Regional Hyperthermia in Conjunction with Definitive Radiotherapy against Recurrent or Locally Advanced Prostate Cancer T3 pN0 M0

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Background and Purpose: Since long-term results of the standard treatment of locally advanced or recurrent prostatic carcinoma are unsatisfactory, the role for additional regional hyperthermia was evaluated in a phase I/II study.
Patients and Methods: From 08/1996 to 03/2000, 22 patients were treated by a standard irradiation regimen (68.4 Gy) in combination with regional hyperthermia (weekly, five to six times), and five of 22 patients received short-term (neoadjuvant) hormonal treatment. Of these, 15 patients had primary prostatic carcinoma T3 pN0 M0 and seven a histologically confirmed local recurrence after radical prostatectomy. Feasibility of hyperthermia, and acute/late toxicity as well as long-term follow-up (prostate-specific antigen [PSA] control, overall survival) were analyzed. Clinical endpoints were correlated with thermal parameters.
Results: Mean maximum temperatures along the urethra of 41.4 °C (41.0 °C for the recurrences), and mean T_{90} values of 40.7 °C could be achieved. Severe acute toxicity of grade 3 occurred at the rectum in three, at the urethra in four, at the intestine in one, and a burn induced by hyperthermia in one of 22 patients. Late toxicity was only observed rectally in one patient (grade 3) and at the urethra in two patients (grade 2). There was no correlation between thermal parameters and any toxicity. The survival curves showed a PSA control for primary prostatic carcinoma > 50% after 6 years, but no long-term PSA control for the recurrences. Overall survival after 6 years was 95% for primary carcinoma, and 60% for the recurrences. There was a clear correlation between higher temperatures or thermal doses with long-term PSA control.
Conclusion: Regional hyperthermia might be a low-toxicity approach to increase PSA control of common treatment schedules. Further evaluation, in particular employing improved hyperthermia technology, is worthwhile.

Key Words: Regional hyperthermia · Prostate carcinoma · PSA control

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Definitive externe Radiotherapie mit regionaler Hyperthermie beim lokal fortgeschrittenen oder rezidivierten Prostatakarzinom Stadium T3pN0M0

Hintergrund und Ziel: Die Langzeitergebnisse der Standardtherapie beim lokal fortgeschrittenen oder rezidivierten Prostatakarzinom sind unbefriedigend. Daher wurde eine zusätzliche regionale Hyperthermie in einer Phase-I/II-Studie evaluiert.
Patienten und Methodik: Von 08/1996 bis 03/2000 wurden 22 Patienten mit einer Standardradiotherapie von 68,4 Gy in Kombination mit regionaler Hyperthermie (wöchentlich, fünf bis sechs Sitzungen) behandelt. Bei fünf von 22 Patienten wurde eine neoadjuvante Hormonbehandlung durchgeführt. Bei 15 Patienten lag ein primäres Prostatakarzinom T3 pN0 M0 vor; sieben Patienten hatten ein histologisch bestätigtes Lokalrezidiv nach radikaler Prostatektomie. Geprüft wurden die Durchführbarkeit der Hyperthermie, die akute und späte Toxizität sowie die Langzeitkontrolle (PSA-Kontrolle [prostataspezifisches Antigen], Gesamtüberleben). Die klinischen Endpunkte wurden mit thermischen Parametern korreliert.
Ergebnisse: Es konnten mittlere Maximaltemperaturen entlang der Urethra von 41,4 °C (41,0 °C für die Rezidive) sowie mittlere T_{90} von 40,7 °C erreicht werden. Schwere akute Nebenwirkungen vom Grad 3 traten am Rektum bei drei, an der Urethra bei vier, am Dünndarm bei einem sowie durch Hyperthermie bedingt (Verbrennung) bei einem von 22 Patienten auf. Spätfolgen wurden nur bei einem Patienten am Rektum (Grad 3) und bei zwei Patienten an der Urethra (Grad 2) festgestellt. Es bestand keine Korrelation zwischen thermischen Parametern und irgendeiner Toxizität. Die Überlebenskurven zeigten eine PSA-Kontrolle von > 50% beim primären Prostatakarzinom nach 6 Jahren, jedoch keine Langzeit-PSA-Kontrolle bei den Rezidiven. Das Gesamtüberleben betrug nach 6 Jahren 95% für die primären Prostatakarzinome und 60% für die Rezidive. Es fand sich eine deutliche Korrelation zwischen hohen Temperaturen bzw. thermischen Dosen und der langfristigen PSA-Kontrolle.

