Strahlentherapie
und Onkologie

Originalarbeit

3D Interstitial HDR Brachytherapy Combined with 3D External Beam Radiotherapy and Androgen Deprivation for Prostate Cancer

Preliminary Results

Thomas Martin[1], Silla Hey-Koch[1], Gerd Strassmann[1], Christos Kolotas[1], Dimos Baltas[1,2], Bernd Rogge[1], Sandra Röddiger[1], Hans-Georg Vogt[1], Reinhard Heyd[1], Thomas Dannenberg[3], Ralf Kurek[3], Ulf Tunn[3], Nikolaos Zamboglou[1,2]

Background: Evaluation of feasibility, tolerance and efficiency for a new 3D interstitial HDR brachytherapy technique combined with 3D external beam radiotherapy and androgen deprivation for prostate cancer.
Patients and Methods: Between January 1997 and August 1998 we treated 35 patients with Stage cT1–3 N0 M0 prostate cancer. Thirty-two patients with a follow-up of 12 to 28 months (median: 18 months) were evaluated. After ultrasound-guided transrectal implantation of 4 non-parallel needles, CT based 3D brachytherapy treatment planning ("Offenbach system") was performed. All patients received 4 fractions brachytherapy using a fractional dose of 5 or 7 Gy. Time between each fraction was 14 days. After brachytherapy 3D external irradiation followed up to 39.6 or 45.0 Gy. All patients received androgen deprivation, starting 2 to 19 months before brachytherapy, ending 3 months after 3D external radiotherapy.
Results: Posttreatment PSA levels dropped to <1.5 ng/ml in 29/32 patients (91%). In 25 patients PSA levels were < 0.5 ng/ml, in 4 patients 0.5 to 1.5 ng/ml. In 2 patients we noted biochemical relapse. Transrectal implantation was very well tolerated. Grade 3 acute urinary toxicity occurred in 1 patient. We noted no Grade 2 or higher acute gastrointestinal toxicity. One patient developed a Grade 3 late urinary toxicity. No patient showed late gastrointestinal side effects. All 140 dose-volume histograms for 3D HDR brachytherapy were analyzed.
Conclusions: The new 3D HDR brachytherapy technique, combined with 3D external irradiation and androgen deprivation, is a feasible, so far well tolerated and effective treatment in the short-time follow-up of median 18 months.

Key Words: Prostate cancer · HDR brachytherapy · 3D external beam radiotherapy · Androgen deprivation · Dose-volume histograms

Interstitielle 3D-HDR-Brachytherapie kombiniert mit externer 3D-Radiotherapie und Androgendeprivation beim Prostatakarzinom: Erste Ergebnisse

Hintergrund: Auswertung der Praktikabilität, Verträglichkeit und Effektivität einer neuen interstitiellen 3D-HDR-Brachytherapie-Technik, kombiniert mit externer 3D-Radiotherapie und Androgendeprivation beim Prostatakarzinom.
Patienten und Methoden: Von Januar 1997 bis August 1998 behandelten wir 35 Patienten mit Prostatakarzinomen im Stadium cT1–3 N0 M0. Die Daten von 32 Patienten mit einer Nachbeobachtungszeit von zwölf bis 28 Monaten (median: 18 Monate) wurden ausgewertet. Nach ultraschallgesteuerter transrektaler Implantation von vier nicht parallelen Nadeln erfolgte die CT-gestützte 3D-Brachytherapie-Planung („Offenbach-System"). Alle Patienten erhielten vier Fraktionen der 3D-Brachytherapie mit einer Einzeldosis von 5 oder 7 Gy im Abstand von jeweils 14 Tagen. Anschließend erfolgte die externe 3D-Radiotherapie bis 39,6 oder 45,0 Gy. Alle Patienten erhielten zusätzlich eine Androgendeprivation, die zwei bis 19 Monate vor der Brachytherapie eingeleitet und drei Monate nach Abschluss der externen Radiotherapie abgesetzt wurde.
Ergebnisse: Bei 29/32 Patienten (91%) sank der posttherapeutische PSA-Wert unter 1,5 ng/ml, davon bei 25 Patienten auf unter 0,5 ng/ml, bei vier Patienten auf 0,5 bis 1,5 ng/ml. Zwei Patienten entwickelten ein biochemisches Rezidiv. Die

[1]Strahlenklinik, Städtische Kliniken Offenbach, Germany,
[2]Institute of Communication and Computer Systems, National Technical University of Athens, Athens, Greece,
[3]Urologische Klinik, Städtische Kliniken Offenbach, Germany.

