3-D Conformal HDR Brachytherapy as Monotherapy for Localized Prostate Cancer

A Pilot Study

Thomas Martin[1], Dimos Baltas[1], Ralf Kurek[1], Sandra Röddiger[1], Marina Kontova[1], Georgios Anagnostopoulos[1], Thomas Dannenberg[2], Thomas Buhleier[2], Georgies Skazikis[1], Ulf Tunn[2], Nikolaos Zamboglou[1]

Purpose: Pilot study to evaluate feasibility, acute toxicity and conformal quality of three-dimensional (3-D) conformal high-dose-rate (HDR) brachytherapy as monotherapy for localized prostate cancer using intraoperative real-time planning.
Patients and Methods: Between 05/2002 and 05/2003, 52 patients with prostate cancer, prostate-specific antigen (PSA) ≤ 10 ng/ml, Gleason score ≤ 7 and clinical stage ≤ T2a were treated. Median PSA was 6.4 ng/ml and median Gleason score 5. 24/52 patients had stage T1c and 28/52 stage T2a. For transrectal ultrasound-(TRUS-)guided transperineal implantation of flexible plastic needles into the prostate, the real-time HDR planning system SWIFT® was used. After implantation, CT-based 3-D postplanning was performed. All patients received one implant for four fractions of HDR brachytherapy in 48 h using a reference dose (D_{ref}) of 9.5 Gy to a total dose of 38.0 Gy. Dose-volume histograms (DVHs) were analyzed to evaluate the conformal quality of each implant using D_{90}, D_{10} urethra, and D_{10} rectum. Acute toxicity was evaluated using the CTC (Common Toxicity Criteria) scales.
Results: Median D_{90} was 106% of D_{ref} (range: 93–115%), median D_{10} urethra 159% of D_{ref} (range: 127–192%), and median D_{10} rectum 55% of D_{ref} (range: 35–68%). Median follow-up is currently 8 months. In 2/52 patients acute grade 3 genitourinary toxicity was observed. No gastrointestinal toxicity > grade 1 occurred.
Conclusion: 3-D conformal HDR brachytherapy as monotherapy using intraoperative real-time planning is a feasible and highly conformal treatment for localized prostate cancer associated with minimal acute toxicity. Longer follow-up is needed to evaluate late toxicity and biochemical control.

Key Words: Prostate cancer · Brachytherapy · HDR monotherapy · Intraoperative real-time planning

Strahlenther Onkol 2004;180:225–32
DOI 10.1007/s00066-004-1215-4

Konformale 3-D-HDR-Brachytherapie als Monotherapie beim lokal begrenzten Prostatakarzinom. Eine Pilotstudie

Ziel: Pilotstudie zur Evaluation der Praktikabilität, Akuttoxizität und konformalen Qualität der konformalen dreidimensionalen (3-D) High-Dose-Rate-(HDR-)Brachytherapie als Monotherapie beim lokal begrenzten Prostatakarzinom unter Einsatz intraoperativer Real-Time-Planung.
Patienten und Methodik: Zwischen 05/2002 und 05/2003 wurden 52 Patienten mit einem Prostatakarzinom, PSA-Wert (prostataspezifisches Antigen) ≤ 10 ng/ml, Gleason-Score ≤ 7 und klinischem Stadium ≤ T2a behandelt. Der mediane PSA-Wert betrug 6,4 ng/ml und der mediane Gleason-Score 5. 24/52 Patienten waren im Stadium T1c und 28/52 im Stadium T2a. Für die TRUS-gesteuerte (transrektaler Ultraschall) transperineale Implantation von flexiblen Plastiknadeln in die Prostata kam das Real-Time-HDR-Planungssystem SWIFT® zum Einsatz. Nach der Implantation wurde ein CT-basiertes 3-D-Postplanning durchgeführt. Alle Patienten erhielten ein Implantat für vier Fraktionen HDR-Brachytherapie in 48 h mit einer Referenzdosis (D_{ref}) von 9,5 Gy bis zu einer Gesamtdosis von 38,0 Gy. Dosis-Volumen-Histogramme (DVH) wurden analysiert, um die konformale Qualität der Implantate mit Berechnung der D_{90}, D_{10} Urethra und D_{10} Rektum zu bestimmen. Akuttoxizitäten wurden unter Verwendung der CTC-Skalen (Common Toxicity Criteria) evaluiert.
Ergebnisse: Die mediane D_{90} betrug 106% von D_{ref} (Range: 93–115%), die mediane D_{10} Urethra 159% von D_{ref} (Range: 127–192%), die mediane D_{10} Rektum 55% von D_{ref} (Range: 35–68%). Die mediane Nachbeobachtungszeit beträgt gegenwärtig 8 Monate. Bei 2/52 Patienten wurden akute urogenitale Grad-3-Toxizitäten beobachtet. Gastrointestinale Toxizitäten > Grad 1 traten nicht auf.

[1] Department of Radiation Oncology, and
[2] Department of Urology, Klinikum Offenbach, Offenbach/Main, Germany.

Received: August 1, 2003; accepted: December 18, 2003.

Schlussfolgerung: Die konformale 3-D-HDR-Brachytherapie als Monotherapie unter Einsatz intraoperativer Real-Time-Planung erweist sich als praktikable und hochkonformale Behandlung mit minimalen akuten Nebenwirkungen beim lokal begrenzten Prostatakarzinom. Eine längere Nachbeobachtungszeit ist zur Beurteilung von Spättoxizitäten und biochemischer Kontrolle notwendig.

