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Hyperthermia for Deep Seated Tumours – Possibilities of Heating with Capacitive Devices

O.K. Kurpeshev[1], J. Van der Zee[2], M. Cavagnaro[3]

1. Siberian Scientific Research Institute of Hyperthermia, Novosibirsk region, Iskitim-5, Russia;
2. Erasmus Medical Centre, University Medical Center Rotterdam, Rotterdam, Netherlands;
3. Sapienza University, Rome, Italy

O.K. Kurpeshev – PhD, MD, consultant; J. Van der Zee – PhD, MD, Member of European Society for Hyperthermic Oncology (ESHO); M. Cavagnaro – Prof., PhD, Member of the Societies of the Institute of Electrical and Electronics Engineers (IEEE), the European Society for Hyperthermic Oncology (ESHO) and the European Association of BioElectromagnetics (EBEA)

Contents

The review examines the general principles of capacitive electromagnetic hyperthermia (EMHT), the distribution of electromagnetic energy in various experimental models and in patients' tumors, the design features of applicators from various capacitive hyperthermic systems and their role in achieving hyperthermic mode in tumors of deep localization. In classical capacitive EMHT, the main obstacle in achieving the required temperature in such tumors is overheating of the subcutaneous fatty tissue under the electrodes. For some capacitive hyperthermic systems, the heating of adipose tissues is enhanced due to the fact that the applicator design does not conform to certain technical requirements. In capacitive EMHT at frequencies of 8–13.56 MHz, obtaining the minimum hyperthermic mode is possible with output powers of 500–800 W, maximum – 1000–1200 W and above.

The results of the use of various hyperthermic capacitive systems in patients with malignant tumors of internal organs are analyzed.

Key words: *radiation therapy, chemotherapy, thermoradiotherapy, thermochemotherapy, thermochemoradiation therapy, electromagnetic fields, hyperthermia, capacitive devices*

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Abbreviations

HT – hyperthermia
RT – radiation therapy
LRHT – loco-regional HT
CT – chemotherapy
CRT – chemoradiotherapy
EMHT – electromagnetic HT
SAR – specific absorption rate
EM – electromagnetic
SCF – subcutaneous fat
RFHT – radiofrequency HT

Introduction

Experimental and clinical studies have shown that loco-regional hyperthermia (LRHT) at temperatures of 40–46 °C is a powerful adjuvant of radio- (RT), chemo- (CT) and chemoradiotherapy (CRT). This is explained by the variety of its biological actions: direct cell kill, radio-, chemo- and immunomodulation, as well as suppressing the development of drug resistance of tumor cells [1–17]. In most studies, the dependence of the results of hyperthermia (HT) on the temperature level and the duration of heating, i.e. on the heat dose, has been demonstrated [8, 18–23]. For LRHT, electromagnetic field (EMF) in the microwave and radio frequency range is mainly used. With EMHT, the intensity of heat generation and the temperature distribution depends on the dielectric and thermodynamic properties of the tissues, the blood perfusion, and the method of heating. Therefore, there is a variation in temperature in the heated volume of tissue and it may change during the HT session. Thermometry is mainly carried out by invasive methods, by introduction of thermal sensors into the tumor. In clinical conditions however, this method of thermometry does not allow the evaluation of the quality of treatment very well, since the number of thermometry sensors introduced into the tumor is limited, and temperature indicators are largely dependent on their location.

The quality of EMHT depends on the degree of temperature rise in the entire heated volume and the temperature distribution in the tumor. The most recent European Society for Hyperthermic Oncology (ESHO) guidelines for deep LRHT prescribe a temperature increase of preferably 1 °C per 5 min heating, ranging from 0.6 to 2.0 °C. In the calculated SAR (specific absorption rate) distribution, the ratio between the average SAR in the target and the average SAR in non-target should be at least 1.5, and the maximum SAR in 0.1 % of the total volume of normal tissue (hot spot) not larger than 4 times the SAR in the target [24]. With an excessive accumulation of energy in certain parts of normal tissues, so-called hot spots are formed. In this case, patients subjectively feel a burning sensation and pain under the applicators, which do not allow a further increase in output power, respectively, temperature in the tumor [25].

In hyperthermic oncology, tumors, according to the depth of location, are divided into 3 types: superficial (up to 3 cm in depth), subsurface (up to 3–6 cm deep) and deep (more than 6 cm) [26]. HT of superficial tumors is mainly carried out with the help of installations generating microwave radiation (434–915 MHz), and the required temperature level is achieved without special difficulties. While the creation of a hyperthermal regime in subsurface and deep tumors, especially internal organs, is problematic. For these purposes, radiofrequency HT (RFHT) is used and the energy is supplied to the target in two ways: multi-phase irradiation and capacitive. In

multi-phase irradiation heating, the effect of RF radiation (70–120 MHz) on the tumor is carried out using 4–8 synchronously operating antennas. They are enclosed in a frame in the form of a ring or ellipse, placed around the treated area of the patient's body. To achieve maximum energy in the target, the phase and output power are adjusted for each antenna separately. In capacitive heating, an alternating EM power (8–40.68 MHz) is created between two or three electrodes opposite each other or at an angle.

This review analyzes the possibilities of heating deep seated tumors using the capacitive RFHT method of various hyperthermia systems.

Capacitive hyperthermic systems

In clinical practice, mainly 2-electrode capacitive HT devices are used. There are 3-electrode, as well as coplanar types, that is, 2 multipolar annular or flat electrodes located in one plane [27, 28]. However, these did not find application in the clinic. In recent years, there was a 2-channel, 4-electrode installation on which only experimental studies were started [29]. In all capacitive hyperthermic systems, the electrode device has a similar construction: on its working surface there is an insert filled with circulating fluid with a high dielectric constant. The side of the insert adjacent to the patient's body is covered with an elastic membrane, which allows you to effectively cool and level the body irregularities in the heating zone. The electrode and the insert form the applicator as a whole. Sometimes, in order to better fill the space between of the applicator and the patient's body, additional bags (boluses) with water are used.