Submitted: 7 Feb 2000; accepted: 12 May 2000.

transrektale Implantation wurde sehr gut toleriert. Ein Patient entwickelte akute Grad-3-Toxizitäten des Harntraktes, kein Patient akute gastrointestinale Nebenwirkungen größer als Grad 1. Eine Grad-3-Spättoxizität des Harntraktes zeigte ein Patient, gastrointestinale Spättoxizitäten entwickelte kein Patient. Alle 140 Dosis-Volumen-Histogramme der 3D-HDR-Brachytherapie wurden ausgewertet.

Schlussfolgerung: Die neue 3D-HDR-Brachytherapie-Technik, kombiniert mit externer 3D-Radiotherapie und Androgendeprivation, stellt eine praktikable, bisher gut verträgliche und effektive Therapiemodalität nach Kurzzeitnachbeobachtung von median 18 Monaten dar.

Schlüsselwörter: Prostatakarzinom · HDR-Brachytherapie · Externe 3D-Radiotherapie · Androgendeprivation · Dosis-Volumen-Histogramme

Prostate cancer is one of the major health problems in Europe and the United States. It is now the most commonly diagnosed carcinoma in older men and the second leading cause of male cancer deaths in Germany [21]. The incidence of localized prostate cancer has significantly increased in the last 10 years as a result of public awareness and improved early detection methods.

Curative treatment options for localized stages include radical prostatectomy, external beam radiotherapy (EBRT) and interstitial brachytherapy. Radical prostatectomy is still the standard therapy option for localized prostate cancer in Germany. However, the American Prostate Cancer Guidelines Panel has analyzed all available literature data on radiation and surgical treatment series and concluded that "there was no clear-cut evidence for the superiority of any one treatment" [18]. For external beam radiation the survival rates were comparable with radical prostatectomy for similar stages [3]. With the introduction of the routinely use of posttreatment PSA level and postradiation biopsies it has been shown that permanent eradication of prostate cancer after external beam radiation is not achieved as often as previously believed [22, 24]. There exists a clear dose-response relationship for the local control of prostatic cancer, and also for late toxicities [11]. Dose escalation trials performing 3D conformal EBRT alone are currently underway to determine the optimal increase in radiation dose to the prostate without increasing late side effects.

Interstitial brachytherapy is the alternative conformal treatment modality with the possibility to deliver a high dose precisely to the prostate gland and to spare at the same time organs at risk because of the steep dose gradient. Transperineal low-dose rate (LDR) brachytherapy using permanent implants of iodine-125 or palladium-103 seeds has been introduced in the 1980s. But LDR brachytherapy is indicated only in patients with organ confined disease, a low initial PSA level and a low Gleason score because of inherent technical and radiobiological problems. In the 1990s high-dose rate (HDR) brachytherapy using temporary Ir-192 implants has become a well established conformal treatment combined with 3D conformal EBRT [1, 13, 23]. Transrectal ultrasound (TRUS) guided transperineal implantation under spinal anesthesia is the standard implantation technique today. The dose-planning procedure for transperineal HDR brachytherapy is commonly based on ultrasound images of the prostate before and after implantation.

In our department we routinely use computed tomography (CT) for HDR brachytherapy planning in order to image the target volume and also the adjacent critical structures [12, 27]. Using the PROMETHEUS software the 3D reconstruction and conformal dose planning of HDR implants with non-parallel configured applicators is possible [4]. Based on this 3D planning approach, we introduced the new transrectal implantation technique for prostate brachytherapy, followed by 3D external beam radiotherapy [16]. Additionally we have integrated neoadjuvant and adjuvant androgen deprivation in our treatment concept with the aim to achieve a significant volume reduction of the prostate gland before brachytherapy and to increase the efficiency using the combined modality [6, 26].

In this publication we report the combined treatment modality, including our new prostate brachytherapy technique, and the preliminary results in 35 patients with localized adenocarcinoma of the prostate.

Patients and Methods

Patients

Between January 1997 and August 1998 a total of 35 patients with localized prostate cancer, without distant and lymph node metastases, were treated in our department using the combination of 3D interstitial HDR brachytherapy, 3D external beam irradiation and androgen deprivation. The mean age of the patients was 69 years (range 57 to 78 years).

Pretreatment investigations included digital rectal examination, transrectal ultrasound and serum PSA level. Lymph node metastases were excluded by CT or MRI of the pelvis. Skeletal metastases were excluded by bone scanning. The patients were clinically staged according to the TNM classification system of 1997 (UICC). All histopathology results were based on TRUS-guided core biopsy material. The WHO classification system was used for the histopathological differentiation. Pretreatment serum PSA levels ranged from 3.5 to 268.5 ng/ml (median: 16.7 ng/ml). All patient characteristics are given in Table 1.

Thirty-two of the 35 patients were eligible for the evaluation of toxicity and biochemical control. Three patients died because of intercurrrent diseases. Follow-up examinations included digital rectal examination, TRUS and serum PSA level on a 3-monthly basis during the first posttreatment year and thereafter every 6 months.

