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Conference Paper

Oncothermia Research at Preclinical Level

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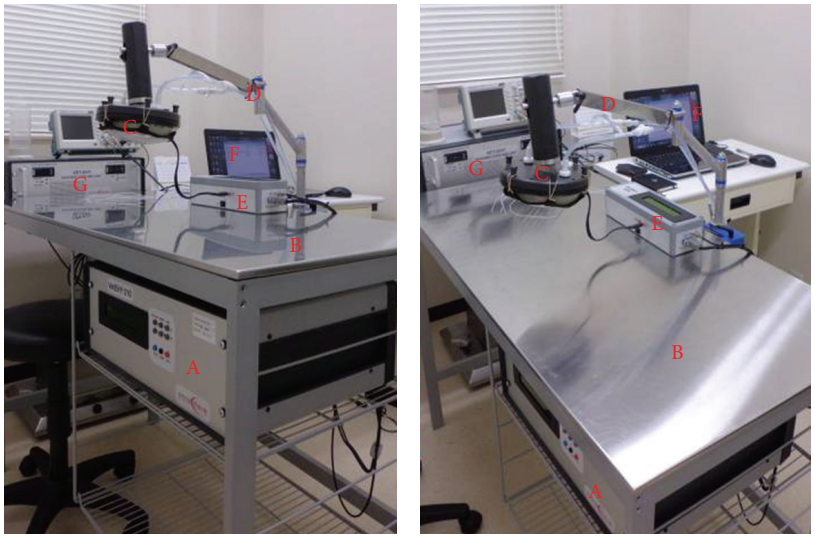
We describe a new electrohyperthermia (oncothermia) method and a tumor treatment system, which was developed to cure companion animals having spontaneously occurring tumors. This dedicated veterinary oncothermia device plays a dual role; this can be a new hope to successfully treat companion animals having tumors. And during these treatments, we can get a large amount of valuable information about the real nature and parameter of the applied electromagnetic field and the behaviour of the tumor under this special modulated radiofrequency field. Then, this experience and knowledge can be transferred directly to the human clinical application to develop more precise treatment systems for human clinical oncology.

1. Background

Oncothermia method (OTM) is a long-time (since 1989) applied electrohyperthermia treatment modality in human clinical oncology [1]. Its clinical results are excellently showing the advantages of the method [2]; however, the details of its mechanism of action are intensively investigated even now. Oncothermia research group conducts investigations at all levels of scientific research, from in vitro studies to human clinical trials [3]. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven in vivo [4], but the complex electromagnetic parameters playing crucial role to achieve these antitumor effects had not yet exactly been determined.

On the other hand, in the veterinary oncology practice there is a huge need for an effective treatment to cure malignant diseases due to the increasing incidence of cancer in pet animals [5]. In the past decades, a lot of hyperthermia methods were developed for human oncological treatments, and many of them were also tested in the field of the veterinary clinical practice. Whole body hyperthermia was used with limited success due to the serious side effects [6–9]; therefore, locoregional hyperthermia techniques became more prevalent. These techniques use the energy of the electromagnetic field to heat up the tumors. Several different radiofrequency (RF) methods were tested, like local current field technology which was very successful to treat surface-localized tumors [10–12]. Interstitial hyperthermia methods when metal needles were placed invasively into the tumor, and RF current was applied via the needles [13, 14]. Microwave (MW) technologies were also tried in veterinary hyperthermia with varying clinical success [15–17]. The most interesting capacitively coupled RF technology was described in [18] where the tumor was heated up selectively with great efficacy. Unfortunately, this very promising technology was forgotten.

Presently, contrary to the huge demand, in the veterinary practice, there is no any really effective, relatively cheap,



(a) (b)

Figure 1: The VetEHY510 system prototype and its main parts: A: main unit, B: metal treating table as a grounded counter-electrode, C: active treatment electrode, D: electrode holder arm, E: patient box, F: controlling computer, and G: table heater and electrode cooling water thermostat and pump unit.

and easy to use tumor treating system in the hand of the veterinarians to fight against pet cancer. For these reasons, Oncotherm created a specialized research device for preclinical investigations/veterinary clinical use, the VetEHY510 system, presented in Figure 1.

The VetEHY510 system was created to serve dual purposes:

(i) give a powerful, effective, and easy to use device for veterinary oncologists to fight against pet cancer and to provide information about the treatment efficacy of oncothermia method for comparative clinical oncology,

(ii) collecting information and a wide range of measured electromagnetic parameters, which can help to optimize the treatment protocols and clarify the real role of electromagnetic treatment parameters which are governing the best clinical outcome.