Currently there are 5 capacitive systems that are commercially available internationally: Synchrotherm (13.56 MHz), Andromedic (13.56 MHz), Oncothermia EHY-2000 (13.56 MHz), Thermotron RF-8 (8 MHz) and Celsius TCS (13.56 MHz). The remaining systems relate to experimental installations, or concern devices for which further information is not available (in particular, systems produced in China).

The **Synchrotherm RF** (13.56 MHz) and **Andromedic** (13.56 MHz) devices were designed in Italy and are rather similar. They are equipped with 2–3 pairs of round applicators of different diameters. Heating is carried out by the classical capacitive method. The maximum output power is 600 watts. The water temperature in the applicators can be adjusted from 6 °C to 20 °C. These installations have four major drawbacks. The first – is that the electrodes are made of a bending material, the second – is that during the HT session, the pair of electrodes are not fixed rigidly relative to each other. This design can create an unstable and unparallel placement of the electrodes on the patient's body, and thereby an uncontrolled distribution of the EM field, which may result in the development of burns on the skin, and/or underheating of the tumor. Thirdly, the applicators are attached to the patient's body using a bandage that interferes with visual monitoring of the water level in them. Fourth, the bolus is as large as the electrode and thus a pronounced edge effect is present. In the available literature, we did not find data on tissue temperatures achieved with these systems, nor on results in cancer patients (to our knowledge, these installations are no longer being made).

The **Oncothermia** system was developed in Hungary and operates at 13.56 MHz. The system which has been installed most (EHY-2000) has a maximum output power of 150 W, other systems have a maximum power output of 250 W (EHY 2030) or 600 W (EHY 3010). Oncotherm systems have an active applicator with a diameter that range from 10 to 30 cm and a second passive applicator which is a large plate covering the entire upper surface of the couch, fixed and grounded. With such a large difference in the size of the electrodes, the energy is concentrated in the superficial tissues under the small electrode. The thickness of the applicator membrane is about 1.5 mm. Due to the large thickness of the membrane of the applicator, when water is circulated under pressure, during the HT procedure, a convex surface is created and thus the possibility of its close contact with the patient's body is excluded. Temperature control on this unit is not provided.

Celsius TCS (13.56 MHz), hereinafter Celsius, was developed in the Federal Republic of Germany and appeared on the medical equipment market in 2006. The unit has a maximum output power of 600 watts. Of the pair of electrodes, the upper one moves with the help of the bracket in horizontal and vertical directions, the lower one – only horizontally by manually moving it from one connector to the other. Thus, the electrodes in relation to the patient can be placed only vertically, a horizontal arrangement is not provided. To control the temperature, fiber-optic flexible thermal sensors are attached to the installation. The main disadvantage is also the high density of the applicator membrane, which has a thickness of about 1.5 mm. Therefore, during treatment under the pressure of circulating water, the membrane of the applicator acquires a convex shape and thereby reduces the area of contact of the applicator with the patient's body. This significantly impairs the main function of the bolus: smoothing out body irregularities and cooling the skin.

Thermotron RF-8 (8 MHz) was developed in Japan in the early 1980**s**. The unit has a maximum output power of 1500 W and is equipped with 6 pairs of applicator electrodes with a diameter of from 70 to 300 mm. A pair of applicators are enclosed in a 360-degree gantry frame and their displacement relative to the patient occurs synchronously in a circle in one plane. Temperature control is carried out by flexible or needle 1–4 element thermoresistance sensors. The membrane of the applicator has a thickness of about 0.7–0.8 mm. The temperature of

the circulating fluid in the applicator can be reduced to 5 °C.

The **Cancermia** system (8 MHz) was developed in South Korea and is mainly used for scientific purposes within the country, and there is no detailed information about its technical characteristics available.

The hyperthermic complexes **Superterm EP-40** (40.68 MHz) and **Extraterm (40.68 MHz**), with a maximum output power of 600 W, was developed in Russia and from 1995 to 2017 was used for scientific purposes at the A.F. Tsyb MRRC. Devices were equipped with applicators of different sizes and shapes (round, rectangular) in the amount of up to 10 pairs on the installation Superterm EP-40, 6 pairs on the installation Extraterm. The applicators met the basic technical requirements: their membranes were made of latex rubber 0.6–0.8 mm thick, the side walls had the shape of a bellows (with corrugated ribs) and covered the electrode area by 1–3 cm.

General principles of capacitive HT and EM energy distribution in modeling or phantom measurements

The advantages of capacitive RFHT are mainly associated with the simplicity of the equipment and the heating procedure. The disadvantage is the overheating of the SCF under the electrodes due to the perpendicularly directed vector of the electric field on the surface of the body [30]. To reduce overheating of the acids, the salt water (0.4–1.0 %) with a temperature of 5–10 °C circulates in the applicator. With larger sizes of the applicator, compared with electrodes, it is possible to avoid overheating of the skin and along the edges of the electrodes, that is, to minimize the so-called edge effect. The cooling efficiency depends on a number of circumstances: the temperature of the circulating fluid in the applicators, the duration of the cooling before the HT procedure, the thickness of the SCF. Therefore, it is recommended to start cooling down 20–30 min before the beginning of HT with a thickness of SCF not more than 2 cm [30–35]. In model calculations and experiments on pigs, Kato H. et al. [34] the cooling effect was observed when the SCF thickness was up to 1.6 cm. According to Brezovich I.A. [30], with the thickness of SCF more than 1 cm, even preliminary cooling cannot bring about the desired result.

The dependence of the efficiency of cooling of the fat tissue is shown in fig. 1 [35].

From fig. 1 it follows that with pre-cooling the surface of the body of patients with water at 10 °C for 20 min, the temperature in the SCF decreases by approximately 3 °C when the thickness is 2–2.5 cm, by 5 °C when the thickness is 1.5 cm, and by 7.5 °C when the thickness is 0.5–1 cm. Thus, the largest effect of pre-cooling the SCF is seen at a thickness of less than 1 cm.