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Schlussfolgerung: Die regionale Hyperthermie könnte eine gut verträgliche Zusatztherapie sein, um die PSA-Kontrolle von üblichen Therapieschemata zu verbessern. Hier ist eine weitere Evaluation sinnvoll, insbesondere auch unter Anwendung verbesserter Hyperthermietechnologien.

Schlüsselwörter: Regionale Hyperthermie · Prostatakarzinom · PSA-Kontrolle

Introduction

For locally advanced prostate cancer cT3/4 with cN0 or pN0, external-beam radiotherapy (EBRT) is accepted as standard treatment.

The role of radical prostatectomy in case of periprostatic tumor extension (T3) is controversially discussed. Reports with large numbers of T3 carcinomas describe a 5-year prostate-specific antigen (PSA) relapse-free survival of only 30–40% paralleled by considerable rates of local recurrences in the range of 20% [12, 24]. These results are similar to those of other nonsurgical series. Therefore, taking the peri-/postoperative morbidity into account, EBRT is widely favored.

However, in T3/T4 tumors definitive radiotherapy alone with standard doses of about 72 Gy is also inadequate. On average, in 60% PSA progression occurs after 5 years and in 80% after 10 years [32]. Innovative strategies include dose escalation by intensity modulation, additive interstitial radiotherapy, and/or cytoreduction by hormonal manipulation, either neoadjuvant and/or adjuvant, for several years. Nonetheless, these approaches could not improve the outcome, but imply some late normal tissue reactions.

Dose escalation with three-dimensional conformal irradiation led to an increased late rectal toxicity ≥ grade 2, and in fact, investigators found a higher rate of proctitis ≥ grade 2 [19, 22]. Long-term hormonal treatment causes specific side effects of the medication, impotency, and increased late reactions [8].

There is currently no standard of care for locally advanced prostatic carcinoma. Regional hyperthermia might be a useful option, because it is known to enhance the locoregional efficacy of radiotherapy [16, 25, 27]. An advantage of regional hyperthermia might be its low toxicity profile, observed in many studies in terms of acute and late reactions [17]. We conducted a phase II study to further investigate the role of regional hyperthermia for locally advanced prostatic carcinoma.

Patients and Methods

We established a protocol for concurrent thermoradiation for locally advanced primary prostatic carcinoma at stage T3 pN0 M0 or recurrent rTx cN0 M0 tumors. This protocol has been approved by the ethics committee of the Charité in November 1996. We enrolled 22 patients with histologically proven primary or recurrent prostatic carcinoma. Capsular penetration was verified either by ultrasound or by clinical examination. Only pN0 categories (verified by lymphadenectomy) were included. Exclusion criteria were severe comorbidity, in particular vascular diseases, and interferences with radio-frequency hyperthermia, cardiac pacemakers and other electronic or metallic implants, e.g. endoprostheses.

External radiotherapy was performed with a linear accelerator (Siemens Mevatron KD, 18 MV) using fractions of 5×1.8 Gy up to 68.4 Gy at the reference point (ICRU). Planning was carried out based on a three-dimensional CT data set using the planning system Helax®. Prostate and seminal vesicles with a safety margin of 1 cm (7–8 mm dorsally to spare the rectum) were specified as planning target volume. A conformal four-field box technique was used.

Regional hyperthermia was carried out about 30 min before or after a single fraction once a week five to six times during the radiotherapy course as described elsewhere [29]. We used the SIGMA-60 applicator of the BSD 2000 system. The midplane (feed points of the antennas, central plane of the applicator) was positioned a few centimeters cranial to the symphysis defining the longitudinal position [21]. The patient was also transversally centered in the applicator (defining the vertical and lateral position). We inserted minimally invasive hyperthermia catheters (closed-end catheters for housing the Bowman thermistors) into the rectum and urethra. In addition, a bladder catheter was positioned parallel to the thin hyperthermia catheter (diameter about 1.6 mm). We could register temperature position curves along the catheters in the rectum and the urethra in 10- to 15-min intervals. For the temperature-time curves in between, we left the point probe at the maximum.