Schlüsselwörter: Prostatakarzinom · Brachytherapie · HDR-Monotherapie · Intraoperative Real-Time-Planung

Introduction

The incidence of prostate cancer is increasing rapidly and has reached 700,000 cases annually in Europe and North America at the beginning of the 21th century [4]. For 2002, there were an estimated 189,000 new cases of prostate cancer diagnosed in the USA alone [11]. The widespread use of the prostate-specific antigen (PSA) test and transrectal ultrasound (TRUS), allowing earlier detection, has resulted in a significant stage downmigration with a majority of patients newly diagnosed with organ-confined disease [12]. Gleason score and pretreatment PSA level have a major impact on the risk of extraprostatic disease, seminal vesicle infiltration and regional lymph node involvement and can be used as prognostic factors for the definition of risk categories in patients with clinically organ-confined stages [25]. Patients with pretreatment PSA levels ≤ 10 ng/ml and Gleason scores 2–6 are considered to belong to the low-risk group, patients with PSA levels ≤ 10 ng/ml and Gleason score 7 to the intermediate-risk group. Curative treatment options for these risk groups of localized prostate cancer include radical prostatectomy (RP), three-dimensional conformal external-beam irradiation (3-D CRT), and interstitial brachytherapy.

Low-dose-rate (LDR) brachytherapy using permanent implants of ^{125}I or ^{103}Pd seeds as monotherapy has become a very popular treatment option in the USA during the last decade. In Germany and other European countries more and more institutions have just started to establish LDR brachytherapy as an alternative to RP and 3-D CRT [35]. Long-term results from large series in North America are now available with encouraging biochemical control rates and acceptable toxicity [10, 27]. However, although improvements have been made in implantation techniques and dose-planning procedures for permanent seed implantation, there are still a number of critical issues to discuss. First of all, there are still potential difficulties to deliver the prescription dose to the entire prostate because of an inherent lack of total control in depositing the seeds precisely to the preplanned position inside the gland [28]. In addition, the postimplant prostate edema results in varying changes of the target volume during several weeks after implantation [34]. Other critical issues concerning the patient and his family are radiation protection after the implantation of permanent radioactive seeds and the risk of seed migration.

High-dose-rate (HDR) brachytherapy using temporary ^{192}Ir implants as a boost in combination with external-beam irradiation was established in the 1990s as conformal treatment technique for prostate cancer [2, 3, 6, 8, 9, 15, 17, 21]. Since 1997, we have treated > 700 patients with prostate cancer in our institution using HDR implants followed by 3-D CRT and combined with temporary androgen deprivation [18, 19]. The ability to optimize dwell times and positions of the ^{192}Ir source along the implant needles allows optimal dose conformity to the prostate, unaffected by the limitations of permanent seed implantation. In 1999, Martinez et al. started a study to investigate conformal HDR brachytherapy as monotherapy for favorable-stage prostate cancer to overcome these limitations. The William Beaumont group concluded, in their publication, that the HDR monotherapy protocol was feasible and very well tolerated with an excellent coverage of the prostate gland [22]. Based on our own experiences with HDR brachytherapy and on published feasibility reports [22, 29, 36], we started a pilot study of 3-D conformal HDR brachytherapy as monotherapy for localized prostate cancer in 2002. We used the newly developed HDR planning system SWIFT® (Nucletron, Veenendal, the Netherlands) for intraoperative real-time planning of HDR brachytherapy during the implantation procedure. The purpose of our study was to evaluate the feasibility and acute toxicity of 3-D conformal HDR brachytherapy as monotherapy. In addition, we evaluated the benefits of the intraoperative real-time HDR planning system SWIFT® by analyzing the conformity and quality of all implants using a dose-volume histogram-(DVH-)based methodology.

Patients and Methods

Patients

Between May 2002 and May 2003, we treated 52 patients with localized prostate cancer using 3-D conformal HDR brachytherapy as monotherapy. The patients' median age was 66 years (range: 45–79 years). Patients were eligible to participate in the pilot study if they fulfilled the following inclusion criteria: biopsy-proven adenocarcinoma of the prostate, clinical stage ≤ T2a, PSA level ≤ 10 ng/ml, and Gleason score ≤ 7. All patients in our series gave their informed consent after detailed information about the aims, risks and technique of the pilot study. 3-D CRT or permanent seed implantation were offered as alternative radiation therapies. Pretreatment investigations included digital rectal examination, TRUS, and serum PSA level. Median volume of the prostate gland before brachytherapy was 35 ml (range: 17–78 ml) The patients were clinically staged according to the TNM classification system

of 1997 (UICC). Stage T1c was diagnosed in 24 and T2a in 28 patients. Median pretreatment PSA level was 6.4 ng/ml (range: 3.0–10.0 ng/ml). 44/52 patients with Gleason 2–6 were in the low-risk and 8/52 patients with Gleason 7 in the intermediate-risk group. In 36/52 patients neoadjuvant androgen deprivation (NAAD) using LHRH agonists was started by urologists before inclusion of the patients into our protocol. The median duration of NAAD was 3 months (range: 2–4 months). The details of patient characteristics are given in Table 1.

Table 1. Patient distribution by clinical stage, Gleason score and pretreatment prostate-specific antigen (PSA) value.

Tabelle 1. Patientenverteilung nach klinischem Stadium, Gleason-Score und prätherapeutischem PSA-Wert (prostataspezifisches Antigen).