2. Materials and Methods

Using the VetEHY device in Tottori University, Veterinary Medical Center, we treated companion animals (dogs and cats) having different kinds of tumors (liver tumor, soft tissue sarcomas, lung tumor, lymphomas, melanoma, etc.) under the supervision of professional vet oncology specialists and kept the animal ethical regulations. The use of the dedicated veterinary device is shown in Figure 2.

These spontaneously occurring tumors are the best "models" of human malignant diseases. Getting treatment information and experiences on behavior of these tumors from these pet patients is extremely valuable, transforming directly to human practice to improve the clinical results (Figure 3).

Scientists in oncology just start to realize the importance of the involvement of veterinarians to a real preclinical research work. The newest edition of Withrow and MacEwen's Small Animal Clinical Oncology [5] briefly summarizes the aspects of companion animal cancer that enables attractive comparative models in a real preclinical investigation. To emphasize the real value the information which can be collected during the experimental treatment of companion animals, we would like to cite some points from the aforementioned book.

(1) Companion dogs and cats are immunologically intact animals (like humans) as opposed to many experimental models of rodents and other animals.

(2) Cancers seen in practice are spontaneously developing as opposed to experimentally induced and better recapitulate the natural human and veterinary condition.

(3) Companion species have a higher incidence of some cancers (e.g., osteosarcoma, non-Hodgkin's lymphoma) than humans.

(4) Most animal cancers progress by more rapid rate than their human counterpart. This permits more rapid and less costly outcome determinations such as time to metastasis, local recurrence, and time of survival.

(5) Because fewer established "gold standard" treatments exist in veterinary medicine compared to human medicine, it is ethically acceptable to attempt new forms of therapy (especially single-agent trials) on an untreated cancer rather than wait to initiate new treatments until all "known" treatments have failed, as is common in the human condition.

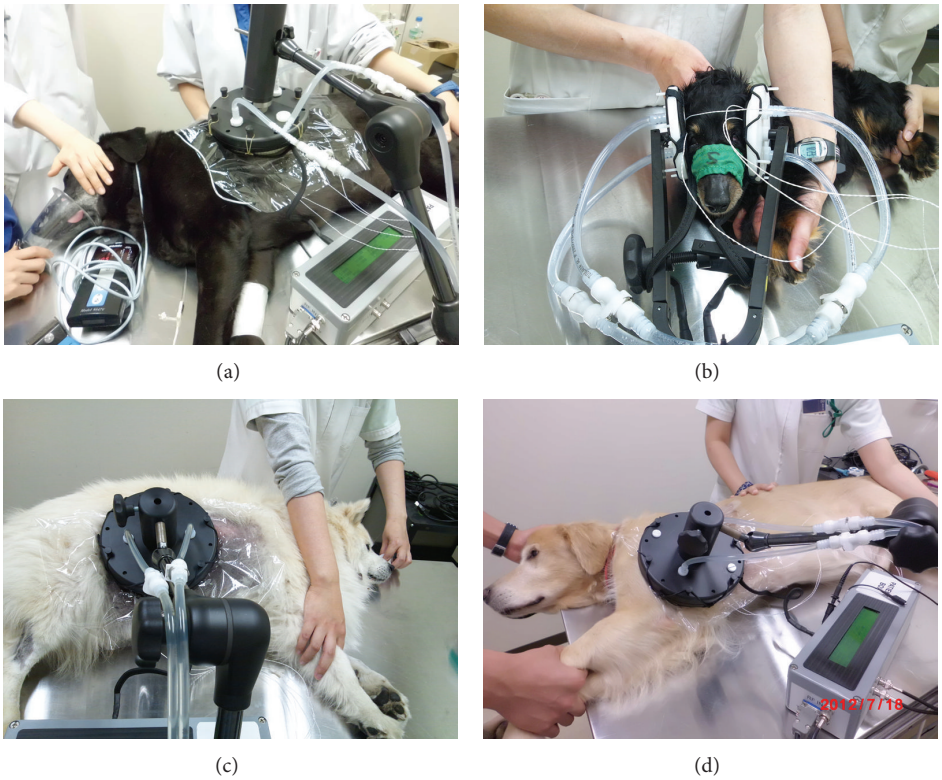


Figure 2: The VetEHY510 system in use, treating different companion animal cancer patients: (a) treatment of a dog having pulmonary metastasis, (b) treatment of a dog having brain tumor (glioblastoma) using a special forceps electrode system, (c) treatment of a dog having liver tumor, and (d) treatment of a dog having a large lesion in the lung originated from a malignant lymphoma.

