

Oncothermia for prostate cancer

Hyperthermia is the oldest treatment in oncology [1]. Oncothermia is a further development of the traditional, more than two thousand years old [2] oncological hyperthermia method. It solves such technical problems, which were blocking the reliable applications of hyperthermia in oncology till now. Oncothermia solves the selective deep action on nearly cellular resolution [3]. The main idea is connected to the electric field effect of cancer, which presently anyway became a hot topic in bio-science, [4], [5], [6], [7], [8]. It is widely applied on lower frequencies also [9], [10], [11] and clinical trials are also in progress [12], [13].

Problematic points in conventional hyperthermia:

- traditional hyperthermia is controlled solely by the temperature. However, the requested job is to kill the malignant cells, for what a definite energy dose is necessary [14]. make the focus artificially has many problems, because the malignant tumors have no real boundary (only the benign tumors have boundary). So the focus never could be proper,
- the problem is even more complex to see the technical complications of the focusing in depth of the human body, avoid the hot-spots, and eliminate the natural and necessary movements (e.g. breathing or other) of the patients, as well as avoid the overheating of the surfaces, when the energy penetrates in to the body.
- there are many theoretical problems of the heat-effects in the tumor and healthy tissues, the interactions with the general physiology (including the HSP the hypoxia, etc.).

Oncotherm approach is different:

1. Oncothermia is based on the paradigm of the energy-dose control, replacing the single temperature concept [15], reapplies the gold standards, the specific energy absorption instead of the temperature.
2. Oncothermia applies such mechanism, which is self-selective, (the focusing in this case would be automatic). It uses the general mechanism of the malignancy: the malignant cells have autonomy (renegades as Weinberg says), they are in permanent competition with the others for the nutrition and for the life-conditions. The healthy cells are generally collective, their control is made by "social signals", no real competition is introduced only a labor division is active. This means, that the active ionic exchange near the malignant cells (in most of the cases) is more intensive than in their healthy counterpart. This allows the introduced current to find the optimal path, which goes through the best conduction way. So the current goes self-selectively to the malignant cells [16]. Technically (in simple speaking) this is nothing else, only to introduce current through the tissue, and that will find the malignant cells automatically. We had experiments in co-cultures, and observed the effect in work.
3. Oncothermia makes such internal energy-distribution, which is not doing an average heating only, but definitively works at the places where the energy could be applied on the most optimal way. Apply energy somewhere could increase the temperature of the target but could do some other works also. Naturally, the absorbed energy increases the temperature. It is, like in the case of ionizing radiation, only a normal "side effect" not that is the desired effect. The expected work is to damage the DNA, to destroy the chemical bonds and rearrange the structure. That is trivial, if the temperature is high enough, could do this rearrangement alone, but of course than everything has this average energy. (If we have a fatty dish after the dinner, we could wash it out by very hot water only, but a clever housewife has detergent to reduce the water temperature, and make the job where it must be done - at the surface of the dish, and not waste energy to the non-important volumes.) To make the temperature arising alone in the tissue, could be a problem of the safety and again comes back the selection task. So we have to give the energy not equivalently into the target but specifically to the place where we want do the distortion (like the ionizing radiation does). What is the target? It could not be the cellular interior (nuclei and DNA) because that by non-ionizing radiation needs again high temperature, and the initial problem is not solved. The target is the cellular membrane! If we keep the current in the extracellular matrix than the energy heats up only this electrolyte, and a heat-flow starts from the extra- to intra-cellular regions through the membrane. This heat-flow accompanied by different ionic flows and water transport, changes the Hodgkin-Huxley equilibrium, the membrane became more transparent, and at the end destroyed [17]. (Anyway the transparent membrane also could be helpful to kill the malignant cells, because large concentration of the intracellular HSP could be expressed extracellularly, which has direct effect on the apoptosis and the stimulation of the systemic immune reactions.)
4. Oncothermia uses the membrane effects of outside electromagnetic fields [18], [19], [20]. Also the modern fluctuation analysis (fractal-physiology, [21], [22], [23]) supports it [24], [25]; as well as the resonance phenomenon is studied and used in the light of a new theory [26]. The hypoxia study [27] and special vector-potential theory [28] helps to complete the method.

The acceptance of the new paradigm is a clear demand of the theory and the practice as well [29], and realized in oncothermia approach [30].

Treat the prostate tumors offers an easy approach to make local treatment by intraluminal (transurethral) manner. There are numerous methods (see table 1.).

Non-heat-connected methods	Heat connected methods
Surgical (open or laparoscopic) techniques	Focused high-energy ultrasound heating/ablation techniques)
Transurethral resection	Interstitial cooling (cryoablation techniques)
Other transurethra surgical techniques	Laser ablation (vaporization) techniques
External ionizing radiation techniques	Hot water transurethral heating
Brachytherapies	Metal-rods, seeds, ferromagnetic particles heating
Chemo-, hormon- and drug/herb- therapies	Magnetic nano-particle suspension heating
	External loco-regional heating techniques
	External systemic (whole-body) hyperthermia
	Transurethral microwave heating
	Electro Cancer Therapy (Galvanotherapy)
	Transurethral oncothermia

Table 1. Some common treatments of prostate tumors.