	Patients (n)
Clinical stage	
T1c	24
T2a	28
Gleason score	
2–4	14
5–6	30
7	8
PSA (ng/ml)	
0–4.0	3
4.1–6.0	17
6.1–10.0	32

Treatment Technique

Transperineal implantation was performed under general or spinal anesthesia with the patient in the lithotomy position. A Foley catheter was inserted, and the bladder was partially filled with 100 cm^3 of sterile water. For the implantation procedure, we used a stepping unit fixed on a positioning and stabilizing system, which was mounted on the patient table. The electronic biplanar 7.5-MHz ultrasound probe (B+K 8658MFI), connected with the ultrasound system (B+K Falcon), was inserted into a plastic probe sheath, filled with saline solution for a better quality of ultrasound imaging. Then, the ultrasound probe and the perineal HDR template were fixed on the stepping unit. In the next step, we introduced the ultrasound probe into the rectum in a position parallel to the urethra. The stepper unit with probe and template was adjusted and fixed, allowing only caudad-cephalad movement of the probe. Before ultrasound image acquisition, we placed two locking needles in the prostate for fixation of the gland. Using transversal ultrasound views, we visualized and identified base and apex of the prostate, urethra, rectum, and bladder. Then, the acquisition of ultrasound images of the prostate was performed continuously from base to apex. These images were acquired in real-time by the SWIFT® system, and a 3-D volume was created out of this. The image in the middle between base and apex was automatically defined as the reference plane. In the next step, we defined the contours of prostate, urethra and anterior rectal wall, visualized on the monitor simultaneously in coronal, transverse and sagittal plane views (Figures 1a to 1c) as well as a 3-D reconstruction. The contouring procedure could be performed using manual, semimanual or automatic contouring tools. The appropriate needle positions were generated intraoperatively using the needle placement tool of SWIFT® (Figures 2a to 2c). The generated virtual needles, the active and inactive source dwell positions, and the resulting isodose distribution were visualized immediately in relation to the anatomy in all plane views (Figures 3a to 3c) and as 3-D reconstruction. In addition, DVHs for prostate, urethra, and rectum were calculated to evaluate the results of the anatomy-based optimization.

After finishing the intraoperative planning, we started with transperineal implantation of flexible plastic needles (20 cm in length and 1.9 mm in diameter) with metal stylets into the prostate through the template under TRUS control.

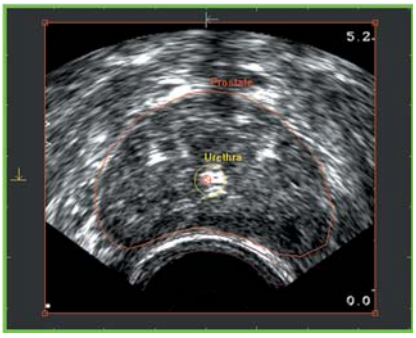

Figure 1a – Abbildung 1a

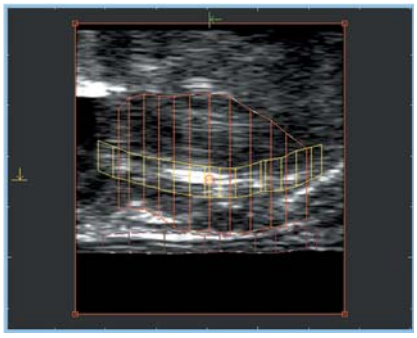

Figure 1b – Abbildung 1b

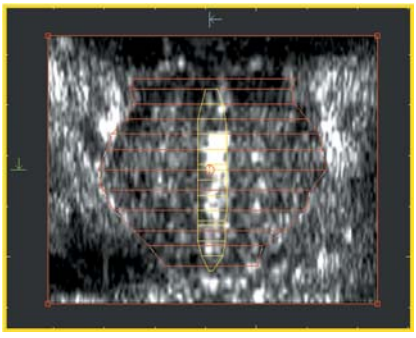

Figure 1c – Abbildung 1c

Figures 1a to 1c. Intraoperative real-time planning for HDR brachytherapy of prostate cancer: contouring of prostate, urethra and anterior rectal wall, visualized simultaneously in transverse (a), sagittal (b) and coronal (c) ultrasound views.

Abbildungen 1a bis 1c. Intraoperative Real-Time-Planung für die HDR-Brachytherapie des Prostatakarzinoms: Konturierung von Prostata, Urethra und anteriorer Rektumwand, simultan abgebildet in transversaler (a), sagittaler (b) und koronaler (c) Ultraschallansicht.

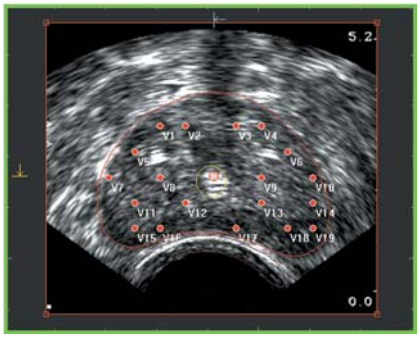

Figure 2a – Abbildung 2a

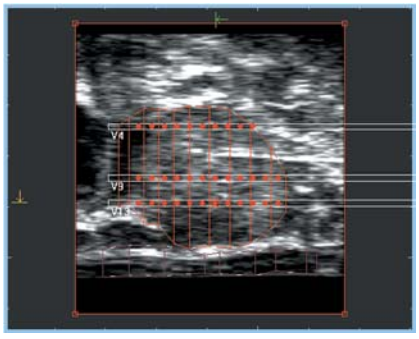

Figure 2b – Abbildung 2b

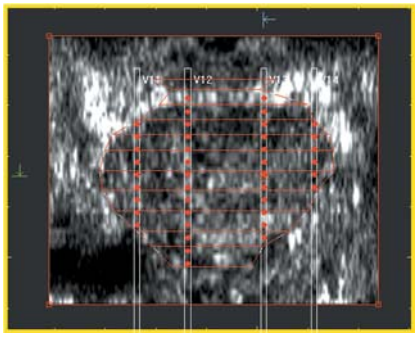

Figure 2c – Abbildung 2c

Figures 2a to 2c. Intraoperative real-time planning for HDR brachytherapy of prostate cancer: needle positions inside the prostate are generated intraoperatively. The generated virtual needles and the active and inactive source dwell positions are immediately visualized in transverse (a), sagittal (b) and coronal (c) ultrasound views.