We assume that these reference points for the temperature-time curves characterize the central part and the periphery of the prostate. Using the temperature-time curves at the beginning (power-on) and at the end (power-off) of heat treatment, we could derive specific absorption rates (SARs) in W/kg at the reference points. We could also derive index temperatures T_{90} and T_{max} (T_{90} is the temperature exceeded by 90% of the tumor/prostate-related measurement points) as well as thermal dose parameter cumulative minutes (cummin) $T_{90} > 40.5$ °C, i.e., the time in minutes for the whole series with a $T_{90} > 40.5$ °C at the prostate [29]. The thermal parameters were correlated with clinical endpoints (toxicity, PSA control).

We started the heat treatment with a total power of 400–500 W (depending on habitus and general status) and synchronous adjustment (0.0; i.e., a phase delay 0 at every channel or antenna pair) or a slight shift to the bottom with a phase delay of 30–50° at the dorsal channel. According to patient tolerance (heat stress, hot spots) and achieved temperatures

in the measurement points (attempting to achieve > 41.5 °C), we increased or reduced the total power and, in particular, the weights at the dorsal or ventral channel or modified the phase delay.

Toxicity was documented according to WHO criteria (acute toxicity) or according to the LENT score (late effects of normal tissues) [18]. For the heat treatments we defined a toxicity score as follows: 0 – no complaints or some discomfort by bolus pressure, thermal stress or positioning; 1 – power-dependent discomfort, which resolves completely at the end of heat treatment; 2 – hot spot sensation, which persists or occurs after the end of heat exposure and resolves in days or (rarely) weeks; 3 – burn or thermal lesion.

The follow-up was based on a PSA monitoring every 4 months. PSA control was defined as a nadir of < 1 ng/ml. PSA progression according to ASTRO was defined for cases exceeding 2 ng/ml. PSA levels between 1–2 ng/ml were also judged to be a progression, if PSA increased at two successive controls. Local progression was defined according to WHO as macroscopic tumor growth of > 25%.

All statistical analyses were conducted with SPSS software version 10 (SPSS Inc, Chicago, IL, USA). Tests for subgroups were performed using the distribution-free Mann Whitney test. Overall survival and biochemical disease-free survival were analyzed using the actuarial method by Kaplan-Meier.

Results

Feasibility

From 1996 until 2000 we included 15 patients with de novo locally advanced prostatic carcinoma and seven recurrences. The patient characteristics are given in Table 1. Some patients with primary carcinoma (n = 6/15) were on LHRH (luteinizing hormone-releasing hormone) agonists before radiotherapy started. In these patients the medication was continued for 2 months and finished at the end of external radiotherapy.

Thermoradiation was well tolerated. The prescribed radiation dose could be delivered to all 22 patients. Concomitant regional hyperthermia was given in four to six sessions to 21 patients. Only in one patient hyperthermia had to be interrupted after the first heat treatment due to patient refusal. The total number of heat treatments was 122. The prescribed endoluminal thermometry in bladder, urethra and rectum could be performed in the majority of heat treatments. In a few patients the routine insertion of a bladder catheter during each heat session had to be waived. Insertion of the small flexible hyperthermia catheters in the urethra, however, was tolerated by most patients at each treatment session.

The statistical evaluation of the temperature position curves along the urethra is shown in Table 2 (see Patients and Methods for definitions). The temperature distribution appears quite homogeneous with a relatively high minimum temperature (T_{90} ~ 40.6–40.7 °C) compared with a series of rectal carcinomas [23]. On the other hand, the specific absorption rate and total power were lower than achieved for rectal cancers. We conclude that perfusion and thermal conduction must be higher in rectal carcinomas preventing temperature increase even for higher SARs. The toxicity per treatment and

Table 1. Characteristics of 22 patients entering the study from 1996 to 2000. PSA: prostate-specific antigen.

Tabelle 1. Patientencharakteristik (22 Patienten; Studienzeitraum 1996–2000). PSA: prostataspezifisches Antigen.

Age	**69 years (56–75 years)**			
Stage	*Primary*		*Recurrent*	
	cT3a pN0	9	rTX cN0	7
	cT3b pN0	6		
Hormonal Manipulation				
	Primary		*Recurrent*	
	None	9	None	7
	Neoadjuvant	6		
Grading	*Primary*		*Recurrent*	
	G1	3	G1	0
	G2	9	G2	1
	G3	3	G3	6
PSA	*Primary*		*Recurrent*	
	< 10 ng/ml	5	< 10 ng/ml	3
	10 – 20 ng/ml	4	10 – 20 ng/ml	4
	> 20 ng/ml	6		
	Mean = 16.7 ng/ml		Mean = 10.8 ng/ml	

Table 2. Thermal parameters (mean ± standard deviation) measured in the urethra (map along the prostatic urethra) and power-related parameters in n = 122 heat treatments. The parameters are differentiated for primaries and recurrences, and compared with corresponding parameters in rectal cancer achieved along endoluminal catheters under similar conditions [17]. P: total power; SAR: specific absorption rate.