List of the generally applied treatment-concepts are listed in the table 2.

Ablation (temperature) concept	Acidosis (heat) concept,	Apoptosis (HSP) concept
<i>Examples: RF-ablation, microwave-ablation, laser-ablation, cryo-ablation, etc.</i>	<i>Examples: RF- and microwave hyperthermia, electro-hyperthermia, etc.</i>	<i>Examples: whole-body hyperthermia, oncothermia electro-cancer therapy, etc.</i>
High temperature in unit volume	Relatively high energy input in unit volume	Relatively small energy input in unit volume
Direct, massive necrosis, scar tissue	Oxygen supply limit, indirect necrosis	Apoptosis and moderate necrosis
Only invasive applications	Invasive, semi-invasive and non-invasive solutions	
Mechanical "focus"	Sophisticated focus	

Table 2. Most common treatment concepts of hyperthermia.

Benign and malignant tumors however need different heating strategies. The benign tumor needs heating for all over the organ; while the malignant one requests only a very local action (part of the tumor in the prostate). The other definite difference the benign tumor could be solved by urethral expansion (eliminate the blockade of the urine passage), the case of malignant tumor needs a complete elimination of the tumor (see table 3.).

Main character	Benign	Malignant
problem	hyperplasia	local tumor
effect	mechanical obstruction	potential metastases
request	urethral expansion	tumor elimination
solution	intraurethral	intraprostatic
organic action	homogeneous	local

Table 3. The action strategy of benign and malignant prostate tumors

Hyperthermia is a rapidly developing treatment for prostate tumors both of malignant and BPH cases, shown by the number of peer-reviewed publications in MedLine, (Fig. 1.).

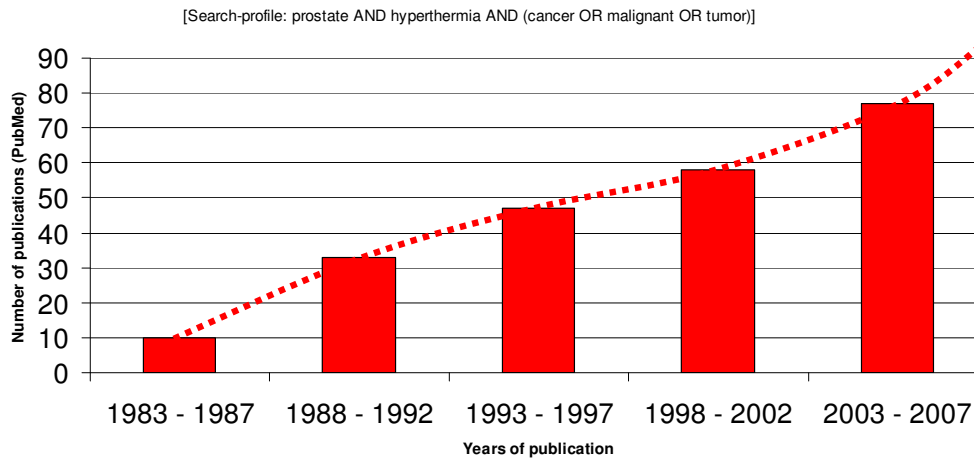


Fig. 1. Development of prostate hyperthermia publications by year (Commulative, PubMed, search-profile: [prostate AND hyperthermia AND (cancer OR malignant OR tumor)])

Oncothermia for prostate tumors is further development of hyperthermia for this organ also. The effects are solved by directed electric field, well designed RF-conducting on 13.56/40 MHz frequency. It is impedance (current-flow) heating, not radiative at all. Oncothermia is controlled with direct feedback of the tissue, which is a part of the applied resonant electric circuit (fig. 2.). The field is distributed like a cone (fig. 3.).