Abbildungen 2a bis 2c. Intraoperative Real-Time-Planung für die HDR-Brachytherapie des Prostatakarzinoms: Nadelpositionen innerhalb der Prostata werden intraoperativ generiert. Die generierten virtuellen Nadeln und die aktiven und inaktiven Haltepositionen der Quelle werden sofort in transversaler (a), sagittaler (b) und koronaler (c) Ultraschallansicht abgebildet.

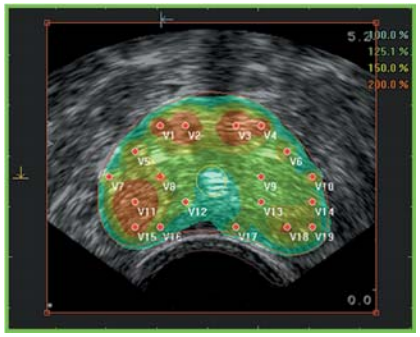

Figure 3a – Abbildung 3a

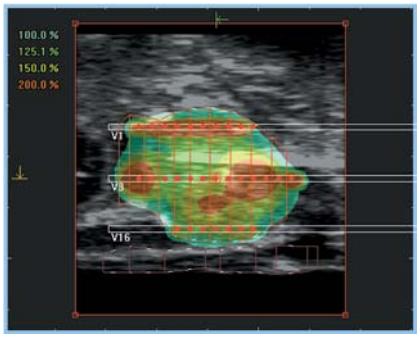

Figure 3b – Abbildung 3b

Figure 3c – Abbildung 3c

Figures 3a to 3c. Intraoperative real-time planning for HDR brachytherapy of prostate cancer: virtual needles, active and inactive source dwell positions and the resulting isodose distribution are visualized immediately after dose optimization in transverse (a), sagittal (b) and coronal (c) ultrasound views.

Abbildungen 3a bis 3c. Intraoperative Real-time-Planung für die HDR-Brachytherapie des Prostatakarzinoms: Virtuelle Nadeln, aktive und inaktive Haltepositionen der Quelle und die resultierende Isodosenverteilung werden sofort nach der Dosisoptimierung in transversaler (a), sagittaler (b) und koronaler (c) Ultraschallansicht abgebildet.

The isodose distribution was continuously updated in real time based on the actual needle location to compensate for organ distortion and to assure conformal prostate coverage. After placement of all plastic needles, we performed a final 3-D ultrasound acquisition to document and verify the final in situ needle positions and to calculate the isodose distribution and DVHs. Then, cystoscopy was used to control urethral and bladder mucosa and to verify tenting of the bladder mucosa by the needles. Finally, we inserted a suprapubic catheter, removed the template and fixed all needles by subcutaneous sutures on the perineal skin to prevent any needle movement.

After implantation, we performed a spiral CT scan of the pelvis (3.0 mm slice thickness) and sent the images to the PLATO BPS workstation for 3-D conformal postplanning. Before CT scanning, the bladder was filled with 50 ml diluted contrast medium for better separation between bladder and prostate base. The silicone Foley catheter, inserted for identification of the urethra in the CT slices, was removed after CT scanning. Contours of the planning target volume (PTV), urethra, and rectum were then delineated in all CT slices. The PTV was defined as the entire prostate gland without margins. The circumference of the whole rectum and urethra was delineated from 10 mm above to 10 mm under the PTV. In the next step, 3-D autoreconstruction of the needles followed using the autoreconstruction module of PLATO BPS 14.2.2. Then, 3-D dose optimization was performed to the PTV surface [14, 37]. To evaluate the conformal quality of the implants, we used DVH-based parameters for PTV, urethra, and rectum. The

D_{10} urethra (dose delivered to 10% of the urethra) was limited to 175% and the D_{10} rectum (dose delivered to 10% of the rectum) to 75% of the reference dose (D_{ref}). Our aim was to achieve a D_{90} (dose delivered to 90% of the PTV) > 90% of D_{ref}. Our dose specification was on the mean dose on the PTV surface.

The reference dose was 9.5 Gy per fraction delivered four times in 48 h to a total dose of 38.0 Gy. The biological equivalent dose (BED) of HDR brachytherapy as monotherapy was estimated by means of the LQ formula. Using an α/β-value of 7 Gy for prostate cancer cells, we reached a BED of 89.6 Gy for a standard external-beam regimen (5 × 1.8 Gy weekly). Alternatively, using an α/β-value of 5 Gy, which is supported by current radiobiological analyses, we reached a BED of 110.2 Gy [5]. The patients were immobilized during the entire treatment and received continuous i.v. infusion with meperidine (10 mg/h) for pain control. The first fraction of HDR brachytherapy was delivered on the day of implantation, second and third fraction on day 1 after implantation, with at least 6 h between the fractions, and the fourth fraction in the morning of day 2 after implantation. Before each fraction, any needle movement in the caudad-cephalad direction was controlled. After the last fraction, all flexible plastic needles were removed. 1 day after the last fraction, the suprapubic catheter was removed, and the patients were discharged home after voiding spontaneously.