Methods

Androgen Deprivation: All patients received different hormonal treatments for neoadjuvant androgen deprivation prior to interstitial brachytherapy. LHRH agonists were

Characteristics	No. of patients
Stage	
cT1	2
cT2	24
cT3	6
Grading	
G1	10
G2	17
G3	5
Pretreatment PSA level (ng/ml)	
<10	9
10–20	13
>20	10

Table 1. Patients characteristics (n = 32).

Tabelle 1. Patientencharakteristika (n = 32).

used in 21 patients, antiandrogens in 8 patients and maximum androgen blockade in 6 patients. Neoadjuvant androgen deprivation times varied between 2 and 19 months. Hormonal treatment continued in all patients for adjuvant androgen deprivation simultaneously to brachytherapy and external beam irradiation and was stopped 3 months after external beam radiotherapy.

3D Interstitial HDR Brachytherapy: All patients received 4 fractions of 3D interstitial HDR brachytherapy in 6 weeks. The time between each fraction was 14 days. For the transrectal implantation procedure the patient was placed in lithotomy position and received an antibiotic prophylaxis using 120 mg Gentamycin. 50 mg Pethidin iv and 5 mg Midazolam iv were given for a sedation analgesic premedication.

The new transrectal implantation technique for HDR brachytherapy was performed in a similar way as the technique for transrectal prostate biopsy. Inserting the 7.5 MHz transrectal ultrasound probe (B+K 8551), the monitor displays a dotted line on the longitudinal image of the prostate. The dotted line represents the projected course of the afterloading needle through the rectal wall into the prostate. One single needle was then inserted through the transducers needle guide until it was visible on the monitor and implanted within the prostate. The ultrasound probe was then removed and used again for the next needle implantation. Four needles per implant were the standard number for the transrectal implantation technique. Two crossing needles were implanted in the upper and lower left and 2 crossing needles in the upper and lower right periphery of the gland. The typical needle configuration is shown in Figure 1. After implantation, urethro-cystoscopy was performed, a silicone Foley catheter was inserted and the bladder was partially filled with diluted contrast medium.

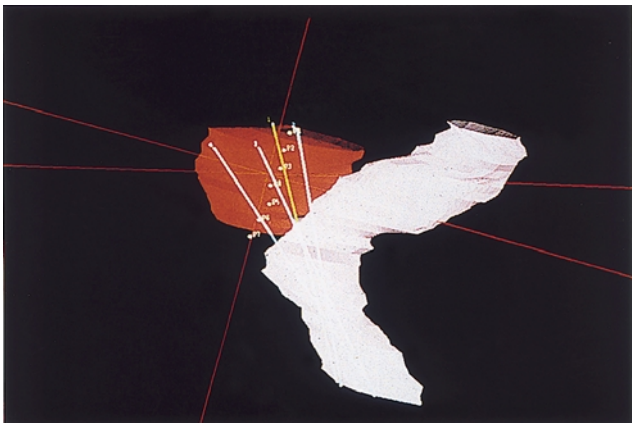

Figure 1. Configuration of the 4 non-parallel needles within the prostate after TRUS-guided transrectal implantation for 3D interstitial HDR brachytherapy.

Abbildung 1. Anordnung der vier nicht parallelen Nadeln in der Prostata nach TRUS-gesteuerter transrektaler Implantation für die interstitielle 3D-HDR-Brachytherapie.

Directly after the implantation procedure, a spiral CT scan of the prostate region was performed (0.3 cm step, 0.3 cm slice thickness) and sent on-line via network to the PLATO BPS planning workstation to the PLATO BPS planning workstation (Nucletron B.V., Veenendaal, The Netherlands). The contours of the planning target volume (PTV) and the critical tissues (urethra, rectum) were defined on all CT slices. The PTV was defined as the whole prostate gland.

In the next step we reconstructed the 4 non-parallel needles using the CT-reconstruction module of the PLATO BPS system. On the PTV surface, equidistant dose points were generated to calculate the mean dose value, which is also specified as the reference dose. The active dwell positions were defined and it was ensured that all of them laid within the PTV. For 3D dose optimization the dose distribution was normalized relatively to the mean value of the calculated dose values on the PTV surface. The reference dose was defined as the 100% value.

For the evaluation of the dose distribution we routinely used dose-volume histograms (DVH) for the PTV and the normal tissues. All isodose lines of interest were built up on the CT slices and evaluated within and surrounding the prostate and within all critical structures. The PTV and the anatomical structures were documented as a three-dimensional image, including the 3D dose distribution. Using various options we could evaluate this 3D image in all sections, including rotation, zooming and changing the degree of transparency of the objects (Figure 2).