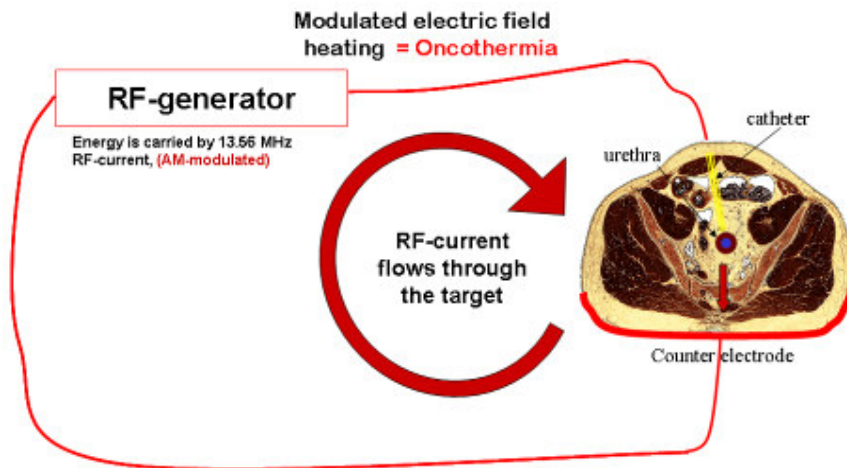
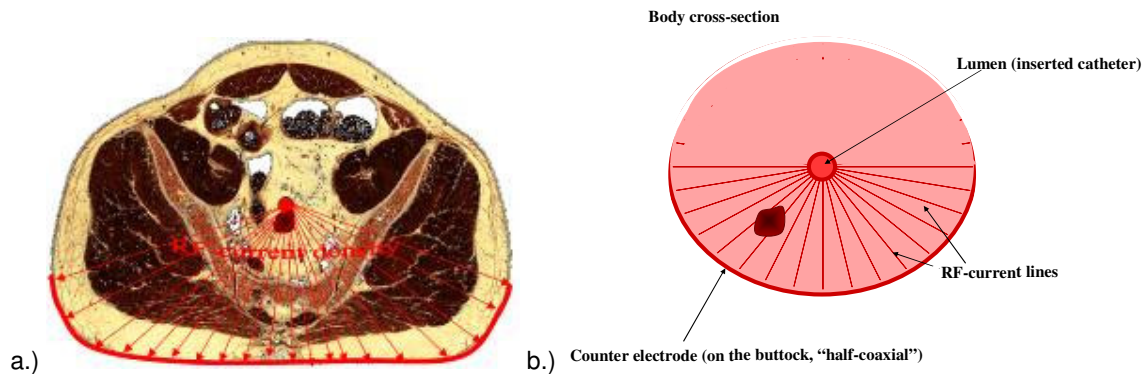


Fig. 2. Simple schematics of oncothermia for transurethral treatment.



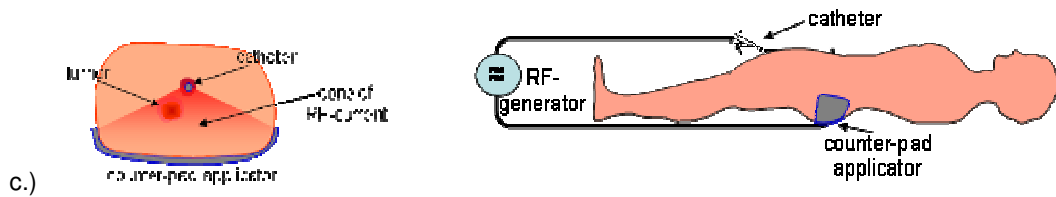


Fig. 3. The distribution of the field by the actual arrangement of the electrodes. The saggital cross section of the body (a), schematics (b) and the position on the patient (c).

The temperature in the wall of urethra is also controlled for the safety reasons, and by the accurately measured absorbed energy controls the treatment efficacy. The highest temperature is reached in the prostate and not on the wall of the urethra (fig. 4.). This torus-like temperature distribution can be measured by thermocamera on autopsy measurements (fig. 5.). The power is ranging up to 80 W, while the temperature could be adjusted up to 70 °C. The phantom model on cattle-liver shows well the “cone” cross-section after cut, fig. 6.

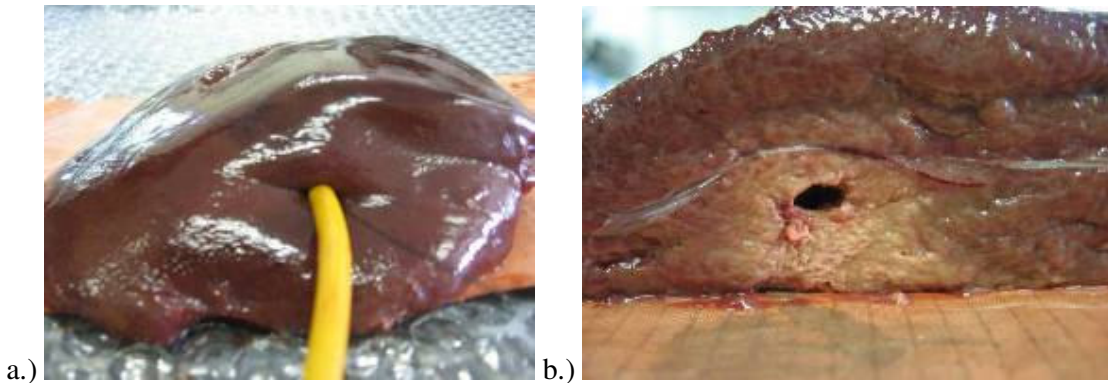


Fig. 6. The phantom heating arrangement (a) and the cut after the treatment (b)

