

## Chapter 7

### Summary and General Discussion

Treatment results after conformal irradiation of locally advanced prostate cancer are insufficient (Zelefsky et al. 1998, Zagars et al. 1999). Adding hyperthermia to the external beam irradiation can be expected to improve treatment outcome (chapter 1) (Ryu et al. 1996, Anscher et al. 1997). A randomized trial will be necessary to prove this benefit. The aim of this thesis was to evaluate the possibilities and usefulness to start a randomized study on hyperthermia for locally advanced prostate cancer. To achieve this goal, several questions were answered. The feasibility was evaluated of interstitial hyperthermia (chapter 2) and regional hyperthermia (chapter 3). Temperature distributions were analyzed (chapters 2 and 3). Perfusion, which mainly determines the temperature distribution, was calculated (chapter 4). The results of follow-up (chapter 6), the side effects (chapter 2, 3, 5, 6) and the influence of hyperthermia on quality of life (chapter 5) were investigated.

In chapter 2 the results of a feasibility study of three-dimensional spatially controlled interstitial hyperthermia for locally advanced prostate cancer were described. Twelve patients with prostate cancer (T3 Nx/0 M0) were treated with conformal external beam radiotherapy (70 Gy) and one interstitial hyperthermia treatment. Hyperthermia was delivered with the 27MHz Multi Electrode Current Source interstitial hyperthermia

technique (MECS-IHT) on outpatient basis. Guided by transrectal sonography, 12 catheters (range 7-16) were placed in the prostate through a template. Two electrodes per probe were inserted. Thermometry (average 100 sensors) was performed from within the probes for online temperature control. Additional thermometry was done in the prostate, rectum, urethra, and bladder. Reconstruction was done by sonography. Prostate perfusion was estimated from the thermal decay at the end of treatment. The full 3D temperature distribution was calculated.

A learning curve was experienced regarding MECS-IHT. At the end of this learning curve, the hyperthermia technique was considered as technically feasible. Toxicities were acceptable. It proved to be possible to calculate the full 3D-temperature distribution in the prostate, using the combination of extensive catheter thermometry and hyperthermia treatment planning simulation (Raaymakers et al. 2001). Based on the average perfusion, 3D calculated temperatures appeared to result in lower temperatures and a more realistic description of the temperature distribution than expected from the measured catheter temperatures. The average measured catheter temperatures were  $T_{90}$  39.9°C and  $T_{50}$  44.1°C, whereas the average calculated temperatures were  $T_{90}$  39.4°C and  $T_{50}$  41.8°C. So, it was not feasible to achieve the goal temperature of 42-43°C in the entire prostate. A high perfusion, to an average level of 47 ml/100gr/min (range 30-65) found at the end of each hyperthermia treatment, resulted in a heterogeneous temperature distribution, with highly peaked temperatures around the electrodes and a sharp temperature drop-off outside the implant volume. Following the quality assurance criteria on interstitial hyperthermia (Emami et al. 1991, 1996), this temperature distribution would be insufficient to treat cancer. Furthermore, prostate cancer has in approximately 80% multiple cancer foci (Chen et al. 2000). Therefore, treatment of the whole prostate is required. There might be possibilities to improve the temperature distribution in the prostate using the MECS-IHT system. The electrode configuration could be adapted to the shape of the prostate. More heating catheters could be introduced (Van der Koijk et al. 1997). But, because of implantation limitations to bladder and rectum, underdosed regions are likely to remain. In our study the macroscopic tumour area reached higher temperatures compared to the whole prostate, with  $T_{90}$  40.7°C, and  $T_{50}$  43.0°C. Therefore, interstitial hyperthermia as a boost might be beneficial, especially regarding thermal enhancement of

irradiation (Ryu et al. 1996) without severe acute (chapter 2 and 6) and without expected late (Gonzalez et al. 1995) toxicities. Other combinations of MECS interstitial hyperthermia with different radiotherapy regimes / techniques (HDR / I-125) are possible and these might be superior to the chosen study design. Concluding, interstitial hyperthermia, in this form, seems insufficient for prostate cancer treatment, because treatment of the whole prostate volume is required.

