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Conformal radiotherapy plus local hyperthermia in patients affected by locally advanced high risk prostate cancer: Preliminary results of a prospective phase II study

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Abstract

Purpose: Hyperthermia has been used in several trials to treat pelvic cancers without excessive toxicity and with positive results. The aim of this study was to evaluate feasibility and results in terms of biochemical recurrence-free, disease-free survival, overall survival, and treatment toxicity profile of hyperthermia combined with radiotherapy in locally advanced high risk prostate cancer.

Patients and methods: From November 1998 to December 2004, 144 patients with locally advanced prostate cancer (LAPC) were enrolled in a phase II study. They were treated using conformal radiotherapy (CRT) plus local hyperthermia (LHT) and androgen suppression therapy (AST). Treatment modalities consisted of: 1) CRT with a mean dose of 74 Gy (2 Gy/fraction/5 fractions per week); 2) LHT: one session per week during the first, second, third, and fourth week of the radiotherapy course; 3) AST was administered as neo-adjuvant and adjuvant therapy in more than 60% of patients.

Results: The median follow-up time was 51.7 months. Four patients were lost at follow-up. Of 140 evaluated patients, four died because of intercurrent diseases and 12 because of progression of disease. Patients were evaluated in terms of five-year overall survival (87%), and five-year biochemical progression-free survival (49%). No significant side effects, except symptoms related to AST have been reported. No late grade 3 toxicity occurred.

Conclusions: In advanced high risk prostatic cancer, hyperthermia is feasible and well tolerated. It may be useful to enhance the radiotherapy efficacy at intermediate dose in order to avoid higher doses of irradiation which increases acute and late sequelae. The advantage of LHT combined with CRT should be confirmed by a randomized phase III trial, comparing irradiation plus AST with or without hyperthermia.

Keywords: *Hyperthermia, prostate cancer, radiotherapy, androgen suppression therapy*

Introduction

The aim of this phase II study was to evaluate the feasibility and efficacy of local hyperthermia (LHT) combined with conformal radiotherapy (CRT) and androgen suppression therapy (AST). After surgery or radiation therapy alone the overall incidence of biochemical progression ranges from 15 to 40% [1–3]. In patients affected by locally advanced prostate cancer (LAPC, stage T3 and T4 of UICC-TNM *Classification of Malignant Tumors* 5th ed.) and/or high risk disease (Gleason score ≥ 7, or serum PSA ≥ 10) a statistically significant benefit in cause-specific and overall survival was seen when treated by using radiation and AST for at least three years [4]. Irradiation plus AST reduced the incidence of five-year biochemical progression to 15–20% [5]. Furthermore, in a subset analysis of patients with Gleason score 8–10, there was a

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significant improvement in absolute and cause specific survival [6]. In patients treated with radiation and long-term hormone therapy the 8 year-local failure rate, distant metastases rate and overall survival were 30%, 52% and 51%, respectively [7].

Randomized clinical trials have demonstrated the efficacy of CRT and LHT in many tumours [8–10]. In the Duke University experience, high risk patients with stage T3 or T4 prostate cancer were treated in a non-randomized study with CRT and LHT to a maximum dose of 70 Gy. The three-year local control and distant failure free survival was 93% and 68% respectively [11]. Stanford University reported patients with recurrent prostate cancer treated originally with brachytherapy, were successively retreated with LHT and irradiation. None of the patients experienced severe rectal or bladder reactions, and 75% achieved a complete clinical response [12]. Karapurakal et al. reported their experience on pre-irradiated patients treated by using RT and LHT [13]. All patients had a positive response to re-treatment, achieving a complete tumour control by two to six months after re-treatment. Only two patients developed a urethral stricture. According to previous clinical studies, the addition of hyperthermia to conventional radiotherapy at doses no higher than 70 Gy seems to be feasible. In this study hyperthermia was combined with CRT at a dose slightly higher (mean dose delivered $\leq$74 Gy) in order to improve results in terms of local control, and disease free survival, without an increase of late toxicity. In spite of the positive results reported in literature by using irradiation plus AST, we expected that adding hyperthermia could achieve an improved local control, avoiding doses higher than 76–78 Gy, which significantly correlate with an increased risk of complications.

