.
ECVT index: GROUP B
Progress: At the time of initial diagnosis, the breast cancer on the right side had metastasized to the lungs and bones, and despite chemotherapy, the breast cancer had spread and invaded the skin (upper left, 10/12, Fig.4). Soon after ECCT treatment was started, the cancer gradually softened and exudate came out. After 3 months, the exudate stopped coming out and slowly decreased until 2 years later. Lung (1/14) and bone (3/14) metastases tended to improve. Three years later, the bone metastasis had not disappeared completely, so chemotherapy and radiation therapy were performed, resulting in liver failure.
Remarks: The patient's cancer ECVT index GROUP was B, and there was no problem with the leakage of dead cancer cells. However, her general condition might not be function well and her immune system was weakened, so the bone metastases did not disappear. Her liver failure maybe caused by chemotherapy and radiation therapy.

Case 2. Female (50 y.o.), Breast cancer (invasive ductal carcinoma) metastasized to bones.
ECVT index: GROUP B
Progress: Although radiation therapy was performed after surgery for the left breast cancer, the cancer had already metastasized to bones throughout the body (Fig.5). For 7 months before ECCT treatment, she was unable to get

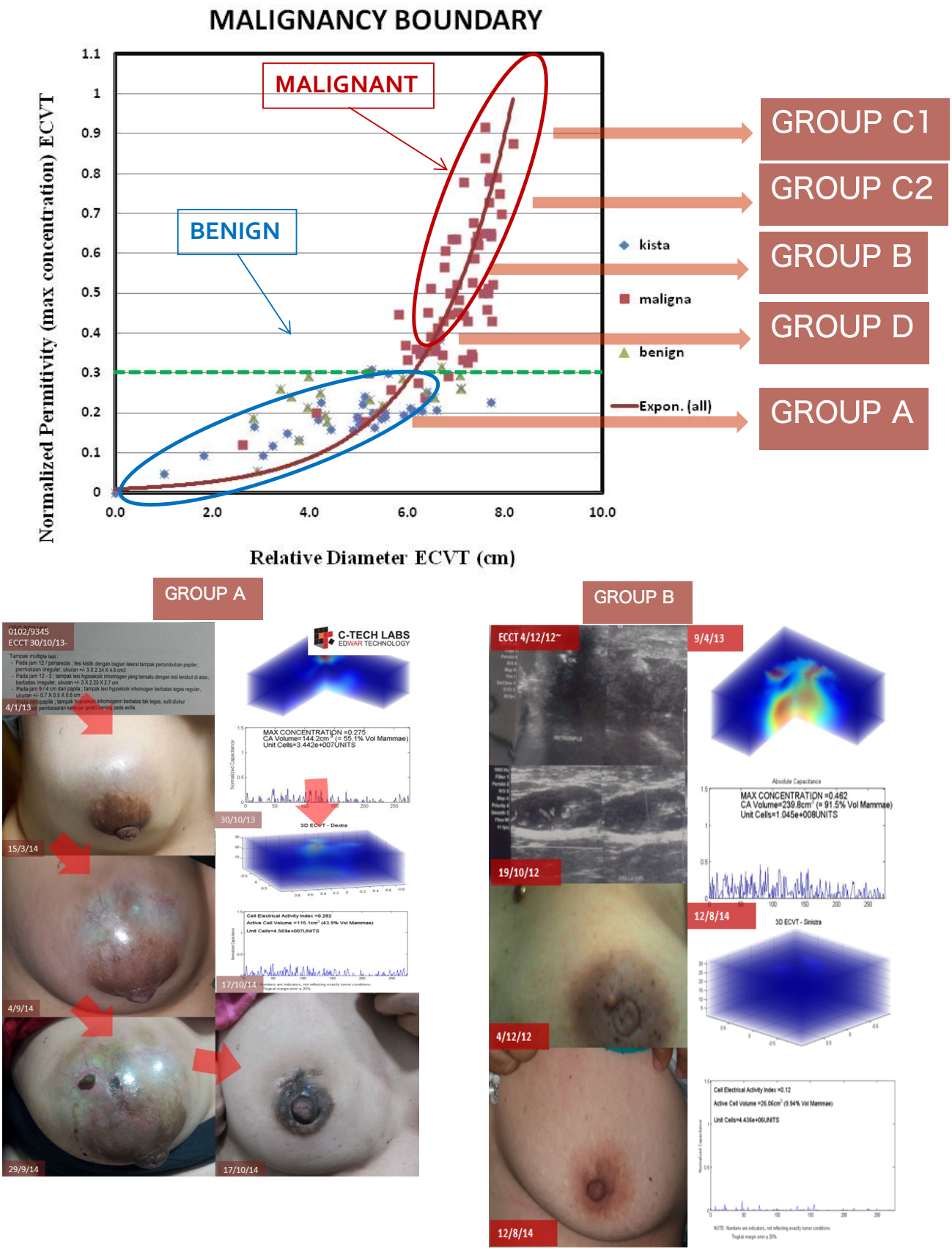
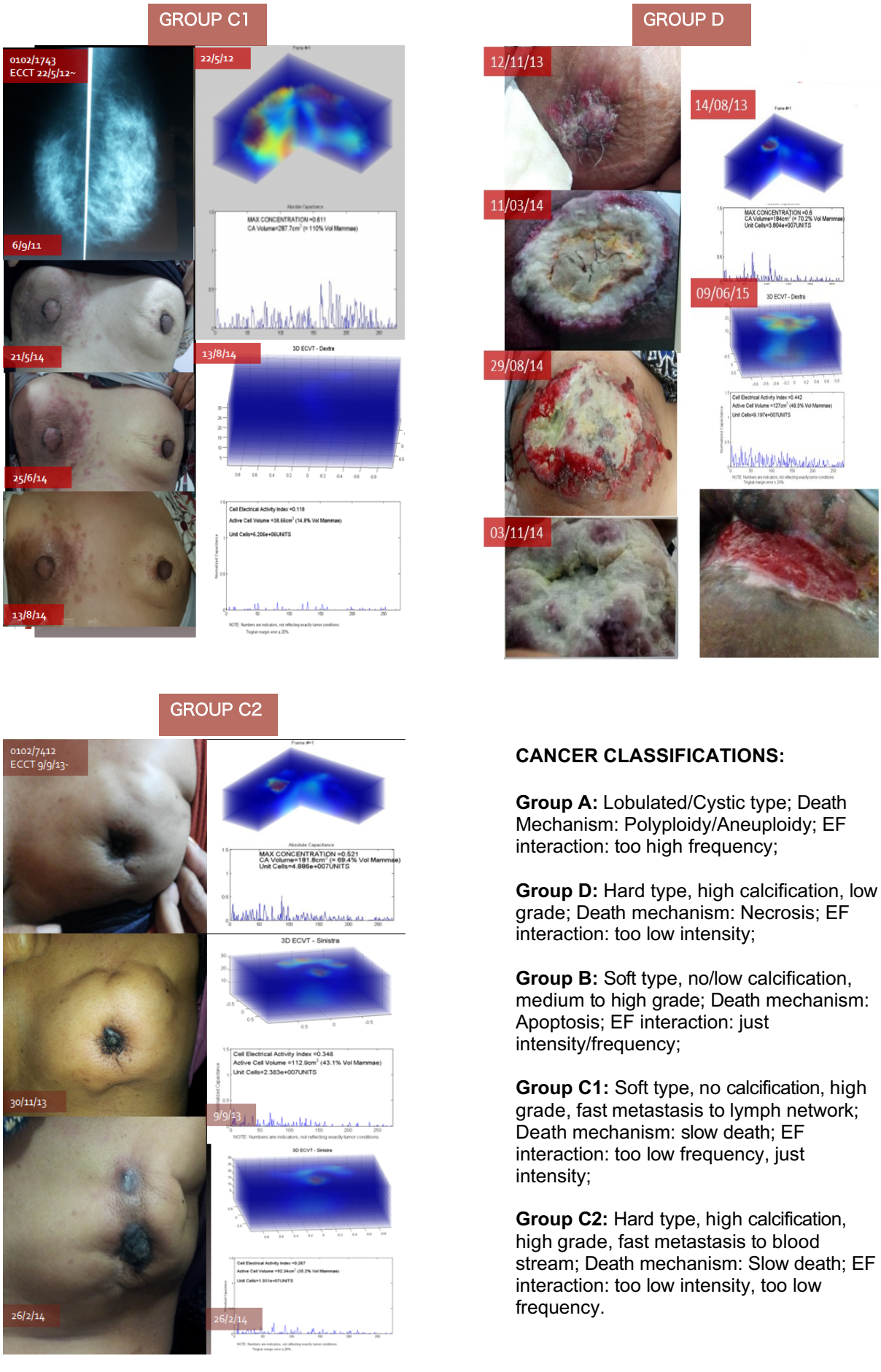