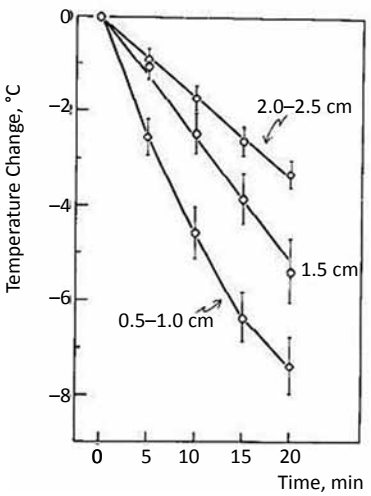

Fig. 1. The degree of cooling SCF with water at 10 °C, depending on its thickness

It should be borne in mind that the bolus can not always fill the space between the patient's skin and the electrode. When even small gaps appear between the applicator and the patient's body, SAR sharply increases on the skin of these areas [36]. To avoid such gaps, Brezovich I.A. et al. [31] recommends that the membrane material should be elastic and have an electrical conductivity, a thickness of 0.1 mm, and recommends further that the bolus should be circulated with 0.4 % saline solutions.

The distribution of absorbed EM power and the resulting temperature in the volume heated with a capacitive technique is determined, apart from the dielectric properties of the tissues and shape and dimension of the body, by the size of the electrodes, the distance between them and their location relative to each other [26, 31, 37, 38].

Of the capacitive hyperthermic systems, the most in-depth studies on the distribution of EMF in models and phantoms were carried out using the Thermotron RF8 [26, 34, 37–39] and a few on Celsius [40, 41].

In fig. 2, shows the temperature distribution at RFHT on the **Thermotron RF-8** device in a phantom of different volumes depending on the size of the electrodes [38]. The skin surface was cooled with water at a temperature of 20 °C.

As can be seen in fig. 2, with identical electrode diameters, which are commensurate with the thickness of the object being heated, considerable part of the energy reaches the deepest parts in a homogeneous volume. If the diameters of both electrodes are less than the thickness of the object, then heating occurs mainly under the electrodes. In case of using electrodes of different diameters, heating will predominantly take place under the smaller electrode. In this case, the larger the difference in electrode size is the more intense the heating will be under the small electrode, and in the center of the target less heat will be generated or it may be completely absent.

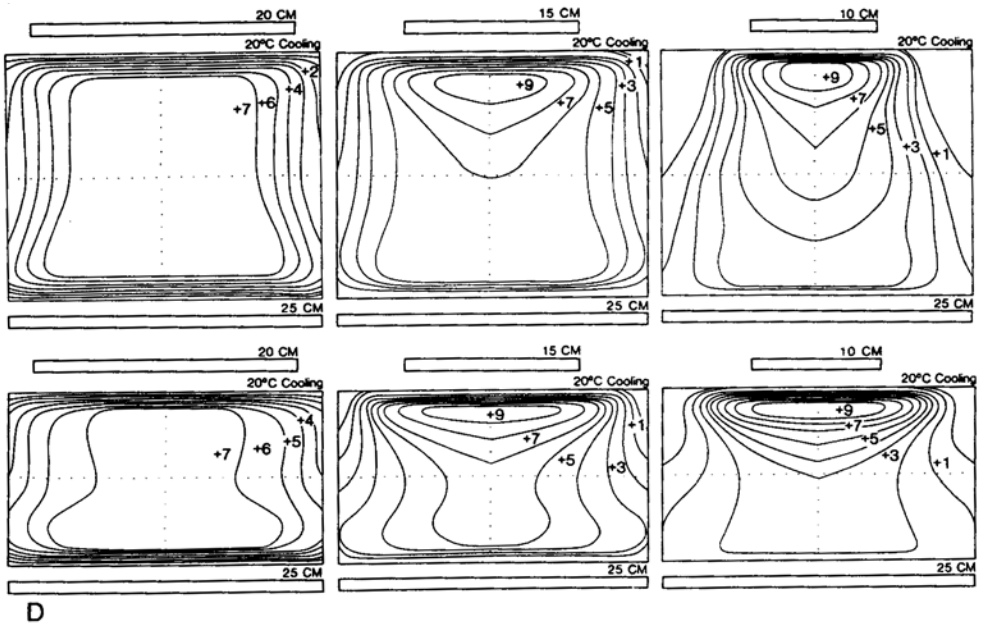

Fig. 2. Temperature distribution in phantom heated with the device Thermotron RF-8. The phantom thickness on the top row is 20 cm, on the bottom one 15 cm. The sizes of the applicators and the temperature levels, for different heating conditions, are given in the figures. The shaded areas under the applicators are hot zones

In other model experiments and on phantoms imitating the human body, for various hyperthermic systems, the distribution of SAR and temperatures in the pelvic organs and tumors was also studied [40, 41]. In the work of Frija E., Cavagnaro M. [40], the phantom was heterogeneous (skin, SCF, muscles) and had a cylindrical shape 85 cm high with the base in the form of an ellipse with semi-axes of 12 and 18 cm. The calculation was carried out for the capacitive system Celsius TCS and the radiative systems BSD-2000 and ALBA-4D, all with an output power of 500 W. SAR was calculated for the small pelvis, SCF, bladder and cervix. The conditions for calculating SAR were as follows: when the bladder was the target, the diameter of the ventral applicator was 15 cm and that of the dorsal applicator 25 cm, when the cervix was the target both applicators were 25 cm.

In fig. 3 and 4 show the distribution of SAR in phantoms with SCF thickness of 1 cm ventrally and 2 cm dorsally.

Calculations showed that the maximum SAR to se Celsius TCS in the bladder was 46.1 W/kg, and in the cervix 10.3 W/kg. The maximum SAR in the SCF under the 15 cm diameter applicator was 2038.9 W/kg, and under the 25 cm applicator it was 588.1 W/ g. Thus, the maximum value of SAR in the SCF is 44 times higher than in the bladder and 57 times than in the cervix. Such high energy levels will result in a burning sensation, and require a decrease of radiated power or, otherwise, significantly increases the risk of burns in the SCF, which significantly limits the use of this device for HT tumors of internal organs. For radiative systems this ratio was much lower: 0.5 and 1.1 for he BSD-2000 system and 1.0 and 2.7 for the ALBA-4D system, respectively, allowing a higher energy levels in the umors of these organs.