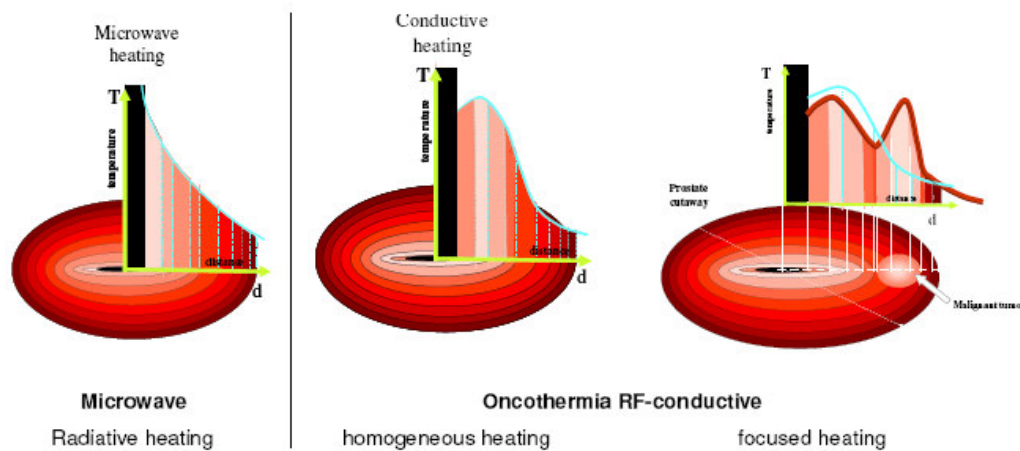


Fig. 4. The temperature distribution for radiative (a), conductive (b) cases. The malignant tumor concentrates the current-flow, absorbs more energy (c).

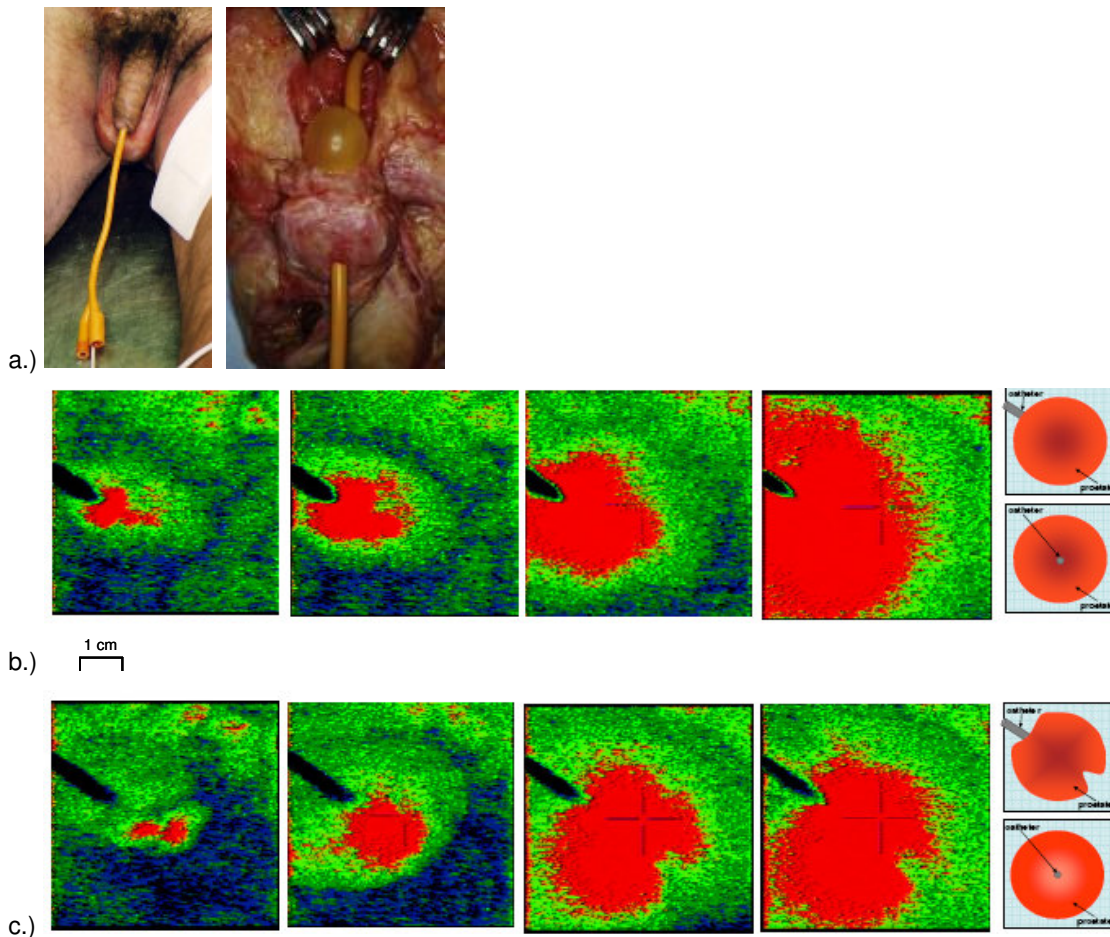


Fig. 5. The cadaver experiment (a) shows clear picture: the radiative heating has a sphere-like (b), while the oncothermia heating a torus-like (c) temperature-pattern.

