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Oncothermia research at preclinical level

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Oncothermia research at preclinical level

Objectives of the work

Our paper has double objectives: first it is connected to the human medicine, aiming to model the natural human tumors much more realistically than the rodent tumor models. In this line we treat spontaneously occurring tumors and metastases on companion animals. During these experimental oncothermia treatments we can collect a huge amount of measured electromagnetic parameters that can help to understand what is really happening during oncothermia treatment and can help to optimize the next generation oncothermia devices. The other goal is to develop a dedicated tumor treating device for the veterinary market because it does not have a really effective, relatively cheap and easy to use method to fight against pet cancer. We show that oncothermia has definite benefit in both the objectives.

Introduction

Contrary to the human hyperthermia applications in oncology, the history of hyperthermia in veterinary medicine has only 50 years. The very first veterinarian oncology case was published in 1962. The tendency of the number of publication was rapidly growing till the 1980s and declined sharply in the next decades (see Figure 1.)

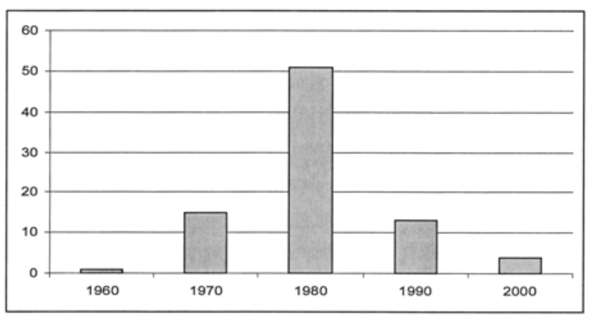

Figure 1. Number of publications on veterinary hyperthermia by decades

The first hyperthermia applications concentrated on the whole-body heating with various techniques. The systemic treatment was devoted to act in the advanced cases of distant metastases. The treatments were used alone or combined with local radiation on the primary tumor. Experiment of rodent tumor models in vivo concluded with unexpected results: the systemic (whole-body) hyperthermia does not able to destroy completely the primary tumor, but it also does not block the metastatic developments, oppositely it promotes the progression of the distant metastases. In veterinarian clinical trial of dogs having osteosarcomas without evidences of metastases, the local radiation combined complementary with whole body hyperthermia was studied. The result was surprisingly bad: the combined treatment was not effective on the primary tumor, but rapid and massive metastases were developed in far distant organs including the lung. This had blocked the research in this direction; the veterinarian application of the hyperthermia even in combined therapies was not plasticized in veterinary field.

Disadvantages of the whole-body hyperthermia had formulated the demand of the local (regional) heating combined with local radiation techniques. At first the ultrasound heating was studied, but its disappointing low efficacy had blocked these trials. The other promising trials were made by infrared laser-heating, but its high expenses and the necessary complications by the invasive way, which was the consequence of the low penetration depth of the radiation; this method has limited spreading in veterinary clinical practices. After these disillusive trials, let us summarize the local (regional) heating methods by electromagnetic effects in veterinary applications.

The aim in the local (regional) heating in general was a selectively achieved high temperature (42-43°C) in the target, and the technical solution of the energy delivery was irrelevant. The invasive interstitial microwave treatment and all the other non-invasive solution were equally handled, the only point was the temperature in the target, irrespective which technique was applied. The so-called LCF (local current field) technique was especially dedicated for veterinarian applications, and it was applied as monotherapy in most of the cases. The device (named RF-22 Thermoprobe) was developed in the early 1970s, and its results were dominantly published in the early 1980s. This device was accumulator operated, handheld construction with 10 W maximal output power, using 2MHz frequency between two sheet electrodes having a distance of 5 mm in 12 cm length.
It was applied solely for small size (max. 5-10 mm diameter) surface-located tumors (mainly squamous cell carcinomas). To avoid the overheating a temperature sensor controlled the process, regulating less than 50°C. There were speculations (R.L. Grier) about a temperature as high as 59°C, because the supposed thermal conduction allows this gradient from critical 50°C measured on the electrode surface. The same author reports very good results in cases of surface-located tumors (malignant melanoma, squamous-carcinoma, fibrosarcoma, perianal adenoma, etc.) of small pets (dogs, cats): a single shot treatment with 30 second had positive response in 85% of the cases, 70% complete remission, 15% partial regression, and 15% had no benefit from the treatment.