In chapter 3 the results of a feasibility study of regional hyperthermia for patients with locally advanced prostate carcinoma (T3/4 Nx/o M0) were described. The primary objective was to analyze the thermometry data with an emphasis on the possibility of replacing invasive thermometry by tumour-related intraluminal thermometry. Fourteen patients were treated with a combination of conformal external beam radiotherapy (70 Gy) and hyperthermia. Hyperthermia was delivered using the Coaxial TEM system, one treatment per week, to a total of five treatments. Thermometry was performed in bladder, urethra, rectum and esophagus. Invasive thermometry in the prostate was carried out during one or two treatments for each patient by placing transperineally a central and a peripheral catheter. At the end of the study, regional hyperthermia in combination with external beam radiotherapy for locally advanced prostate carcinoma was regarded as clinically feasible. No severe complications occurred. The maximum body, bladder and rectum temperatures remained below safety limits. The most frequently observed complaint necessitating a power reduction was local pain due to hot spots. Absorbers (Kroeze et al. 2003) were used successfully to treat and prevent this local pain. Systemic stress developed seldomly and was never treatment limiting. Temperatures were low, but are comparable with the results of other centers (Tilly et al. 2001). Our mean invasive  $T_{90}$  was  $40.2 \pm 0.6^{\circ}\text{C}$  and  $T_{50}$  was  $40.8 \pm 0.6^{\circ}\text{C}$ . The mean dose, described as Cum min  $T_{90} > 40.5^{\circ}\text{C}$ , per treatment was 22 minutes (range 0-50). We measured heterogeneous temperature distributions in the prostate. The average invasive temperature range was  $1.1^{\circ}\text{C}$ . Due to the temperature heterogeneity and a limited number of thermometry sensors (mean 7, range 2-13) a large variability between treatments and patients existed regarding achieved temperatures and dose. Overall, the invasively measured temperatures were lower than the intraluminal temperatures, as was also found by Tilly et al. (2001). Importantly, intraluminal temperatures did not

reliably predict invasively measured temperatures. Invasive thermometry therefore remains compulsory to calculate a thermal dose for an individual patient. Changes in temperature during treatment, measured by the urethral sensors, corresponded well with changes in temperature measured by the individual invasive sensors. Similar comparison of rectal temperature changes with intraprostatic temperature changes was not as predictive. The similarity in temperature changes between the urethral and invasive sites, suggests that urethral temperatures are sufficient for treatment optimization. The SAR profile did not correspond with the temperature profile indicating a heterogeneous perfusion. Regarding the temperature, SAR and perfusion heterogeneity in the prostate, the question remains how many invasive catheters and sensors are required to calculate a reliable thermal dose. Due to the limited number of treatments with invasive thermometry in the present study no minimum number of sensors or catheters can be recommended. In our study, invasive thermometry did not cause severe toxicities. Others left the catheters in the body for several days (Van der Zee et al. 1998, Wust et al. 1998), which might explain the large percentage of infections their patients experienced. Together with Sneed et al. (1998) we conclude that it is preferable to remove all catheters after each hyperthermia session to reduce the number of complications. Based on the practical experience from this study we conclude that increasing the number of invasive catheters above two would cause an unacceptable increase in perineal pain complaints and therefore should be avoided. Unfortunately, in this study, two catheters for invasive thermometry seems not sufficient. Some centers are developing non-invasive thermometry based on MR imaging during the hyperthermia treatment, but several major problems still have to be solved (Hoffmann et al. 2002, Wust et al. 2002). Therefore, MR thermometry probably will not be available in the near future. In this study, hyperthermia treatment planning was performed for each patient, using our Hyperthermia Treatment Planning system (van de Kamer et al. 2001). Using Houndsfield Unit based thresholding and manually outlining of the tumor, a 40 cm CT data set (slice thickness of 5 mm) was segmented and down scaled to a resolution of 1 cm. Next, the SAR model was used to make several SAR computations: in different treatment positions and with or without absorbers. Because the patient anatomy is highly structured on a millimeter scale and the calculated SAR distribution is only limited to a centimeter resolution, due to current computer limitations, quasistatic zooming has been developed (Van de Kamer et al.

2001). With this technique a high-resolution SAR distribution within a volume of interest can be calculated. The intraluminally and invasively measured SAR distributions are yet compared with the calculated SAR profiles. When validated, the hyperthermia treatment plan might predict an accurate SAR and temperature distribution and might estimate a reliable thermal dose. One or two invasive catheters then could be used for extra thermometry to confirm the calculated temperature distribution. Further improvement of our planning system is expected from efforts to generate a generic prostate model, which incorporates vasculature and a temperature dependent perfusion.

Increasing the body temperature in this study moderately increased the tumour temperatures, but not statistically significant (De Leeuw et al. 2003). Kapp (1996) and Thrall et al. (1997) showed evidence for an increased risk of distant metastasis when increasing the body temperature. In animal studies on experimental sarcoma tumours, they increased the body temperature up to 41.8<sup>0</sup>C (whole body hyperthermia). In our study the body temperature was only moderately elevated (average maximal body temperature 38.6<sup>0</sup>C). Our results on clinical outcome for prostate cancer (chapter 6), and for cervical cancer (Warlam-Rodenhuis et al. 2000) do not indicate an increased risk of distant metastasis. Van der Zee et al. (2002) even reported a reduced number of distant metastasis after regional hyperthermia for cervical cancer. Repasky and Issels (2002) recently discussed the possible benefits of fever and heat shock proteins on the immune response in cancer treatment (chapter 1). Therefore, we conclude that the risk of increased metastasis is not applicable for our patient group.