Fig. 3 Clinical classification of ECCT response and ECVT index (continued)



CANCER CLASSIFICATIONS:

Group A: Lobulated/Cystic type; Death Mechanism: Polyploidy/Aneuploidy; EF interaction: too high frequency;

Group D: Hard type, high calcification, low grade; Death mechanism: Necrosis; EF interaction: too low intensity;

Group B: Soft type, no/low calcification, medium to high grade; Death mechanism: Apoptosis; EF interaction: just intensity/frequency;

Group C1: Soft type, no calcification, high grade, fast metastasis to lymph network; Death mechanism: slow death; EF interaction: too low frequency, just intensity;

Group C2: Hard type, high calcification, high grade, fast metastasis to blood stream; Death mechanism: Slow death; EF interaction: too low intensity, too low frequency.

Fig. 3　Clinical classification of ECCT response and ECVT index

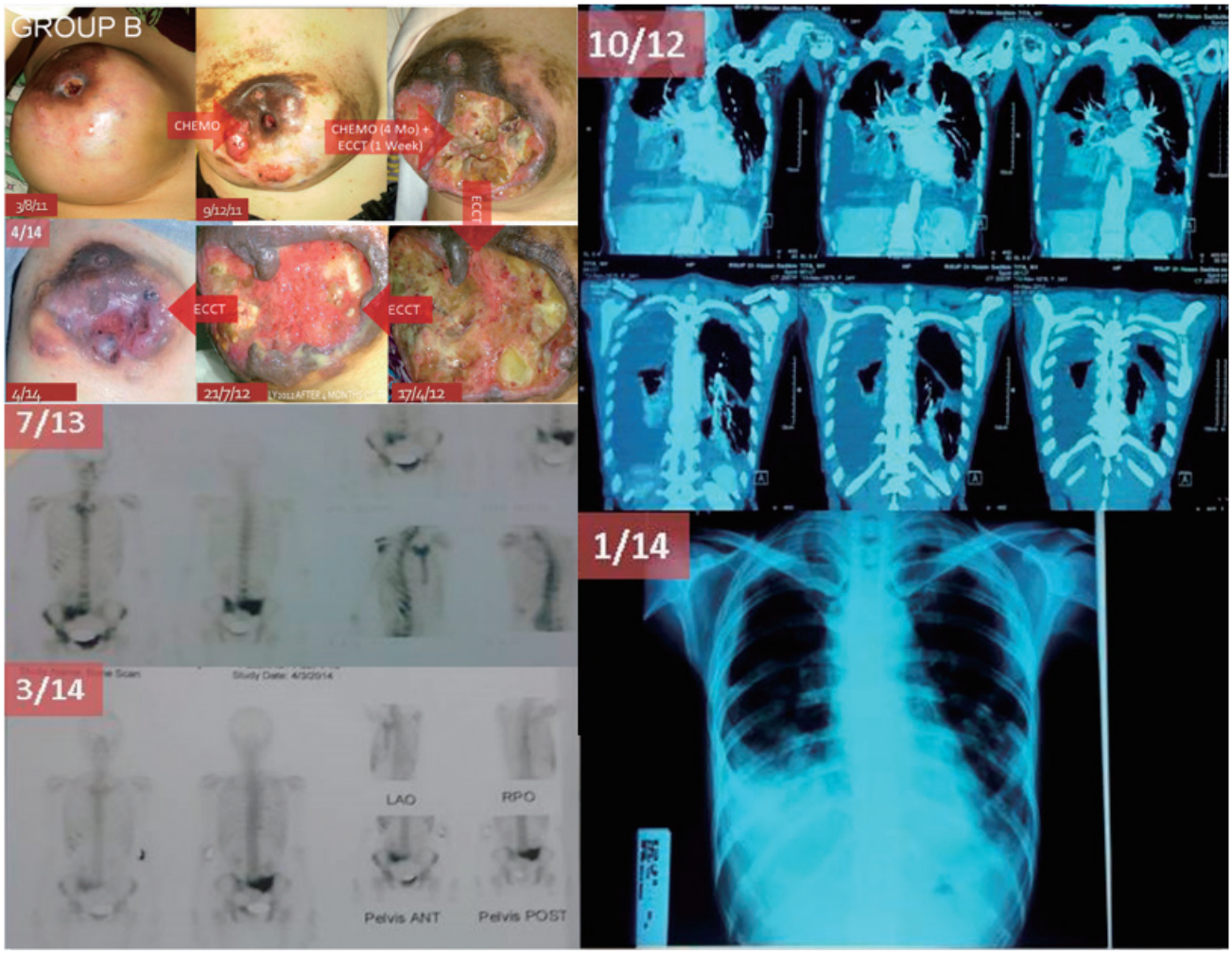


Fig. 4 Case 1. Female (36 yo), Breast cancer

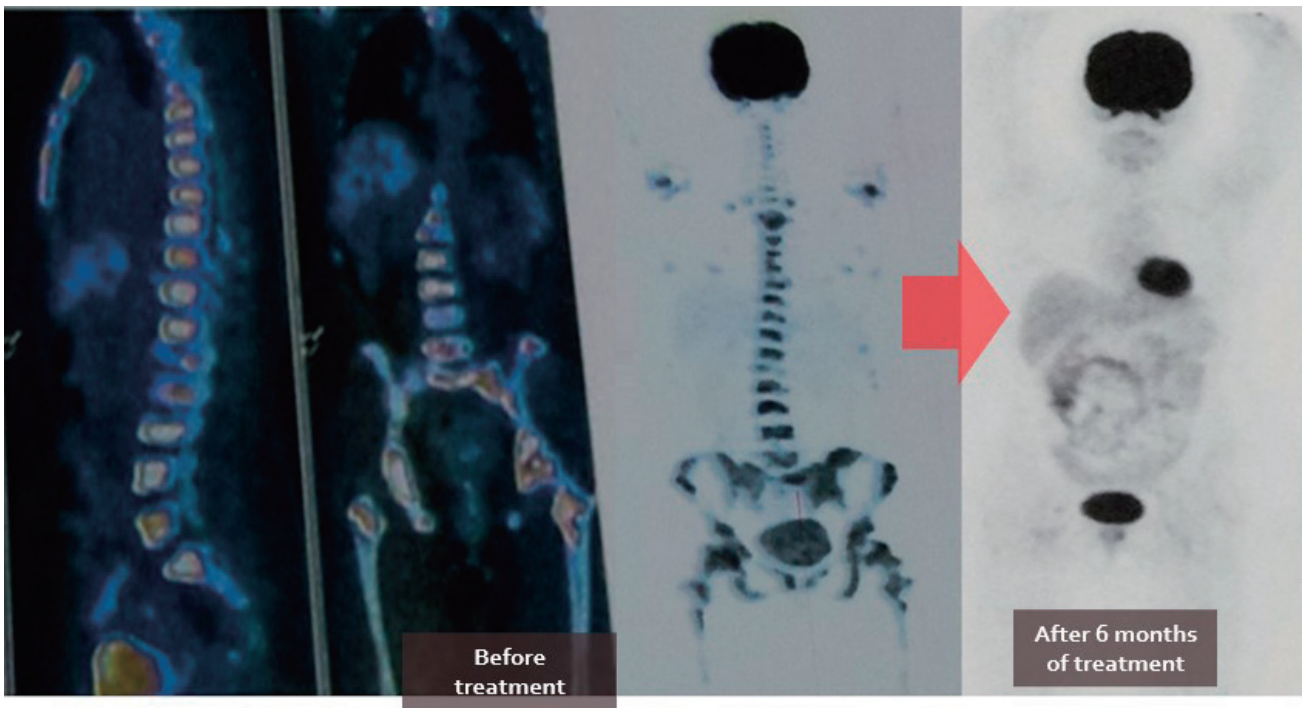


Fig. 5 Case 2. Female (50 y.o.), Breast cancer

out of bed due to pain in her spine and pelvis. After starting ECCT, the patient's pain gradually decreased and her general condition improved, and she became asymptomatic 7 months later. PET-CT 6 months after ECCT treatment revealed that the cancer had disappeared. All blood tests then were also normal. Five years later, she was confirmed to be alive.

Remarks: In ECVT index GROUP B, dead cancer cells are easily excreted from the body, as is the case with medium to high grade invasive ductal carcinoma. In GROUP D type patients with bone metastases, dead cancer cells are typically hard to kill. For GROUP C2 type patients with bone metastases, the cancer progresses and metastasizes quickly, making difficult to achieve CR and not recommended alone.