Tabelle 2. Thermische Parameter (Mittelwert ± Standardabweichung) in der Urethra (Scan entlang dem Prostataabschnitt der Urethra) und leistungsabhängige Parameter bei n = 122 Wärmebehandlungen. Aufteilung der Parameter bei primären und rezidivierten Karzinomen und Vergleich mit den Ergebnissen beim Rektumkarzinom (Scan mittels endoluminaler Katheter) unter ähnlichen Bedingungen [17]. P: Leistung; SAR: „spezifische Absorptionsrate".

	Prostate Cancer		**Rectal Cancer**	
	Primary	**Recurrent**	**Primary**	**Recurrent**
T_{90} (°C)	40.7 ± 0.3	40.6 ± 0.8	40.2 ± 1.2	40.7 ± 0.4
T_{max} (°C)	41.4 ± 0.4	41.0 ± 0.7	41.4 ± 0.6	41.7 ± 0.5
Cummin T_{90} ≥ 40,5 °C (min)	179 ± 92	148 ± 138	110 ± 93	184 ± 85
SAR (W/kg)	31.9	21.9	36.3	30.8
P (W)	525	425	615	580
Rel. SAR (W/kg/100 W)	6.9	5.3	5.9	5.3
Mean toxicity (per treatment)	0.5	0.5	0.6	0.8
Maximal toxicity (per patient)	1.2	1.6	1.2	1.6

Table 3. Acute toxicity according to WHO and CTC (above). For the toxicity score of hyperthermia see text. Late toxicity (below) is scored according to LENT (late effects of normal tissues) [18].

Tabelle 3. Akute Toxizität gemäß WHO and CTC (oben). Toxizitätsgrade der Hyperthermie s. Text. Die Spättoxizität (unten) wurde nach dem LENT-Score klassifiziert (Spätwirkungen auf das Normalgewebe) [18].

Acute	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Rectum	2	10	7	3	–
Bladder/urethra	3	3	12	4	–
Intestine	12	5	4	1	–
Skin	5	15	2	–	–
Heat	1	8	12	1	–

Late	Grade 1	Grade 2	Grade 3/4
Gastroinestinal	2/20 (10%)	0	1/20 (5%)
Urogenital	1/20 (5%)	2/20 (10%)	0

patient was comparable for both tumor entities. However, tolerance was generally reduced in recurrent tumors. This corresponds to a higher total power and gained SAR in primary tumors compared with recurrences. Nevertheless, the temperatures achieved for recurrences are similar or even higher, which is probably based on a reduced perfusion and perfusion regulation capacity.

Table 2 illustrates that primary prostatic carcinomas are easier to heat than primary rectal carcinomas with higher relative SAR and T_{90} (for lower total power) [21, 23]. However, this is not the case for recurrent prostatic carcinoma as compared to recurrent rectal cancer (see Discussion).

Toxicity

Acute and late reactions are summarized in Table 3. Acute reactions were acceptable. Only 14% grade 3 reactions at the rectum, 18% at the urethra (dysuria), < 5% at the small intestine and hyperthermia-related (burn), respectively, were observed. Grade 2 reactions at the urethra or caused by heat (persistent hot spot sensations) are frequent (55%), but moderate urinary toxicity is common during radiotherapy. Persistent hot spots (muscle-skeletal pain syndrome) heal within a few days or, at most, several weeks without any late morbidity.

No correlation was observed between thermal parameters (T_{max}, T_{90}) and acute toxicity. Conversely, we even found a trend linking higher temperatures with less acute radio-induced toxicity. However, this might be explained by an increased tolerance for more aggressive heating in cases of less radio-induced toxicity.

Late reactions (see Table 3 below) were moderate. Follow-up was at least 24 months in 20 patients. Of these, only 5% had rectal toxicity grade 3 (with permanent loss of mucus and urgency) and 10% (n = 2/20) suffered from long-term urinary reactions grade 2 (intermittent urgency and dysuria). Our analysis showed no correlation between thermal parameters and chronic toxicity.