Beck M. et al. [41] studied the SAR distribution achieved with the Celsius TCS in homogeneous phantoms of 10 and 14 cm thickness. The applied power was 100 W and both electrodes had a diameter of 25 cm. The results showed a sharp decrease in UPM in depth, a decrease by 50 % took place already at a depth of about 3 cm, by 75 % – by 5 cm. Since there is a between the SAR and the temperature, a the same sharp decrease in the level of heating in the depth of the fabric.

It should be noted that in studies of Frija E., Cavagnaro M. [40] and Beck M. et al. [41] do not take into account the heat carryover by the bloodstream, which during moderate HT rises in patients with tumors and prevents the rise in temperature. In addition, in their work did not take into account the fact that the applicators on the Celsius TCS unit in clinical conditions does not completely adhere to the heated surface, which further increases the temperature gradient along the depth.

Kok H.P. et al. [42] performed calculations of the distribution of the EM field for the irradiation (70 MHz) and capacitive systems, in frequency similar to Celsius TCS (13.6 MHz), in heterogeneous phantoms, imitating human pelvis, without SCF or with its thickness of 1 and 2 cm. The SAR was calculated for conditional tumors located in the center of the phantom (cancer of the cervix and prostate gland) and eccentric (cancer of the bladder and rectum). In addition, the calculations were also carried out for modeled patients with cancer of the pelvic

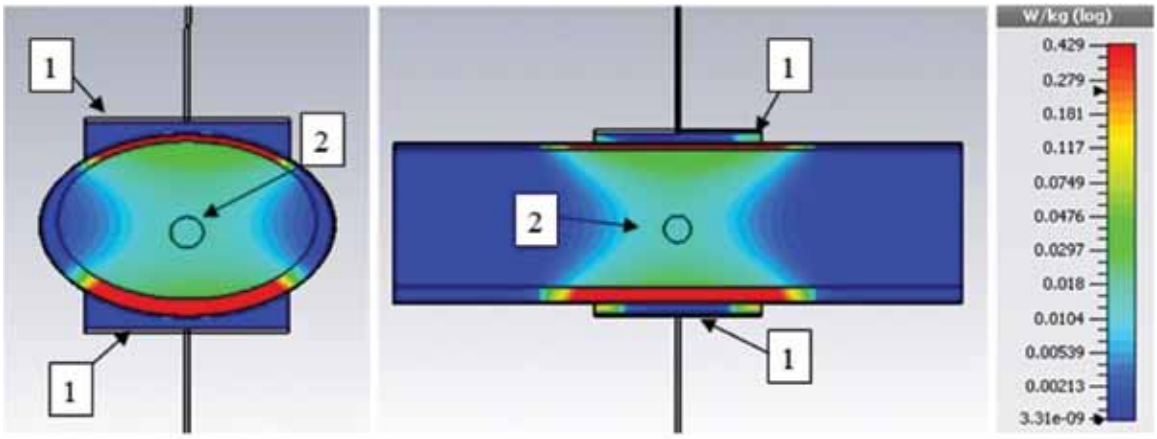

Fig. 3. Distribution of EM energy in the phantom simulating the pelvis with the uterine cervix, when heated with the Celsius TCS. 1 – applicators, 2 – cervix

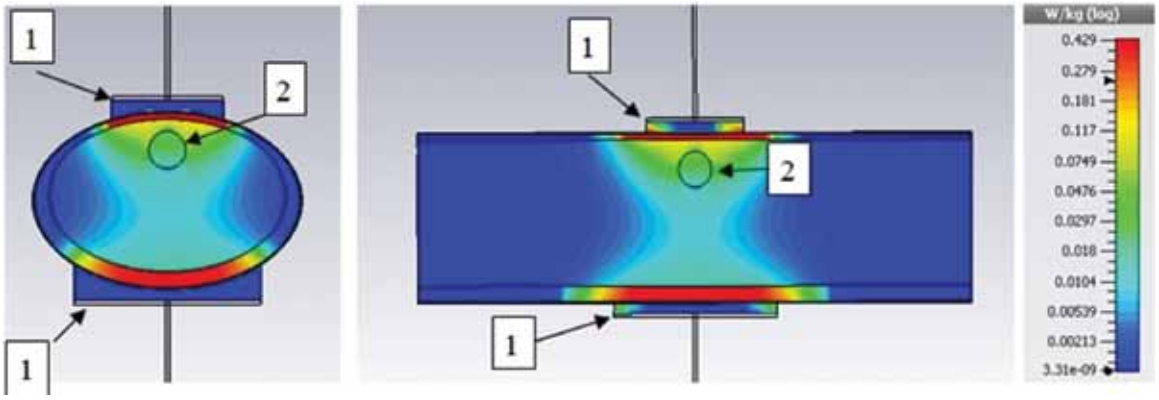

Fig. 4. Distribution of EM energy in the phantom simulating the pelvis with the bladder, when heated with the Celsius TCS. 1 – applicators, 2 –bladder

organs, with various types of bolus filling and skin cooling. The authors showed that with capacitive heating, any fat layer reduces the energy transmitted in depth.

Only the lack of fat in patients allows to reach temperatures above 40 °C in the selected target located. Calculations on patient models showed that the T90 (the temperature level reached in at least 90 % of the target) is approximately 37.3 °C in cervical and prostate cancer, 38–38.3 °C in bladder, and 37.5–38 °C in rectal cancer.