HDR brachytherapy was given using a dose per fraction of 5 or 7 Gy specified as described above. The choice of the fractional dose was made following assessment of the DVHs and depended on the maximum and mean doses to the critical organs. A dose of 5 Gy was given in 46 implants and a dose of 7 Gy in 82 implants. Giving 4 fractions per patient we reached a total HDR brachytherapy dose of 20 Gy in 3/35, 22 Gy in 4/35, 24 Gy in 12/35, 26 Gy in 6/35 and 28 Gy in 10/35 patients.

3D External Beam Radiotherapy: Two weeks after the last HDR brachytherapy fraction 3D external beam irradiation started. All patients were treated in a 4-field box technique with individual shaped blocks using 23 MV photon beams from a linear accelerator. A CT based conformal 3D dose plan was created individually for each patient. The PTV was defined as the prostate gland plus the seminal vesicles with a margin of 1.5 cm around. External beam irradiation was given using a fractionation of 5 times 1.8 Gy per week, specified at the isocenter. The EBRT dose was 39.6 Gy, if the brachy-

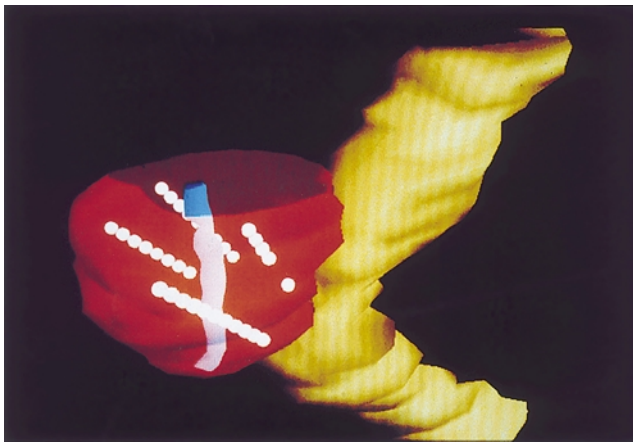

Figure 2. PTV (= prostate), rectum and urethra documented in a CT-based 3D image, including the optimized HDR source positions.

Abbildung 2. Dokumentation von PTV (= Prostata), Rektum und Urethra als dreidimensionale Abbildung auf CT-Basis, inklusive der optimierten Haltepositionen der HDR-Quelle.

therapy dose was 26 to 28 Gy or 45.0 Gy, if brachytherapy dose was 20 to 24 Gy.

Results

The median follow-up at the time of evaluation of posttreatment PSA level and toxicity was 18 months (range 12 to 28 months).

Biochemical Control

The posttreatment PSA levels dropped to less than 1.5 ng/ml in 29/32 patients (91%). PSA levels of 25 patients were less than 0.5 ng/ml (78%) and PSA levels of 4 patients were 0.5 to 1.5 ng/ml (13%).

In 3/32 patients (9%) we noted rising PSA levels at 11, 12 and 12 months after therapy. One patient showed only 1 single rise and 2 patients showed 3 consecutive rises of PSA >1.5 ng/ml. The distribution of the posttreatment PSA levels is given in Table 2.

According to the definition of biochemical failure after radiotherapy of the ASTRO Consensus Panel [2] we noted 2/32 patients (6%) with biochemical relapse in our series. In 1 of the 2 patients we found a histopathologically proven local progression without metastasis. The other patient presented no clinical evidence of persistent or recurrent tumor or distant metastasis.

Posttreatment PSA level	No. of patients (%)
< 0.5 ng/ml	25 (78%)
0.5–1.5 ng/ml	4 (13%)
One PSA rise	1 (3%)
PSA relapse (3 consecutive rises)	2 (6%)

Table 2. Posttreatment PSA levels after a median follow-up of 18 months (range: 12 to 28 months).

Tabelle 2. Posttherapeutische PSA-Werte nach medianer Nachbeobachtungszeit von 18 Monaten (Range: zwölf bis 28 Monate).

Toxicity

The transrectal implantation procedure was very well tolerated by all patients under sedation analgesic premedication. We noted no serious bleeding or acute complications during any of the implantations. One of the 35 patients developed a periprostatic hematoma 2 days after implantation which required surgical intervention, but he could continue with brachytherapy 2 weeks later.

Acute side effects were evaluated according to the RTOG/EORTC toxicity criteria. Most patients experienced increased frequency of micturition and mild or moderate dysuria (Grade 1 to 2) following HDR brachytherapy and during external beam irradiation. Urinary retention requiring suprapubic catheterization (Grade 3) occurred in 1 patient, lasting 2 weeks. No patient showed Grade 2 or higher gastrointestinal side effects. We noted no rectal infection.

Late side effects were evaluated according to the LENT-SOMA score criteria. Three patients experienced persistent dysuria as a Grade 2 late urinary toxicity. One patient developed a radiation cystitis with bladder stricture (Grade 3) requiring endoscopic operation. No patient showed late gastrointestinal side effects. We noted no proctitis, no rectal bleeding and no fistula. The distribution of the side effects is given in Table 3.