From published data it seems that the technical developments in regional hyperthermia systems resulted in an improvement of the achieved temperatures. Anscher et al. (1997) used the BSD Sigma 60 hyperthermia applicator on patients with prostate cancer. They achieved a mean T<sub>90</sub> of 39.3<sup>0</sup>C and T<sub>50</sub> 40.4<sup>0</sup>C. Our mean prostate temperatures using the Coaxial TEM were higher: T<sub>90</sub> 40.2<sup>0</sup>C and T<sub>50</sub> 40.8<sup>0</sup>C and are comparable with recent achievements of others (Tilly et al. 2001). Further improvements may be expected in the near future. Theoretical studies show that a multi-phase amplitude controlled system might optimize the prostate temperature (Paulsen et al. 1999, Wust et al. 2001, Kroeze et al. 2001b). A new radiative applicator will be developed in our department (Kroeze et al. 2001b). This multi-ring annular array of antennas will optimize the steering possibilities,

resulting in an improvement of the achieved temperature distribution and a reduction of side effects.

In chapter 4, prostate perfusion was estimated in patients with locally advanced prostate carcinoma, treated with a combination of external beam irradiation and regional (10 patients) or interstitial hyperthermia (8 patients). Perfusion values were calculated from temperature elevations due to constant applied power and from transient temperature measurements following a change in applied power. The student t-test was used for comparison of perfusion values in time and between groups. At the start of the regional hyperthermia treatments, the mean perfusion was estimated  $10 \pm 8$  ml/100gr/min. At the end of those treatments, perfusion increased to  $14 \pm 2$  ml/100gr/min ( $p < 0.01$ ). At the end of the interstitial hyperthermia treatments, perfusion was estimated  $47 \pm 5$  ml/100gr/min, which was significantly different compared with the end of regional hyperthermia ( $p < 10^{-7}$ ). The achieved temperatures and temperature distributions were described in chapter 2 and 3 (see above) and differed considerably between both hyperthermia techniques. Furthermore, the systemic temperature increased in regional hyperthermia up to  $38.6^{\circ}\text{C}$ , whereas in interstitial hyperthermia the body temperature was not elevated. Because an increase of temperature results in an increase of perfusion (Larson et al. 1995, Vujaskovic et al. 2000), higher maximum temperatures in interstitial hyperthermia may explain this difference in perfusion. Another explanation for the significant difference in estimated perfusion between the two hyperthermia techniques might be a stealing effect (Cai et al. 2000). Due to a high body temperature in regional hyperthermia, as a physiologic cooling reaction of the body, a redistribution of blood flow may take place, e.g. to the skin. This would cause prostate perfusion in regional hyperthermia to be lower compared to perfusion in interstitial hyperthermia where the body temperature is not elevated. Due to the very high perfusion, a non-optimal temperature distribution was existing in interstitial hyperthermia (chapter 2). A possible improvement may be obtained by increasing the body temperature during interstitial hyperthermia. This might stimulate the steal effect and in this way reduce prostate perfusion. It remains questionable whether a steal effect really exists. Other reasons for the higher end-perfusion values in interstitial hyperthermia might be: trauma from the needle insertion (Larson et al. 1995), epidural anesthesia which dilates the blood

vessels below the anesthesia level, and the higher temperatures reached in MECS-IHT. Further study on the steal effect is needed.