Results of experimental and clinical research on capacitive hyperthermic systems

HTM3000P (13.56 MHz) system. Testing of this system was conducted in Dutch in 11 patients with recurrent rectal and sigmoid carcinoma. From 496 measurements of the temperature in the tumor in 288 (58 %), it was below 40 °C. The mean thickness of the SCF in the anterior abdominal wall was 1.5 ± 0.3 cm (1–2.7 cm), in the dorsal region it was 2.1 ± 0.7 cm (1.2–3.1 cm). The skin was pre-cooled with water circulating in the bolus at 5–10 °C for 30 min. RFHT was carried out using large electrodes (300 cm^2) in various set-ups at an average output power of 700 W (maximum power of the unit was 1400 W). Heating with a higher output power was limited due to patients' complaints of burning sensations and pain under the applicators due to overheating of the SCF. The temperature at the border of the SCF-muscle was above 44 °C [33].

Superterm EP-40 (40.68 MHz), **Extraterm** (40.68 MHz). Clinical studies on these installations have also shown that, with the thickness of SCF more than 1,5–2,0 cm, it is practically impossible to reach therapeutic temperatures in tumors of internal organs. With a smaller thickness of SCF, it is possible in malignant neoplasms of the lung, liver and rectum, as well as soft tissue sarcomas and osteogenic sarcomas with deep localization [43].

Cancermia GHT-RF8 (8 MHz). Experimental and clinical studies on this setup are rare [44, 45]. Seong J. et al. [44] LRHT performed 84 patients with unresectable primary liver cancer on this unit. HT with a duration of 30–60 min was carried out for 30 min after the remote RT (TD 30.6 Gy / 3.5 weeks). The maximum, minimum and

average temperatures in the tumor were 41.9 ± 1.3 °C, 39.9 ± 1.0 °Cand 40.8 ± 0.9 °C, respectively. During treatment, 51.2 % of patients felt pain in the area of heating and as a result, 13.1 % developed SCF necrosis. The results of the treatment, evaluated in 67 patients, showed that in 27 (40 %) tumors regressed by more than 50 %, including 2 with a full response. Symptomatic improvement was observed in 78.6 % of patients. Acute toxicity in the form of pain was observed in 51.2 % of patients, and necrosis of the SCF in 13.1 %. The actuarial 1, 2 and 3-year survival rates were 44.8 %, 19.7 %, 15.6 %, respectively. The median survival was 6 months. Kim S-W. et al. [45] compared the effectiveness of neoadjuvant CRT and termochemoradiotherapy (TCRT) in patients with locally advanced rectal cancer. In the group of patients with TCRT, compared with CRT, there was a tendency to a decrease in the stage of the disease (p = 0.060) and an increase in the frequency of the pathological complete tumor response (p = 0.064). Overall survival was significantly higher (p = 0.014) in the study group.

Oncothermia (13.56 MHz). Lee S-Y. et al. [46] report temperatures during treatment of 20 patients with cervical cancer (FIGO stage IIb–IVb). Patients were treated during 60 min, with a 30 cm diameter electrode at power levels of 80 W for10 min, 120 W for10 min and 150 W for 40 min. The temperature in the lumen of the cervix had increased from 36.7 ± 0.2 to 37.5 ± 0.5 °C after 30 min from start of treatment, and to 38.5 ± 0.8 °C at the end of the session.

One of the authors (Kurpeshev O.K.) has observed a treatment with the Oncotherm device in one of the oncological centers of Russia, in a patient with cervical cancer [8]. The patient was frail physique with a height of 164 cm and weight of 50 kg. The anterior-posterior diameter in the pelvic region was 13 cm, and the thickness of the SCF in the anterior abdominal wall was 0,9 cm. Thermometry was performed using an alcohol thermometer and fiber optic sensors. The pelvic region was treated by using an active electrode of 30 cm in diameter. The exposure was started with 60 W, and power was stepwise increased to 110 W within the next 60 min and continued with the same power level until the end of treatment of total 90 min. A further increase in power was impossible, because of a strong burning sensation in the skin under the active electrode. At the end of the session, the temperature in the rectum was 37.2 °C, in the vagina 37.1 °C, and in the urethra 36.9 °C.

The data suggests that on the Onkoterm facility, in tumors of deep localization, it is not possible to create a hyperthermic regime in a classical sense. Moreover, the developers of the method themselves, in the description of this technology approved by the ministry of Health of Russia [47] also point out the absence of a hyperthermic regime in the tumor. On page 5, they write: "…. in the theory of oncothermia (this is the name of the treatment named after the device – authors' notes), the static / hyperthermic phase is perceived as undesirable". But, further they write: "... the temperature during oncothermia is responsible for less than a quarter of the total efficiency of the method, while the rest ¾ provide non-thermal factors (field, electrodynamic)". We can agree with the authors' statements about the minimal contribution of HT to the therapeutic effect; moreover, we believe that at such temperatures that are achieved at this facility in tumors of the internal organs, it can be completely absent.

Celsius TCS. During the existence of this facility on the market of medical devices (over 12 years), full-fledged thermometric studies in the clinic have not been carried out. The failure of achieving therapeutic temperatures in a patient with rectal cancer treated with this device was observed by one of the authors (Kurpeshev O.K.) in one of the oncological clinics in Russia [8]. The anterior-posterior size of the patient in the pelvic region was 13.5 cm, the thickness of the SCF in this region was maximum 1,2 cm. RFHT was applied to the pelvic region, during 60 min with a pair of electrodes of diameter of 25 cm each. The temperature was monitored intrarectally using an alcohol thermometer with a 0,5 cm reservoir in close contact to the tumor. The heating was started with an output power of 50–60 W and for 40 min it was brought up to 130 W, for 50 min – up to 150 W. A further increase in power was not possible due to the appearance of a strong burning sensation on the skin under the applicators. Peritumoral temperature on the 40th minute of heating was 38 °C, and at the end of the session (60 min) – 38.5 °C.

Experiments on pigs also have shown the problem of heating at depth with this device Noh J.M. et al. [48]. Pigs weighing 40 kg were treated under general anesthesia. During one day the animals were exposed to 6 treatment sessions of 60 min, at intervals of 30 min. Despite the decrease in blood flow in the liver and thereby decrease in heat removal, due to general anesthesia, the maximum temperature increase of 2.7 °C took place only at the end of the sixth session when the power input had increased to 200 W. Thus, even in this experiment on a low-weighted and anesthesized pig, it was not possible to obtain therapeutic temperature.