Patients and methods

From November 1998 to December 2004, 144 patients with stage T3-T4, or T2 high-risk prostate cancer (Gleason score $\geq$ 7, or serum PSA $\geq$ 10) were treated by using CRT plus LHT and AST. Mean PSA level and mean Gleason score were 13 ng/ml (range 6–90) and 7 (range 4–10), respectively. Radiation therapy commenced from 12 to 24 weeks after the start of AST: a mean dose of 74 Gy was administered to the prostate and seminal vesicles (range 70–76 Gy) considered at high risk of invasion. Daily tumour dose was 1.8–2 Gy, 5 days per week, in 7–8 weeks. Linear accelerators were used with photon energies $\geq$6 MV with typical 4 or 6 field techniques. The posterior wall of the bladder was included in the planning target volume, receiving the same dose as the tumoural volume. Doses to the inferior third of the rectum did not exceed 50–55 Gy, and a small portion of the anterior rectal wall received the same dose as the prostate. In eleven patients with clinically positive lymph nodes, regional lymphatic area was irradiated. Patients were monitored during the radiotherapy course with weekly blood counts, and tolerance to treatment was documented. Particular side effects were considered such as skin reactions, abdominal cramping, diarrhoea, rectal urgency, urinary frequency, dysuria, haematuria, urinary tract infections and incontinence. Morbidity of irradiation was scored by using RTOG/EORTC toxicity criteria.

Patients were enrolled in this study by following the inclusion criteria shown in Table I and assigned to receive CRT plus LHT alone when they refused side effects of hormonal manipulation. CRT plus LHT and AST were administered in patients with higher risk of recurrence, who, after informed consent, accepted symptoms associated with AST. AST was delivered as both neoadiuvant (97% of cases) and adjuvant treatment (76% of cases). Patients undergoing CRT-LHT-AST combined treatment received an analogue of luteinizing-hormone releasing hormone (LHRH) plus an antiandrogen both steroidal or non-steroidal in 64% of cases. In 36% of cases, patients received only an antiandrogen. AST was administered starting three to six months before CRT plus LHT and contined for two or five years. AST was scheduled for two years in patients with PSA $\leq$ 10, and Gleason

Table I. Inclusion criteria.

- Biopsy proven locally advanced prostate cancer (clinical stage T3/T4 with any Gleason score and serum PSA or clinical stage T2 and Gleason score >7 and/serum PSA > 10 ng/ml)
- Patient with a life expectancy of at least 2 years
- Patients under treatment for concurrent disease will be eligible if the medical condition will neither interfere with the process of the treatment nor the analysis
- No prior radical prostatectomy or cryosurgery for prostate cancer
- No prior pelvic RT or orchiectomy
- No previous chemotherapy for malignancy within five years
- No previous or concurrent invasive cancers other than superficial non-melanomatous skin cancers unless disease free for at least five years
- All patients must have signed an informed consent form prior to the registration on the study.

score > 7, and for five years in those with PSA > 20 or T4 N1. Before undergoing AST by an LHRH analogue patients received an antiandrogen orally for four weeks in order to prevent the flare resulting from the surge in testosterone. The CRT-LHT-AST treatment group included 89 patients (63.5%) of whom 14 interrupted or modified AST for reasons including referral urologist's recommendations, general physician's suggestions, patient's wish or inter-current side effects. AST was given following the initial prescription in only 75 patients. The characteristics of the patients are given in Table II.

LHT was delivered combined with external radiation therapy by using radiofrequency equipment (BSD 2000 with Sigma-60® applicator) working in the range from 60–120 MHz and maximum forward power to 2000 Watts. All treatments reported in this study were performed at 90 MHz. The hyperthermia course started following two to four radiotherapy fractions and it was delivered once a week, within 15 to 30 minutes of an irradiation fraction. It was continued until completion of the radiotherapy course. If the patient tolerance allowed it, hyperthermia was delivered throughout the entire course of radiation therapy, without exceeding one treatment per week, for a maximum of five treatments. All physical parameters of hyperthermia sessions were automatically recorded. Hyperthermia toxicity has been assessed using the formulation reported by the NCI criteria. *Acute toxicity* was defined when occurring during the session and dependent on application of power. *Sub-acute toxicity* was defined when occurring within 24 h of a session and persisting for >24 h thereafter. *Severe complications* were defined as the adverse reactions requiring treatment interruption and/or medical or surgical intervention.

