

500 kHz intracavitary hyperthermia in the treatment of patients with cervical and endometrial cancer – preliminary results and treatment description

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The effectiveness of elevated temperature (hyperthermia) in cancer treatment is a well-known issue. However, due to technical problems with generating hyperthermia within the tumour and, at the same time, sparing the healthy tissues, in practice this modality is not widely used.

Method. Local hyperthermia was induced by a computer-controlled generator (500 kHz) with three amplifiers transmitting energy to the lesion via a modified uterine brachytherapy applicator. Temperature was measured with 3 thermocouples. Total treatment time was 60-90 minutes.

Material. 10 patients with cervical and endometrial cancer were enrolled into this study and 11 procedures were performed. Prior to hyperthermia all patients were treated with external field irradiation to the pelvis to the dose of 45-46 Gy. Intracavitary LDR/HDR brachytherapy (dose of 45 Gy/point "A" in two fractions) with colpostat used for the hyperthermia procedure was than performed.

Results. In all cases, except one, caused by equipment failure, biologically stable temperature was observed. No severe side effects of treatment were observed. There was no need to terminate treatment due to high temperature intolerance.

Wewnątrzjamowa hipertermia 500 kHz w leczeniu chorych na raka szyjki i trzonu macicy – opis metody i wstępne wyniki

Terapeutyczne możliwości zastosowania podwyższonej temperatury w leczeniu nowotworów znane były od dawna. Trudności techniczne w uzyskaniu adekwatnej temperatury w guzie, z jednoczesną ochroną tkanek zdrowych, są jak dotąd podstawowym czynnikiem, limitującym szersze praktyczne zastosowanie metody.

Material i metody. Do przeprowadzenia zabiegów zastosowano sterowany komputerowo generator i 3 wzmacniacze fal radiowych o częstotliwości 500 kHz, przekazujący chorym tkankom energię za pomocą zmodyfikowanego aplikatora (kolpostatu) Fletcher'a. Pomiar temperatury odbywał się za pomocą zestawu trzech termopar. Praktyczny czas przeprowadzenia zabiegu wynosił 60-90 minut. Przeprowadzono 11 zabiegów u 10 chorych z rozpoznaniem raka szyjki macicy i trzonu macicy. Przed rozpoczęciem hipertermii wszystkie chore na raka szyjki poddane zostały napromienieniu z pól zewnętrznych na obszar miednicy małej do dawki 45-46 Gy. Zabieg hipertermii bezpośrednio poprzedzał śródjamową brachyterapię LDR/MDR (dawka 45 Gy/punkt "A" w dwóch etapach), przeprowadzaną za pomocą tego samego kolpostatu. Po poinformowaniu o charakterze zabiegu nagrzewania każdorazowo uzyskiwano zgodę chorej na jego przeprowadzenie.

Wyniki. Poza jednym przypadkiem (awaria aparatu) u wszystkich leczonych udało się uzyskać stabilne w czasie terapeutyczne wartości temperatur, a w kilku przypadkach temperatury dochodzące nawet do 48 °C były dobrze tolerowane przez chore. Nie stwierdzono żadnych poważniejszych objawów ubocznych zabiegów; nie zaszła konieczność ich przerwania ze względu na brak tolerancji chorej.

Key words: hyperthermia, gynecological brachytherapy

Słowa kluczowe: hipertermia, brachyterapia ginekologiczna

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Introduction

The therapeutic effects of high temperature has been widely known since ancient times. Hippocrates mentions it to be as effective as pharmacology and surgery [1]. In 1866 spontaneous regression of a soft tissue sarcoma was described in a patient with fever caused by erysipelas. In 1893 Coley tried to adapt high temperature therapy into practice – he caused fever in patients with cancer by giving them *Streptococcus* toxin [2]. Progress in surgical techniques, incorporation of cytostatics into oncological therapy and the development of ionizing radiation have overshadowed hyperthermia for many years. The interest in it revived again in the 1970-s.

Biological background

High temperature affects both the cellular and the tissue level. Its cytostatic effect reflects damage to cell membrane, contractile fibre, cell skeleton, lysosomes, mitochondria and nuclear DNA structure accompanied by interference with reconstruction and replication of the structures. At the tissue level elevated temperature leads to impaired blood perfusion, caused by vessel embolism, resulting in necrosis. High temperature alone permits to obtain partial (> 50%) or complete regression of the tumor, in 30 and 15% of cases respectively. Unfortunately the effect is short lasting. This may be explained by the repair of lesions induced by elevated temperature after the temperature is reduced back to the physiological ranges. The thermotolerance phenomenon also seems a relevant issue. Thermotolerance represents resistance to elevated temperatures noted after 10 to 20 hours of incubation in 37°C. Heat shock proteins are responsible for this effect. Cells exposed within a short time (30-45 min) to both elevated temperatures and ionising radiation behave in a different manner: they become more sensitive to ionising radiation. Radiobiology explains the phenomenon by a lower sensitivity to high temperatures observed in G2 and M phases of the cell cycle. In contrast, the radioresistant S phase is more sensitive to elevated temperatures. Considering tumor cells to represent poorly oxygenated and, thus, radioresistant tissue elements, one finds them more sensitive to elevated temperatures, which produce synergistic effects at the tissue level. As compared to normal tissue, tumors with pathological vascular supply may be more sensitive to vascular changes provoked by increased temperature [1].