Results

All 52 patients successfully received 38.0 Gy HDR brachytherapy in four fractions of 9.5 Gy each over 48 h. For the entire treatment, patients stayed in hospital for 5–7 days. We observed no complications during any of the implantations. The mean duration for transperineal implantation using the real-time planning system SWIFT® was 60 min. All patients tolerated the implantation procedure and subsequent delivery of four fractions of HDR brachytherapy very well with minimal discomfort. Using prophylactic analgesia with continuous meperidine i.v. infusion, perineal pain was adequately controlled.

Median follow-up time is currently 8 months (range: 3–15 months). Acute toxicity was evaluated according to the Common Toxicity Criteria (CTC version 2.0). 32/52 patients experienced increased frequency of micturition and mild or moderate dysuria as acute grade 1–2 genitourinary toxicity. Urinary retention requiring suprapubic catheterization for > 6 weeks as acute grade 3 GU toxicity was observed in 2/52 patients. We noted no grade 4–5 acute genitourinary toxicity. 11/52 patients developed increased stool frequency as acute grade 1 gastrointestinal toxicity, no patient developed acute grade 2–5 gastrointestinal side effects. Toxicity data are presented in Table 2.

CT-based DVH parameters were used for dosimetric analysis of all HDR implants to evaluate and document the quality of 3-D conformal HDR brachytherapy. In 52/52 implants we noted a D_{90} > 90% of D_{ref}. The mean D_{90} was 106% of D_{ref} with a range of 93–115%. The mean D_{10} rectum was 55% of D_{ref} with a range of 35–68%, and the mean D_{10} urethra was 159% of D_{ref} with a range of 127–192%. DVH parameters are presented in Table 3.

Discussion

HDR brachytherapy as monotherapy for patients with localized prostate cancer is a new conformal treatment technique which aims to overcome the potential limitations of LDR brachytherapy using permanent implants of ^{125}I or ^{103}Pd seeds. The well-known phenomenon of prostate edema after seed implantation can strongly affect the aim to deliver 100% of the D_{ref} to the entire gland [34]. Martinez et al. treated 41 patients with HDR brachytherapy as monotherapy using one implant for four fractions of 9.5 Gy each. They found a significant increase of the prostate volume very shortly after needle implantation, but very little change of the volume during the subsequent 32–36 h of HDR treatment delivery. Since dosimetry

Table 2. Acute genitourinary and gastrointestinal toxicity (CTC version 2.0) after 3-D conformal HDR brachytherapy as monotherapy.

Tabelle 2. Akute urogenitale und gastrointestinale Toxizität (CTC Version 2.0) nach konformaler 3-D-HDR-Brachytherapie als Monotherapie.

Toxicity	Patients (n)
Genitourinary	
Grade 1	24/52
Grade 2	8/52
Grade 3	2/52
Grade 4	0/52
Gastrointestinal	
Grade 1	11/52
Grade 2	0/52
Grade 3	0/52
Grade 4	0/52

Table 3. Dosimetric analysis of CT-based dose-volume histogram (DVH) parameters to evaluate the conformal quality of 52 HDR implants. D_{90}: dose delivered to 90% of the prostate; D_{10} urethra: dose delivered to 10% of the urethra; D_{10} rectum: dose delivered to 10% of the rectum.

Tabelle 3. Dosimetrische Analyse von CT-basierten Dosis-Volumen-Histogramm-(DVH-)Parametern zur Evaluierung der konformalen Qualität von 52 HDR-Implantaten. D_{90}: verabreichte Dosis auf 90% der Prostata; D_{10} urethra: verabreichte Dosis auf 10% der Urethra; D_{10} rectum: verabreichte Dosis auf 10% des Rektums.

	D_{90} (Gy)	(% of D_{ref})	D_{10} urethra (Gy)	(% of D_{ref})	D_{10} rectum (Gy)	(% of D_{ref})
Median	10.1	106	15.1	159	5.2	55
Minimum	8.8	93	12.1	127	3.3	35
Maximum	10.9	115	18.2	192	6.5	68

for the HDR implants was based on TRUS images at the time of the first fraction with all needles in situ, these images incorporated the postimplant edema and, therefore, had no negative effects on the ability to deliver the full prescription dose to the entire prostate. This has been shown by analyzing the D_{90} at the first and last fraction, which did not change significantly [22]. Based on these results, we used the same approach of generating a single treatment plan after implantation for the following four fractions of HDR brachytherapy. In our series, we performed CT-based 3-D postplanning directly after implantation [1, 14, 37]. The isodose distribution was evaluated in all CT slices within and surrounding the prostate and within normal tissues (Figure 4). To evaluate the quality of the implants, we used DVH parameters for prostate, urethra and rectum and documented the D_{10} of organs at risk and the D_{90} of the prostate.

It is strongly recommended to evaluate the D_{90} and the rectal and urethral doses after permanent seed implantation, because these data provide an evaluation of the overall quality of the implant [13, 23, 35]. Especially the D_{90} parameter has a major impact on prediction of biochemical control after brachytherapy. Stock et al. noted a biochemical control rate of 92% after permanent seed implants with a $D_{90} > 140$ Gy, but a control rate of 68 % after implants with a $D_{90} < 140$ Gy [31]. In a prospective study on 719 patients treated with permanent seed implants, Potters et al. found that a $D_{90} \geq 90\%$ can be used as a factor for predicting PSA relapse-free survival [26]. Using HDR brachytherapy as monotherapy, Martinez et al. reported a mean D_{90} of 104% with a range of 95–106% for ten analyzed implants [22]. In our series, the mean D_{90} was 106% with a range of 93–115% for 52 implants. Rodriguez et al. treated 63 patients with two implants and three fractions of 7 Gy per implant for HDR brachytherapy as monotherapy. This group noted a $V_{100} > 95\%$ in all implants [29]. These dosimetric data demonstrate that the approach of HDR brachytherapy as monotherapy using intraoperative real-time planning results in an excellent conformal 3-D dose distribution and coverage of the prostate gland with better D_{90} values compared to most published results of LDR brachytherapy [16, 24, 30].