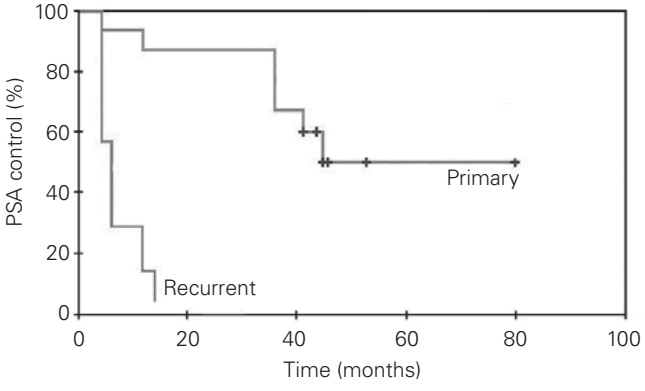

Figure 1. Survival under PSA control (ASTRO consensus, < 1 ng/ml) for primary carcinomas (15 patients) and recurrences (seven patients).

Abbildung 1. Überleben unter PSA-Kontrolle (ASTRO-Konsensus, < 1 ng/ml) bei primären Karzinomen (15 Patienten) und Rezidiven (sieben Patienten).

Follow-Up

A subdivision of the clinical events according to death, PSA failure, local progression, and distant metastases is shown in Table 4. During a median observation time of 6 years (42–80 months) only one patient deceased in the primary group and three patients in the recurrence group. Relapse-free survival (i.e., PSA control) is shown in Figure 1, and overall survival in Figure 2. We found a PSA control of about 50% after 6 years. Much less favorable was the PSA control for (macroscopic) recurrences, where PSA progression occurred in all patients after 18 months. However, local progression of a recurrence verified by ultrasound was only seen in one patient. In four of seven patients (57%) a salvage androgen ablation kept the progressive disease under control. One patient developed

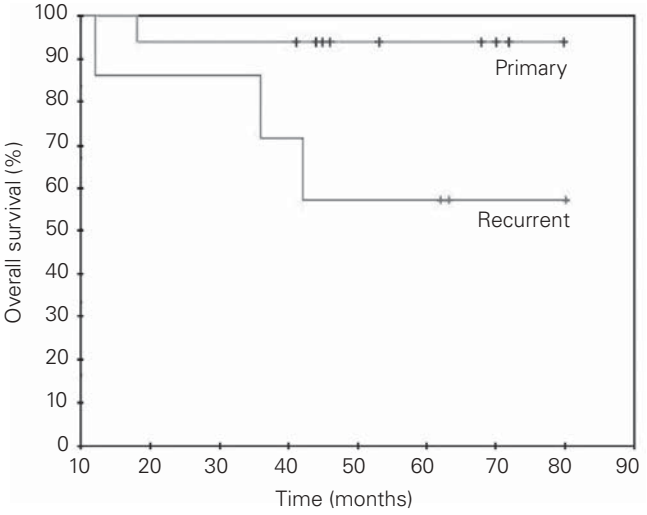

Figure 2. Overall survival for primary carcinomas and recurrences.

Abbildung 2. Gesamtüberlebenszeit bei primären und fortgeschrittenen Karzinomen.

early distant metastases of unproven origin and was excluded from the analysis of local control.

Overall survival after 6 years reached 95% in the primary group and about 60% in the recurrence group (Figure 2).

A clear correlation was found between the quality of heat treatments (T_{max}, T_{90}, cummin) and the PSA control according to Table 5. In the group with PSA control (n = 8) significantly higher temperatures and thermal doses were achieved (p-values of 0.01–0.02) in spite of the small number of patients. The best distinction was achieved for mean T_{max} (measured in the urethra). In fact, T_{max} was the only relevant predictive factor for PSA control with five local PSA failures for patients with $T_{max} < 41.2$ °C and only one PSA failure for $T_{max} \geq 41.2$ °C ($p = 0.037$, Mann-Whitney test).

Even though the (pretherapeutic) PSA value is well established as prognostic factor (see, e.g., [14]), the correlation between the initial PSA and the PSA control was not as high in this small group according to Table 5. Surprisingly, the thermal parameters are better correlated with the outcome than the pretreatment PSA values. For example, in the group with an initial PSA > 20 ng/ml, a PSA control of 33% is found as compared to 67% for a PSA ≤ 20 ng/ml ($p = 0.22$, Mann-Whitney test).

Table 4. Subdivision of the clinical endpoints in the follow-up of 22 patients with a mean observation time of 6 years (42–80 months).