Table II. Patient characteristics.

No. of patients	144
Median age (yrs) (range)	3 (42–86)
Race (white)	144
Clinical stage	
T2b	21
T3	116
T4	7
Gleason grade	
Not graded	11
4	3
5	9
6	45
7	32
8	22
9	16
10	6
Radiotherapy dose (Gy)	
70	9
72	10
74	95
76	30
No. of hyperthermia treatments	
1	3
2	4
3	12
4	121
5	3
8	1
Median follow up (months)	51.7
Range (months)	10–86

For each treatment session, the intraluminal temperature was measured by inserting two closed catheters into the bladder and the rectum, respectively. Thermal mapping was performed within the catheters by moving, with a step of 1 cm, the temperature probes on a length of at least 10 cm in the rectum and bladder, near the prostate region and by repeating data collection every 10 minutes during the treatment course. A minimum of four averaging multiple dipole E-field sensors were placed on the patient's surface in longitudinal direction such that the sensor is longitudinally centred within the device. Phase and amplitude steering were tested at low levels of forward power (<250 W) to attempt to maximize the ratio of E-field strengths detected in the tumour to normal tissue. Single Bowman sensors were mapped manually and/or automatically within the entire thermometry catheter length in tissue during each hyperthermia session, when technically feasible. Systemic temperatures were determined by intermittent rectal and bladder measurements. The temperature of the circulating coupling medium was also recorded.

In order to prevent any hyperthermia-related complications, some patient parameters and emergency rules were observed throughout the treatment, such as continuous clinical observation of patient, monitoring of oxy-haemoglobin saturation, heart rate, and blood pressure. Some conditions such as patient anxiety, continuous pain, nausea or vomiting, pulse rate > 150, normal tissue temperature > 43°C, blood pressure maximum > 180 mmHg, and altered mental status were considered for reducing applied power or in stopping the treatment. Emergency cardiopulmonary resuscitation was on regular stand-by availability and patients had to be observed post treatment until core temperature, haemodynamic parameters and mental status had normalized.

Results

Four out of 144 patients, from extra-regional sites, were lost at follow-up. Of 140 patients evaluated, four died because of inter-current disease and 12 because of progression of disease. The duration of progression-free and overall survival was measured from the time of inclusion in the study to the

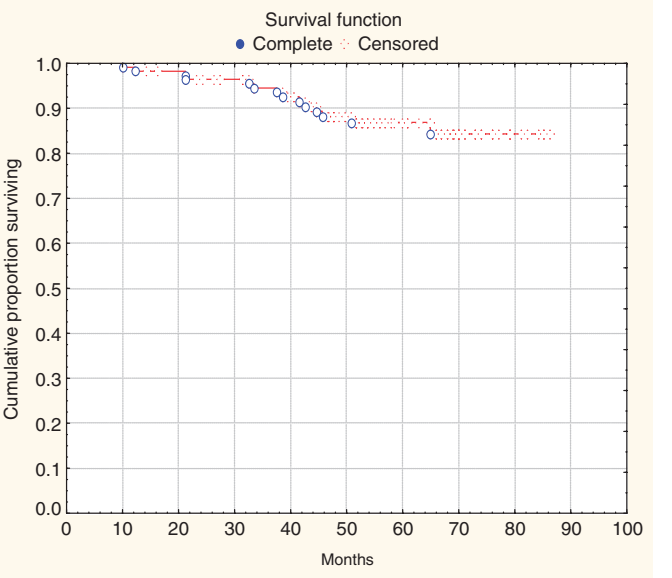

Figure 1. Overall survival. Cumulative proportion surviving (Kaplan–Meier method).