Treatments having no benefit were in cases when the tumor was expanded deeper than 2 mm. This author has treated large animals (horse, cattle) with this LCF technique too. 50% of these tumors were resistive against other therapies like surgery, radiation or immunotherapy. The LCF treatments, made by max. 3 times and max. during 30 seconds, were successful: 80% had complete remission, while 16% was reacting partially. In conclusion cases of large tumors (larger than 5 cm) or deeply extended locations (deeper than 2-3 mm) the LCF method is not effective. Kainer treated eyelid squamous carcinomas of cattles, and reporting 91% complete remission in all the cases. The last reference which we found in the literature was published in 1990, showing the case of squamous carcinoma on the eye of a high-values sport horse. The LCF was successfully applied in combination with brachytherapy (Au^{198}). From this time we could not found any published data with this method, which anyway was applied successfully for small, surface located tumors.

Numerous methods were developed for deeper applications of RF-current. The simplest one, when the tumor selection is made by the needle insertion into the tumor volume. Such method was used in combination with radiation therapy for nasomaxillar fibro sarcomas dogs, which anyway has very bad prognosis (median survival time is 1 month). Numerous needles were inserted from the nose-surface of the dog according to the contour of the deep-seated tumor, oppositely in two rows. The needles were wired in one row, and the rows were supplied by 500 kHz RF generator. The temperature was measured by invasive sensors in the tumor, controlling the maximal temperature to 43 °C. This was reached by 5-15 W output power. The heating up period was 15 min, and there was a plateau keeping the tumor on 43 °C for 30 min. 2-4 treatments were applied in 72 h intervals in four treated animals. Complete remission was reached in case of three out of four. One was no successful. One had recidive in follow up, while two was completely free of disease. Dewhirst and collaborators had continued the practice of 500 kHz interstitial treatment, but mixed with the 2.4 GHz microwave application, taking care only on the temperature as parameter, keeping the 43°C as the "dose". Reviewing later, the authors remark the better observed effects in case of 500 kHz than 2.4 GHz applications. This needle invasive modality has a pure electric field version (ECT) too, which became increasingly popular.

Magnetic methods were applied also in veterinarian practice, and intensive research is made in this field nowadays. There are numerous problems arisen compared to the non-invasive heating methods: (a) the focusing is artificial, where the magnetic material is inserted, the energy absorption is concentrated, (b) the magnetic fluid spread by diffusion and blood-perfusion from the target, (c) the temperature can not be concentrated in a localized volume among the well conductive heat-exchanging conditions like the living state, (d) the method is invasive, having numerous problems of possible infection, bleeding, inflammation and cellular dissemination, (e) the inserted material has to be annulled at finishing the treatment procedures (f) it is too expensive and complicated for veterinary use.

The microwave radiation as a well oriented energy beam could be easily used for hyperthermia therapies. Radiotherapy was combined with sophisticated 433 MHz and 915 MHz hyperthermia systems; and only 51% of the cases were complete remission, and 35% was partially responding. No response was observed in 14%, despite of the combined therapies. Despite the theoretically easy focusing of microwaves, numerous practical problems occur: at large tumors to construct a unified temperature distribution was not possible, while in small tumors the focusing was problematic, burning the connective tissues as well.

Other microwave treatment was done by the ring-array focusing at 140 and 433 MHz frequencies. The temperature was measured invasively.