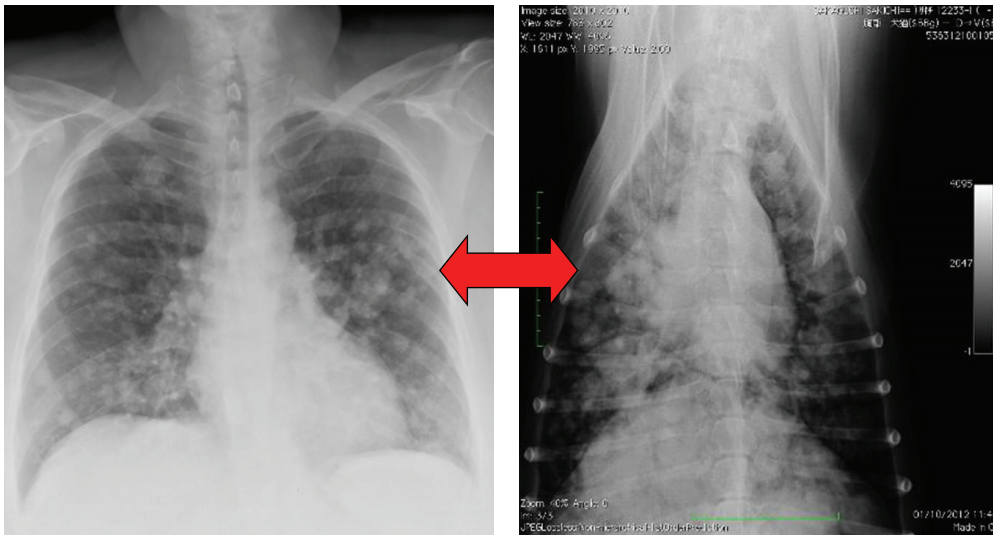
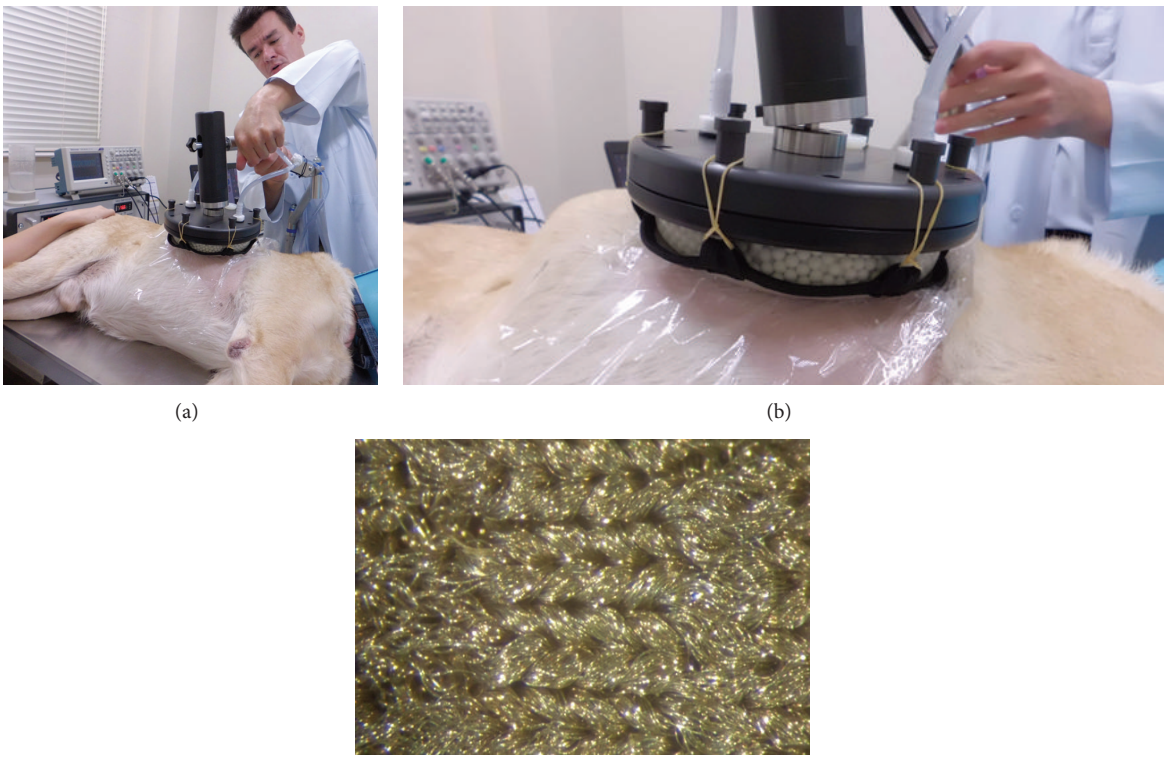