Case 3. Male (22 y.o.), Brain cancer

ECVT index: GROUP D

Male diagnosed with brain tumor at the pineal area extended to thalamus: The tumor mass is located at the mesenchepalon (pineal region) pressing to thalamus, causing impaired vision and severe headaches to the patients (23/11/12, Fig.6). After 4 months of ECCT treatment, the tumor size gradually decreases (1/4/13) and the patient continues to improve clinically. After 15 months of treatment, the tumor mass is almost undetectable by MRI (6/3/14) and the patient's condition almost recovered to normal. The tumor mass in this case is located in the area linked to the fourth ventricle through where the complete disposal of the resulted dead cells can occur. Using the ECCT the entire tumor in this case could be expected to disappear completely without surgery.

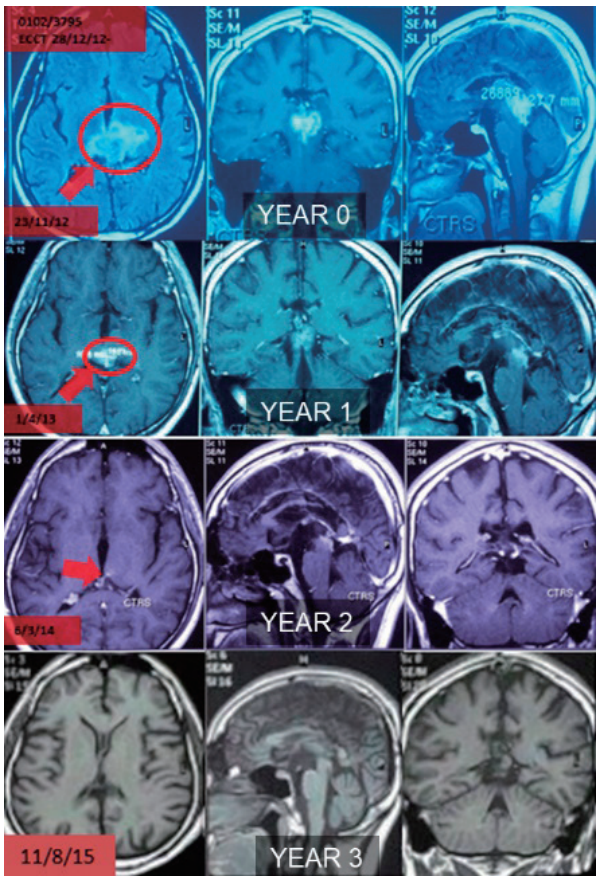


Fig. 6　Case 3. Male (22 y.o.), Brain cancer

Case 4. Male (9 y.o.), Brain cancer (WHO Grade 3, Pineal Parenchymal Tumor).

The tumor was close to the fourth ventricle (17/9/13, Fig.7). The dead cells that occur in the brain owing to ECCT. Treatment excreted into spinal fluid. 6 months later MRI (1/3/14) revealed that his hydrocephalus had improved.

Case 5. Male (41 y.o.), Lung cancer metastasized to pleura.

The patient was diagnosed with lung cancer in the left lung sized 6.8x12.5cm at the hilar; the mass stuck to the heart, the main artery and esophagus, and a massive pleural effusion identified (22/6/13, Fig.8). The initial condition of the patient was complaining with shortness of breath, coughing and chest pain. The presence of

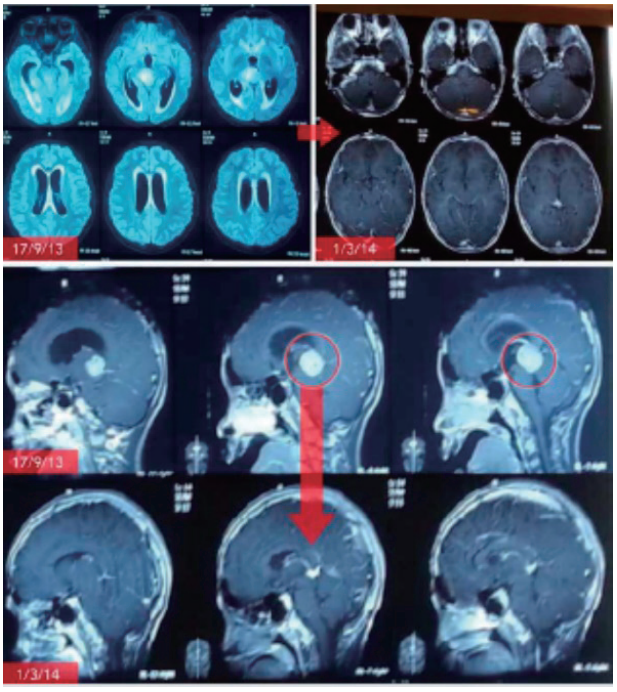


Fig. 7　Case 4. Male (9 y.o.), Brain tumor (pineal gland cyst tumor)

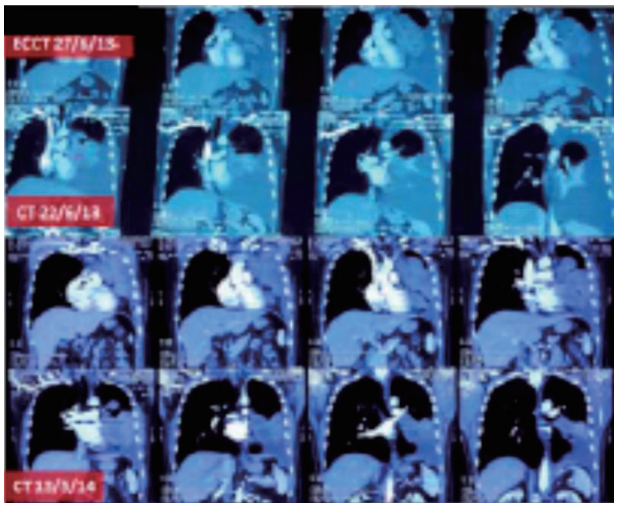


Fig. 8 Case 5. Male (41 y.o.), Lung cancer

pleural effusion required the patient to get drainage of the fluid every 5 days of up to 2000ml. In the early use of ECCT, the shortness of breath, coughing and pleural fluid increased, but the pain quickly reduced. However, after 3 months of treatment, the coughing, shortness of breath and pleural fluid in the lungs began to disappear, and after 1 year of treatment the size of the mass began to shrunk (13/5/14). The last condition of the patients (as of June, 2015): the shortness of breath almost gone, coughing completely gone. The lung fluid was no more identified, but the solid residue from the settling lung fluids was still remaining.

