Health-Related Quality of Life after Permanent Interstitial Brachytherapy for Prostate Cancer

Correlation with Postimplant CT Scan Parameters

Michael Pinkawa[1], Karin Fischedick[1], Marc D. Piroth[1], Bernd Gagel[1], Holger Borchers[2], Gerhard Jakse[2], Michael J. Eble[1]

Purpose: To determine dosimetric risk factors for increased toxicity after permanent interstitial brachytherapy for prostate cancer.

Patients and Methods: Quality of life questionnaires (Expanded Prostate Cancer Index Composite) of 60 and 56 patients were analyzed after a median posttreatment time of 6 weeks (A – acute) and 16 months (L – late). The corresponding CT scans were performed 30 days after the implant. The prostate, rectal wall, and base of seminal vesicles were contoured. Prostate volume, number of seeds and needles as well as dosimetric parameters were correlated with the morbidity scores.

Results: For a prostate volume of 38 ± 12 cm^3 (mean ± standard deviation), 54 ± 7 ^{125}I sources (Rapid Strands®, activity of 22.6 ± 3.0 MBq [0.61 ± 0.08 mCi]) were implanted using 20 ± 6 needles. Improved late urinary function scores resulted from a higher number of sources per cm^3 ($\geq$ 1.35). A prostate D_{90} < 170 Gy (A)/< 185 Gy (L) and base of seminal vesicle D_{10} < 190 Gy (A and L) were associated with higher urinary function scores. Late rectal function scores were significantly higher for patients with a prostate V_{200} < 50% and V_{150} < 75%. Patients with a prostate volume < 40 cm^3 reached better sexual function scores (A and L). A higher number of needles per cm^3 ($\geq$ 0.5) resulted in improved late urinary, bowel and sexual function scores.

Conclusion: Quality of life after a permanent implant can be improved by using an adequate amount of sources and needles. With an increasing number of seeds per cm^3, dose homogeneity is improving. A prostate D_{90} < 170 Gy and a base of seminal vesicle D_{10} < 190 Gy (as an indicator of the dose to the bladder neck and urethral sphincter) can be recommended to maintain a satisfactory urinary function.

Key Words: Quality of life · Prostate neoplasm · Brachytherapy · Dosimetry

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Lebensqualität nach permanenter interstitieller Brachytherapie beim Prostatakarzinom. Korrelation mit Parametern des Postimplantations-CT

Ziel: Analyse dosimetrischer Risikofaktoren für erhöhte Toxizitätsraten nach permanenter interstitieller Brachytherapie beim Prostatakarzinom.

Patienten und Methodik: Fragebögen zur Lebensqualität (Expanded Prostate Cancer Index Composite) von 60 bzw. 56 Patienten wurden 6 Wochen (A – akut) und 16 Monate (S – spät) nach Therapie analysiert. Die entsprechenden Postimplantations-CTs wurden 30 Tage nach der Behandlung durchgeführt. Die Prostata, Rektumwand und Basis der Samenblasen wurden konturiert. Prostatavolumen, Seed- und Nadelanzahl sowie dosimetrische Parameter wurden mit den Punktwerten der Fragebögen korreliert.

Ergebnisse: Zur Behandlung eines Prostatavolumens von 38 ± 12 cm^3 (Mittelwert ± Standardabweichung) wurden 54 ± 7 ^{125}I-Seeds (Rapid Strands®) der Aktivität 22,6 ± 3,0 MBq (0,61 ± 0,08 mCi) über 20 ± 6 Nadeln implantiert. Verbesserte späte Blasenfunktionswerte resultierten bei einer höheren Seedanzahl pro cm^3 ($\geq$ 1,35). Ein Prostata-D_{90}-Wert < 170 Gy (A)/< 185 Gy (S) und ein Samenblasen-D_{10}-Wert < 190 Gy (A und S) waren mit verbesserten Blasenfunktionswerten assoziiert. Späte Funktionswerte für den Stuhlgang waren bei Patienten mit Prostata-V_{200}-Werten < 50% und -V_{150}-Werten < 75% signifikant höher. Patienten mit einem Prostatavolumen < 40 cm^3 erreichten bessere Werte in der Sexualität (A und S). Eine höhere Nadelanzahl pro cm^3 ($\geq$ 0,5) resultierte in verbesserten späten Funktionswerten in allen Domänen.