Figure 3: Representative example of the similarity of the clinical manifestation between humans and companion animals. (a) X-ray image of the pulmonary metastases from recurrent melanoma in a human patient (image courtesy of Dr. D. G. Borgeson), (b) X-ray image of the pulmonary metastases from melanoma in a Labrador dog (patient from our veterinary hospital).

Figure 4: Newly developed technical solutions in the VetEHY510 system. The main unit contains a dynamic real-time tuner system which can keep the SWR in optimal range during the treatment in real time.

Figure 5: The patient box and its display during treatment.



(a) (b) (c)

Figure 6: The treating electrode system. (a) Adjusting the electrode holder, (b) the shape-adapting electrode-holder bolus and the flexible textile electrode in contact with the body, and (c) microscopic image of the fiber structure of the electroconductive textile material. The fibers are coated with palladium-copper-silver alloy.

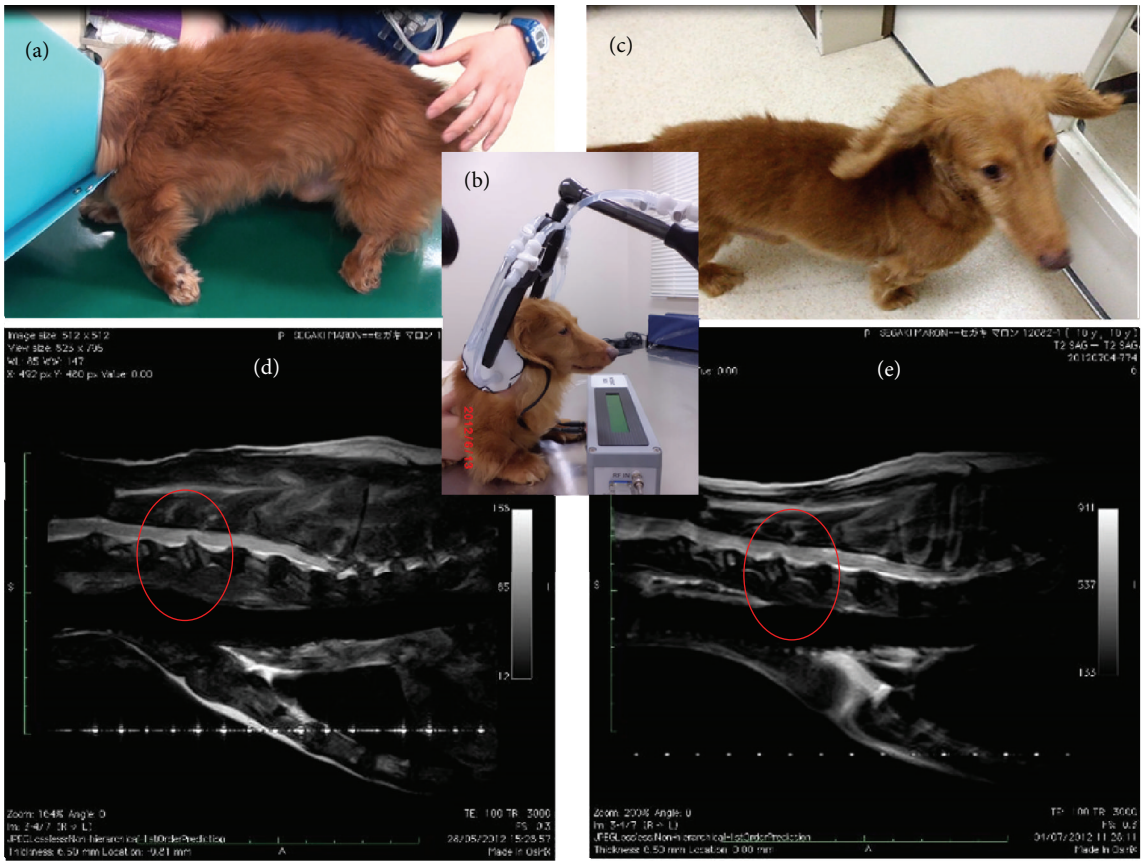


Figure 7: Summary of Case 1. (a) The dog at the time of the hospitalization, suffering from severe ataxia and hemiparesis before the treatment, (b) the dog during the oncothermia treatment, using a special forceps electrode, (c) the dog after several treatments can walk and run again without problem, (d) the MRI image before the treatment showed a lesion in the cervical region (c3) which compressed the spinal cord causing the severe symptoms, and (e) after the first treatment session, the size of the lesion was decreased as shown on this MRI image, and the spinal cord had been released from the pressure.

(6) Companion species' cancers are more akin to human cancers than are rodent tumors in terms of patient size and cell kinetics. Dogs and cats also share similar characteristics of physiology and metabolism for most organ systems and drugs. Such correspondence allows better and safer comparison of treatment modalities such as surgery, radiation, and chemotherapy between animals and humans to be made.