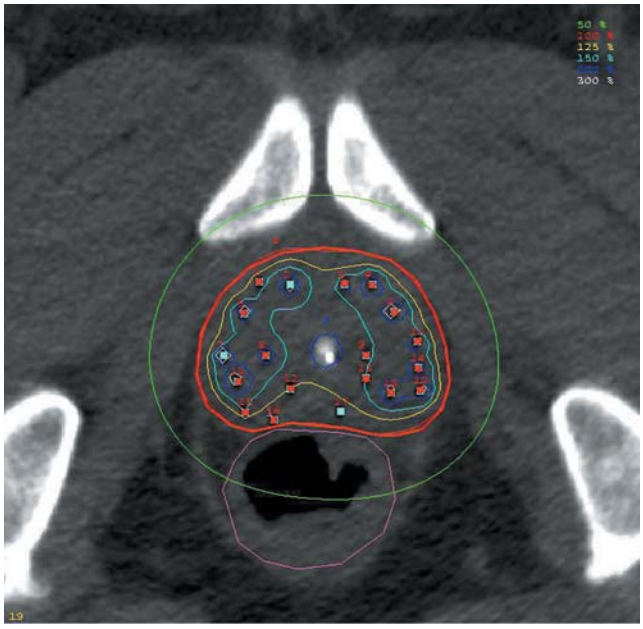

Figure 4. CT-based 3-D postplanning after implantation: evaluation of the isodose distribution in one representative CT slice within and surrounding the prostate and within the normal tissues (green: 50% isodose; red: 100% isodose; yellow: 125% isodose; light blue: 150% isodose; dark blue: 200% isodose).

Abbildung 4. CT-basiertes 3-D-Postplanning nach Implantation: Evaluation der Isodosenverteilung in einem repräsentativen CT-Schnitt innerhalb und außerhalb der Prostata und innerhalb der Normalgewebe (grün: 50%-Isodose; rot: 100%-Isodose; gelb: 125%-Isodose; hellblau: 150%-Isodose; dunkelblau: 200%-Isodose).

Treatment-related toxicity has also been correlated with postimplant dosimetry results in permanent seed implantation. Wallner et al. reported that both the dose and length of the irradiated urethra were related to urinary morbidity. Analyzing 45 patients treated with ^{125}I implants, they found that in patients who developed RTOG grade 0–1 urinary toxicity an average of 10 mm of the urethra was irradiated to doses > 400 Gy compared to 20 mm in patients who developed grade 2–3 urinary toxicity [32]. For ten implants of HDR brachytherapy as monotherapy, Martinez et al. reported a mean urethral D_{10} of 122% (range: 114–142%) for fraction 1 and 132% (range: 114–157%) for fraction 2 [22]. In our series, we noted a mean urethral D_{10} of 159% with a range of 127–192% for 52 implants. These data demonstrate lower doses to the urethra compared to published results of permanent seed implants [7, 32]. When examining rectal morbidity of permanent seed brachytherapy, Wallner et al. found that in patients developing RTOG grade 1–2 rectal toxicity, an average of 17 mm^2 of the rectal wall was irradiated to doses > 100 Gy, compared to 11 mm^2 for patients experiencing no rectal morbidity [32]. Martinez et al. limited the dose to any segment of the rectum to < 75% of the prescription dose of HDR brachytherapy, but reported no rectal D_{10} parameters [22]. In our series, we noted a mean rectal D_{10} of 55% with a range of 35–68% for 52 implants. Estimating a BED of 110 Gy for the rectum, using an α/β-value of 5 Gy, we therefore observed a BED of 61 Gy for 10% of the rectum volume. This demonstrates also lower doses to the rectum compared to published results of permanent seed brachytherapy [32, 33].

We used the newly developed real-time HDR planning system SWIFT® to achieve a conformal dose distribution with HDR brachytherapy. Using SWIFT®, we had the advantage of visualizing the ultrasound images of prostate, urethra and rectum simultaneously in transverse, sagittal and coronal plane views and as 3-D reconstruction in real time. Based on this improved imaging technology, we were able to define the contours of prostate and organs at risk with high efficiency. In addition, we were able to generate optimal needle positions in-

traoperatively without performing an extra TRUS study for preplanning few days before implantation. During the entire implantation procedure, we evaluated the actual isodose distribution interactively in relation to the target volume and organs at risk. Intraoperatively, we could control the conformal quality of the implant including all dosimetric parameters of interest by using DVHs.

For an accurate treatment delivery of fractionated HDR brachytherapy using one implant and one single treatment plan, it is important to observe the degree of needle movement that may occur between the fractions. Martinez et al. noted a range in caudad shift of implanted needles between fraction 1 and 2 from 0 to 3 cm and corrected this with the aid of fluoroscopy. Movement between the remaining fractions was minimal to none. In our series, all plastic needles were sutured to the perineal skin. We verified the needle positions before the delivery of HDR brachytherapy clinically and by using CT scans. Only in one patient a significant caudad movement of one needle was noted before fraction 2. For this patient, we performed a new CT-based treatment plan before continuing with the next fraction.