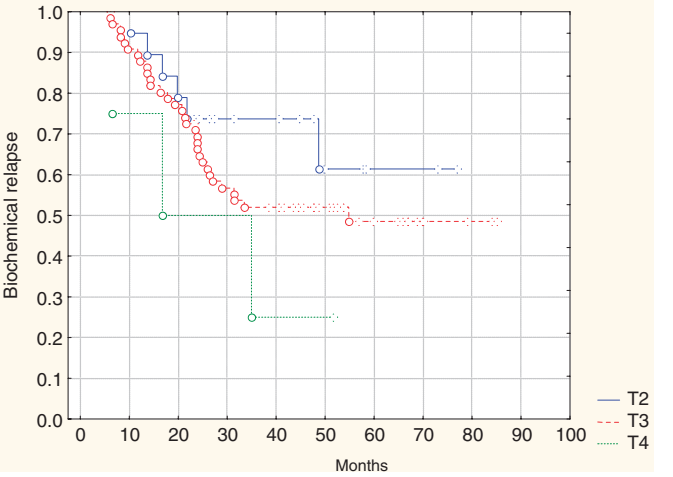

Figure 2. Progression free survival (biochemical relapse). Cumulative proportion surviving (Kaplan–Meier method). T2 *vs.* T3 *vs.* T4

documentation of progression or until death. Median follow-up was 51.7 months (range 10.1 to 86.2, STD 17.2) with endpoints being overall survival, and disease-free survival or biochemical progression (Figures 1 and 2). Biochemical progression was defined as a consistent and significant rise in the PSA, according to the ASTRO consensus definition. The overall survival and disease-free survival (biochemical recurrence) rates are 87% and 49% at 60 months, respectively.

Statistical analysis: Difference in variables with a continuous distribution across dichotomous categories were assessed with the use of the Mann-Whitney U test. The Kaplan–Meier method was used to calculate survival. Analysis was performed with the Cox proportional hazard regression model. Statistical significance in this study was set as $p < 0.05$. All p value are two-sided.

Regarding hyperthermia, the thermal treatment goal was to keep a T90 (temperature that was equalled or exceed by 90% of the measured points along each track in the thermal mapping) greater than 40°C for about 30 minutes (actually, the data reported was 24.4 minutes with 14.4 to 34.4 95% CI). The mean maximum temperature achieved was 42.7°C (rectal wall measurement), whereas the average of T90 and the 95% interval in the rectum and in the bladder were 40.2°C (38.4 to 42°C), and 41.3°C (39.5 to 42.3°C), respectively.

No significant acute hyperthermia-correlated toxicity was reported. With regard to the gastro-intestinal (GI) and genito-urinary (GU) acute toxicity, some

grade 1 side effects were reported, whereas grade 2 urinary side effects occurred in very few cases, related to the probe positioned in the urethra. All GI and GU grade 1 acute toxicities disappeared within one month after the completion of the therapy course. No late hyperthermia-related toxicity occurred. GI and GU acute and late effects did not correlate with temperature achieved during hyperthermia treatment. No more genito-urinary side effects occurred when probes were positioned by using more appropriate catheters than previously used. In conclusion, only a few cases reported thermometry-correlated side effects. Probably due to intermediate dose and conformal technique, no radiotherapy grade 2 acute toxicity was reported. A late CRT-related toxicity occurred in 2.7% of cases with GI grade 2, whereas GU toxicity rate was greater (6.7%) but limited to grade 1. No GU grade 2 late complications were reported. No GI or GU late grade 3 or greater toxicity occurred in our patients within a median follow-up of 51.7 months.

Discussion

There is growing use of hyperthermia in the treatment of pelvic deep-seated tumours, especially after the finding of an improved response and overall survival by adding thermal therapy to radiation therapy [10].

The consensus conference held in Osaka in 2004 (Kadota Forum), having evaluated the role of hyperthermia according to the criteria of Evidence Based Medicine (EBM), did not consider prostate cancer as a tumour which can be treated with a level 1-2 of EBM. In spite of the lack of evidence, in many centres patients affected by advanced prostate cancer have been treated with hyperthermia combined with radiotherapy, achieving positive results in terms of feasibility and very low toxicity [11, 13, 14]. In human prostatic cancer cells, the combination of fractionated irradiation with continuous heating at 40°C or a single acute dose radiation following heat treatment at 41°C, achieves a thermal enhancement ratio (TER) in the range of 1.4 to 2.0 even if a mild hyperthermia is given [15]. In prostate cancer LHT does not increase late effects when added to conventional radiotherapy and it seems to enhance efficacy of combined treatment [11, 13].