(7) Dogs and cats have intact immune systems as opposed to many rodent model systems, which allows immunologic assays and treatment approaches to be explored.

(8) Companion animal trials are generally more economical to perform than human trials.

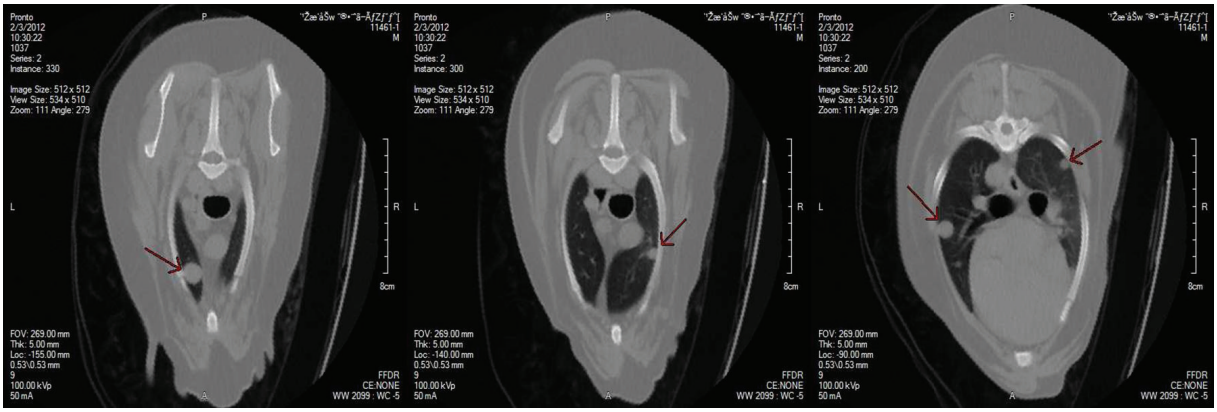
(9) Companion animals live long enough to determine the potential late effects of treatment.

(10) Dogs and cats are large enough for high-resolution imaging studies and multiple sampling opportunities, as well as for surgical intervention.

(II) The VetEHY510 device contains many new technical solutions, which can base the further development of the human clinical device. The main unit contains an E-class type resonant RF source operating at 13.56 MHz, and the high precision dual-directional coupler for precise forwarding and reflected RF power measurement. The main unit also contains a 6 bands wide range, real-time automatic tuner system with autocalibration function for proper impedance matching for any kind of load impedance, according to the high variability of the companion animal's body size and anatomical shape. This tuner system has an ultrafast real-time interfering dynamic element, so the continuous changes of the load impedance (e.g., according to the breathing movement of the animal) can be balanced in every second to keep the standing wave ratio (SWR) value in optimal range during the whole duration of the treatment (Figure 4).

There is a very special part of the VetEHY510 system, the so-called patient box (Figure 5). This device is a small box on the top of the treating table in a close proximity of the patient and makes the RF contact between the main unit and the treating electrode system. This unit is full with highly specialized measurement electronics and is able to

(a) (b) (c)