After the short-term follow-up of median 8 months (range: 3–15 months), acute genitourinary toxicity was mild or moderate with only two patients requiring suprapubic catheterization for 8 and 10 weeks, respectively, as grade 3 genitourinary toxicity. Both patients had a prostate volume < 50 ml but symptoms of benign prostatic hyperplasia prior to brachytherapy. To minimize the risk of urinary retention, we currently include only patients with a prostate volume < 60 ml and an International Prostate Symptom Score (IPSS) < 10 into the protocol. No patient in our series developed acute gastrointestinal toxicity > grade 1. This is consistent with toxicity rates from other series of HDR monotherapy. Rodriguez et al. noted no acute gastrourinary or gastrointestinal toxicity > grade 2 after a median follow-up of 40.8 months [29]. Yoshioka et al. treated 22 patients with one implant and a fractional dose of 6 Gy twice daily to a total dose of 48–54 Gy HDR brachytherapy in 5 days. After a median follow-up of 31 months, they noted no acute toxicity > grade 2 [36]. Martinez et al. compared acute and late toxicity rates of 68 patients treated with HDR brachytherapy as monotherapy to 79 patients treated with permanent seed implantation (^{103}Pd) as monotherapy. The median follow-up time was 22 months. HDR brachytherapy alone was associated with reduced rates of acute grade 1–3 dysuria (33% vs. 66%; $p < 0.001$), urinary frequency or urgency (54% vs. 91%; $p < 0.001$), and rectal pain (6% vs. 22%; $p < 0.009$). Long-term urinary frequency and urgency as late toxicity was also reduced with HDR brachytherapy (24% vs. 62%; $p < 0.004$) compared to ^{103}Pd seed implantation [20].

A potential advantage of HDR monotherapy compared to seed implantation might be the laboratory and clinical evidence that the α/β-ratio for prostate cancer is significantly lower than for other tumors [5]. This would imply an increased sensitivity of prostate cancer cells to large doses per fraction, such as those delivered with HDR brachytherapy as the sole treatment. Whether this radiobiological issue will result in an improved outcome remains to be seen in the future. Since follow-up time after HDR monotherapy is still too short in all published series, there is only few preliminary data for biochemical control rates. Rodriguez et al. noted a 5-year bNED rate of 91% after a median follow-up of 40.8 months. Interestingly, the median time to PSA nadir was 24 months (range: 6–57 months), which is significantly longer than for external-beam irradiation or permanent seed implantation. In our series, we noted dropping PSA values in all patients, but longer follow-up is necessary to report biochemical control rates.

Another potential advantage of HDR monotherapy compared to permanent seed implantation is the elimination of radiation protection and safety issues for the patient, his family and friends. Many patients are concerned about radiation exposure to their partner, children and friends and the potential for seed migration. This safety issue was important for most patients in the decision-making process to participate in our pilot study of HDR brachytherapy as monotherapy.

Conclusion

3-D conformal HDR brachytherapy as monotherapy using the intraoperative real-time planning system SWIFT® for 52 patients with localized prostate cancer was a feasible and well-tolerated treatment modality after the short-term follow-up of median 8 months. The dosimetric results of all implants using CT-based DVH analysis have demonstrated excellent coverage of the prostate gland with highly conformal dose distribution. Clinical and biochemical control rates and late toxicity will be reported as soon as longer follow-up time is available. Further developments of our conformal HDR brachytherapy technique include the use of a newly developed template which is fixed to the perineum for the entire treatment and the use of the ultrasound-based real-time HDR treatment plan for delivering the first fraction HDR brachytherapy intraoperatively.

References

1. Anagnostopoulos G, Baltas D, Geretschläger A, et al. In vivo TLD dose verification of transperineal ^{192}Ir HDR brachytherapy using CT-based planning for the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 2003; 57:1183–91
2. Andreopoulos D, Piatkowiak M, Krenkel B, et al. Combined treatment of localized prostate cancer with HDR-iridium 192 remote brachytherapy and external beam irradiation. Strahlenther Onkol 1999;175:387–91.
3. Borghede G, Hedelin H, Holmang S, et al. Irradiation of localized prostatic carcinoma with a combination of high dose rate iridium-192 brachytherapy and external beam radiotherapy with three target definitions and dose levels inside the prostate gland. Radiother Oncol 1997;44:245–50.
4. Boyle P. Prostate cancer 2000: evolution of an epidemic of unknown origin. In: Denis L, ed. Prostate cancer 2000. Berlin–Heidelberg–New York: Springer, 1994:5–11.
5. Brenner DJ, Martinez AA, Edmundson GK, et al. Direct evidence that prostate tumors show high sensivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys 2002;52:6–13.