Practical aspects of hyperthermia application

The practical use of elevated temperature is still seen as a kind of medical experiment even if the mechanism by which it acts is more or less known. The main problem in obtaining therapeutic ranges of temperature (42.5-48°C) in the tumor involves the risk of exposing the neighbouring healthy tissues to such temperatures. A variety of techniques have been used to elevate tissue temperature. Some authors used hot air or hot water, circulating inside

thin catheters inserted to the target tissue. More sophisticated methods have involved heating of in-flowing blood using the equipment for extra-corporeal circulation, microwaves, ultrasound, radio waves. The last two techniques seem to be the most effective and the most widely practised. Reliable monitoring of temperature remains a vital function in any hyperthermia system. Invention of non-metallic thermometers and thermocouples, miniature and resistant to noise effects, allows to establish the temperature level in a simple and credible way. Till now, most of the experience with clinical practice and application of hyperthermia has been related to radiotherapy. The combined therapeutic approach consists either of hyperthermia and a second course of radiation therapy (salvage radiotherapy with a limited radiation dose) or primary radiotherapy of a standard dose, combined with heating. In the first case, application of hyperthermia opens up a chance for reducing the dose of radiation. In many groups of patients, frequently with more than 100 subjects enrolled, with head and neck, skin, breast, gastrointestinal tract and urino-genitary tumors regression of lesion was noted 1.5-2.5-fold more frequently after the combined therapy, as compared to radiotherapy alone. The most severe side effect of hyperthermia is risk of thermal damage (burns) to the surrounding normal tissue. The patient may also suffer from local discomfort caused by elevated temperature during the treatment [1].

Method

Local hyperthermia was induced by an Ht-1 system developed at the Gdańsk Institute of Technology. The system consisted of a computer-controlled generator (500 kHz) with three amplifiers which transmitted energy to the pathological tissue via a modified (electrically insulated) uterine brachytherapy applicator (Fletcher – type, Nucletron). A colostat served as an active antenna to pass energy to the tissue. Its parts, including the intrauterine probe and two vaginal applicators, could be controlled separately by changing amplitudes and phases of transmitted energy. Specific distributions of temperature could be obtained, depending upon the patient's clinical condition. Taking into account the wave frequency (500 kHz), it is necessary to apply a grounding electrode, which involved aluminium foil wrapped around the patient's pelvis. Temperature was monitored by three thermocouples. Due to their small size (diameter <0.5 mm), the temperature could be assessed, as indicated, in the uterus, in direct vicinity of active antennas, in the anus, urinary bladder and/or interstitially. Physical variables of the induced waves (frequency, phase, power) and electrical impedance of patient's tissue were evaluated in a real time in accordance with data obtained during the assessment of temperature distribution in "in vitro" experiments and computer simulations [3]. During the procedure temperature of at least 42,5°C in minimum 45 minutes was observed in the treated volume. Total treatment time was 60-90 minutes. All parameters of each procedures were recorded in the computer software.

Material

Ten patients were enrolled into the study. Eleven procedures were performed: 9 in patients with uterine cervix cancer IIb and IIIb FIGO stage, 2 in one patient with endometrial cancer. All patients with cervical cancer were treated once and the patient with endometrial cancer received two procedures.

According to the treatment protocol all the patients with uterine cervix cancer were treated with external field irradiation to the pelvis to the dose of 45-46 Gy (1.8-2 Gy/fraction). Intracavitary LDR/HDR brachytherapy (dose of 45 Gy/point "A" in two fractions) using colpostat for hyperthermia procedure was then performed. In the case of the patient with endometrial cancer case only LDR/MDR (dose 50 Gy/point "A" in two fractions) brachytherapy was performed due to the patient's poor general condition. In every case informed consent was obtained. Except for one case, when we observed equipment failure, stable temperature was documented. In a few cases the temperature of 48°C could be maintained and was well tolerated by the patients. In 10 cases no signs of intolerance were observed, however in 2 cases a discomfort (verbalised as a sensation of heat in the lower abdomen) forced us to lower the power supplied by the amplifier. In one case a 1 x 0.5 cm thermal lesion was accidentally induced due to contact of an improperly insulated part of the colpostat with the vaginal mucosa. This lesion disappeared spontaneously. In none of the cases we had to discontinue the treatment due to intolerance of the elevated temperature.