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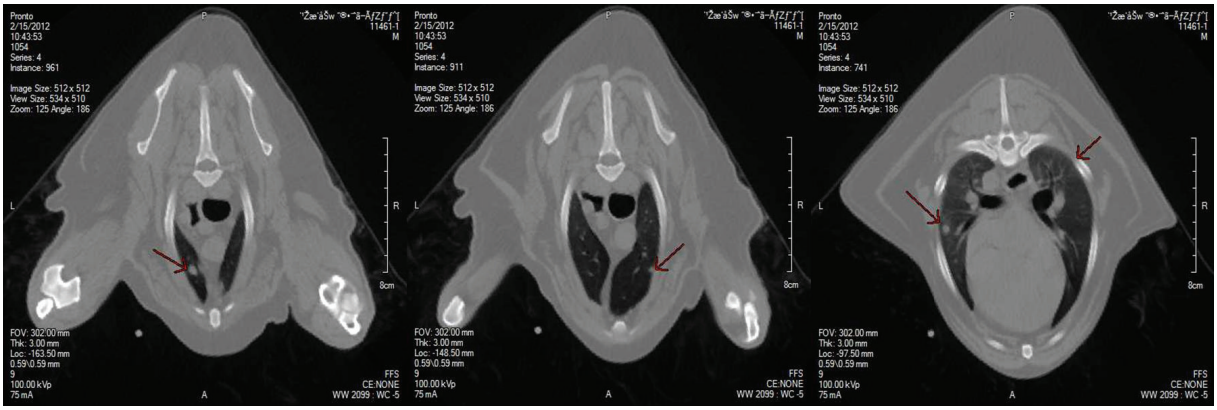

(e)

Figure 8: Summary of Case 2. (a) X-ray image of the primary melanoma on the toe of the right hind leg, (b) the dog during oncothermia treatment, (c) the dog is still alive and has a good condition, without symptoms. (d) CT image series in different slices of the lung before the treatment. Several large lesions can be visible in the lung, marked with red arrow, and (e) CT image series of the same slices of the lung after the treatment. The size of the lesions is dramatically decreased and in some cases completely disappeared.

measure the extended amount of electromagnetic and thermal parameters during the treatment. These are the electrode voltage, load currents, and their phase together with the impedance matching parameters and the temperature. These measured parameters can be seen on Figure 10 in a graph series. This unit also contains a precise, four-channel temperature measurement system which is completely insensitive to the strong electromagnetic field according to its unique electronic solution, so this system is capable of measuring temperature under the treating electrode.

The treating electrode system is also a new development. The shape-adapting electrode-holder bolus together with the flexible electrode material can be seen in Figure 6.

3. Results

(i) Shrinkage of tumor size, decreasing the tumor-associated pain, and improvement of the quality of life of the animals were observed after oncothermia