The 2.4 GHz microwave treatment combined with radiotherapy was successfully applied in cases of canine's hemangiopericitoma. The complete remission rate was 82% while the overall response rate was 91%. Important observation was made in spontaneous canine soft-tissue sarcomas by comparison of the various temperature levels. The measurements show certainly higher blood-perfusion rate in the tumors on lower temperatures than in higher ones, which has definite importance in the combined therapy with radiation.
Special microwave application was done for cats, increasing the intake of the 99mTc labeled liposomal radiofarmacons.
Treatments of the surface tumors were made by RF (13.56 MHz) treatment combined with the magnetic targeting (Magnetrode) in deeper regions. This study showed the improved tumor-selection effect of this frequency, but the method was not further-developed afterwards.

Oncothermia method (OTM) has been applied in human oncology since 1989. Its clinical results excellently show the advantages of the method, however, the details of its mechanism are being intensively investigated even now. Oncothermia research group conducts investigations at all levels of scientific research, from in vitro studies to human clinical trials. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven in vivo, but the complex electromagnetic parameters playing crucial role in achieving these antitumor effects have 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 incidences of cancer in pet animals, and the lack of a really effective and relatively cheap method to cure.

Materials and methods

Oncotherm created a specialized research device for preclinical investigations/veterinary clinical use, the VetEHY510 system. This Oncotherm-veterinarian device is developed to eliminate the previous problems and fulfill the demands above. The system is capacitive coupled and simple for use. Its schematics are shown below. The VetEHY510 system was created to serve dual purposes:
I. To 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. To Collect information and a wide range of measured electromagnetic parameters, which can help to optimize the treatment protocols and clarifying the real role of electromagnetic treatment parameters could provide the best clinical outcome.
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 device works on the basis of RF-current flowing through the chosen part of the animal. This has various effects:
General heating by the absorbed energy of the current
Automatically focuses on the tumor-lesion
Selectively targets the malignant cells
Initializing special membrane associated effects (signal pathways), promote natural processes (apoptosis) to kill the cancerous cells.
Builds up again some cellular connections (adherent connections and junctions) blocking the dissemination of the malignant cells.
Vet-EHY treatment-device is designed for treating of oncology cases of companion animals (dogs, cats). It is a brand new development, with automatic tuning and many extra features for the veterinary applications and users' convenience.
It is built in a high-tech electronics based on the wide knowledge of the oncothermia applications in human oncology. The electrodes are flexible and widely consumable for various applications. It could fit for every body/forms and lesions.
Technical parameters
13.56 MHz output carrier frequency
0-80 W adjustable output power
LCD screen to display actual treatment parameters
Digital power and treatment time control
Microprocessor controlled, fast tuning
Latest developments of fractal fluctuation modulation
RS232 output for treatment data logging and full computer control of the device
Vet-EHY makes conductive heating. It is a modulated radiofrequency-current flowing through the targeted volume. The patient is a part of the electric circuit, fully and permanently controlled by the electronics and the treatment is carefully adjusted to optimal in-situ. The treated tissue is imperfect dielectric-material of the condenser of the circuit.
The method is self-selective, using the better conductivity of the extracellular electrolyte around the malignant cells due to their higher metabolic activity and lower pH.

The VETEHY device was designed to fit all the clinical demands in veterinary oncological practice:
The applied frequency is accurately 13.56 MHz (free frequency, no shielding is required, harmonized with the electromagnetic compatibility standards.)
The applied power limit is 80 W, which could be adjusted in 1W steps.
The tuning is fully automatic, (auto-matching).
The standing wave ratio is measured, the S11 attenuation is indicated on the display in dBm. (Approximately 20 dBm corresponds to SWRl.l, and the SWR decreases to 1.01, 1.001 ... by 30, 40, .. dBm, respectively. (The SWR roughly could be described as the sum of the forwarded and reflected power divided by their difference. Consequently, SWR=1 means the ideal situation when no reflected power is present, all the forwarded power is absorbed by the target.
The device has RS232 standard serial port to register the actual treatment, and all the parameters can be controlled by an external PC.
The electrode was designed to fit automatically into all the shapes and form of the animals body due to the significant anatomical differences of the different dog breeds.