Tabelle 4. Aufschlüsselung der klinischen Endpunkte bei 22 Patienten im Beobachtungszeitraum bei einer mittleren Beobachtungszeit von 6 Jahren (42–80 Monate).

	Alive	PSA progression	Local progression	Distant metastases
Primary n = 15	14	6	0	1
Recurrent n = 7	4	4	1	2

Discussion

We evaluated a regimen of a standard radiotherapy using moderate doses of 68.4 Gy in combination with regional hyperthermia, which causes low acute or late morbidity. Such a regimen appears feasible in order to improve outcome with a good therapeutic ratio.

Generally, long-term PSA control is unsatisfactory, if macroscopic infiltration of the periprostatic tissue is diagnosed by clinical criteria or imaging. The widespread therapeutic option was radiotherapy alone with radiation doses of 66–70 Gy resulting in a long-term PSA control of only 30% for observation times > 5 years [31]. PSA control in a similar range is achieved for high-risk tumors (e.g., T3/4) by other groups applying standard radiotherapy, e.g., a 5-year PSA control of 35% [28] or a 3-year PSA control of 60% [6]. Therefore, various approaches have been considered to enhance the effectiveness of the standard treatment.

In a large study, Zietman et al. [32] prescribed a tumor dose of 68.4 Gy, and found a biochemical control of < 40% after 5 years declining to < 20% after 10 years. Additional hormonal treatment was suggested for these cases (see [10] for a survey). Two RTOG trials addressing locally advanced prostate cancer are available. RTOG trial 85-31 [11] compared radiotherapy alone with radiotherapy plus long-term adjuvant hormonal treatment in patients with either lymphatic involvement (pN+) or clinical stage T3 (palpable tumor infiltration beyond the capsula). A large improvement of biochemical control was seen after 5 years (55% vs. 20%). RTOG trial 92-02, dealing with a patient group similar to ours (T2c–T4 tumors), found a biochemical control of 21% after 5 years in the reference arm with radiotherapy and neoadjuvant androgen suppression (2 months), while additional long-term androgen deprivation improved PSA control to 46% [8].

An EORTC trial [4] investigated a patient group of 415 men with locally advanced prostate cancer treated with either EBRT or radiotherapy and long-term androgen deprivation. This study exclusively showed a survival benefit for the combined treatment group of 79% versus 62%. Unfortunately, the biochemical control was not documented in this trial making a comparison with other studies difficult.

Another strategy to enhance the local effectiveness of standard radiotherapy is a dose escalation. These techniques mainly used intensity-modulated radiotherapy or high-dose-rate brachytherapy. Various studies have consistently confirmed a dose-response relationship for the PSA control.

Most dose escalation studies of prostatic carcinomas treat patients with T1–3 tumors, i.e., locally advanced carcinomas are only a small part of the whole patient group. Therefore, a

Table 5. Univariate analysis of thermal parameters correlates the effectiveness of the heat treatments with the major clinical endpoint PSA control (for primary prostatic carcinoma, 14 patients alive). The one patient with metastatic disease was excluded from the thermal analysis (n = 6), which can only characterize local PSA control, whereas the whole patient group is described by the initial PSA value (n = 7).

Tabelle 5. Univariate Analyse der thermischen Parameter zur Korrelation der Effektivität der Wärmebehandlungen mit der PSA-Kontrolle (beim primären Prostatakarzinom, 14 lebende Patienten). Der Patient mit metastasierender Erkrankung wurde aus der thermischen Analyse genommen (n = 6), da diese nur die lokale PSA-Kontrolle betrifft, während die gesamte Patientengruppe (n = 7) durch den initialen PSA-Wert beschrieben wurde.

	T_{90}	T_{max}	Cummin T_{90} ≥ 40.5 °C	PSA (initial)
PSA control (≤ 1 ng/ml) (n = 8)	40.8 °C	41.7 °C	202 ± 92 min	13.3 ng/ml
PSA progression (n = 6)	40.4 °C	40.9 °C	93 ± 35 min	26.6 ng/ml (n = 7)
p	0.013	0.010	0.020	0.18

proper selection of patients for such a comparison is difficult. Pollack et al. [15] performed a randomized dose escalation study (70 vs. 78 Gy) in 305 T1–T3 patients including 20% (60 patients) with T3. The 5-year PSA control for T3 carcinoma is comparable to our data (40%).