Case 6. Female (66 y.o.), Lung cancer (small cell carcinoma) metastasized to lungs.
ECVT index: GROUP C1

Due to multiple lung metastases from lung cancer, she was forced to lose a lot of weight due to coughing and chest pain (29/8/14, Fig.9). 3 months after starting ECCT, her chest pain and cough subsided (4/2/15). Her appetite had recovered completely. But she could not survive more than 3 years for lack of monitoring.

Remarks: ECVT index GROUP C1 lung cancers are highly progressive and fast metastasize to both lungs and other organs, mainly lymphatic system and brain. Though good progress was achieved, long-term and intensive monitoring and care must be given for the type of cancers. Otherwise, short-term outcomes may not benefice for long-term survival.

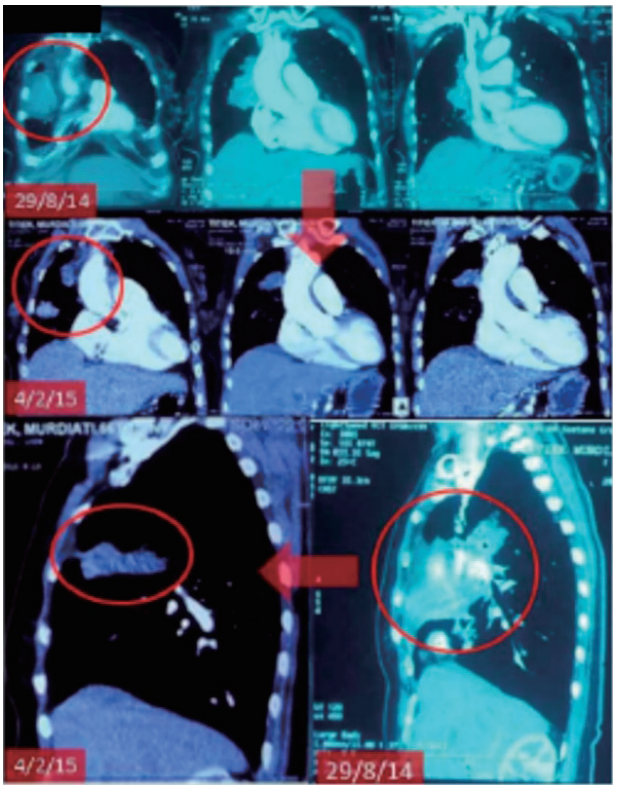


Fig. 9 Case 6. Female (66 y.o.), Lung cancer

Case 7. Female (66 y.o.), Lung cancer metastasized to bones.

Lung cancer with bone metastasize: The patient was diagnosed with a tumor mass in the right lung at the suprahilar with metastasize on the spine (CT 2/10/13, Fig.10). The patient initially could only lie on the bed, and was very weak and feeling shortness of breath due to pleural effusion in the both lungs. During early use of ECCT, the patient felt severe pain on the bones so the usage was very limited. After one month of treatment, the pain on the bones began to decrease, and after 3 months the general condition began to improve. After 7 months of treatment, the tumor mass on the lung and the bones showed significant reduction (CT 25/5/14), and the patient showed significant clinical improvement, having able to stand up and walk slowly, and the shortness of breath, coughing and lung fluid was completely gone.

Case 8. Female (55 y.o.), Malignant Lymphoma (Non-Hodgkin's lymphoma).
ECVT index: GROUP C1

Progress: Non-Hodgkin's lymphoma had spread from the neck, around the esophagus, to the mediastinum area, and was in contact with the heart (15/8/13, Fig.11A). She was unable to eat or drink water, was in poor general

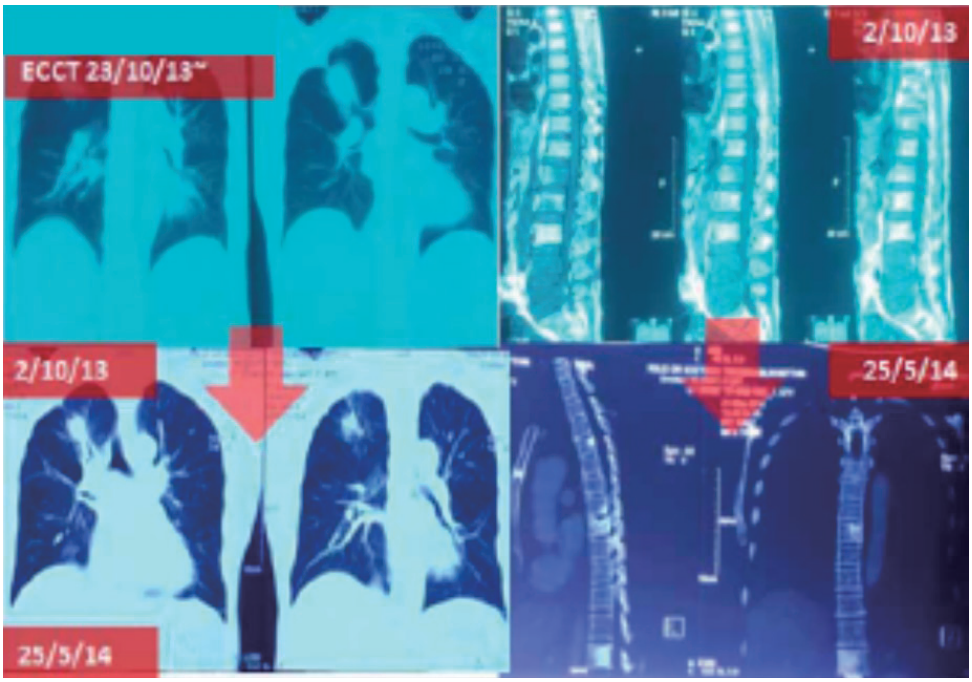


Fig. 10 Case 7. Female (66 y.o.), Lung cancer metastasized to bones

condition, and remained in a hospital bed for two weeks without treatment. After starting ECCT, she improved day by day and was able to walk again, and was discharged from the hospital in 2 weeks. The lesion in her neck shrank within two months, and a photograph taken nine months later confirmed that the lesion in her neck and thoracic cavity had disappeared (Fig.11B). She is still alive after 7 years with no recurrence.