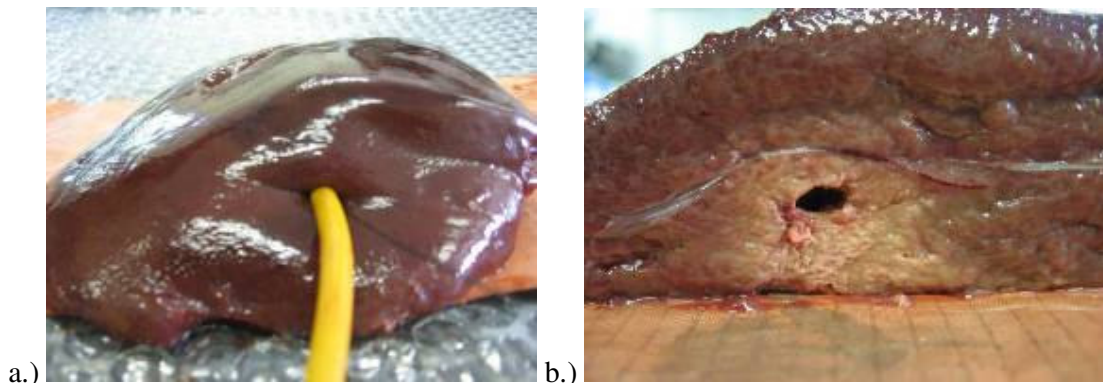


Fig. 6. The phantom heating arrangement (a) and the cut after the treatment (b)

Oncothermia is selective by the higher conductivity and higher permittivity of the extracellular matrix of malignant tissue. (This high complex dielectric constant is effective in the microscopic level as well, [31].) The current flows automatically on the better conductive areas, focusing the energy delivery on these spots (Fig. 7.). The focusing is directed by the position of the counter-electrode (ground, reference electrode, fig. 8) self-adhesively placed on the skin of the patient (fig. 9.). No cooling in the catheter or in the rectum is applied. The capacitive arrangement is cylindrical (not plan-parallel as in the general loco-regional treatments) and it has precise temperature measurement built in the catheter. The most sensitive and hottest area is checked for its temperature: the surface of the urethra, the area of the prostate directly touched by the electrode. The conductive heating has

Its effect is not only the heating but mainly the electric field [32], which arranges apoptotic cell-

destruction in the tumor, [33]. The field effect could be well demonstrated on the ECT results for prostate cancer. The electric field cancer treatment (ECT) device was applied for many patients mainly in China (fig. 10.), [34], [35].

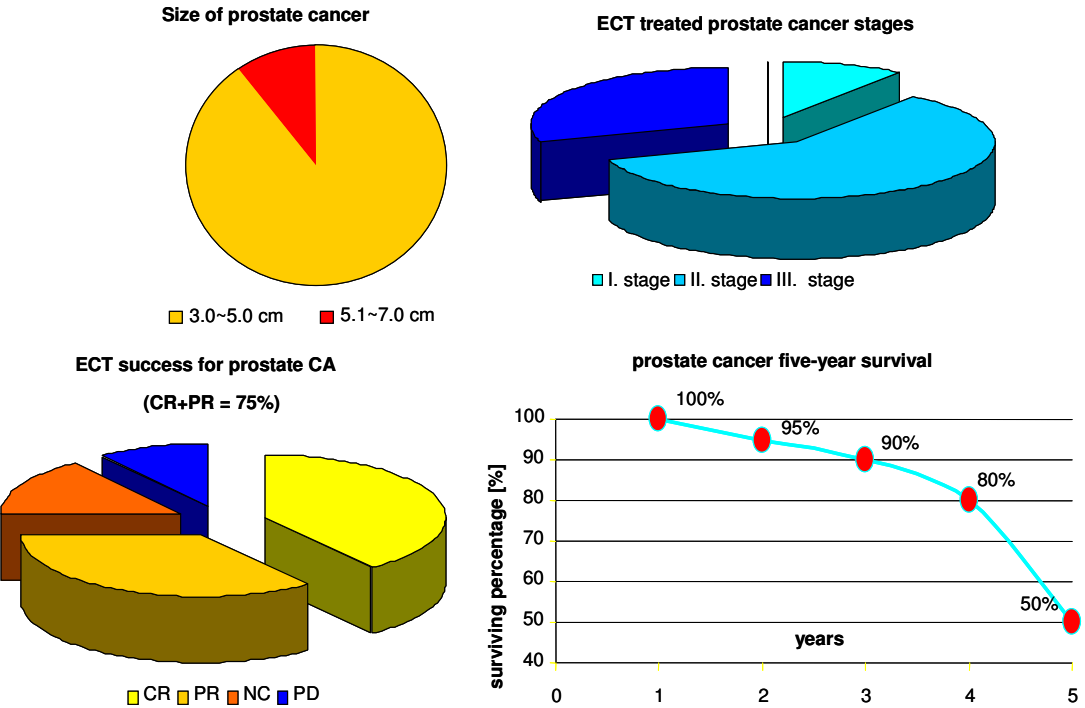


Fig. 10. Prostate cancer treated by ECT (n=20) (Xin Youling: Clinical Applications of ECT in Treatment of Tumors, 1999.China-Japan Friendship Hospital)

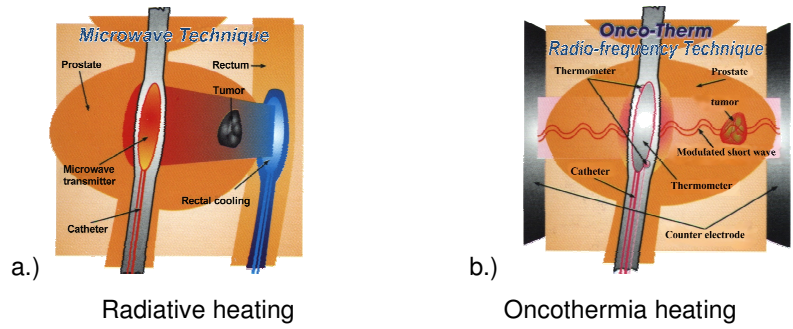


Fig. 7. Comparison of the heating methods radiative heating technique (a) and oncothermia (b).

