

Current Role and Future Perspectives of Hyperthermia for Prostate Cancer Treatment

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Abstract. *Prostate cancer is the second most common cause of death in men. Between 10%-60% of patients experience biochemical recurrence associated with treatment failure. No consensus on optimal therapy for advanced prostate cancer exists and even though hormonal therapy and radiotherapy are standards, different groups have included hyperthermia associated with radiotherapy to increase its efficacy. We have tried to analyze these studies to evaluate if this association can ameliorate the therapy in the advanced disease state. From the analysis of these studies, it appears that no amelioration can be obtained adding hyperthermia and the principal cause of this failure appears to be due to the incorrect timing of hyperthermia application and probably the abrogation of androgen receptor expression in androgen-dependent cells.*

Prostate cancer is the most commonly diagnosed cancer in males and about 30% will develop microscopic prostate cancer during their lifetime. This increased incidence is attributable to early detection programs and to a complex series of initiation and promotional events under genetic and environmental influences. Androgen dependence, previous inflammatory reactions of prostate cancer and a Western lifestyle are recognized important factors that may contribute to its carcinogenesis (1, 2). The natural history of this tumor is long and complex, determining a nonuniform practical therapeutic guideline. As outlined by Dahm *et al.*, over the course of the disease the patient can be faced with a myriad of therapeutic choices not recognized critically important according to evidence-based practice (3). According to these

authors, there is an urgent need for standardizing guidelines for the management of patients affected by prostate cancer. The appropriate use of worldwide accepted therapies is becoming urgent and this urgency becomes even more evident if new forms of therapies for prostate cancer treatment, such as hyperthermia, are used. According to the consensus conference held in Osaka (2004), there is no 1-2 level of evidence-based medicine regarding hyperthermia use in prostate cancer treatment. In spite of a lack of evidence, in many radiotherapy departments where hyperthermia devices are present, the association of hyperthermia with radiotherapy is practiced. In this overview, we will briefly describe the hyperthermia methods used for treating prostate cancer and compare the different studies that have added hyperthermia to the standard therapies. The purpose is to suggest the right time of application of hyperthermia and to evaluate the efficacy of its association with radiotherapy.

Hyperthermia Methods

The growing use of hyperthermia has permitted the development of new devices for treating pelvic tumors. There are at least 3 types of hyperthermia devices for treating deep tumors. They differ according to the source of energy, uniformity of heat deposition and application to the body. In fact, heat can be generated through ultrasound (US), radiofrequency (RF) or microwave (MTA) applicators. These applicators can be positioned externally, intraluminally (transrectally, transurethrally) or interstitially. Although complete tumor eradication is the primary goal in prostate cancer, achieving this is more complex than in other varieties of tumors. The prostate is surrounded by important structures such as neurovascular bundles, urethra, bladder and rectum that must be spared (4, 5).

Microwave ablation (MTA). MTA can be performed in a percutaneous manner, or by placing an antenna in the prostatic urethra. It is possible to reach a temperature in the

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order of 55-70°C and to treat a prostate volume ≤ 50 g. Percutaneous MTA is performed in the dorsal lithotomic position and a total of 4-5 microwave antennae are used with urethral and rectal cooling.

Interstitial hyperthermia (IH). IH is performed similarly to brachytherapy and is performed with the patient under epidural or general anesthesia. Generally 12 catheters, each with an electrode, are placed in the prostate through a template under transrectal ultrasonography guidance (4, 6). Another interstitial method is that proposed by Tucker *et al.* (7). In this method, a biocompatible rod (93% palladium-7% cobalt) is permanently placed in the prostate and submitted to a electromagnetic field at frequencies between 50-200 Hz. Heat is generated by the Curie effect (4). Heat is delivered uniformly but the rod positioning is uncomfortable for the patient.