Remarks: ECCT is highly effective against malignant lymphoma in general. However, ECVT index GROUP C1 cancers progress quickly, metastasize quickly, and are prone to recurrence, so long-term observation is recommended. Non-Hodgkin's Lymphoma is a good indication for high-grade lymphoma, and the response is slow for low-grade Hodgkin lymphoma.

Case 9. Female (44 y.o.), Breast Ca. post ope. Post chemo+RT, brain, lung, bone, L/N metastasis (Non-Hodgkin's lymphoma).
ECVT index: GROUP C1
Progress: This patient had conducted radical mastectomy, radiotherapy and chemotherapy, but the cancer has spread to the bones, lungs, lymphatic system and brain (22/1/13, Fig.12). The patient's condition before ECCT

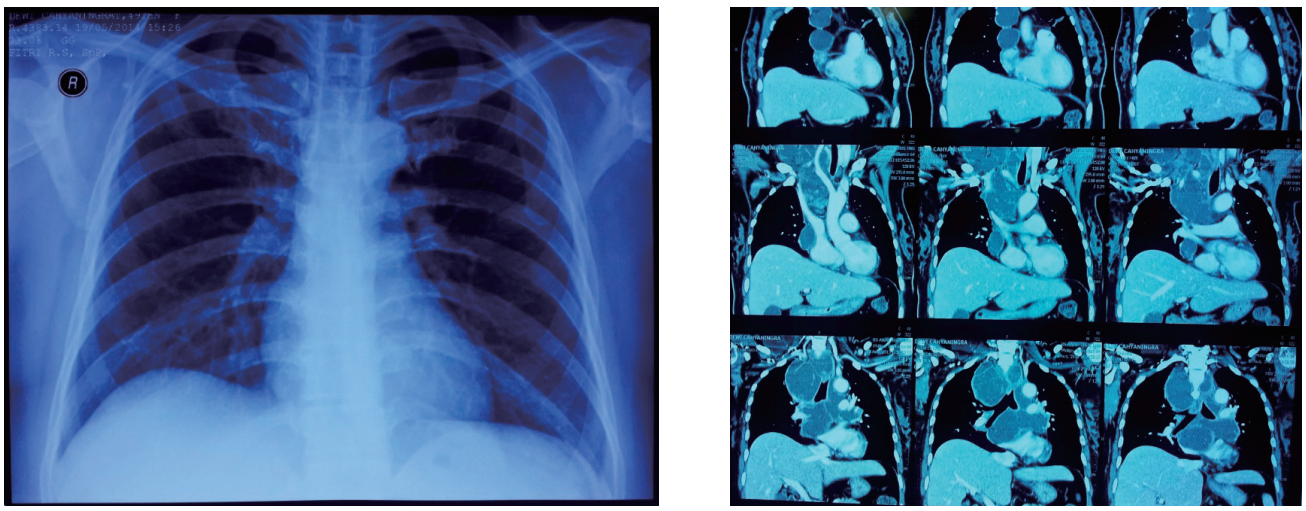


Fig. 11A Case 8. Female (55 y.o.), Malignant Lymphoma

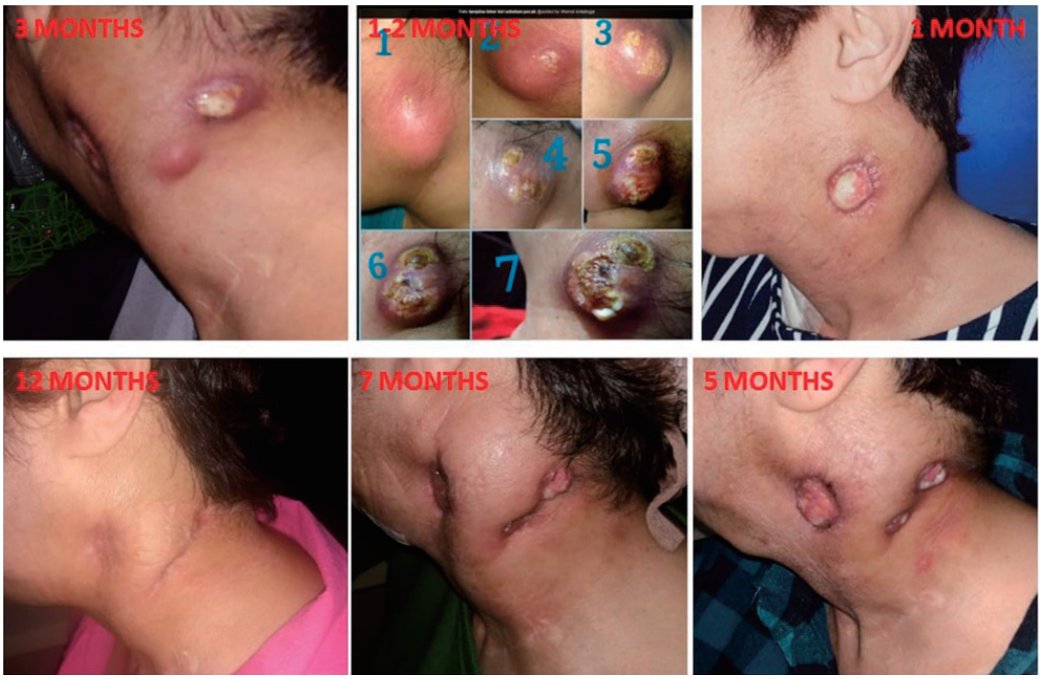


Fig. 11B Case 8. Female (55 y.o.), Malignant Lymphoma

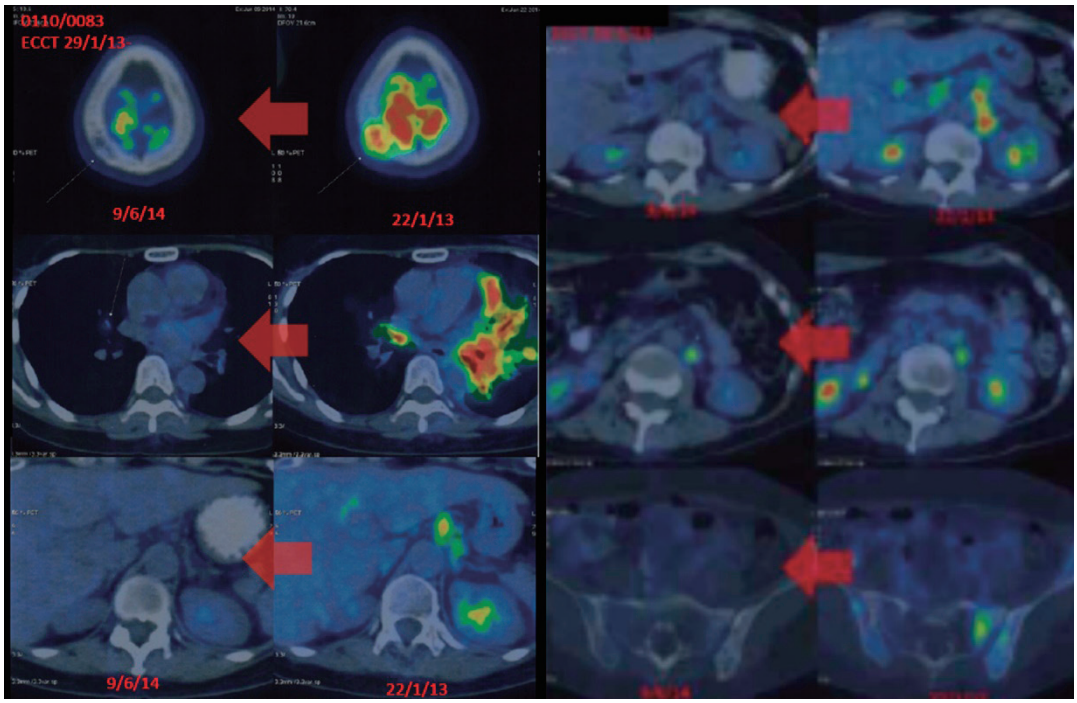


Fig. 12 Case 9. Female (44 y.o.), Breast Ca. post ope. Post chemo+RT, brain, lung, bone, L/N metastasis

treatment was weak and feeling intense pain in her bones. After ECCT treatment of 1-2 months, the pain on the bone gradually diminished. After 1.5 years of ECCT treatment, the PET-CT scan (9/6/14) showed the metastasized nodules have almost completely gone. Her condition was improving very well with no essential complaints and all indicators in normal levels during 2 years of treatment and monitoring, but no long-term monitoring was done for this patient.