The treatment time could be adjusted and shown by count-down in minutes (maximum 90 min). The treatment power is in Watts (W), (maximum 80 W).
The tuning in the beginning of the treatment is made by 3 W power. The increasing of the power is only possible, if the tuning is finished.
The treatment pad has the electrode holder and the counter electrode is a metallic sheet of the treatment table, or a forceps counterpart.

Results & discussion

The literature clearly shows the problems of the hyperthermia in veterinary practice. Until now such a device does not exist for veterinary use, which
Is effective enough for treatment,
Has universal, versatile applications
Could be applied as monotherapy in cases when no other possibilities are available
Is easy to use in veterinary practices
Is inexpensive, or its investment turns back quickly.
Scientists in oncology are just starting to realize the importance of the involvement of veterinarians in a real preclinical research work. The newest edition of Withrow and MacEwen's Small Animal Clinical Oncology briefly summarizes the aspects of companion animal cancer that enables attractive comparative models in a real preclinical investigation.

To emphasize the real value of the information which can be collected during the experimental treatment of companion animals, we would like to cite some points from the afore-mentioned book:
Companion dogs and cats are immunologically intact animals (like humans) as opposed to many experimental models of rodents and other animals.
Cancers seen in practice has spontaneously developed as opposed to experimentally induced, and they recapitulate the natural human and veterinary condition better.
Companion species have a higher incidence of some cancers (e.g., osteosarcoma, non-Hodgkin's lymphoma) than humans.
Most animal cancers progress by more rapid rate than their human counterpart. This permits more rapid and less costly outcome determinations such as time until the metastasis, local recurrence, and time of survival.
As 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 to wait to initiate new treatments until all "known" treatments have failed, as it is common in the human condition.

1. 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 to be made between animals and humans.
2. Dogs and cats have intact immune systems as opposed to many rodent model systems, which allows immunologic assays and treatment approaches to be explored.
3. Companion animal trials are generally more economical to perform than human trials.
4. Companion animals live long enough to determine the potential late effects of treatment.
5. Dogs and cats are large enough for high-resolution imaging studies and multiple sampling opportunities, as well as for surgical intervention.

These spontaneously occurring tumors are the best "models" of human malignant diseases. Getting treatment information and experiences on the behavior of these tumors from these pet patients are extremely valuable. These info can be directly transformed to human practice to improve the clinical results. (Figure 2.)

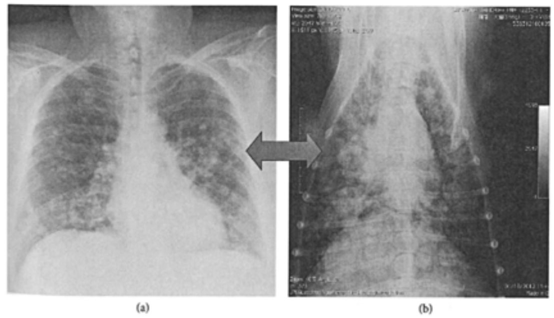

Figure 2. A representative example of the similarity of the clinical manifestation between humans and companion animals. A: X-ray image of the pulmonary metastases from recurrent melanoma in a human patient (image courtesy of Dr. D.G. Borgeson), B: X-ray image of the pulmonary metastases from melanoma in a labrador dog (patient from our veterinary hospital)

Shrinkage of tumor size, decrease of the tumor-associated pain and improvement of the quality of life of the animals were observed after oncothermia 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, 8 years old mini dax. Symptoms: severe ataxia, the dog was not able to move and keep his balance. Diagnosis: supposed meningioma 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 3.)