In the absence of clinical research, the developers of Celsius TCS recommend using specific schemes of power increase for clinical applications. The treatment involves 10 sessions of HT for 60 min, with a gradual increase in the radiation power during the procedure. In particular, in the treatment of patients with liver tumors in the 1st session, treatment begins with 40 W and ends at 100 W. In each subsequent session, the output power is increased by 10–20 W. At the 10th session, treatment begins with 100 W and for 50 min increases to 170 W, then for 10 min, if the patient's condition allows, it is allowed to rise to

the maximum tolerated power. But, as practice shows, an output of 200 W with HT tumors of internal organs in this unit is very problematic.

Such a scheme of power increase for the Celsius TCS device was applied by Yu J.I. et al. [49], in combination with radiation therapy, in patients with metastases (MTS) of colorectal cancer in the liver. As can be seen in table, they started with 40 W at the beginning of the first session and increased power during 60 min to 100 Watts. In the subsequent 4 sessions, the starting power was increased from 50 to 85 W, and the maximum power from 120 to 200 W. Five sessions of HT and seven fractions (3 Gy each) of total liver irradiation were applied. Unfortunately, the authors did not measure the temperature in MTS. Taking into account the general laws of distribution of EM energy at this facility [40, 41] and the results of research on other such systems, it can be assumed that in MTS, at the EMF facilities used, the hyperthermic regime was not achieved. Perhaps for this reason, the contribution of HT to the effectiveness of RT was not obtained. The treatment results in ten patients were as followed. Within 1 month, a partial response was achieved in 3 (30 %) patients, stabilization in 4 (40 %), and pain reduction in 4 (40 %). At 3 months, local progression free survival was 30 % (median 2.2 months) and pain progression free survival was 58.3 %. At that time, 1 patient had died from progression of MTS in the pleura, and 3 patients had developed grade III toxicity. Comparison of the obtained results with previous studies of MTS of colorectal cancer in the liver, including Radiation Therapy Oncology Group (RTOG) studies, did not show clear differences in effects on pain [50–52]. In the RTOG study, pain decrease 1 month after treatment was observed in 50 % of patients, which was higher than in the group treated with thermoradiation (TRT). The liver function and general condition of patients tended to worsen after TRT, whereas in the RTOG study these improved in 40 % and 49 %, respectively. That is why, Yu J.I. et al. [49] conclude that they could not demonstrate an improvement in results of the treatment with the Celsius device.

Thus, experimental studies on phantoms, animals, as well as a single temperature measurement in a patient show that it is impossible to create a hyperthermic regime in tumors of deep localization using the Celsius device. As already mentioned, the table data offered for work in the clinic (used and in the experiment) provide for an increase in power from 60–90 to 160–190 W during the 40–50 min of treatment, and for the remaining 10 min allowed to increase it to the maximum portable.

However, due to the peculiarities of the applicator design, the output of 200 W in the clinical environment is very problematic. Comparative analysis with literature data shows that the RF field used at the Celsius TCS turned out to be significantly lower than at devices of this type carried out by other researchers [33, 45, 53–55]. In these studies, it was shown that with using capacitive RFHT at frequencies of 8 and 13.56 MHz, the minimum RF field required to achieve the minimum hyperthermic regime in tumors of internal organs varies from 500–800 W, the maximum – 1000–1200 watts and above. In particular, according to Van Rhoon G.C. et al. [33] on the HTM3000P device (13.56 MHz) with an average thickness of the SCF of the anterior abdominal wall 1.5 ± 0.3 cm (1–2.7 cm), the sacrum area 2.1 ± 0.7 cm (1.2–3.1 cm) and the use of electrodes with an area of 300 cm^2, the average power used was 700 W, the maximum – 1400 W.

Kim S-W. et al. [45] for TCRT patients with locally advanced colorectal cancer, the Cancermia GHT-RF8 (8 MHz) machine used an average output power of an average of 800 ± 229 W, and a maximum of 1005 ± 232 W.

In studies of Harima Y. et al. [54–55] used output power at Thermotron ranged from 800 to 1500 W. The reason for the impossibility of increasing the power of EMF to these values is the appearance of a burning sensation on the skin and pain under the applicators, which indicates a wrong approach to treatment and selection of patients or non-compliance of the design of applicators with the technical requirements.

On the basis of the available experimental clinical data and the results of model calculations and measurements on phantoms [8, 40, 41, 48, 49], we believe that the data of some publications that are not fully justified say that in tumors of the internal organs of patients (lung cancer, cervix, rectum), on the installation Celsius TCS reaches a

Table

The calculated settings used by Yu J.I. et al. [49] in the treatment of patients with metastatic colorectal cancer in the liver*

Session №№	Radiated power (W) for different levels (L) irradiation during the session					The total dose (kJ) (60 min)
	L1	L2	L3	L4	L5	
1	40	60	70	90	100	240
2	50	70	85	100	120	285
3	60	80	100	120	150	342
4	75	100	130	160	180	432
5	85	110	135	160	200	465