Radiofrequency tumor ablation (RFTA). RFTA is a method which delivers a high-frequency monopolar or bipolar alternating current (100-500 Hz) to target tissue. The electromagnetic energy transmitted is converted to heat through the frictional energy generated by the ions that follow the alternating current direction. The heat is generated near the electrode tip and dissipates rapidly with increasing distance (8). According to Gillet *et al.* (4) its use in prostate cancer is entirely experimental. These authors also outline that if radical prostatectomy is not reached after RFTA, pronounced complications are observed (4).

High-intensity focused ultrasound (HIFU). The HIFU method is gaining greater acceptance in the scientific community as an ablative tool. HIFU is generally performed in patients with low clinical stage disease (CT1-CT2), Gleason grades 5 to 7 and prostate volume ≤ 30 g (9). Initially HIFU was used for benign prostatic hyperplasia, but is now used for prostate cancer too. The treatment is generally performed under general or epidural anesthesia. One hour of HIFU is sufficient to treat 10 g of tissue. The procedure is not yet approved by the FDA for use in the USA and HIFU is not devoid of side-effects such as incontinence.

Locoregional hyperthermia (LH). LH or external hyperthermia is a noninvasive, well-accepted heat modality for delivering heat to a patient. It is performed by a coaxial (phase array) or capacitive system. The frequency generally used is between 8-13.5 MHz. The great drawback of capacitive hyperthermia is a nonuniform distribution of heat in the pelvic region. This is less evident with phase array methodology. An accurate device for temperature measurement is necessary and a skilled nursing staff is necessary for avoiding side-effects such as skin burning (6). All the advantages and disadvantages of these methodologies are given in Table I.

Standard Therapy in Advanced Prostate Cancer

Treatment for prostate cancer depends upon its stage. T3 and T4 tumors that lack involvement of lymph nodes or of distant organs are considered locally advanced. Therapeutic options for this stage include external beam radiotherapy with androgen ablation. Androgen ablation (ADT) is used because around 75% of advanced cancer has been demonstrated to remain hormone sensitivity (10, 11). ADT is not without side-effects but its association with conformal radiotherapy (CFRT) and brachytherapy has shown a benefit in overall survival compared to radiation alone (10, 11). Biochemical failure (BF), defined as a progressive increase in prostate-specific antigen (PSA) level without radiographic metastatic disease, is present in a median of 35% of patients. It is also expressed as biochemical disease free-survival (BDFS). Patients with high-risk features (PSA level ≥ 30 ng/ml and tumor grade 3 or 4) show a BF of 80%, 3 years after radiotherapy (12). Three levels of risk have actually been recognized by the Radiation Oncology Group (RTOG) and the American Society for Therapeutic Radiology and Oncology (ASTRO) and are: T stage, Gleason score and PSA level (13). ASTRO has also defined that a patient's risk group is indicated by the single highest factor present among T stage, Gleason score and PSA level (13). The best percentage of BDFS is obtained using ADT + CFRT and is more than 70% (14).

Hyperthermia as reported by Villa (6) was added to radiotherapy with the intent to obtain a radical treatment. This author found that reports of the association of deep hyperthermia with radiation are few, as are the numbers of patients treated (6). Most studies tested with HT have been carried out using brachytherapy or external radiotherapy (ERT). ERT is delivered five days per week for 7-8 weeks and the target is the prostate gland plus seminal vesicles. In fact, ERT is being replaced by CFRT and a dose of ≥ 70 Gy is considered the gold standard as radical treatment for advanced prostate. A dose ≥ 72 Gy seems to be associated with a lesser biochemical recurrence as demonstrated by Kupelian *et al.* (15).

To adequately treat a patient with hyperthermia, it is necessary to offer the best traditional treatment and add hyperthermia for obtaining an amelioration. For amelioration, we believe that hyperthermia can positively change the following criteria: increase quality of life (QL), decrease of biochemical recurrence and increase in overall survival (OS). Using these criteria, we have compared five studies (see Table II) to verify if hyperthermia ameliorates the best classical therapy in use, CFRT + ADT. The study of Bruns *et al.* was used as a standard of comparison for the excellent results obtained (14). This study was compared to the other four studies which used hyperthermia + ADT + CFRT (16-19).