Remarks: This is a ECVT index GROUP C1. The cancer can relapse easily when the body immune system weakened. The patient, though got a good progress in the with ECCT treatment, long term monitoring and continued treatment with ECCT is needed for long-term survival.

Median OS was 28.9months (95% CI, 27.5-65.5) in the ECCT arm and 15.6months (95% CI, 13.3-19.1) in the Temozolomide (TMZ) arm (Fig.13).

Following the results of a pilot study demonstrating the safety and tolerability of ECCT since 2010 in newly diagnosed and recurrent GBM patients were analyzed. Baseline characteristics were not balanced between the study arms receiving either ECCT or TMZ alone: N = 28 for ECCT and N = 105 for TMZ alone (6). The enrolled patients had a median age of 46 years, ECOG-PS (Eastern Cooperative Oncology Group-Performance Status) 0-4, and had been diagnosed a median of 11.8 months. The primary endpoint was OS; quality of life (QoL), and safety. Radiologic response was evaluated by brain MRI. QoL was determined by an EORTC-developed questionnaire (23), and measurements were repeated every 2 months (24). Results showed a median survival of 28.9 versus 15.6 months in ECCT treatment versus Temozolomide alone, respectively. We don't evaluate statistical significance of the two arms because we couldn't obtain TMZ alone data except OS and patients baseline characteristics of GBM treatment. As for QOL and safety, ECCT treatment resulted in a higher QOL and less adverse event (2% vs. 16%). The most common side effect observed was local pain (3%) at the site of cancer although it's difficult to distinguish between tumor growth or destruction and side effects of treatment. Further, we could apply ECCT treatment on cancer patients of PS 3, 4 with some evident recovery.