Local hyperthermia in prostate cancer is possible using several different methods, such as interstitial, endoluminal, and external hyperthermia. LHT permits a uniform heat distribution in the prostate and in seminal vesicles, with optimal temperature levels. The use of LHT could avoid the hazard of radiotherapy dose escalation, which increases grade 2–3 rectal complications from 12% to 26% when the total dose is increased from 70 to 78 Gy [16]. The possibility to omit invasive thermometry in prostate cancer is still uncertain, and if a thermal dose in the individual patient is required, an invasive measurement will be needed [17]. Nevertheless, in many tumours a strong correlation exists between endoluminal and invasive thermometry [18] and similarly in prostate cancer a non-invasive measurement could replace the intratumoural thermometry [11]. In conclusion, urethral temperature is sufficient for treatment optimization, because of the similarity between temperature changes in urethral and interstitial sites. However, the question about the role of invasive measurement remains [19]. The intraluminal approach is not suitable to measure the exact intra-tumoural temperature, but it reduces toxicity and complications following invasive methods, in the meantime increasing the compliance of patients to the treatment. Temperature changes within a hyperthermia session in invasive and urethral border sensor measurements corresponded well [20] even if intraluminal data, such as urethral border, may exhibit higher values than the invasive measurement. Local hyperthermia is feasible and well tolerated with no apparent significant toxicity and without severe complications [14, 20, 21]. The duration of hyperthermia shows a trend toward the significance for overall survival and seems to compare favourably with most series using irradiation alone [14, 20].

In our experience, LHT added to CRT at intermediate dose seems to be a favourable approach in terms of treatment related toxicity if compared to 33% grade 2 and 7% grade 3 late toxicity reported after 78 Gy by RTOG 9406 trial, including only stage T1-T2 patients [22]. The very low toxicity that occurred in our study should be particularly appreciated, considering the positive results in terms of overall and disease-free survival associated with more advanced disease and high risk patients. The toxicity profile and the promising results referred in the present study represent an important step towards the implementation of LHT combined with radiation therapy and AST in prostate cancer treatment. Further studies and a longer follow-up are needed in order to know the long-term results and assure the complete safety of thermal therapy.

Conclusions

In high-risk LAPC, hyperthermia seems to be useful to enhance the efficacy of radiotherapy course at intermediate dose (not exceeding a mean dose of 74 Gy). LHT combined with CRT achieves positive results in terms of overall and disease-free survival, similar to results obtained by delivering higher doses, without exceeding the dose that significantly increases acute and late toxicity. Although getting further improvements in prostate cancer seems to be

unlikely considering the optimal results already achieved by AST-CRT combined therapy, to evaluate the exact gain of adding hyperthermia to radiotherapy in high risk-LAPC, a randomized phase III study, comparing CRT plus AST with or without LHT, could be proposed.