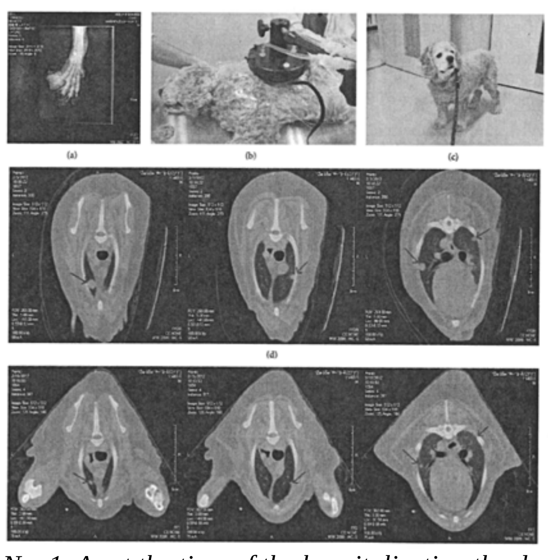

Figure 3. Summary of case No. 1. A: at the time of the hospitalization the dog was suffering from severe ataxia and hemiparesis before the treatment, B: the dog during the oncothermia treatment, using a special forceps electrode, C: after several treatments the dog could walk and run again without any problem, D: before the treatment the MRI image showed a lesion in the cervical region (c3) which compressed the spinal cord causing the severe symptoms, E: after the first treatment session, the size of the lesion was decreased as shown in this MRI image, and the spinal cord was released from the pressure

Case 2 Case No.:11461, a 8 years old castrated male 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: low dose Carboplatine (2 times, 100mg/m2, what is 1/3 of the prescribed dose) + Oncothermia treatment (10 times in 2-3 days interval). Summary of case No.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, E: CT image series of the same slices of the lung after the treatment. The size of the lesions are dramatically decreased and in some cases completely disappeared

Case 3 Case No.:9417, 9 years old, castrated male golden retriever. Diagnosis: lymphoma in the thoracal cavity. Treatment: 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 case is shown in Figure 3.

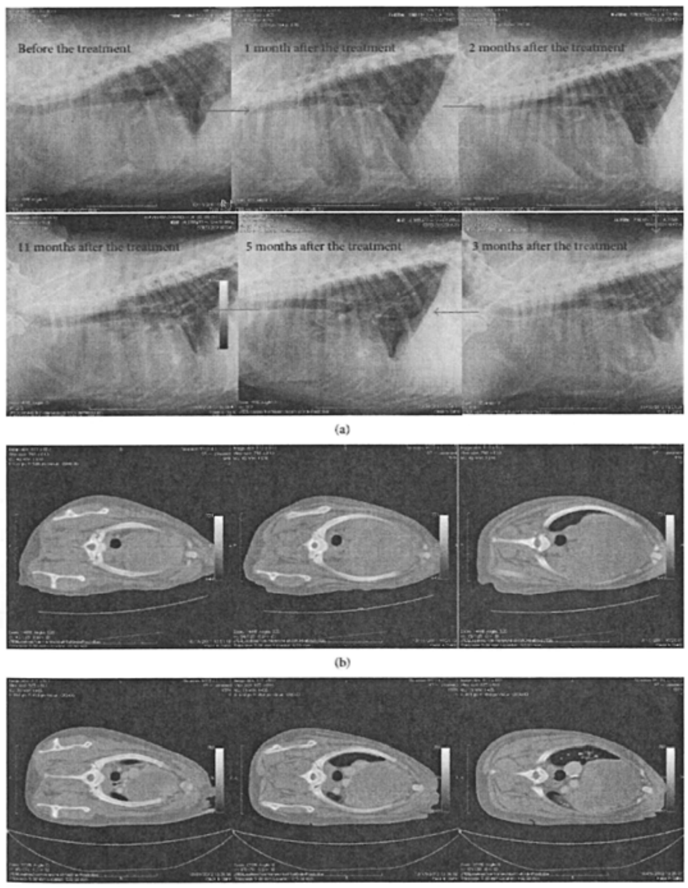

Figure 3. Summary of case No.3. A: In this X-ray image series the changes of the status of the lesion in the thoracal cavity can be tracked. B: CT image series in different slices of the lung before the treatment. The large tumor mass can be visible in the mediastinum, compressing the large part of the 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, the lung was partially released from the compression

This case was a typical example of a rapidly progressing deadly disease becoming a manageable chronic disease.

During these treatments we 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.

Conclusions

Oncothermia method and the VetEHY510 system is a new hope to effectively cure 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.

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