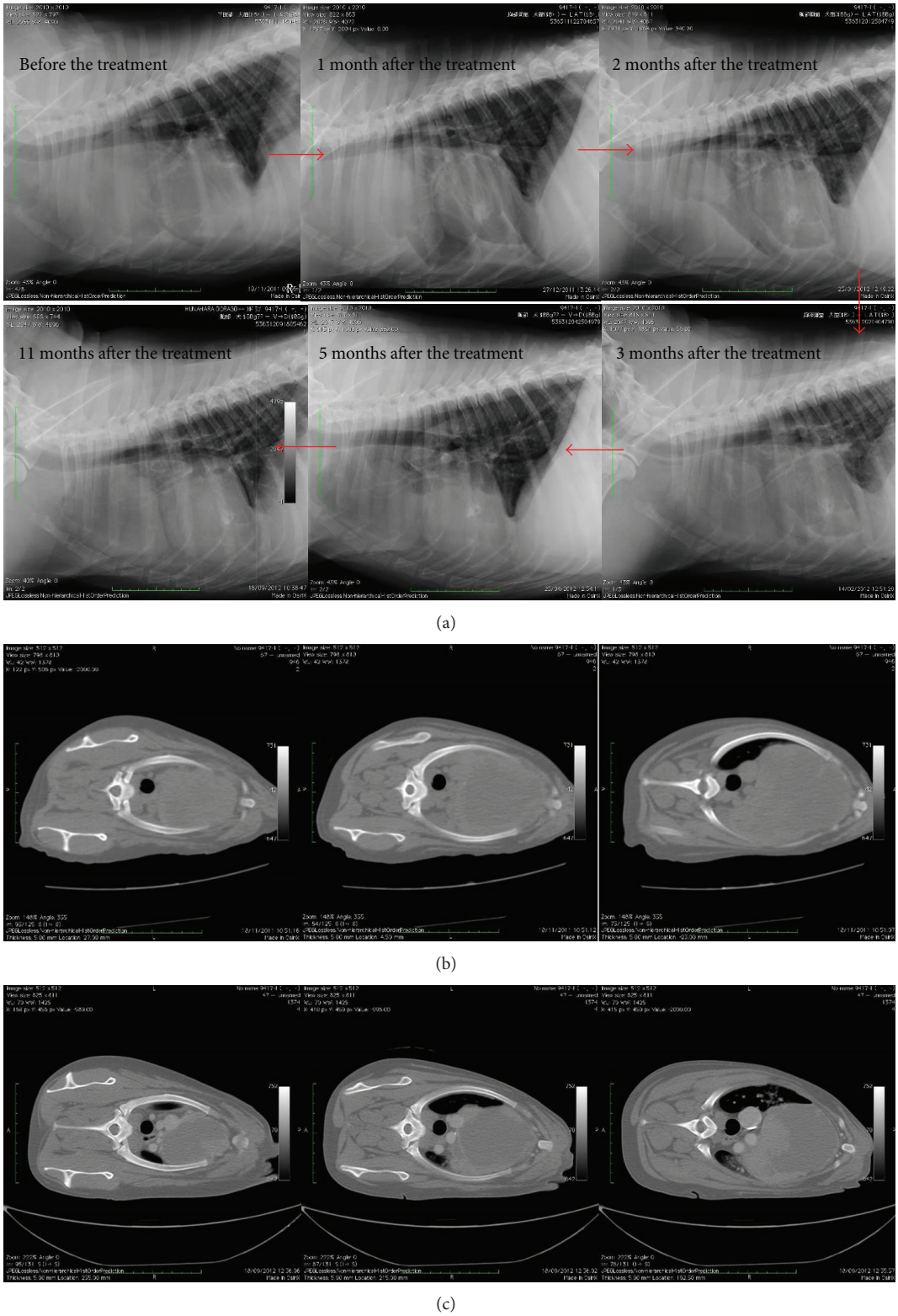

Figure 9: Summary of Case 3. (a) In this X-ray, image series can be tracking the changes of the status of the lesion in the thoracal cavity. (b) CT image series in different slices of the lung before the treatment. The large tumor mass can be visible in the mediastinum, compressing the large part of the lung making serious difficulties in breathing. (c) CT image series of the same slices of the lung 11 months after the treatment started. The size of the lesion significantly decreased, and the lung had been partially released from the compression. This case was a typical example when a rapidly progressing deadly disease became a manageable chronic disease.