* – for clarity, the table is fully photographed from the article

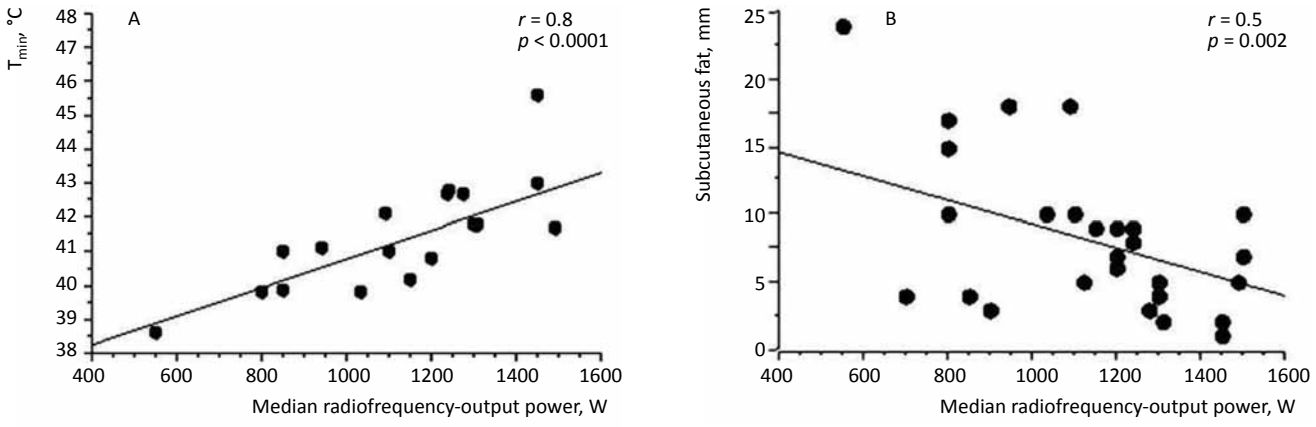

Fig. 5. Correlation between output power and minimum temperature in the esophagus (A), as well as the thickness of the SCF (B)

temperature of 41–45 °C [56, 57]. In this regard, the high results of HT obtained in this setting in patients with these tumor sites require careful analysis and discussion..

Thermotron RF-8. At this device, the largest number of experimental and clinical studies on HT. Several of these studies have shown a direct relationship between the temperature in deep seated tumors, the EM power applied, and the thickness of the SCF [6, 26, 32, 37–39, 53–55, 58–70]. In this setting, 7 randomized studies were performed on patients with malignant neoplasms of internal organs. Five of them showed a high contribution of HT to the antitumor treatment, 2 it was absent due to underheating of the tumor and / or a small sample [8].

In an multi-institutional study, Abe et al. [26] showed that the temperature and also the immediate response of the tumor, depended on the depth of the tumor. In the total group of 63 patients, the average temperature was 42.5 ± 0.5 °C. In superficial tumors (depth up to 3 cm), the complete response rate was 68 %, for tumors at a depth of 3–6 cm it was 54 %, and for tumors located at more than 6 cm depth it was 23 %. In seven of 20 (35 %) tumors located at >6 cm depth, a temperature of more than 42 °C was not achieved. In these patients, the SCF thickness was more than 2 cm.

Ohguri T. et al. [53], in 35 patients with non-small-cell lung cancer stage III, statistically significant correlations were established between the esophageal temperature, the output power, the thickness of the SCF, and the results of treatment. Heating was performed using electrodes with diameters of 30 cm, and with an output power ranging from 548 to 1560 W. Thermometry in the esophagus was performed in 22 patients. The temperature varied from 39 to 48 °C and depended on the size of the thorax and the thickness of the SCF. A significant increase in overall survival (p = 0.01), local control (p = 0.004), and distant metastasis free survival (p = 0.02) was observed when the median applied power was minimum 1200 W. With such high power, the minimum temperature in the esophagus was > 41.5 °C (fig. 5A). These high temperatures were achieved in patients with a mean SCF thickness of 0.75 cm. (fig. 5B). In these works, the median intra-esophageal minimum (41.7 °C) and maximum temperature (43.2 °C) highly correlated with the corresponding medians of the output power, which were 548 and 1679 W, respectively.

According to Harima Y. et al. [54] in a multicenter randomized clinical trial in patients with cervical cancer with IIIB st. HT significantly increased the results of CRT. In these cases, the average temperature of 40.6 °C in the tumor was achieved with an output power of 800–1500 W. However, with the expansion of patients to IIA–IVA st. no significant contribution of HT to efficacy of CRT was obtained, although 5-year survival rates (total, disease-free, recurrence-free) were 9–13 % higher compared to control [55]. The output power from 800 to 1500 W was used in the work. At these capacities, the maximum temperature in the rectum and vagina ranged from 40.1 to 44.6 °C (average 42.2 °C), the average – from 39.6 to 42.5 °C (average 41.1 °C), CEM43T90 – from 0.1 to 46.6 min (average 3.8 min).

Hiraoka M. et al. [58, 59] studied the relationship between SCF thickness and maximum temperature in tumors with a localization at a depth of more than 5 cm (head and neck region, thorax, abdominal region, pelvic organs, lower limbs). The skin was cooled with the bolus water at 5–10 °C. The dimension of the water bolus for cooling exceeded the size of the electrode by at least 6 cm. In 38 % of tumors they achieved a temperature above 43°C, in 44 % between 41 and 43 °C, and in the remaining 18 % it was below 41 °C. The objective response rates for these various temperature groups were 53, 82 and 33 %, respectively. During treatment, 27 (68 %) of 40 patients experienced pain, which had disappeared after completion of HT in 20 patients. However, four (10 %) patients

developed SCF necrosis, two (5 %) had a 2nd degree skin burn, and four (10 %) had visible edema in the treated area. When the SCF thickness was 0,5 cm, a maximum tumor temperature of over 41 °C was achieved in 86 % of cases (6/7), for 0.5–1.0 cm in 89 % (16/18), for 1.0–1.5 cm in 95 % (18/19), for 15–20 in 60 % (6/10), and for more than 20 mm in only 17 % (1/6). The authors conclude that for capacitive RFHT, the thickness of the SCF should not exceed 1.5 cm.

A randomized, multicentric study on the effect of HT in cervical cancer showed that in only 2 of 4 cancer centers, tumors reached temperatures above 41 °C. In the two other centers this was from 40.2 to 40.6 °C, and from 37.5 to 39 °C [60]. It should be noted that patients with a SCF thickness of up to 3 cm were included in this study, and that at least half of the patients were treated with an additional intravaginal electrode with the temperature measured in contact with this electrode, where it can be expected to be the highest. Even greater temperature variations were noted in a study by Konishi et al. [61] in patients with rectal cancer (n = 17). The intratumor temperature varied from 38 to 44 °C, with an average of 41 °C. Low temperatures were also associated with thicker SCF layers.

