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A new method of investigating the efficacy of regional thermotherapy in subcutaneous xenografts of nude mice*

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Summary. A new method of investigating the efficacy of regional thermotherapy in subcutaneous xenografts of nude mice is reported. The use of high frequency hyperthermia was well tolerated by the sensitive animals and allowed an exact continuous temperature measurement in different tumor regions. The interstitial procedure in this model could be the best approach for later clinical use in urology, e.g. for prostate treatment and is an alternativ to the transrectal hyperthermia application.

Key words: Nude mouse model – Thermotherapy model – Interstitial thermotherapy

Introduction

The importance of regional hyperthermia in tumors is unclear. Experimental models to investigate the possible application of hyperthermia are increasingly important.

For many years the nude mouse model has produced solid human tumors [2]. The problem of homogenous temperature distribution within the target area appears to be solvable by interstitial application.

Methods

For tissue heating we used a specially constructed high frequency generator (Fa. Geltinger, Neubiberg, FRG) at a frequency of 920 MHz with an infinitely variable performance of up to 20 Watt (Fig. 1). The performance could be generated either by one or two coaxial antennas (BSD med. cor. mod. MA 250). Subsequently we tried to find out whether hyperthermia could be conducted in subcutaneously transplanted tumors of the nude mouse and whether these grafts were locally tolerated. The subcutaneous tumors of about 7×7×1.5 mm (BPH grafts) or 12×10×8 mm size (autonomously growing malignancies) size were tangentially tunnelled using 14G Abocath cannulae under chloral hydrate anaesthesia

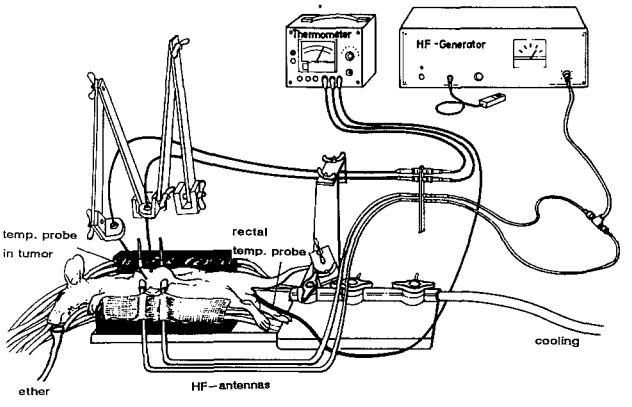

Fig. 1. Experimental design of the high frequency generator, thermometer and nude mouse holder during hyperthermia. Water cooling at 20°C. The animal is positioned onto a cooling mat during the treatment

Fig. 2. Tangential puncturing of Abocath cannulate to place high frequency antennas

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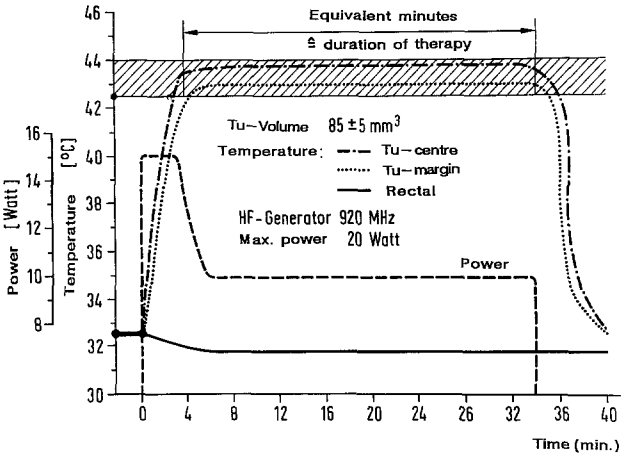

Fig. 3. Temperature course during interstitial hyperthermia in xenotransplanted subcutaneous tumors of the nude mouse. The treatment time begins when a temperature of 42.5°C at the tumor margin is reached. The initial performance was 15 Watt and may be maintained at about 10 Watt when a steady state condition is reached. Due to the cooling effect the rectal temperature slightly decreases during treatment

Table 1. Complications after 30 min of interstitial hyperthermia at 42.5 to 43.5°C ($N=91$ treatments) in the case of subcutaneously xenotransplanted prostate tumors in thymusdysplastic mice

	N	%
Local burns	15	16.4
Wound infection	13	14.3
Body temperature > 36°C	5	5.5
Death during hyperthermia	1	1.1

(0.01 ml/kg bodyweight i.p.) so that the high frequency antennas could be introduced. (Fig. 2). In addition to rectal temperature monitoring the temperature in the tumor center at different measurement points of the tumor margin was continuously monitored using puncture temperature probes (Yellow Springs Instruments, Probe 524), and a temperature between 42.5 and 43.5°C was maintained.

Results

In subcutaneously xenotransplanted tumors (BPH grafts, prostate, bladder and kidney carcinomas) of the nude mouse it was possible to elevate the temperature within 3 min from 32°C (initial value, since the body temperature of nude mice is reduced) to 43.5°C in the tumor center and 42.5°C at the tumor margin (Fig. 3). This temperature could be maintained over different areas of tissue by controlling the frequency application. Hyperthermia was well tolerated by the animals for two hours at maximum. The continuous cooling avoided an increase in body temperature. When the high frequency generator was switched off the temperature within the tumors tissue decreased to the initial value within a few minutes.

In a total of 91 treatments there were 15 cases of local burns, 13 cases of wound infections, 5 cases of increasing body temperature prior to the introduction of cooling and one death.

Discussion

The reported method of interstitial hyperthermia of subcutaneous xenografts of human tumors transplanted on nude mice has proven efficient and confirmed the idea of Mechling et al. [5].

In contrast to hyperthermia in heated waterbath which is mostly conducted in small animals, this procedure allows precise and continuous temperature measurement in different tumor regions. It is not sufficient to measure the exact temperature distance in a phantom since the blood circulation heavily influences this distribution [6].

The interstitial hyperthermia in this animal model could be applied to clinical use in urology, e.g. for prostate treatment. In this case the procedure would be an alternative to the use of a transrectal probe which is already available for clinical practice [7]. The intended temperature of 42.5°C to43.5°C could be reached homogenously in the tumor tissue within a short period of time and could be maintained constant by continuous measurement and additional control of the high frequency performance.

Hyperthermia could be conducted in the same animal without requiring further invasive procedures and yielded constant and reproducible results in different animals and varying tumor sizes. Animal models are useful to check the efficacy of hyperthermia if used alone or in combination with other therapeutic modalities since the multiple physiological influences during hyperthermia in vitro cannot be reproduced [3]. In addition, the nude mouse tumor model allows the effects of local hyperthermia, combined with chemotherapy, irradiation and/or hormone therapy as a multimodal therapy concept for the treatment of different urological tumors, to be exanuiced.

It will be seen whether the good results obtained with thermochemotherapy in soft tissue sarcomas in the true pelvis [4] or the therapeutic effects obtained with a combination of radiotherapy and hyperthermia [1] can expected in prostatic carcinoma, bladder tumors and perhaps also kidney tumors.

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