6. Demanes DJ, Rodriguez RR, Altieri GA. High dose rate prostate brachytherapy: the California endocurietherapy (CET) method. Radiother Oncol 2000; 57:289–96.
7. Desai J, Stock RG, Stone NN, et al. Acute urinary morbidity following iodine-125 interstitial implantation of the prostate gland. Radiat Oncol Investig 1998;6:135–41.
8. 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.
9. Galalae RM, Kovacs G, Schultze J, et al. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 2002;52:81–90.
10. Grimm PD, Blasko JC, Sylvester JE, et al. 10-year biochemical (prostate-specific antigen) control of prostate cancer with ^{125}I brachytherapy. Int J Radiat Oncol Biol Phys 2001;51:31–40.
11. Jemal A, Thomas A, Murray T, et al. Cancer statistics 2002. CA Cancer J Clin 2002;52:23–47.
12. Jones GW, Mettlin C, Murphy GP, et al. Patterns of care for carcinoma of the prostate gland: results of a national survey of 1984 and 1990. J Am Coll Surg 1995;180:545–54.
13. Kaulich TW, Lamprecht U, Paulsen F, et al. Physical and technical quality assurance and radiation protection in transperineal interstitial permanent prostate brachytherapy with 125-iodine seeds. Strahlenther Onkol 2002; 178:667–75.
14. Kolotas C, Baltas D, Zamboglou N. CT-based interstitial HDR brachytherapy. Strahlenther Onkol 1999;175:419–27.
15. Kovacs G, Galalae R, Loch T, et al. Prostate preservation by combined external beam and HDR brachytherapy in nodal negative prostate cancer. Strahlenther Onkol 1999;175:Suppl 2:87–8.
16. Lee WR, de Guzman AF, Bare RL, et al. Postimplant analysis of transperineal interstitial permanent prostate brachytherapy: evidence for a learning curve in the first year at a single institution. Int J Radiat Oncol Biol Phys 2000;46:83–8.
17. Lennernas B, Holmang S, Hedelin H, et al. High-dose rate brachytherapy of prostatic adenocarcinoma in combination with external beam radiotherapy – a long-term follow-up of the first 50 patients at one center. Strahlenther Onkol 2002;178:537–41.
18. Martin T, Hey-Koch S, Strassmann G, et al. 3D interstitial HDR brachytherapy combined with 3D external beam radiotherapy and androgen deprivation for prostate cancer – preliminary results. Strahlenther Onkol 2000; 176:361–7.
19. 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.
20. Martinez AA, Grills I, Huang R, et al. Image-guided conformal brachytherapy as monotherapy for early stage prostate cancer: reduced toxicity with high-dose-rate brachytherapy compared to permanent palladium seed implants. Radiother Oncol 2003;66:Suppl 1:8.
21. Martinez AA, Kestin LL, Stromberg JS, et al. Interim report of conformal high-dose-rate brachytherapy for patients with unfavorable prostate cancer: the William Beaumont phase II dose-escalating trial. Int J Radiat Oncol Biol Phys 2000;47:343–52.
22. Martinez AA, Pataki I, Edmundson G, et al. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. Int J Radiat Oncol Biol Phys 2001;49:61–9.
23. Nag S, Beyer D, Friedland J, et al. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. Int J Radiat Oncol Biol Phys 1999;44:789–99.
24. Nath R, Roberts K, Ng M, et al. Correlation of medical dosimetry quality indicators to the local tumor control in patients with prostate cancer treated with iodine-125 interstitial implants. Med Phys 1998;25:2293–307.
25. Partin AW, Kattan MW, Subong ENP, et al. Combination of prostate-specific antigen, clinical stage and Gleason score to predict pathological stage of localized prostate cancer. JAMA 1997;277:2445–51.
26. Potters L, Cao Y, Calugaru E, et al. A comprehensive review of CT-based dosimetry parameters and biochemical control in patients treated with permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2001; 50:605–14.
27. Ragde H, Abdel-Aziz AE, Snow PB, et al. Ten-year disease free survival after transperineal sonography-guided iodine 125 brachytherapy with or without 45 Gray external beam irradiation in the treatment of patients with clinically localized, low to high Gleason grade prostate carcinoma. Cancer 1998;83:989–1001.
28. Robertson PL, Narayana V, McShan DL, et al. Source placement error for permanent implant of the prostate. Med Phys 1997;24:251–7.
29. Rodriguez RR, Demanes DJ, Altieri G. California endocurietherapy cancer centers HDR monotherapy program for prostate cancer: early results. Abstract and Slide Compendium of the 11th International Brachytherapy Meeting, Santa Fe, June 19–22, 2002.
30. Stock RG, Stone NN, Lo YC, et al. Postimplant dosimetry for (125) I prostate implants: definitions and factors affecting outcome. Int J Radiat Oncol Biol Phys 2000;48:899–906.
31. Stock RG, Stone NN, Trabert A, et al. A dose-response study for I-125 prostate implants. Int J Radiat Oncol Biol Phys 1998;41:101–8.
32. Wallner K, Roy J, Harrison L. Dosimetry guidelines to minimize urethral and rectal morbidity following transperineal I-125 prostate brachytherapy. Int J Radiat Oncol Biol Phys 1995;32:465–71.
33. Waterman FM, Dicker AP. Probability of late rectal morbidity in ^{125}I prostate brachytherapy. Int J Radiat Oncol Biol Phys 2003;55:342–53.
34. Waterman FM, Yue N, Corn BW, et al. Edema associated with I-125 or Pd-103 prostate brachytherapy and its impact on post-implant dosimetry: an analysis based on serial CT acquisition. Int J Radiat Oncol Biol Phys 1998; 41:1069–77.
35. Wirth MP, Hermann T, Alken P, et al. Recommendations for treatment with permanent, interstitial brachytherapy alone in locally limited prostate cancer. Strahlenther Onkol 2002;178:115–9.
36. Yoshioka Y, Nose T, Yoshida K, et al. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys 2000;48:675–81.
37. 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, 1998:312–26.

Address for Correspondence
Thomas Martin, MD
Department of Radiation Oncology
Klinikum Offenbach
Starkenburgring 66
63069 Offenbach/Main
Germany
Phone (+49/69) 8405-3335, Fax -3334
e-mail: Doc-Martin@t-online.de