Similar results were obtained in patients with liver and pancreatic cancer [26, 62–64]. Yoshida M. et al. [62] with capacitive RFHT, 24 patients with pancreatic cancer in 15 (62.5 %) reached a temperature in the tumor above 42 °C. Nagata T. et al. [63, 64] also showed the dependence of achieved tumor temperature on the tumor type and SCF thickness. In hepatocellular carcinoma, the maximum temperature reached 41.2 ± 0.2 °C, the average temperature was 40.3 ± 0.3 °C, and the minimum temperature was 40.1 ± 0.2 °C. For a massive tumor these values were 41.1 ± 0.2 °C and 40.0 ± 0.2 °C respectively, for a nodal type 41.0 ± 0.3 °C and 40.0 ± 0.4 °C, for diffuse tumors 42.1 ± 0.6 °C and 40.6 ± 0,5 °C. For metastases MTS the maximum temperature was 42.4 ± 0.2 °C, the average temperature 41.8 ± 0.2 °C, and the minimum 40.7 ± 0.2 °C. The maximum temperature in the liver parenchyma averaged 39.6 ± 0.2 °C (38.2–41.4 °C), and in the SCF – 40.3 ± 0.3 °C (38.7–41.4 °C). The thickness of the SCF ranged from 0.3 to 1.2 cm (with an average of 0.8 cm). The immediate response of tumors were associated rather with the maximum than with the minimum temperature. Necrosis of SCF developed in 20 (12 %) patients, gastric ulceration in four (2 %), and liver necrosis in one (1 %). Consequences of thermometry were severe peritoneal pain in seven (11 %) patients, intraperitoneal hematoma in one (1 %) and pneumothorax in one (1 %).

In a modelled patient with hepatocellular cancer, the calculated average tumor temperature during 50 min heating with the Thermotron device was 39.7 °C. In the real treated patient the average measured temperature was 40.3 °C, that is, it differed not much [39].

Hamazoe R. et al. [65] analyzed 318 hyperthermia treatments of 39 patients with recurrent or inoperable malignant tumors of the digestive system. Although it was difficult to heat the bile duct and pancreatic tumors to 42 °C, they observed a high correlation between the maximum output power of EM energy and the maximum temperature in the tumor (p < 0.001). Moreover, a correlation was found between tumor response and applied RF power. A high response rate was observed with an average output power of 1000 W, a minimum of 700 W, after four or more HT sessions. The authors conclude that the level of maximum applied power can be a good indicator of the effectiveness of the treatment for abdominal tumors.

Further studies have shown that with the Thermotron device, heating of deep seated tumors to temperatures of 40 °C and higher is possible when the SCF thickness is less than 1.5 cm [66–70].

Discussion

The main problem of the classical capacitive EMHT of malignant neoplasms of deep localization is overheating of the SCF, up to the development of burns. Thermal load on it can be reduced by intensive cooling of the skin. The resulting high temperature can be decreased by extensive cooling of the skin with the SCF less than 1.5–2 cm thick. This means that the capacitive system is not always applicable in patients with tumors of deep localization. Another disadvantage of capacitive heating is the limited ability to control power to bring maximum energy to the tumor. This is achieved only by selecting the size and location of the electrodes above the tumor. To improve the depth of heating, when using these systems, it is necessary to comply with a number of technical requirements and conditions of the HT. First of all, it concerns the characteristics of the membranes of applicators and additional water boluses. They must be elastic and thin – no more than 0.7–0.8 mm. This contributes to a better fit of the membranes to the body of the patient, that is, without the formation of air gaps between them and the body of the patient. To reduce the edge effect, the size of the bolus should be larger than the size of the electrodes, that is, cover the heating area. In a capacitive RFHT at frequencies of 8–13.56 MHz, obtaining the minimum hyperthermic mode is possible with output powers of 500–800 W, maximum – at 1000–1200 W and above.

Conclusion

The results of both experimental and clinical studies show that with the help of some capacitive systems presented in this review, it is impossible to create

hyperthermic regimens in tumors of deep localization. Such installations can be used for HT superficial, in some cases, subsurface tumors. Finally, temperature measurement with HT is the fundamental basis for applying this type of treatment.

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О.К. Курпешев[1], Я. ван дер Зее[2], М. Кавагнаро[3]

ГИПЕРТЕРМИЯ ОПУХОЛЕЙ ГЛУБОКОЙ ЛОКАЛИЗАЦИИ: ВОЗМОЖНОСТИ ЕМКОСТНОГО МЕТОДА*

1. Сибирский научно-исследовательский институт гипертермии, Новосибирская обл., Искитим-5;
2. Эразмусский медицинский центр, Университетский медицинский центр Роттердама, Роттердам, Нидерланды;
3. Университет Сапиенца, Рим, Италия

О.К. Курпешев – д.м.н., консультант; Я. ван дер Зее – д.м.н., член ESHO;
М. Кавагнаро – проф., д.м.н., член IEEE, ESHO и EBEA

Содержание

Рассмотрены общие принципы проведения емкостной электромагнитной гипертермии (ЭМГТ), распределение электромагнитной энергии в различных экспериментальных моделях и опухолях больных, особенности конструкции аппликаторов различных гипертермических систем и их возможности в создании гипертермического режима в новообразованиях глубокой локализации. При классической емкостной ЭМГТ основным препятствием в достижении необходимого температурного режима в таких опухолях является перегрев подкожно-жировой клетчатки под электродами. При некоторых емкостных гипертермических системах нагрев жировой ткани еще больше усиливается из-за несоответствия конструкции аппликаторов техническим требованиям. При емкостной ЭМГТ на частотах 8–13,56 МГц получение минимального гипертермического режима возможно при выходных мощностях 500–800 Вт, максимального 1000–1200 Вт и выше.

Анализируются результаты применения различных емкостных гипертермических систем у больных со злокачественными новообразованиями внутренних органов.

Ключевые слова: *лучевая терапия, химиотерапия, термолучевая терапия, термохимиотерапия, термохимиолучевая терапия, электромагнитные поля, гипертермия, емкостной метод*

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