Analysis of Dose-Volume Histograms in HDR Brachytherapy

We routinely used DVHs for each brachytherapy fraction to evaluate and document the quality of the conformal interstitial implants. We have analyzed all 140 DVHs in our series for the coverage of the PTV by the reference dose, for the maximum and mean doses to the rectum and the maximum and mean doses to the urethra. The mean values of this DVH analysis are given in Table 4.

Toxicity	No. of patients
Acute urinary	
Grade 1	8
Grade 2	3
Grade 3	1
Acute gastrointestinal	
Grade 1	6
Grade 2	0
Grade 3	0
Late urinary	
Grade 1	2
Grade 2	3
Grade 3	1
Late gastrointestinal	
Grade 1	0
Grade 2	0
Grade 3	0

Table 3. Acute (RTOG/EORTC toxicity criteria) and late (LENT-SOMA score criteria) toxicities after a median follow-up of 18 months (range: 12 to 28 months).

Tabelle 3. Akut- und Spättoxizität nach einer medianen Nachbeobachtungszeit von 18 Monaten (Range: zwölf bis 28 Monate).

n = 140	Mean value
PTV coverage by the reference dose	82% (range: 73–89%)
Maximum rectal dose	7.7 Gy (range: 5.9–11.6 Gy)
Mean dose to the whole rectum	1.8 Gy (range: 1.2–2.4 Gy)
Maximum urethral dose	15.3 Gy (range: 9.6–25.2 Gy)
Mean dose to the whole urethra	8.7 Gy (range: 5.3–11.5 Gy)

Table 4. Analysis of 140 dose-volume histograms for 3D interstitial HDR brachytherapy. Mean values for the PTV coverage by the reference dose and the maximum and mean doses to rectum and urethra.

Tabelle 4. Analyse von 140 Dosis-Volumen-Histogrammen der interstitiellen 3-D-HDR Brachytherapie. Mittelwerte für die Erfassung des Planungszielvolumens durch die Referenzdosis sowie für die maximale und mittlere Dosisbelastung von Rektum und Urethra.

Discussion

The surgical treatment of localized prostate cancer using radical prostatectomy still remains one of the most effective therapies with 10-year survival rates of 65 to 77% in Stages T1/T2 and 38% in Stage T3 [19, 29]. However, postoperative complications of impotency, urinary incontinence, and a relatively high incidence of positive surgical margins, are obviously disadvantages of the surgical approach [10].

Conventional external beam radiotherapy of Stage T1/T2 prostate cancer, delivering total doses below 70 Gy, results in survival rates of 59% at 10 years, reported by Bagshaw et al. [3]. For locally advanced stages Perez et al. [20] reported 5-year survival rates of 56%. Toxicity rates of 3.3% for Grade 3 gastrointestinal side effects and 7.7% for late Grade 3 urinary side effects were reported after conventional external beam irradiation treatment [15].

To improve local control and survival rates after definitive radiotherapy, an increasing of the total radiation dose can be considered, but an increased external beam dose will at the same time increase the toxicity rate. Therefore, a significant increase in radiation dose to the prostate can only be accomplished by performing a conformal radiotherapy technique.

3D conformal EBRT produces an optimal dose distribution by conforming the dose maximally to the target with a dose reduction to the surrounding organs. The preliminary results of dose escalation trials using 3D conformal EBRT are encouraging. PSA relapse-free survival was significantly improved compared to conventional EBRT [28]. This seems to be a promising conformal approach, but long-term results of local control, survival and late side effects are not yet available.

Interstitial brachytherapy is another attractive conformal treatment modality which aims to improve the treatment outcome in localized prostate cancer. LDR brachytherapy using permanent implants of iodine-125 or palladium-103 seeds has been used in the last 30 years and became more and more popular in the United States with more than 10,000 treated patients in 1996. Blasko et al. [5] reported a 5-year biochemical control rate of 93% and a 5-year disease-specific survival of 100% in 320 patients with Stage T1/T2, Gleason <6 and median initial PSA level of 7.9 ng/ml treated with iodine-125 seeds. Critz et al. [8] reported favorable results using the combination of permanent iodine-125 implants and external beam radiotherapy. Although improvements have been made in the implantation technique and dose planning of permanent seeds during the last decade by using the ultrasound guided transperineal approach, it is radiobiological less desirable and contraindicated in locally advanced tumors, high initial PSA level and in patients with prior transurethral resections.