Radical prostatectomy, eventually combined with postoperative radiotherapy, might be the treatment option with maximum effectiveness. However, a summary of studies showed that the long-term biochemical control of the surgical approach is not superior to conservative treatments, achieving a PSA control of < 40% [19] and even with postoperative radiotherapy of only 57%. Complications and burden are not negligible for this radical treatment with long-term incontinence in 20–30% of patients, a postoperative morbidity around 30%, late urinary complications of 20–30%, and a surgery-related mortality of 0.5% [3].

From these data we may conclude, that a combined and/or more aggressive treatment strategy can improve the 5-year biochemical control of radiotherapy alone from 20–40% up to slightly > 50%. On the other hand, overall survival at 10 years is not depending on the treatment. It can be 80% (at 5 years) under favorable conditions, or 62% for radiotherapy alone [4]. In particular, surgery plus radiotherapy is not increasing survival as compared to other less aggressive procedures. Therefore, a careful evaluation of all treatment combinations with respect to toxicity is required.

In our small series we gained a long-term PSA control (> 5 years) of 50%, and an excellent overall survival of > 90% for primary locally advanced prostatic carcinoma T3 pN0. This is near the biochemical control achieved with the most aggressive regimens such as radiotherapy plus long-term androgen suppression or radical prostatectomy plus adjuvant radiotherapy. Therefore, regional hyperthermia appears to enhance the effectiveness of standard radiotherapy [9] as suggested in various trials of other tumor entities [30].

Remarkably, regional hyperthermia is very untoxic and is not increasing radiation-induced toxicity. This has already been shown in other prospective trials reported by Rau et al. or van der Zee et al. [17, 25]. In our study, the frequency of chronic side effects is only 10% for grade 3 urinary toxicity and 5% for grade 3 rectal toxicity. This is in the range (or even lower) what we would expect from radiotherapy at a standard dose of 70 Gy. The acute hyperthermia-specific toxicity is acceptable to the patients and, in every case, reversible. No long-term toxicity can be addressed to hyperthermia. Therefore, hyperthermia might increase efficacy, but is not increasing toxicity.

In a study including 26 patients, van Vulpen et al. [26] added either interstitial or regional hyperthermia. They found – after a shorter observation time – a 3-year biochemical control of 70%, which is fairly in agreement with our data (see Figure 1). Anscher et al. [2] performed an earlier study in 18 patients adding regional hyperthermia to a standard radiotherapy regimen. The 3-year biochemical control was only 25%, which looks worse as compared to our results. However, the distribution of prognostic factors was more unfavorable in this patient group. In particular, the average pretreatment PSA value was much higher (38 ng/ml in the work of Anscher et al. [2] versus 17 ng/ml in our study).

Conclusion

Regional hyperthermia is a very feasible and well-tolerated procedure, which might increase the local effectiveness of radiotherapy or any combination therapy against locally advanced prostate cancer. Regional hyperthermia might further enhance the effectiveness of more aggressive treatments such as radiotherapy plus long-term androgen suppression or dose-escalated EBRT. Then, a long-term PSA control better than 50–60% is expected. Regional hyperthermia might as well replace dose-intensifying modules of higher toxicity. For example, standard radiotherapy plus regional hyperthermia might be as effective as standard radiotherapy plus long-term androgen suppression or a dose-escalated schedule, but less burdensome (or less expensive). Further investigations in a randomized study are highly desirable.

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References

1. Aebersold DM, Isaak B, Thalmann G, et al. Applicability and dosimetric impact of ultrasound-based preplanning in high-dose-rate brachytherapy of prostate cancer. Strahlenther Onkol 2004;180:351–7.
2. Anscher MS, Samulski TV, Dodge R, et al. Combined external beam irradiation and external regional hyperthermia for locally advanced adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys 1997;37:1059–65.
3. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002;346:1138–44.
4. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300.
5. De Meerleer G, Vakaet L, De Gersem W, et al. Direct segment aperture and weight optimization for intensity-modulated radiotherapy of prostate cancer. Strahlenther Onkol 2004;180:136–43.
6. Geinitz H, Zimmermann F, Wedel E von, et al. Biochemische Kontrolle nach konformaler, dreidimensionaler Strahlentherapie des Prostatakarzinoms. Strahlenther Onkol 2002;178:369–77.
7. Gellermann J, Wlodarczyk W, Ganter H, et al. A practial approach to perform the thermography in a hyperthermia/MR hybrid system – validation in an anthropomorphous phantom. Int J Radiat Oncol Biol Phys 2005;61: in press.
8. Hanks GE, Lu JD, Machtay M, et al. RTOG protocol 92-02: a phase III trial of the use of long term total androgen suppression following neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2000;48:Suppl:112.
9. Hildebrandt B, Wust P, Ahlers O, et al. The cellular and molecular basis of hyperthermia. Crit Rev Oncol Hematol 2002;43:33–56.
10. Lawton CA. Hormones and radiation therapy in locally advanced adenocarcinoma of the prostate. Semin Radiat Oncol 2003;13:141–51.
11. Lawton CA, Winter K, Murray K, et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavourable prognosis carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001;49:937–46.