Schlussfolgerung: Die Lebensqualität nach permanenter Brachytherapie kann durch den Einsatz einer adäquaten Menge Seeds und Nadeln verbessert werden. Mit höherer Seedanzahl pro cm^3 verbessert sich die Homogenität der Dosisverteilung. Ein Prostata-

[1] Department of Radiotherapy, RWTH Aachen, Germany,
[2] Department of Urology, RWTH Aachen, Germany.

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D_{90}-Wert < 170 Gy und ein Samenblasen-D_{10}-Wert < 190 Gy (als ein Indikator für die Dosisbelastung im Bereich des Blasenhalses und des Sphinkters) können zur Erhaltung einer guten Blasenfunktion empfohlen werden.

Schlüsselwörter: Lebensqualität · Prostatakarzinom · Brachytherapie · Dosimetrie

Introduction

Permanent prostate brachytherapy (PPB) is increasingly utilized for localized prostate carcinoma [11, 21]. An advantage of PPB compared to fractionated conformal radiotherapy is the treatment duration of only 1 day [23]. Due to a stable prostate, margins of ≥ 1 cm around the target volume [4, 30] are not needed and irradiation of rectum and bowel loops can be minimized [6, 26]. The efficacy of the treatment has been well documented [2, 13, 14, 21].

Urinary irritative and obstructive symptoms are the most common side effects, resolving within 6–12 months in most patients [31]. Transient urinary retention has been reported in 5–22% of patients [29, 33, 35]. During the weeks following the implant, there may be changes in bowel habits, tenesmus, and rectal pressure [3, 9]. The most common late injury is proctitis, which often presents as painless bleeding that is usually self-limited [36]. Rectal bleeding has been reported in 2–10%, most often between 6–18 months after implantation [9, 31].

Judicious patient selection and careful adherence to dosimetric parameters are necessary to reduce treatment toxicity. Issues about quality of life are increasingly important. Many reports contain physician-acquired information that has been shown to poorly correlate with data collected from patient self-assessment questionnaires [10, 17–19, 27]. Health-related quality of life (HRQoL) questionnaires have the advantage of revealing all grades of toxicity from the patient's perspective [8].

This study sought to correlate dosimetric and treatment-related parameters with subjective, patient-assessed toxicity based on the Expanded Prostate Cancer Index Composite (EPIC) [34] both in the acute and late phase, and find cutoff values that might be helpful to improve the implantation technique and treatment tolerance.

Patients and Methods

Patients

A total of 76 consecutive patients with prostatic carcinoma of a low risk (T-stage ≤ cT2a, prostate-specific antigen [PSA] < 10 ng/ml, and Gleason Score < 7), treated with permanent interstitial brachytherapy as monotherapy, were included in the analysis. Only patients with a urinary flow rate > 15 ml/s and no significant residual urine were selected. A validated questionnaire (EPIC), comprising 50 items concerning the urinary, bowel, sexual and hormonal domains for function and bother, was answered by the patients after a median posttreatment time of 6 weeks (range 4–30 weeks; group A – acute) and 16 months (range 12–24 months; group L – late) with a response rate of 79% (60 patients in group A) and 74% (56 patients in group L). The multi-item scale scores were transformed linearly to a 0–100 scale, with higher scores representing better HRQoL. Questionnaire A was either answered during a personal visit in the hospital or sent to the patients. Questionnaire L was always sent to the patients with a return envelope. If the questionnaire was not returned within 4 weeks, patients were contacted by telephone and urged to complete it. The questionnaires of 60 patients with prostate cancer without a prior treatment rendered the baseline values (C – control). To make a comparison with the study group possible, only low-risk patients up to an age of 75 years were accepted. As a consequence, all patients were low-risk patients with a median age before radiotherapy of 68 years (both in the study group and control group).

Treatment and Postimplant CT Scan

A transrectal ultrasound with images in 5-mm increments was performed intraoperatively before interstitial brachytherapy with permanent ^{125}I implants. The images were digitalized and transferred to a commercial planning program (Variseed®). The prescription dose was 145 Gy (100% isodose) in accordance with the recommendations of the ESTRO [1] and American Brachytherapy Society [22]. The urethra D1 (maximum dose to the urethra) and D_{30} (dose to 30% of the urethra volume) were limited to 250 Gy and 220 Gy. The dose to 10% of the anterior rectal wall was restricted to 145 Gy. For a prostate volume of 38 ± 12 cm^3 (mean ± standard deviation), 54 ± 7 ^{125}I sources (Rapid Strands®, activity of 22.6 ± 3.0 MBq [(0.61 ± 0.08 mCi]) were implanted using 20 ± 6 needles and a modified peripheral loading technique.