Transperineal HDR brachytherapy using temporary Ir-192 implants combined with external beam radiotherapy was established in the 1990s for the conformal treatment of prostate cancer. Kovacs et al. [14] reported in a large series of 171 patients an excellent local control rate of 89% for T1/T2 and 85% for T3 Stages using 2 HDR brachytherapy fractions of each 15 Gy combined with 50 Gy of EBRT. Borghede et al. [7] and Dinges et al. [9] reported promising preliminary results of transperineal HDR brachytherapy combined with EBRT. Borghede et al. [7] treated patients with 50 Gy of external irradiation combined with 2 HDR fractions of each 10 Gy, Dinges et al. [9] treated with 45 Gy of EBRT combined with 2 HDR fractions of each 9 Gy. The North American groups of Stromberg et al. and Syed et al. reported encouraging results using new fractionation schemes. Stromberg et al. treated 33 patients with 45 Gy EBRT and 3 HDR implants of 5.5 to 6 Gy performed during week 1, 2 and 3 of external radiation. PSA levels normalized in 91% of the patients with 9% acute Grade 3 side effects in a median follow-up of 13 months. Martinez at al. [17] updated this series with similiar results. Syed et al. [25] performed 4 fractions of HDR brachytherapy during 48 hours to a total dose of 20 to 22 Gy followed by 39.6 Gy external radiotherapy. All 40 patients showed posttreatment PSA levels below 4 ng/ml in median follow-up of 12 months. In this series no Grade 3 or higher toxicities were noted.

Based on these experiences and encouraged by these results we have created and introduced a new technique of implantation and treatment planning for HDR brachytherapy of prostate cancer. Using the new transrectal implantation approach, we implanted the 4 non-parallel needles in a technique routinely used and well known by most urologists for prostate biopsy. This transrectal implantation procedure was very well tolerated by all patients using only sedation analgesic premedication and took only 10 to 15 minutes. General or spinal anesthesia was not required. A template for parallel needle implantation was not necessary and neither a larger number of needles.

We evaluated relatively high doses around the 4 needles and a non-homogeneous dose distribution within the prostate. But the mean value for the reference dose covering the PTV was 82% in our series and the high-dose regions of 200 or 300% of the reference dose were within the prostate, where the tumor cells are located. In the same time we were able to keep the intraprostatic urethra outside of these high-dose regions. In our series the mean value for the maximum dose to the urethra was 15.3 Gy per fraction, but this dose was delivered only to less than 0.5% of the volume of the whole urethra, which we could prove by using dose-volume histograms. The value for the mean dose to the whole urethra was 8.7 Gy per fraction, which is below the assumed tolerance level of this organ (see Table 4).

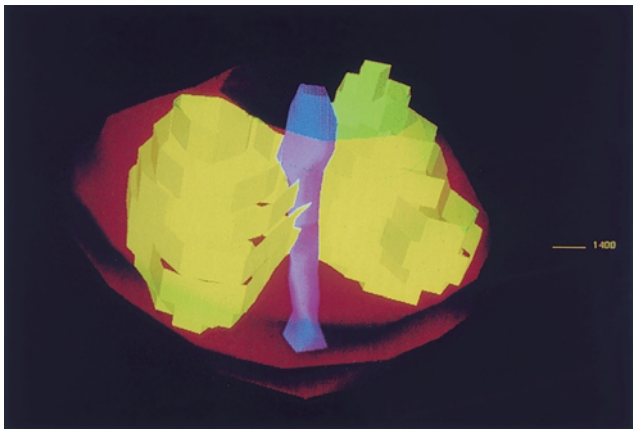

Figure 3. 3D evaluation of the dose distribution. 3D documentation of the 200% isodose (reference dose = 7 Gy) inside the PTV in relation to the intraprostatic urethra.

Abbildung 3. Dreidimensionale Evaluation der Dosisverteilung. 3D-Dokumentation der 200%-Isodose (Referenzdosis = 7 Gy) innerhalb des PTV in Bezug zur intraprostatischen Urethra .

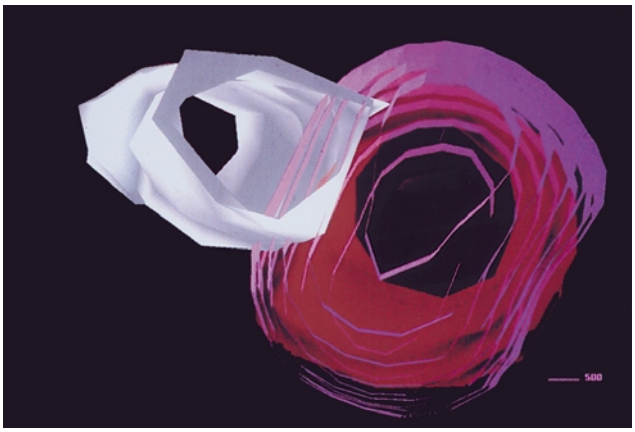

Figure 4. 3D evaluation of the dose distribution. 3D documentation of the 100% isodose (reference dose = 5 Gy) on the PTV surface in relation to the rectal wall.