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References

1. Krumholtz JS, Andriole GL. The surgery of prostate cancer: An update of contemporary radical prostatectomy and brachytherapy series. Sem Surgical Oncology 1999;17(3): 213–218.
2. Ragde H, Elgamal AA, Snow PB, Brandt J, Bartolucci AA, Nadir BS, Korb LJ. Ten-year disease free survival after transperineal sonography-guided iodine-125 brachytherapy with or without 45-Gy external beam irradiation in the treatment of patients with clinically localized, low to high Gleason grade prostate carcinoma. Cancer 1998;83(5):989–1001.
3. Shipley WU, Thames HD, Sandler HM, Hanks GE, Zietman AL, Perez CA, Kuban DA, Hancock SL, Smith CD. Radiation therapy for clinically localized prostate cancer: A multi-institutional pooled analysis. J American Med Association 1999;281(17):1598–1604.
4. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Gil T, Collette L, Pierart M. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and Goserelin. N Eng J Med 1997;337(5):295–300.
5. Pilepich MV, Caplan R, Byhardt RW, Lawton CA, Gallagher MJ, Mesic JB, Hanks GE, Coughlin CT, Porter A, Shipley WU, Grignon D. Phase III trial of androgen suppression using Goserelin in unfavorable prognostic carcinoma of the prostate treated with definitive radiotherapy: Report of RTOG 85-31. J Clin Oncol 1997;15:1013–1021.
6. Lawton CA, Winter K, Murray K, Machtay M, Mesic JB, Hanks GE, Coughlin CT, Pilepich MV. Updated results of the phase III RTOG trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001;49:937–946.
7. Horwitz EM, Winter K, Hanks GE, Lawton CA, Russell AH, Machtay M. Subset analysis of RTOG 85-31 and 86-10 indicates an advantage for long-term vs. short-term adjuvant hormones for patients with locally advanced non metastatic prostate cancer treated with radiation therapy. Int. J Radiat Oncol Biol Phys 2001;49:947–956.
8. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, van Putten WL, van Rhoon GC, van Dijk JD, Gonzalez Gonzalez D, Liu FF, Goodman P, Sherar M. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer. Results from five randomized controlled trials. International Collaborative Group. Int J Radiat Oncol Biol Phys 1996;35:731–744.
9. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, Arcangeli G, Dahl O, Mella O, Bentzen SM. Hyperthermia as an adjuvant to radiation therapy of recurrent or metastatic malignant melanoma. A multicentre randomized trial by the European Society for Hyperthermic Oncology. Int J Hyperthermia 1996;12(1):3–20.
10. Van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomized, multicentre trial. Lancet 2000;355:1119–1125.
11. Anscher MS, Samulski TV, Dodge R, Prosnitz LR, Dewhirst MW. Combined external beam irradiation, & external regional hyperthermia for locally advanced adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys 1997; 37(5):1059–1065.
12. Kaplan I, Kapp DS, Bagshaw MA. Secondary external beam radiotherapy and hyperthermia for local recurrence after 125-Iodine implantation in adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys 1991;20:554.
13. Kalapurakal JA, Mittal BB, Sathiaseelan V. Reirradiation and external hyperthermia in locally advanced, radiation recurrent, hormone refractory prostate cancer: A preliminary report. Br J Radiology 2001;74:745–751.
14. Algan O, Fosmire H, Hynynen K, Dalkin B, Cui H, Drach G, Stea B, Cassady JR. External beam radiotherapy and hyperthermia in the treatment of patients with locally advanced prostate carcinoma. Cancer 2000;89(2):399–403.
15. Ryu S, Brown SL, Kim SH, Khil MS, Kim JH. Preferential radiosensitization of human prostatic carcinoma cells by mild hyperthermia. Int J Radiat Oncol Biol Phys 1996;34(1): 133–138.
16. Pollack A, Zagars GK, Smith LG, Lee JJ, Eschenbach AC, Antolak JA, Starkschall G. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 2000;18(23):3904–3911.
17. van Vulpen M, De Leeuw AA, Van De Kamer JB, Kroeze H, Boon TA, Warlam-Rodenhuis CC, Lagendijk JJ, Battermann JJ. Comparison of intraluminal versus intra-tumoral temperature measurements in patients with locally advanced prostate cancer treated with coaxial TEM system: Report of a feasibily study. Int J Hyperthermia 2003;19(5):481–497.
18. Wust P, Gellerman J, Harder C, Tilly W, Rau B, Dinges S, Schlag P, Budach V, Felix R. Rationale for using invasive thermometry for regional hyperthermia of pelvic tumors. Int J Radiat Oncol Biol Phys 1998;41(5):1129–1137.
19. van Vulpen M, De Leeuw JR, Van Gellekom MP, Van Der Hoeven J, De Graeff A, Van Moorselaar RJ, Van Der Tweel I, Hofman P, Lagendijk JJ, Battermann JJ. A prospective quality of life study in patients with locally advanced prostate cancer, treated with radiotherapy with or without regional or interstitial hyperthermia. Int J Hyperthermia 2003;19(4):402–413.
20. Van Vulpen M, De Leeuw AA, Raaymakers BW, van Moorselaar RJ, Hofman P, Lagendijk JJ, Battermann JJ. Radiotherapy and hyperthermia in the treatment of patients with locally advanced prostate cancer: Preliminary results. British J Urology 2004;93(1):36–41.
21. Tilly W, Gellermann J, Graf R, Hildebrandt B, Weissbach L, Budach V, Felix R, Wust P. Regional hyperthermia in conjunction with definitive radiotherapy against recurrent or locally advanced prostate cancer T3 pN0 M0. Strahlenther Onkol 2005;181(1):35–41.
22. Michalski JM, Winter K, Purdy JA, Parliament M, Wong H, Perez CA, Roach M, Bosh W, Cox JD. Toxicity after three-dimensional radiotherapy for prostate cancer on RTOG 9406 dose Level V. Int J Radiat Oncol Biol Phys 2005;62(3): 706–713.