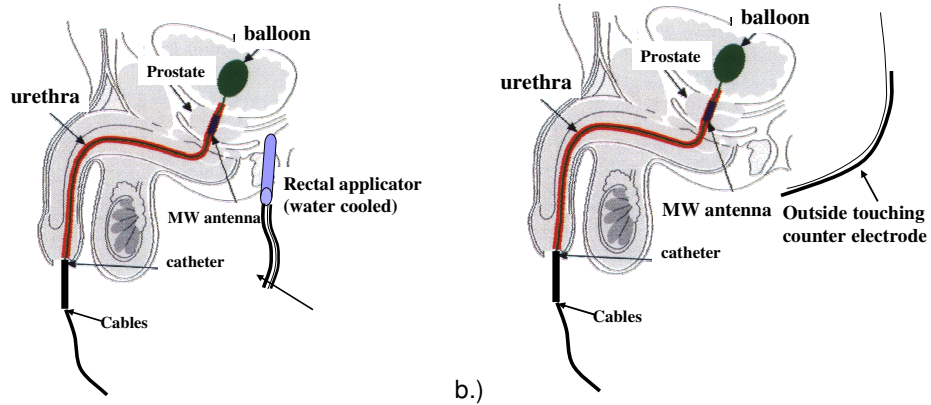


Fig. 8. Positioning the heating elements: radiative heating (a) and oncothermia (b).

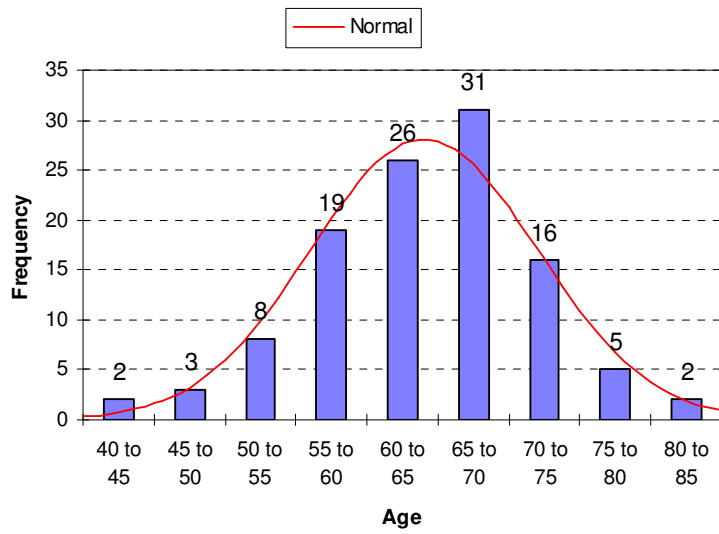


Fig. 9. Placement of the counter electrode and the catheter for the patients.

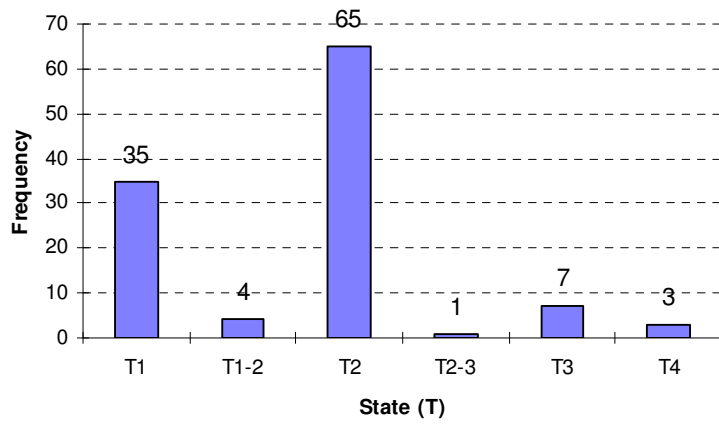
The treatment is highly personalized, and so an overall protocol can not be constructed. The state-of-art of prostate treatment by hyperthermia does not fix any proposal on the treatment temperature. Indications in the literature show a wide range of applied temperatures. The generally accepted consensus for an average treatment is:

- apply it two times,
- having at least 48 hours in between but not more than 3 days,
- each treatment session is 60-120 minutes long,
- the applied temperature is between 42 – 50 °C.