Abbildung 4. Dreidimensionale Evaluation der Dosisverteilung. 3D-Dokumentation der 100%-Isodose (Referenzdosis = 5 Gy) auf der Oberfläche des PTV in Bezug zur Rektumwand.

It is not the aim of 3D conformal brachytherapy to achieve a high degree of dose homogeneity within the prostate, but to achieve precisely an effective dose to the tumor cells and to spare at the same time the critical tissues within and surrounding the prostate. To achieve this aim with only 4 non-parallel needles, we used a CT based system for 3D brachytherapy planning ("Offenbach system"). We therefore did not require pre-planning procedures or radiographs for localizing the needles. Based on a spiral CT scan we reconstructed the non-parallel needles, defined an individual planning target volume, optimized the 3D dose distribution and immediately evaluated the conformal quality of the HDR implant. For each of the 140 brachytherapy fractions, we used 3D documentation of anatomy and dose distribution, including DVHs (Figures 3 and 4).

The biological equivalent dose (BED) of the combined treatment is difficult to estimate because of the problems encountered when adding brachytherapy to external beam doses. However, the LQ model was used to transform the high single doses of brachytherapy to a series of 5 times weekly 2 Gy fractions. The brachytherapy dose per fraction was 5 or 7 Gy at each of the 4 sessions. Using an α/β-value of 10 Gy for the prostate tissue we reached a BED of 25 and 40 Gy, respectively. In addition to the external beam doses, these resulted in a total BED of 70.0 or 79.6 Gy to the surface of the PTV. Alternatively, using an α/β-value of 6 Gy for highly differentiated prostate cancer cells we reached an even higher total BED of 72.5 or 85.1 Gy. Within the prostate we documented regions receiving 200% of the reference dose. For these high-dose regions, receiving 10 or 14 Gy per fraction, we reached a total BED of 125.0 and 179.6 Gy, respectively.

The median follow-up time after the combined treatment is currently 18 months with a range of 12 to 28 months. In this time we have noted in only 1 patient acute Grade 3 urinary side effects. Mild or moderate dysuria in the posttreatment period was reported by 11/32 patients, but only 1 showed persistent dysuria. Furthermore, we noted no acute Grade 2 or higher gastrointestinal side effects. In the still limited follow-up time of 12 to 28 months no patient experienced an urethral necrosis or stricture. In our series we noted no late gastrointestinal side effects, especially no rectal bleeding and no rectal fistula.

We noted only 2 patients with a biochemical relapse in our series. Both patients had locally advanced T3 tumors and initial PSA levels >20 ng/ml as high-risk pretreatment prognostic factors. The efficiency of our combined conformal treatment with an initial response of normalized posttreatment PSA levels in 91% of the patients is promising.

Conclusions

The new approach of transrectal implantation and CT-based 3D treatment planning for 3D interstitial HDR brachytherapy of localized prostate cancer, combined with 3D external beam irradiation and androgen deprivation, is a feasible and so far well tolerated modality in the short-time follow-up of median 18 months. Of course, a longer follow-up time is needed for a definite evaluation of radiation induced long-term complications.

It seems to be an effective conformal treatment based on the encouraging rate of normalization of PSA levels. The simplicity of the transrectal implantation technique and CT based 3D planning procedure, requiring no intensive costs and human resources, and the short treatment times are also economic advantages of this new HDR brachytherapy technique for prostate cancer.