A postimplant CT analysis in 3-mm slices was performed 30 days after the implant. The prostate, rectal wall (part behind the prostate plus two to three slices above and below the prostate), and base of seminal vesicles (part localized behind the prostate) were contoured. No urethral catheter was used. Prostate volume, number of seeds and needles used as well as dosimetric parameters were correlated with the morbidity scores. The following dosimetric parameters were tested for a correlation: prostate V_{200} and V_{150} (prostate volume inside the 200% and 150% isodose, i.e., high dose areas,) prostate D_{90} (minimum dose including 90% of the prostate volume, i.e., lower dose area), rectal wall V_{100} and D_1, and base of seminal vesicle D_{10}.

Statistical Analysis

The questionnaires A and L were analyzed independently. The statistical software SPSS 12.0 for Windows was used. Analysis of variance (ANOVA) was performed to assess treatment

group differences in HRQoL scores (questionnaires C, A, and L), and the Bonferroni method was applied to adjust for multiple comparisons. Comparisons between two groups with or without a risk factor were made using the t-test. Cutoff numbers were defined as numbers that discriminate best (lowest p-value) between high and low morbidity scores. Contingency table analysis with the χ^2-test was done to compare treatment groups with respect to categorial variables. To assess the correlation between the risk factors (as continuous variables), Pearson's correlation index was determined. All p-values reported are two-sided, $p < 0.05$ is considered significant.

Results

Morbidity Scores

Morbidity scores and representative answers are shown in Tables 1 and 2. Urinary domain scores demonstrated the steepest decline (≥ 15 points). Bowel function and bother scores dropped only marginally in the acute phase (< 10 points). Sexual bother scores gradually decreased. Long-term scores were statistically not different from the baseline scores of the control group.

Dose-Volume-Related Risk Factors

Improved late urinary function scores resulted from a higher number of needles per cm^3 (absolute number ≥ 20 additionally significant) and a higher number of sources per cm^3. A prostate D_{90} < 170 Gy (A)/< 185 Gy (L), base of seminal vesicle D_{10} < 190 Gy (A and L), and a lower seed activity (< 24 MBq [0.65 mCi], A) were associated with higher urinary function scores (Table 3). Comparing the influence of the mentioned dose values on symptom rates for "pain with urination at least once a day" and "at least one pad to control daily leakage" after > 12 months, a stronger impact of a D_{90} ≥ 185 Gy was found for "pain with urination" (55% vs. 9% < 185 Gy; $p < 0.01$), while a base of seminal vesicle D_{10} ≥ 190 Gy significantly increased the rate of patients using pads (28% vs. 8% < 190 Gy; $p < 0.01$).

Late rectal function and bother scores were significantly higher for patients with a prostate V_{200} < 50% ("≥ rare rectal bleeding" in 0% vs. 19% with a prostate V_{200} ≥ 50%; $p < 0.01$) and V_{150} < 75% (A and L; Table 4). Patients with a prostate volume < 40 cm^3 reached better sexual function scores (A and L; Table 5; no sexual intercourse in 16% vs. 53% with a prostate volume ≥ 40 cm^3 after 16 months; $p < 0.01$). Apart from improved urinary function, a higher number of needles per cm^3 (≥ 0.5) also resulted in better bowel (L) and sexual (A and L) function scores.

No rectal wall dose parameters with a significant influence on bowel function and bother scores were found. The total implanted activity had no impact on toxicity scores.

The evaluated risk factors are not independent factors (Table 6). High dose areas (prostate V_{200}/V_{150}) were increasingly found in larger prostates, using a higher seed activity and a lower seed number per cm^3. A high number of needles per cm^3 and a small prostate volume, having an important influence on sexual function, significantly correlate – i.e., a high number of needles per

Table 1. Function and bother scores (mean ± standard deviation).

Tabelle 1. Funktions- und Belastungswerte (Mittelwert ± Standardabweichung).