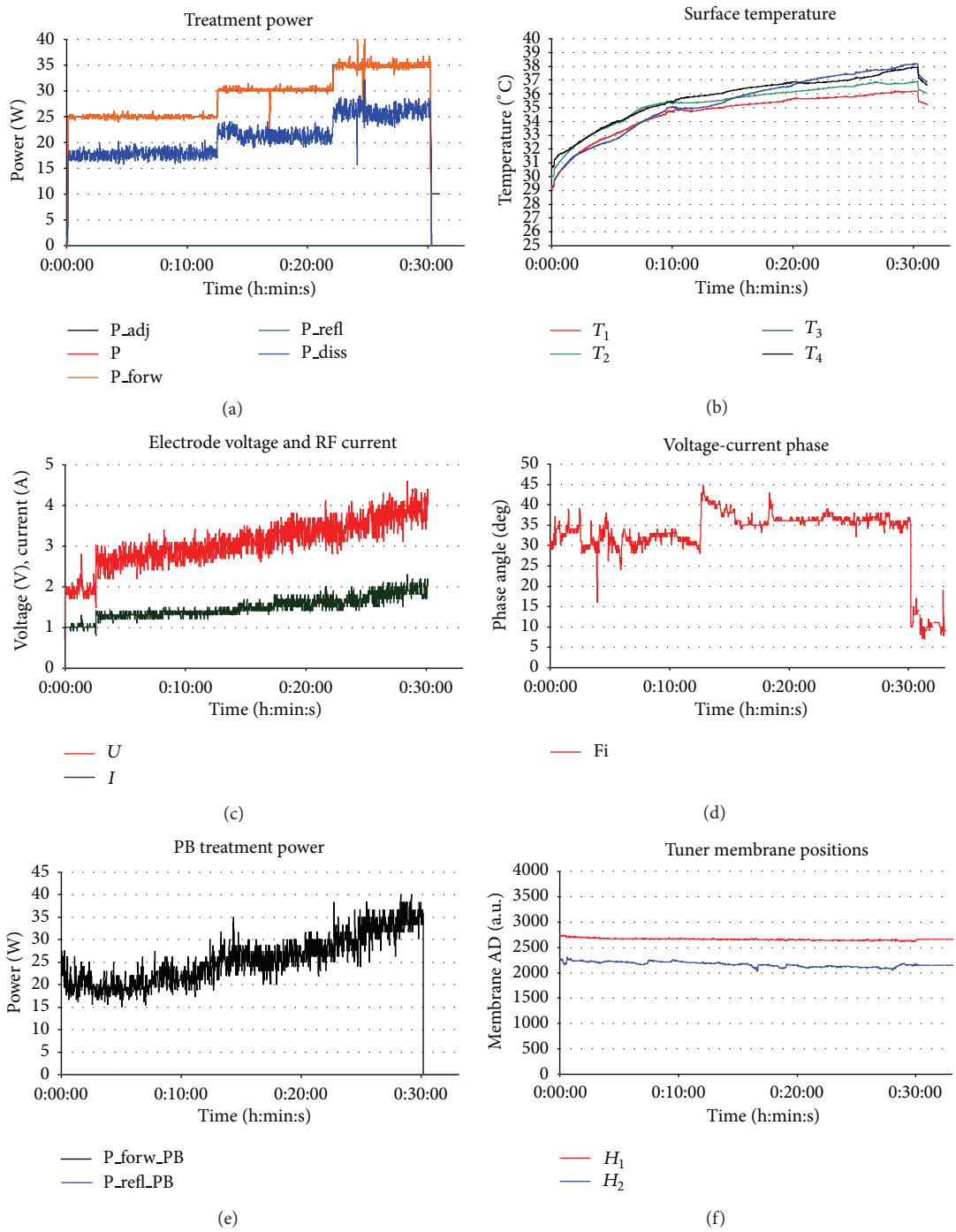

Figure 10: Graph series of the most important measured electromagnetic and thermal parameters during a standard 30 min treatment. (a) Treatment power (forwarding and reflected) measured in the main unit RF generator and dissipated power measured in the patient box. (b) Skin surface temperatures under the treating electrode. (c) Electrode voltage and load current measured in the patient box. (d) The phase of the electrode voltage and load current. (e) Treatment power measured by the power meter in the patient box. (f) Tuner parameters.

monotherapy treatments. More emphasized beneficial effects were observed, when oncothermia was used in combination with low-dose chemotherapy. Veterinary oncothermia clinical investigations are still in progress. To illustrate the clinical success in relatively severe cases, some case reports are presented.

Case 1. Case no. 12082 is an 8-year-old mini Dax. Symptom is severe ataxia; the dog was not able to move and keep his balance. Diagnosis is supposed includes meningeoma in the cervical region (C3) as revealed by MRI investigations. Treatment: oncothermia treatment as a monotherapy (1 session-6 times in 2 weeks, after oncothermia

treatment 1-2 times/month) using the special forceps electrode (Figure 7).

Case 2. Case no. 11461 is an 8-year-old castratedmale Cocker spaniel. Diagnosis: melanoma was found on the toe of the right hind leg, which was surgically removed. Then, severe lung metastases were developed. Treatment includes lowdose Carboplatin (2 times, 100 mg/ m2, which is 1/3 of the prescribed dose) + oncothermia treatment (10 times in 2-3 days interval). The summary of this case can be seen in Figure 8.

Case 3. Case no. 9417 is a 9-year-old castrated male golden retriever. Diagnosis is lymphoma in the thoracal cavity. Treatment includes low-dose COP (Cyclophosphamide-Oncovin-Prednisolon coctail, 2 times, 1/3rd of the prescribed dose) + oncothermia (15 times at the first session then 1-2 times/month). The summary of this case can be seen in Figure 9.

(ii) During these treatments, we had measured and collected many valuable electromagnetic parameters which can help to understand what is really happening during oncothermia treatment in electromagnetic sense.

Our opinion is that the accurate analysis of these precisely measured treatment-related electromagnetic parameters can help to reveal the most critical electromagnetic parameter to achieve the best biological response. Using the results of these measurements, we can optimize the technical solutions of further developments of the oncothermia devices for the human oncological applications and for the veterinary practice too.

4. Conclusions

Oncothermia method and the VetEHY510 system is a new hope to cure effectively companion animal cancer patients, fulfilling the huge demand from veterinary market. The newly developed VetEHY510 device is a powerful research tool for comparative clinical oncology and to understand the role of critical electromagnetic parameters to improve the oncothermia method in human clinical practice too.

Acknowledgments

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