In chapter 5, quality of life (QoL) was investigated prospectively in patients with locally advanced prostate carcinoma treated with conformal radiotherapy (70 Gy) and the influence of adding regional or interstitial hyperthermia was evaluated. Patients treated with radiotherapy alone (n=58) or combined with regional (n=8) or interstitial hyperthermia (n=12) completed the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (C30+3), the EORTC prostate cancer module (PR25) and the Rand 36 health survey before treatment and 1 and 6 months after completion of treatment. Analysis of Variance (ANOVA) for repeated measurements has been performed to describe the data. We found no statistically significant differences in QoL between patients receiving regional (n=8) or interstitial hyperthermia (n=12). No statistical differences in QoL were found between the hyperthermia group (n=20) and the group of patients receiving irradiation alone (n=58). Hyperthermia therefore does not seem to worsen QoL at the measurement points used. The hyperthermia patient group is rather small, so a small difference in QoL could be missed. Furthermore, many selection criteria were applied in the hyperthermia group, which were absent for the radiotherapy only group. A change of QoL in time has been observed in the data of all patient groups together (n=78). Only a temporary deterioration occurred concerning social, psychological and prostate cancer related symptoms. Six months after the baseline measure only sexual dysfunction remained, as was reported previously (Joly et al. 1998, Lilleby et al. 1999, Bacon et al. 2001). When comparing our results to studies on patients with predominantly localized cancer (T1, 2) treated with conventional external beam irradiation, no significant differences in outcome can be noticed (Lim et al. 1995, Litwin et al. 1995, Joly et al. 1998, Lilleby et al. 1999, Bacon et al. 2001, Lee et al. 2001, Janda et al. 2000, Clark et al. 1999, Davis et al. 2001, Eton et al. 2001). Concluding, adding regional or interstitial hyperthermia to external beam irradiation does not seem to decrease QoL. Only a phase III study will be able to prove that QoL is no significant issue in prostate hyperthermia.

## *Chapter 7*

In chapter 6 an interim clinical evaluation was performed on the patients treated with interstitial (12) or regional (14) hyperthermia, as described above. Mean initial PSA was 26 ng/ml. Three patients had a T4 tumour, 23 were staged as T3. Tumours were classified as well (4), moderately (16) and poorly (6) differentiated. Two out of 26 patients received adjuvant androgen suppression. Mean follow up was 36 months. In the combined treatments no toxicities above grade 2 (common toxicity criteria, version 2) were seen. Achieved temperatures and temperature distribution were described above. All patients survived. Seven patients had a biochemical relapse (27%), 3 in the regional and 4 in the interstitial hyperthermia group. The actuarial probability of freedom from biochemical relapse was 70 % at 36 months for all patients together, 79 % for the regional hyperthermia patients and 57 % for the interstitial hyperthermia patients. No factors were found to predict relapse. These results on clinical outcome compare favorable to series on patients treated with radiotherapy alone (Zagars et al. 1988, Pilepich et al. 1995, 1997, Laverdiere et al. 1997, Bolla et al. 1997, 2002, Horwitz et al. 2001). However, the duration of follow-up and the number of patients in our studies are very limited. Up to now, the optimal treatment temperature, the required number of hyperthermia treatments and treatment duration are still unclear (chapter 1 and 6). It seems advisable to use the current hyperthermia regimens, because this has proved effective e.g. in cervical cancer (Van der Zee et al. 2000, 2002). Temperature heterogeneity, as was measured in our interstitial or regional hyperthermia treatments, seemed not properly incorporated in the present thermal dose concepts. Calculation of a thermal dose, using the present dose concepts, therefore seems not useful. We are planning to develop a model for calculating tumour control probability (TCP) in hyperthermia. Such a model could overcome the limitations of the present thermal dose concepts by calculating the combined effect of radiotherapy and hyperthermia per clonogen.

A marked improvement of treatment outcome in locally advanced prostate carcinoma is seen when using androgen suppression adjuvant to conventional irradiation (Zagars et al. 1988, 1999, Pilepich et al. 1995, 1997, Laverdiere et al. 1997, Bolla et al. 1997, 2002, Horwitz et al. 2001). Although androgen deprivation does not act by radiosensitizing prostate cancer cells to radiotherapy, the additive cell death and growth inhibitory effects of androgen suppression plus irradiation are clinically meaningful

(Pollack et al. 2001). Unfortunately, androgen suppression deteriorates quality of life severely (Lubeck et al. 2001), whereas hyperthermia does not seem to decrease quality of life (Chapter 5). The combination of hyperthermia, androgen suppression and radiotherapy may further improve clinical outcome. On the other hand, because clinical results after combined hormonal treatment and irradiation are already near the top of the S curve on outcome, hyperthermia probably will not be able to improve outcome very much and it will be difficult to proof a beneficial effect. A phase III trial without hormonal treatment therefore seems necessary to show a gain of hyperthermia on clinical outcome. Regarding the promising results of Anscher et al. (1997) and our results after irradiation combined with regional hyperthermia, and the deterioration of QoL after hormonal treatment (Lubeck et al. 2001), a phase III trial without hormonal therapy can be defended.

Concluding, a future phase III trial on hyperthermia for locally advanced prostate cancer can be justified. To proof a beneficial effect, the study should be performed without adjuvant hormonal therapy. Regional hyperthermia would be the technique of choice. It seems advisable to use the current hyperthermia regimens. Urethral temperatures alone are sufficient for treatment optimization. The question on the importance of invasive thermometry remains. Hyperthermia treatment planning has to be validated and should be performed for each patient in the phase III study. Toxicity and QoL have to be registered prospectively.