	Control (n)	Acute (n)	Late (n)	Significant difference
Urinary function	92 ± 15 (60)	77 ± 22 (60)	88 ± 18 (55)	Control vs. acute (p < 0.01) Acute vs. late (p = 0.01)
Urinary bother	82 ± 19 (60)	65 ± 24 (55)	74 ± 26 (52)	Control vs. acute (p < 0.01)
Bowel function	93 ± 7 (59)	86 ± 13 (59)	91 ± 9 (55)	Control vs. acute (p < 0.01) Acute vs. late (p = 0.04)
Bowel bother	95 ± 8 (59)	87 ± 17 (59)	91 ± 11 (54)	Control vs. acute (p < 0.01)
Sexual function	42 ± 25 (47)	32 ± 23 (48)	34 ± 24 (46)	–
Sexual bother	61 ± 34 (55)	55 ± 33 (52)	53 ± 38 (48)	–

Table 2. Representative answers.

Tabelle 2. Repräsentative Antworten.

	Control (n)	Acute (n)	Late (n)	Significant difference
Pain with urination at least once a day	5% (60)	42% (60)	18% (55)	Control vs. acute (p < 0.01) Control vs. late (p = 0.03) Acute vs. late (p = 0.01)
At least one pad to control daily leakage	5% (60)	18% (60)	16% (55)	–
Moderate/big problem from frequent urination	20% (60)	48% (59)	27% (56)	Control vs. acute (p < 0.01) Acute vs. late (p = 0.02)
Moderate/big problem from urinary dysfunction	15% (59)	38% (60)	27% (56)	Control vs. acute (p < 0.01)
Rectal urgency at least once a day	17% (60)	32% (60)	16% (56)	–
Bloody stools ≥ rare	3% (59)	15% (60)	7% (55)	Control vs. acute (p = 0.03)
Moderate/big problem from bowel dysfunction	3% (60)	12% (60)	7% (56)	–
Poor or no ability to have an erection	20% (54)	33% (51)	32% (50)	–
No sexual intercourse	34% (53)	48% (50)	29% (48)	–
Moderate/big problem from sexual dysfunction	31% (55)	42% (53)	45% (49)	–

cm^3 was predominantly used for the treatment of smaller prostates.

Discussion

This study could find several treatment technique-related and dosimetric risk factors for increased toxicity after PPB. The main problem is the urinary domain with the lowest scores compared to baseline values. Symptoms sometimes need > 12 months to improve [5, 12, 32, 37]. Zelefsky et al. [37] demonstrated a likelihood of resolution or improvement of grade 2 urinary symptoms of 59% within 36 months. Merrick et al. [20] used the EPIC questionnaire to survey urinary symptoms after PPB. No significant differences of the urinary function and bother subscales were discernible after a median follow-up of 64 months.

We have found that patients with a higher amount of needles per cm^3 and seeds per cm^3 reached better urinary function scores. These patients particularly had smaller prostate volumes, and a lower seed activity was used. The dosimetric consequence of an increased number of seeds per cm^3 (with a lower activity) was a lower prostate V_{200} and V_{150} (significant correlation, Table 6) – i.e., an increased homogeneity inside the target volume.

As reported by Lee et al. [16], an excessively high number of needles (cutoff 33 needles vs. median number of 20 needles in our study) can, on the other hand, increase the obstruction rate. The number of periurethral needle manipulations can contribute to urinary toxicity [7]. Increasing the number of seeds without decreasing the activity will likewise diminish long-term urinary function [35]. In a treatment-planning study [23], a similar prostate coverage and dose to organs at risk could be demonstrated with high- versus low-activity seeds in case of an ideal source positioning. With high-activity seeds, the number of needles and needle manipulations can be minimized. However, a displacement of a high-activity seed will have a greater impact on the dose distribution compared to a low-activity seed. Taking perturbations of the optimal seed arrangement

Table 3. Factors influencing urinary scores (mean ± standard deviation).

Tabelle 3. Faktoren mit Einfluss auf Blasenwerte (Mittelwert ± Standardabweichung).