Discussion

Alive cells apply electric fields associated with cell function (25). The intensity of the electric fields within a cell is less than 10 V/cm (14), but within cell membrane they may reach 105V/cm, and cancer cells possesses higher cellular potential than normal cells (26). Homogenous electric fields align their force lines to direct centrioles (27), whereas inhomogenous electric fields direct centrioles toward higher field intensity, demonstrating dielectrophoresis (28, 29). Therefore, AC fields of 100 kHz or above are known to have no significant biological effects (13). The force applied by electric fields on centrioles is maximal when the dipole is oriented in the direction of the fields (30). Under this circumstance, cancer cells during mitosis contain highly

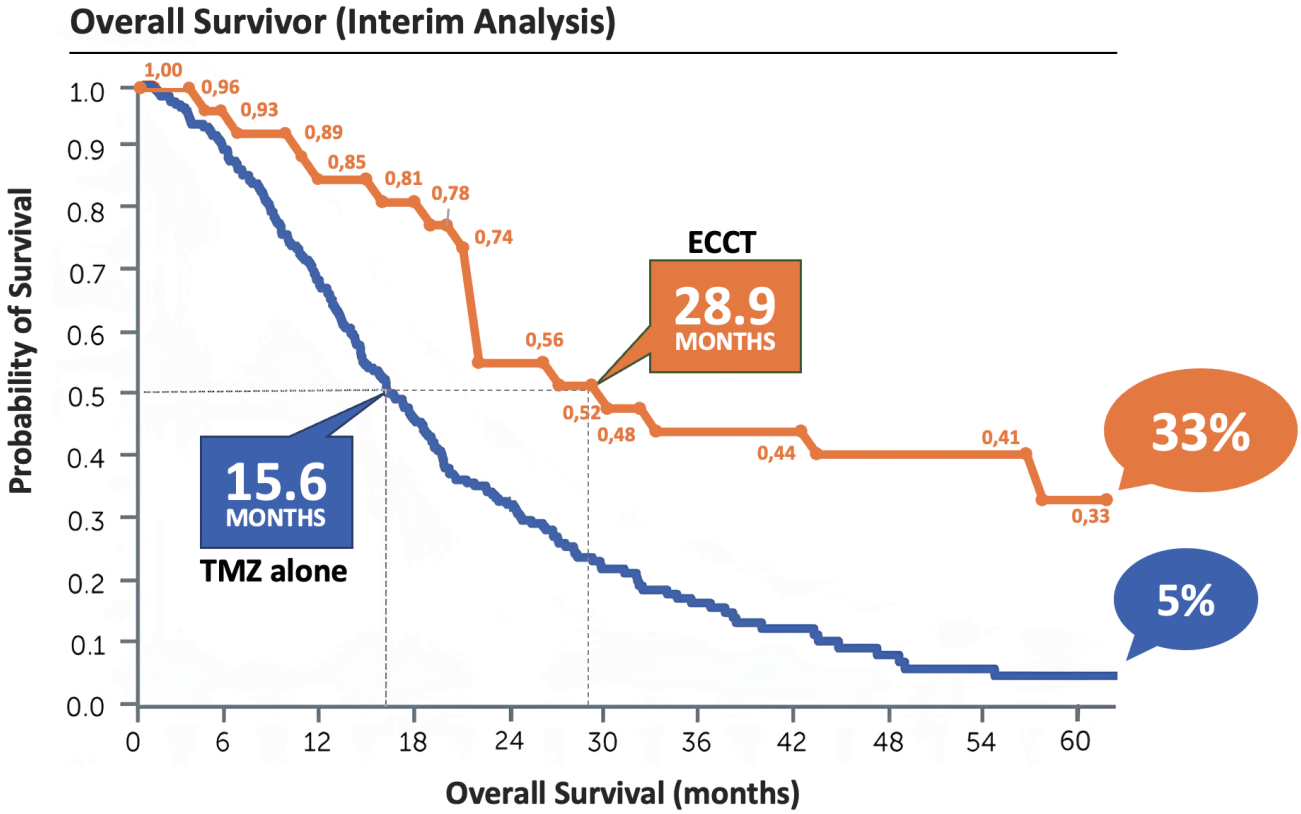


Fig. 13　Kaplan-Meier analysis for patients with GBM treated with ECCT or temozolomide alone
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polar, spatially oriented microtubules (31) and that they would be affected with maximal force when the mitotic process oriented along the lines of force of the fields (13). The spatially oriented microtubules consist of α and β tubulin heterodimers that have large electric dipole moments (31), thus could be disoriented by the forces of the electric fields (32, 33). Our preliminary clinical cases manifest that ECCT has potential to destruct cancer tissue without suffering from severe side effects even in PS 3-4 cancer patient. In addition, ECVT index may predict clinical outcome of ECCT treatment.

Recently, Purnami SW, et al. reported significance of ECCT against three solid cancers (breast cancer, brain cancer, and lung cancer) by demonstrating cox model survival analysis. Of note, the hazard ratio (HR) value ranges from 0.8-0.9 (34). In this Kaplan-Meier analysis of ECCT against GBM, the data has updated and reveals improvement of median OS even though including cancer patients of PS3-4.

Currently, preclinical study manifests moderate outcomes of ECCT against solid cancer universally. In addition, latest advancement of C-Tech Labs EDWAR Technology led by Warsito PT enables shorting of treatment time from average 4 to 12 hours per day. Although there is still a long way to go to improve outcomes for solid tumors other than GBM, such as curing all patients treated with ECCT, this advancement will undoubtedly benefit more patients.

To consider its limited side effect of ECCT compared to other conventional modalities, this is highly recommended for those who suffering from adverse effects of chemo- and/or radiotherapy to achieve long survival benefit. Likewise, combining this with immune checkpoint inhibitors may ameliorate treatment outcome although it requires further investigation. Observations of clinical benefit that are made from the real-world use of a cancer therapeutic are increasingly being utilized to support U.S. Food and Drug Administration (FDA) decision-making and the acceleration of new drug approvals, more innovation is clearly needed. It is desirable to have a treatment like EF, which has few side effects, can be started quickly, and is not affected by genetic abnormalities in the cancer. ECCT is a promising microtubule target cancer treatment. Further evaluation in each cancer type is still necessary. Possible directions may include modifications in the intensity and frequency applied and further optimization of the array layout. We've been extending our scope of ECCT to any solid cancers.

Conclusion

Here, we describe the clinical profile of ECCT, an investigational, microtubule-directed, in retrospective analysis for safety, tolerability and efficacy in patients with advanced or intractable solid cancers. ECCT is an innovative and noninvasive therapeutic approach to cancer therapy. For better understanding of ECCT properly, future clinical investigation about other cancers should be extended.

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