12. Lerner SE, Blute ML, Zincke H. Extended experience with radical prostatectomy for clinical stage T3 prostate cancer: outcome and contemporary morbidity. J Urol 1995;154:1447–52.
13. Martin T, Baltas D, Kurek R, et al. 3-D conformal HDR brachytherapy as monotherapy for localized prostate cancer. A pilot study. Strahlenther Onkol 2004;180:225–32.
14. Mayer R, Pummer K, Quehenberger F, et al. Analysis of competing risk parameters in irradiated prostate cancer patients. Strahlenther Onkol 2003; 179:452–6.
15. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: Results of the M.D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002;53:1097–105.
16. Overgaard J, Gonzalez-Gonzalez D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. Lancet 1995;345:540–3.
17. Rau B, Wust P, Tilly W, et al. Preoperative radio-chemotherapy in locally advanced recurrent rectal cancer: regional radiofrequency hyperthermia correlates with clinical parameters. Int J Radiat Oncol Biol Phys 2000; 48:381–91.
18. Rubin P, Constine L, Fajardo L. Overview: late effects of normal tissues (LENT) scoring system. Int J Radiat Oncol Biol Phys 1995;31:1041–2.
19. Skinner EC, Glode LM. High-risk localized prostate cancer: primary surgery and adjuvant therapy. Urol Oncol 2003;21:219–27.
20. Skwarchuk MW, Jackson A, Zelefsky MJ, et al. Late rectal toxicity after conformal radiotherapy of prostate cancer (I): mutivariate analysis and dose-response. Int J Radiat Oncol Biol Phys 2000;47:103–13.
21. Sreenivasa G, Gellermann J, Rau B, et al. Clinical application of the hyperthermia treatment planning system HyperPlan – comparison of algorithms and clinical observables. Int J Radiat Oncol Biol Phys 2003;55:407–19.
22. Storey MR, Pollack A, Zagars G, et al. Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys 2000;48:635–42.
23. Tilly W, Wust P, Rau B, et al. Temperature data and specific absorption rates in pelvic tumours: predictive factors and correlations. Int J Hyperthermia 2001;17:172–88.
24. Van den Ouden D, Hop WC, Schroder FH. Progression and survival of patients with locally advanced prostate cancer (T3) treated with radical prostatectomy as monotherapy. J Urol 1998;160:1392–7.
25. Van der Zee J, Gonzalez Gonzales D, van Rhoon GC, et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumors: a prospective, randomised, multicentre trial. Lancet 2000; 355:1119–25.
26. Van Vulpen M, De Leeuw AAC, Raaymakers BW, et al. Radiotherapy and hyperthermia in the treatment of patients with locally advanced prostate cancer: preliminary results. BJU International 2004:93;36–41.
27. Vernon C, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. Int J Radiat Oncol Biol Phys 1996;35:731–44.
28. Wachter-Gerstner N, Wachter S, Goldner G, et al. Biochemical response after 3-D conformal radiotherapy of localized prostate cancer to a total dose of 66 Gy. Strahlenther Onkol 2002;178:542–7.
29. Wust P, Gellermann J, Harder C, et al. Rationale for using invasive thermometry for regional hyperthermia of pelvic tumors. Int J Radiat Oncol Biol Phys 1998;41:1129–37.
30. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in a combined treatment of cancer. Lancet Oncol 2002;3:487–97.
31. Zagars GK, Pollack A, Smith LG. Conventional external-beam radiation therapy alone or with androgen ablation for clinical stage III (T3, Nx/N0, M0) adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys 1999;44: 809–19.
32. Zietman AL, Coen JJ, Dallow KC, et al. The treatment of prostate cancer by conventional therapy: an analysis of long-term outcome. Int J Radiat Oncol Biol Phys 1995;32:287–92.

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