References

1. Andreopoulos D, Piatkowiak M, Krenkel B, et al. Die kombinierte Behandlung des lokal begrenzten Prostatakarzinoms mit HDR-Iridium-192-Nachlade-Brachytherapie und perkutaner Bestrahlung. Strahlenther Onkol 1999;175:387–91.
2. ASTRO Consensus Panel. Consensus statement: Guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys 1997;37:1035–41.
3. Bagshaw MA, Cox RS, Ramback JE. Radiation therapy for localized prostate cancer: justification by long-term follow-up. Urol Clin North Am 1990;17:787–802.
4. Baltas D, Tsalpatouros A, Kolotas C, et al. PROMETHEUS: Three-dimensional CT based software for localisation & reconstruction in HDR brachytherapy. In: Ed. Zamboglou N. New developments in interstitial remote controlled brachytherapy, 1st edn. Munich: Zuckschwerdt, 1997:60.
5. Blasko JC. Ultrasound guided LDR brachytherapy for prostate cancer In: Speiser BL, Mould RF, eds. Brachytherapy for the 21st century. Veenendaal: Nucletron B. V., 1998:167–80.
6. Bolla M, Gonzales D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:304–9.
7. Borghede G, Hedelin H, Holmäng S, et al. Irradiation of localized prostatic carcinoma with a combination of high dose rate iridium-192 brachytherapy and external beam radiotherapy with 3 target definitions and dose levels inside the prostate gland. Radiother Oncol 1997;44:245–50.
8. Critz FA, Tarlton RS, Holladay DA. Prostate specific antigen-monitored combination radiotherapy for patients with prostate cancer: I-125 implant followed by external beam radiation. Cancer 1995;75:2383–91.
9. Dinges S , Deger S, Koswig S, et al. High-dose-rate with external beam irradiation for localized prostate cancer – results of a prospective trial. Radiother Oncol 1998;48:197–202.
10. Fowler JF, Roman A, Barry MJ, et al. Patient-reported complications and follow-up treatment after radical prostatectomy – the national Medicare experience: 1988-1990. Urology 1993;42:622–9.
11. Hanks GE, Martz KL, Diamond JJ. The effect of dose on local control of prostate cancer. Int J Radiat Oncol Biol Phys 1988;15:1299–305.
12. Kolotas C, Baltas D, Zamboglou N. CT-based interstitial HDR brachytherapy. Strahlenther Onkol 1999;175:419–27.
13. Kovacs G, Galalae R, Wirth B, et al. Optimierung der interstitiellen 12. Brachytherapie beim lokal begrenzten Prostatakarzinom mit einer neuen Implantationstechnik. Strahlenther Onkol 1995;171:685–8.
14. Kovacs G, Wirth B, Bertermann H, et al. Prostate preservation by combined external beam and HDR brachytherapy at node negative prostate cancer patients – an intermediate analysis after 10 years experience. Int J Radiat Oncol Biol Phys 1996;36:198–204.
15. Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 1991;21:935–9.
16. Martin T, Kolotas C, Dannenberg T, et al. New interstitial HDR brachytherapy technique for prostate cancer: CT based 3D planning after transrectal implantation. Radiother Oncol 1999;52:257–60.
17. Martinez A, Wallace M, Gustafson G, et al. Biochemical control and acute toxicity associated with high dose rate conformal boost brachytherapy for prostate cancer: Comparison of 3-implant vs 2-implant regimens. Proc 40th Annual ASTRO Meeting, Phoenix, 1998:221.abstract No. 1025.
18. Middleton RG, Thompson IM, Austenfeld MS. Prostate cancer clinical guidelines panel summary report on the management of clinically localized prostate cancer. J Urol 1995;154:2144–8.
19. Partin AW, Pound CR, Clemens JQ, et al. Prostate-specific antigen after anatomic radical prostatectomy: the John Hopkins experience after ten years. Urol Clin North Am 1993;20:730–9.
20. Perez CA, Pilepich MV, Zivnuska F. Tumor control in defenitive irradiation of localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1986;12:523–31.
21. Sack H. Prostatakarzinom. In: Scherer E, Sack H, eds. Strahlentherapie, 4th edn. Berlin–Heidelberg–New York: Springer, 1996:551–65.
22. Scardino PT, Wheeler TM. Local control of prostatic cancer with radiotherapy: frequency and prognostic significance of positive results of post-irradiation prostate biopsy. Natl Cancer Inst Monogr 1988:95–103.
23. Schwarzer JU, Hofmann R, Kneschaurek P, et al. High-dose-rate-Brachytherapie des Prostatakarzinoms mit Iridium-192. Strahlenther Onkol 1992;168:17–22.
24. Stamey TA, Ferrari MK, Schmid HP. The value of serial prostate specific antigen determinations 5 years after radiotherapy: steeply increasing values characterize 80% of patients. J Urol 1993;150:1856–9.
25. Syed AM, Puthawala AA, Barth N, et al. High dose rate brachytherapy in the treatment of carcinoma of the prostate: Preliminary results. J Brachyther Int 1997;13:315–31.
26. Whittington R, Broderick GA, Arger P, et al. The effect of androgen deprivation on the early changes in prostate volume following transperineal ultrasound guided interstitial therapy for localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1999;44:1107–10.
27. Zamboglou N, Kolotas C, Baltas D, et al. Clinical evaluation of CT based software in treatment planning for interstitial HDR brachytherapy. In: Speiser BL, Mould RF, eds. Brachytherapy for the 21st century. Veenendaal: Nucletron B. V., 1998:312.
28. Zelefsky MJ, Leibel SA, Kutcher GJ, et al. Three-dimensional conformal radiotherapy and dose escalation: Where do we stand? Semin Radiol Oncol 1998;8:107–14.
29. Zincke H, Utz DC, Benson RC Jr, et al. Bilateral pelvic lymphadenectomy and radical retropubic prostatectomy for Stage C adenocarcinoma of the prostate. Urology 1984;24:532–9.

Address for Correspondence:
Dr. Thomas Martin, Strahlenklinik, Städtische Kliniken,
Starkenburgring 66, D-63069 Offenbach/Main, Germany,
Phone (+49/69) 8405-3335, Fax -3334,
e-mail: Doc-Martin@T-online.de