Discussion

The basic limitations for a wider usage of hyperthermia as a method adjuvant to radiotherapy is the lack of a simple and effective way of obtaining elevated temperature within the tumor only, at the same time sparing the surrounding healthy tissues. Solving this problem seems to be the easiest in the case of uterine neoplasms. Unfavourable treatment results with radio- and radio-chemotherapy call for developing new therapeutic modalities. Several recently published papers show a higher index of clinical effectiveness after incorporating hyperthermia into radiotherapy treatment. Some of the most relevant are the results of the *Dutch Deep Hyperthermia Group*. Their prospective, randomised, multicentred based study analysed the treatment results of 358 patients with cervical, rectal and bladder cancer. In this group 114 patients with cervical cancer were divided into two subgroups – 58 patients received radiotherapy and hyperthermia and 56 – radiotherapy alone. Local control rates were 61% and 41%, respectively, with 3-year survival time of 51% and 27% respectively – thus statistically significant. In the subgroup of patients with rectal cancer (143 pts) no statistically relevant difference was observed but again, the ratio of local control was 16% and 8%, with 3-year survival 22% and 13%, respectively. For the 101 patients with bladder cancer the respective values were 42% versus 33% and 28% versus 22% [4]. It is very important to stress that these results were obtained using "external heating", which is not as effective as intracavitary, due to treatment intolerance and lower range of temperatures.

Van der Zee et al. observed skin reactions after radiotherapy performed for breast cancer recurrence on the thoracic wall. Two adjacent skin areas were irradiated with the same dose, but in one field, additionally, hyperthermia was used. In the part of the skin which received combined therapy significantly lesser teleangiectasiae were observed. This phenomenon can be explained by

a faster reconstruction of radiation damaged blood vessel endothelium [5].

In the randomised trial by Harima et al. assessing the concentrations of Bax and Bcl-2 proteins in irradiated cervical carcinoma cells significantly different protein concentrations were found when hyperthermia was applied together with radiotherapy versus radiotherapy alone. This positively correlated with the ratio of complete tumor regression (83.3% in the hyperthermia combined group vs. 52.6% in the radiotherapy alone group). Negative correlation was observed with lack of response (5.6% vs. 21.1%, respectively) [6].

The queries concerning the adequate number of procedures seem to be solved by the results presented by Valdagni et al [7] and Archangeli et al. [8]. No difference was found when response rates were compared between 2 and 6 hyperthermia sessions, but 4 procedures were more effective than one. This suggests 2 as the most reasonable number of hyperthermia sessions.

Conclusions

All the experiences cited and described above provide the background for future studies. More sophisticated equipment allows to plan a more precise real-time temperature distribution. We have planned further investigations in order to definitely assess biological effect of 500 kHz intracavitary hyperthermia in cervical and endometrial cancer patients. Hyperthermia treatment will be performed as the single adjuvant modality between 7 and 21 days before radical surgery. Each patient will receive 2 hyperthermia sessions of at least 45 minutes effective time of heating (> 42.5°C). To avoid the effect of thermotolerance treatment sessions will be separated by at least a 48 hour gap. Histopathological examination shall help to evaluate biological effectiveness and optimization of treatment. The objectives of the trial will include definition of how to practically include hyperthermia in radiation therapy, at least in selected groups of patients (recurrences after primary irradiation or lack of response to conventional radiotherapy).

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References

1. Overgaard J. The current and potential role of hyperthermia in radiotherapy. *Int J Radiat Oncol Biol Phys* 1989; 16: 535-49.
2. Perez C, Emami B, Myerson R, Roti Roti J. Hyperthermia. In: *Principles and practice of radiation oncology*. Philadelphia: J.B. Lippincott Comp.; 1992, 396.
3. Debicki M, Mrozowski M, Zieliński J et al. Localized current field hyperthermia in carcinoma of the cervix: 3D computer simulations of SAR distributions. *Int J Hyperthermia* 1999; 15: 427-40.

4. van der Zee J, Gonzales Gonzales D, van Rhoon G. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumors: a prospective, randomised, multicentre trial. *Lancet* 2000; 355: 1119-25.
5. van der Zee J, Wijnmaalen AJ, Haveman J et al. Hyperthermia may decrease the development of teleangiectasia after radiotherapy. *Int J Hyperthermia* 1998; 14: 57-64.
6. Harima Y, Nagata K, Harima K et al. Bax and Bcl-2 protein expression following radiation therapy versus radiation plus thermoradiotherapy in stage IIIb cervical carcinoma. *Cancer* 2000; 88: 132-8.
7. Valdagni R, Liu FF, Kapp DS. Important prognostic factors influencing outcome of combined radiation and hyperthermia. *Int J Radiat Oncol Biol Phys* 1988; 15: 959-72.
8. Arcangeli G, Nervi C, Cividalli A. Problem of sequence and fractionation in the clinical application of combined heat and radiation. *Cancer Res* 1984; 44: 4857-63.

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