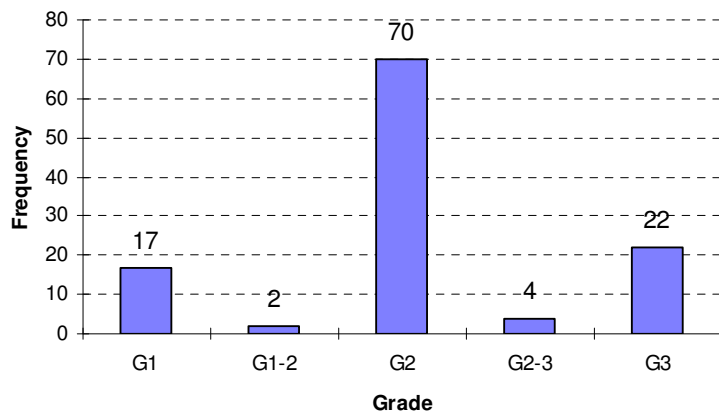
Oncothermia clinical results for prostate cancer



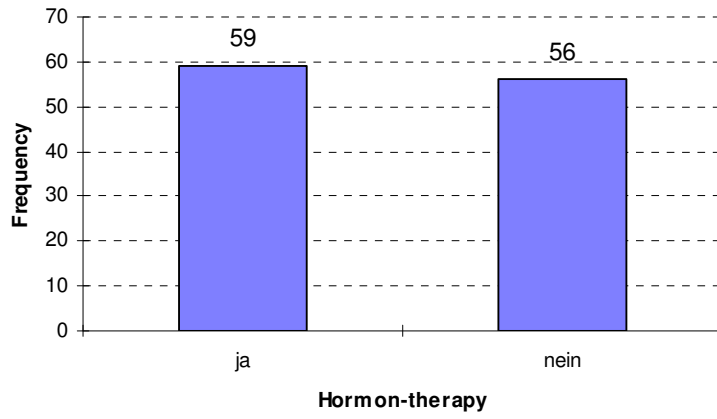
State (T)