From this analysis, it appears that the QL does not decrease, there is no OS gain and a worse effect is obtained

Table I. Advantages and disadvantages of different types of heat application.

Type of hyperthermia	Advantages	Disadvantages
Interstitial	Necrosis Immune stimulation No androgen resistance Targeted area	Requires skilled physician
Intraluminal	Targeted area Can develops Androgen resistance	Requires skilled physician
Capacitive	Simple Well tolerated Poorly targeted area Can develop Androgen resistance	Requires skilled nursing staff Non-uniform temperature distribution Side-effects (burning)

Table II. Comparison between CFRT and some recent studies using CFRT+HT.

	Bruns (14)	Maluta (16)	Algan(19)	Van Vulpen (17)	Tilly (18)
No. of patients	99	144	25	12	22
CFRT	70 Gy	70 Gy	60-70 Gy	70 Gy	70 Gy
ADT	+	+	+	+	+
OS	80%	87%	73%	NA	95% PC- 60% PR
BDFS	78%	49%	35%	NA	NA
QL	NA	↑	NA	↑	↑

CFRT: conformal radiotherapy; ADT: androgen ablation therapy, OS: overall survival; BDFS: biochemical disease free-survival; QL: quality of life; NA: not acquired; PC: primary prostatic carcinoma; PR: recurrent prostatic carcinoma.

regarding biochemical recurrence. At first sight, there are no great differences regarding the doses of radiotherapy used. In fact, a standard dose of 70 Gy was used by all the authors and all patients received ADT. Notwithstanding the use of the best therapy, biochemical recurrence occurred more in the group treated with hyperthermia. The possible mechanisms which can explain this failure are androgen resistance induced by hyperthermia as demonstrated by Pajonk *et al.* (20). These authors investigated, *in vitro*, the effects of hyperthermia on different cell culture lines (PC-3, LnCaP, DU-145 human and TRAMP-C2 murine prostate cancer cells). They demonstrated that in all human cell lines studied, hyperthermia can cause apoptosis, radiosensitization and a decrease of 26S proteasome activity. They also demonstrated that hyperthermia decreases the androgen receptor expression to about 40% in LnCap androgen-dependent cell lines (20). This decrease in receptors can have dramatic clinical consequences and can explain biochemical recurrence (21). ADT typically results in a positive response that is nearly universally followed by relapse to a refractory stage in which the cells proliferate and survive, despite the low-androgen environment. Hyperthermia

can facilitate malignant progression and androgen resistance. In fact, Tsukada *et al.* have demonstrated that androgen receptors are temperature sensitive and that heat can develop androgen resistance (22).

Conclusion

From the analysis of Table II appears that the considerations of Villa are still valid and that HT does not seem to significantly improve the effect of CFRT, if this last technique is appropriately used (6). It also appears, according to Pajonk *et al.*, that HT must be applied with caution. In our opinion and in accordance with Kalapurkal *et al.* (23, 24), the patients eligible for hyperthermia treatment in association with CFRT are those who have developed androgen resistance and are hormone refractory, or have received a high dose of radiotherapy, or may develop radiotoxicity to vital organs such as the rectum. In fact, all authors who have used hyperthermia in association with radiotherapy agree that it does not add side-effects beyond those present with single radiotherapy treatment (15, 16, 21, 22).

The studies of Kalapurakal *et al.* (23, 24) on patients with advanced hormone-refractory disease have shown that these patients are good candidates for being treated with hyperthermia. Temperature distribution inside the prostate gland is a problem that must not be underestimated. Structurally, the prostate is a nonuniform structure; heat deposition is not uniform and the PSA level is temperature sensitive as demonstrated by Tilly *et al.* (18). The association of hyperthermia with chemotherapy warrants further study. In fact, the recent introduction of adjuvant chemotherapy in advanced stages of the disease has obtained positive results using taxanes, or mitoxantrone plus prednisone. These two drugs have shown an additive effect with heat, so their application with HT is worthwhile (25, 26).

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