		Acute	Late
Prostate D_{90} ≥ 170 Gy (acute)/≥ 185 Gy (late) vs. < 170 Gy (acute)/< 185 Gy (late)	Urinary function	66 ± 29 vs. 81 ± 19 (p = 0.03)	78 ± 18 vs. 90 ± 18 (p = 0.04)
	Urinary bother	52 ± 29 vs. 69 ± 22 (p = 0.03)	60 ± 30 vs. 78 ± 23 (p = 0.06)
Base of seminal vesicle D_{10} ≥ 190 Gy vs. < 190 Gy	Urinary function	72 ± 25 vs. 82 ± 20 (p = 0.09)	83 ± 23 vs. 93 ± 10 (p = 0.04)
	Urinary bother	58 ± 26 vs. 71 ± 21 (p = 0.06)	66 ± 29 vs. 83 ± 18 (p = 0.01)
Needle number per cm^3 < 0.5 vs. ≥ 0.5	Urinary function	76 ± 24 vs. 78 ± 22 (p = 0.73)	81 ± 23 vs. 92 ± 12 (p = 0.02)
	Urinary bother	62 ± 27 vs. 66 ± 23 (p = 0.51)	66 ± 29 vs. 80 ± 21 (p = 0.06)
Seed number per cm^3 < 1.35 vs. ≥ 1.35	Urinary function	69 ± 25 vs. 80 ± 21 (p = 0.09)	79 ± 26 vs. 91 ± 13 (p = 0.03)
	Urinary bother	61 ± 24 vs. 66 ± 25 (p = 0.49)	72 ± 30 vs. 75 ± 24 (p = 0.63)
Seed activity ≥ 24 kBq (0.65 mCi) vs. < 24 kBq (0.65 mCi)	Urinary function	60 ± 29 vs. 80 ± 20 (p = 0.01)	80 ± 26 vs. 89 ± 17 (p = 0.20)
	Urinary bother	49 ± 25 vs. 67 ± 24 (p = 0.08)	71 ± 33 vs. 75 ± 24 (p = 0.74)

Table 4. Factors influencing bowel scores (mean ± standard deviation).

Tabelle 4. Faktoren mit Einfluss auf Stuhlgangwerte (Mittelwert ± Standardabweichung).

		Acute	Late
Prostate V_{200} ≥ 50% vs. < 50%	Bowel function	81 ± 20 vs. 88 ± 10 (p = 0.08)	88 ± 10 vs. 93 ± 8 (p = 0.02)
	Bowel bother	79 ± 25 vs. 89 ± 14 (p = 0.05)	87 ± 14 vs. 93 ± 9 (p = 0.03)
Prostate V_{150} ≥ 75% vs. < 75%	Bowel function	82 ± 20 vs. 88 ± 10 (p = 0.14)	87 ± 11 vs. 94 ± 7 (p < 0.01)
	Bowel bother	82 ± 22 vs. 88 ± 15 (p = 0.24)	88 ± 13 vs. 92 ± 11 (p = 0.25)
Needle number per cm^3 < 0.5 vs. ≥ 0.5	Bowel function	85 ± 17 vs. 87 ± 11 (p = 0.42)	88 ± 10 vs. 94 ± 7 (p = 0.01)
	Bowel bother	86 ± 21 vs. 87 ± 15 (p = 0.69)	88 ± 13 vs. 93 ± 9 (p = 0.11)

Table 5. Factors influencing sexual scores (mean ± standard deviation).

Tabelle 5. Faktoren mit Einfluss auf Sexualwerte (Mittelwert ± Standardabweichung).

		Acute	Late
Needle number per cm^3 < 0.5 vs. ≥ 0.5	Sexual function	20 ± 20 vs. 39 ± 21 (p < 0.01)	25 ± 21 vs. 41 ± 23 (p = 0.02)
	Sexual bother	55 ± 37 vs. 55 ± 31 (p = 0.99)	44 ± 41 vs. 60 ± 35 (p = 0.16)
Prostate volume ≥ 40 cm^3 vs. < 40 cm^3	Sexual function	22 ± 24 vs. 37 ± 20 (p = 0.02)	21 ± 23 vs. 38 ± 20 (p < 0.01)
	Sexual bother	53 ± 33 vs. 57 ± 34 (p = 0.69)	53 ± 38 vs. 53 ± 34 (p = 0.95)

Table 6. Pearson's correlation index between risk factors. NS: not significant.

Tabelle 6. Pearson-Korrelationskoeffizient zwischen Risikofaktoren. NS: nicht signifikant.