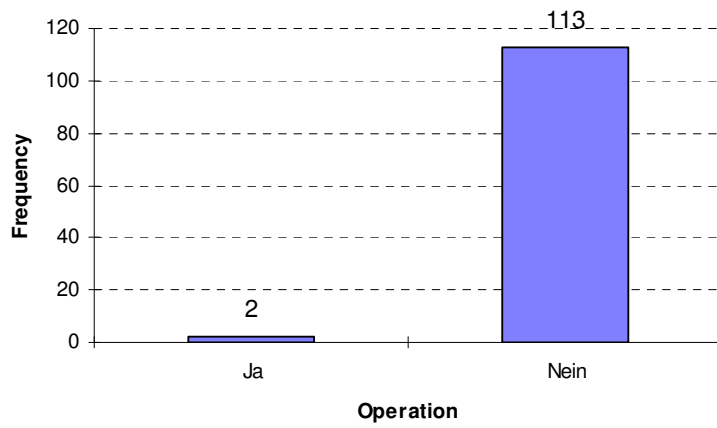
Grade



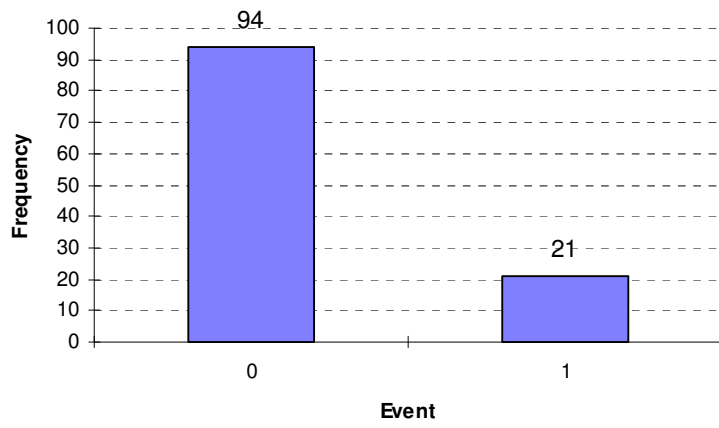
Hormon-therapy



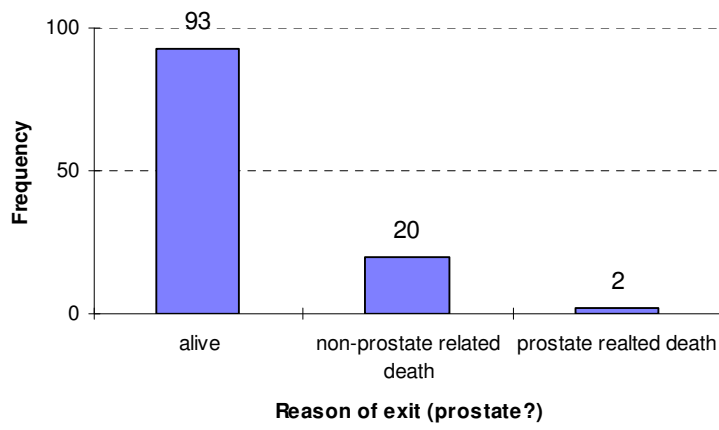
Operation

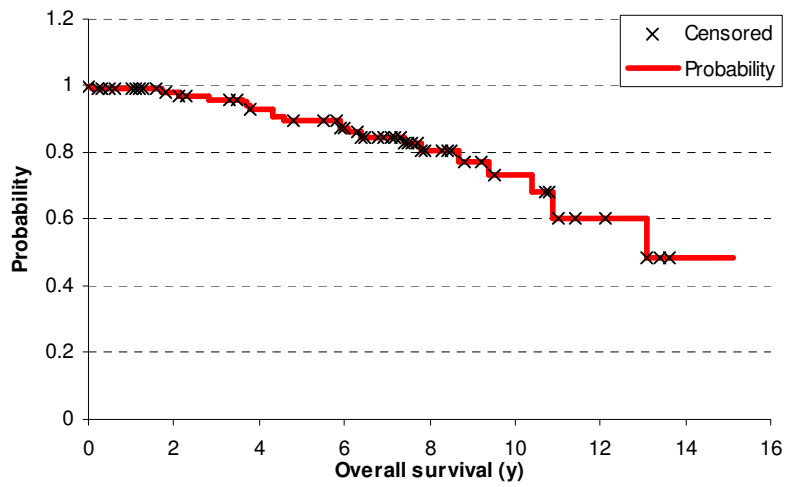
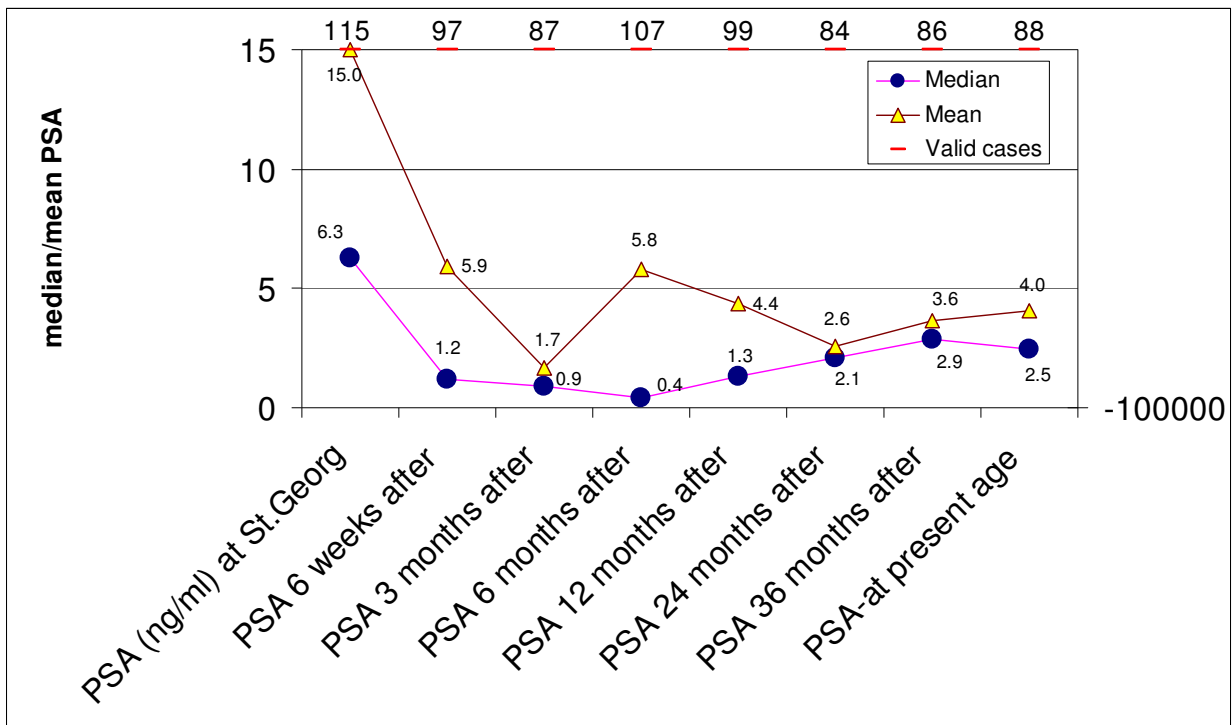


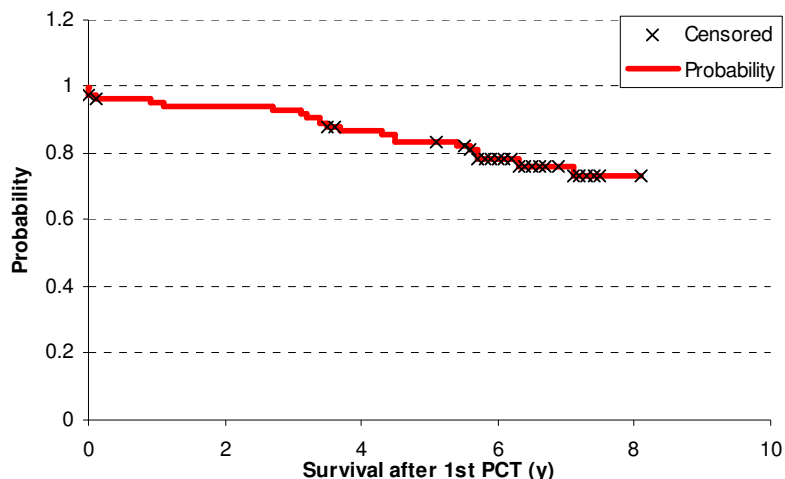
Event



Reason of exit (prostate?)







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