	Seminal vesicle D_{10}	Prostate V_{200}	Prostate V_{150}	Prostate D_{90}	Needle number per cm^3	Seed number per cm^3	Seed activity	Prostate volume
Seminal vesicle D_{10}	–	NS	0.30 ($p = 0.01$)	0.42 ($p < 0.01$)	NS	NS	NS	NS
Prostate V_{200}	NS	–	0.91 ($p < 0.01$)	0.73 ($p < 0.01$)	NS	–0.31 ($p < 0.01$)	0.49 ($p < 0.01$)	0.27 ($p = 0.02$)
Prostate V_{150}	0.30 ($p = 0.01$)	0.91 ($p < 0.01$)	–	0.83 ($p < 0.01$)	NS	–0.31 ($p < 0.01$)	0.46 ($p < 0.01$)	0.24 ($p = 0.04$)
Prostate D_{90}	0.42 ($p < 0.01$)	0.73 ($p < 0.01$)	0.83 ($p < 0.01$)	–	NS	NS	NS	NS
Needle number per cm^3	NS	NS	NS	NS	–	0.72 ($p < 0.01$)	–0.39 ($p < 0.01$)	–0.53 ($p < 0.01$)
Seed number per cm^3	NS	–0.31 ($p < 0.01$)	–0.31 ($p < 0.01$)	NS	0.72 ($p < 0.01$)	–	–0.73 ($p < 0.01$)	–0.80 ($p < 0.01$)
Seed activity	NS	0.49 ($p < 0.01$)	0.46 ($p < 0.01$)	NS	–0.39 ($p < 0.01$)	–0.73 ($p < 0.01$)	–	0.56 ($p < 0.01$)
Prostate volume	NS	0.27 ($p = 0.02$)	0.24 ($p = 0.04$)	NS	–0.53 ($p < 0.01$)	–0.80 ($p < 0.01$)	0.56 ($p < 0.01$)	–

into account, Sloboda et al. [28] recommend an activity of 0.4–0.6 mCi per seed for the best prostate coverage and urethral protection.

A prostate $D_{90} > 140$ Gy [15] or > 130 Gy [24] was found to significantly correlate with PSA relapse-free survival. Although a $D_{90} > 170$ Gy has not been shown to improve biochemical control any more, it had a significant impact on urinary toxicity in our study and should, as a consequence, be avoided.

Patients with a seminal vesicle $D_{10} < 190$ Gy, being an indicator of the dose to the bladder neck and the urethral sphincter muscle, reached late urinary function and bother scores that have not been lower compared to the control group scores before brachytherapy. By increasing the dose in this area, particularly the risk of urinary incontinence is raised.

The bowel domain has not been impaired seriously in the majority of patients. Prostate V_{200} and V_{150} can be more consistent parameters than the dose to the rectal wall. As indicators of dose inhomogeneity and the presence of larger areas with particularly high dose peaks, we have to assume an influence not only on the rectal wall and mucosa itself but also on the vascular supply around the rectal wall.

Finally, patients with smaller prostates (cutoff < 40 cm^3 found significant) were found to reach better acute and late sexual function scores. In a simultaneously submitted study [24], examining the changes of dose delivery within the 1st month after a permanent implant, we could demonstrate the development of a larger edema in smaller prostate volumes and a consequential lower dose in the periphery (rectum V_{100} and prostate D_{90}). Apparently, due to this effect, the dose to the neurovascular bundles is likewise lower.

Conclusion

HRQoL of patients treated with a permanent implant can be improved by using an adequate amount of sources and needles, resulting in a better dose homogeneity without impairing prostate D_{90}. Areas covered by an excessively high dose may contribute to brachytherapy-related morbidity. A prostate $D_{90} < 170$ Gy and a base of seminal vesicle $D_{10} < 190$ Gy (as an indicator of the dose to the bladder neck and urethral sphincter) can be recommended to maintain a satisfactory urinary function. A prostate $V_{200} < 50\%/V_{150} < 75\%$ proved to be associated with best rectal function scores.

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Address for Correspondence
Dr. Michael Pinkawa
Klinik für Strahlentherapie
Universitätsklinikum Aachen
Pauwelsstraße 30
52057 Aachen
Germany
Phone (+49/241) 808-9260, Fax -8425
e-mail: mpinkawa@ukaachen.de