Single-Institution Results of Primary External-Beam Radiation for the Treatment of T1–T3 Prostate Cancer

Wolfgang Weiss[1], Wolfgang Horninger[2], Britta C. Forthuber[1], Hanno Ulmer[3], Peter Lukas[1], Reinhart A. Sweeney[1]

Purpose: To evaluate survival and toxicity rates after primary external-beam radiation for the treatment of prostate cancer.
Patients and Methods: Data of 306 patients treated with conformal external beam radiation between 1996 and 2001 were collected. These were evaluated in terms of overall, cause-specific and disease-free survival as well as toxicity. Furthermore, an investigation of possible risk factors was performed.
Results: Toxicity rates compared favorably with other series with 5.2% RTOG 1–2 and no RTOG > 2 long-term side effects. Actuarial 5-year overall survival rates with and without biochemical failure were 77% versus 78%, cancer-specific survival was 85.41% versus 100%, and disease-free survival was 71.54%, respectively. Potential risk factors for cancer-related death were biochemical failure, initial serum prostate-specific antigen (PSA) and Gleason score.
Conclusion: Toxicity rates were found to be surprisingly low compared to other series, which is likely due to low daily dose and consistent MR-based treatment planning. In terms of survival, no significant differences to other trials could be observed. Initial PSA and Gleason score were significant predictors for treatment outcome in terms of survival.

Key Words: Prostate cancer · Radiotherapy · Toxicity · Survival

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Ergebnisse der primären perkutanen Radiatio in der Behandlung von T1–T3-Prostatakarzinomen

Ziel: Evaluierung von Überleben und Toxizität nach primärer perkutaner Strahlentherapie in der Behandlung des Prostatakarzinoms.
Patienten und Methodik: Die Daten von 306 zwischen 1996 und 2001 mittels konformaler externer Radiatio behandelten Patienten wurden erhoben und ausgewertet. Anschließend wurden die Ergebnisse im Hinblick auf Gesamtüberleben, tumorspezifisches Überleben und rezidivfreies Überleben sowie Toxizität analysiert. Zusätzlich wurde versucht, Risikofaktoren zu finden, welche mit einem schlechteren Outcome assoziiert sind.
Ergebnisse: Im Vergleich mit anderen Studien wurden deutlich niedrigere Toxizitätsraten festgestellt, mit Langzeitnebenwirkungsraten im urogenitalen Bereich von 5,2% RTOG 1–2 und keinerlei Grad-3- und Grad-4-Toxizität. Das aktuarische 5-Jahres-Gesamtüberleben betrug 77% bzw. 78% in Abhängigkeit vom Auftreten eines biochemischen Rezidivs. Das tumorspezifische Überleben betrug 85,41% bzw. 100%, das rezidivfreie Überleben 71,54%. Als potentielle Risikofaktoren für tumorspezifische Todesfälle erwiesen sich sowohl das biochemische Rezidiv als auch initiales Serum-PSA (prostataspezifisches Antigen) und Gleason-Score.
Schlussfolgerung: Verglichen mit anderen Studien wurde ein überraschend günstiges Nebenwirkungsprofil festgestellt, welches mit hoher Wahrscheinlichkeit auf niedrigere Einzelfraktionsdosen sowie konsequente MR-basierte Bestrahlungsplanung zurückzuführen ist. Hingegen konnte im Hinblick auf die Überlebensraten kein wesentlicher Unterschied zu Vergleichsarbeiten beobachtet werden. Initialer PSA-Wert und Gleason-Score scheinen die signifikantesten Parameter im Hinblick auf das Überleben zu sein.

Schlüsselwörter: Prostatakarzinom · Strahlentherapie · Toxizität · Überleben

[1] Department of Radiotherapy, University Hospital of Innsbruck, Austria,
[2] Department of Urology, University Hospital of Innsbruck, Austria,
[3] Department of Biostatistics, University Hospital of Innsbruck, Austria.

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Introduction

Prostate cancer is one of the leading malignant tumor entities amongst men with an incidence of 60 new cases per 100,000 per year. Aside from surgery, the only other curative therapy is radiation therapy. In addition to lowering mortality rates, long-term toxicity must be taken into account as criteria for evaluating the quality of a given therapy, especially in a disease with favorable prognosis. The introduction of conformal irradiation techniques must be considered a major achievement for the patient, as it allows the radiooncologist to deliver higher doses to the target tissue without a significant increase in toxicity [9, 17]. Nonetheless, there is no international or even national consensus in planning or performing external-beam radiation treatment. This study retrospectively analyzes the results of a large, homogeneously treated patient collective of a single institution in regard to parameters of prognostic relevance in etiopathology, and toxicity rates compared to published series.

Patients and Methods

Between 1996 and 2001, 360 men with primary disease were treated at the authors' department. The following inclusion criteria for this evaluation had to be fulfilled:

- patients suffering from prostate cancer at any tumor stage < T4 (diagnostic imaging reports, however, did not differentiate between cT1c and cT2 from 1996 to 2000; therefore, a preponderance of cT1c could be observed),
- clinical absence of lymph node or distant metastasis at the time of diagnosis, regardless of serum prostate-specific antigen (PSA) concentration (based upon data delivered by diagnostic imaging reports from CT and/or bone scans),
- knowledge of comorbidity and symptoms prior to radiotherapy,
- known PSA at the time of diagnosis,
- known PSA at last follow-up,
- last follow-up not more than 0.5 years ago,
- known patient's status.

In close collaboration with the Department of Urology and surrounding local urologists, all necessary data was collected. To complete datasets still lacking important information, the patients' general practitioners were contacted as required. 306 men fulfilled the aforementioned criteria (a total of 15% were lost to follow-up) and provided enough essential data to be included in the study. A distinctive advantage of this retrospective evaluation is the information offered by the provincial cancer registry, which provided us with data concerning the patients' survival status. Thus, at least concerning overall survival, very few patients could be considered "lost to follow-up", namely only those who died after moving away from Tyrol so they would not have been registered. Migration patterns especially for the senior population in Tyrol, however, show very sedentary characteristics [1].

Increasing serum PSA concentration was chosen as an endpoint for clinical outcome in terms of disease-free survival (Houston criteria for biochemical failure: PSA level ≥ 2 ng/ml above nadir [8, 15]). Local failure could not be evaluated due to the immediate onset of androgen deprivation therapy following biochemical failure without the existence of imaging or biopsies to prove failure. Distant failure was proven by radionuclide bone scan and/or CT and/or MR imaging.

Parameters for Irradiation

Radiotherapy consisted of 16-MV photon beams delivered to the prostate and/or seminal vesicles up to a total of 70.2 Gy in 1.8 Gy per fraction via a four-field technique. Clinical tumor volume (CTV) was defined as the prostate including seminal vesicles up to 50.4 Gy at which point the CTV was reduced to the prostate only. The CTV was always defined individually according to pelvic coronal and sagittal MR images projected onto the respective fluoroscopic images at simulation [18]. Planning target volume (PTV) was defined as CTV plus 1.5 cm in all directions. Care was always taken not to include the entire rectal circumference by placing an individual rectal block according to contrast application under fluoroscopy, if necessary. Patients were asked not to void at least 2 h prior to radiotherapy to ensure some consistency in bladder filling. The dose was prescribed to the central part of the PTV on the central axis of the beam intersections as recommended by the International Commission On Radiation Units and Measurements (ICRU).

Follow-Up

Clinical symptoms were monitored at least once weekly during radiotherapy. At the last treatment, patients were physically examined and asked for subjective discomfort. All symptoms were recorded with special focus on gastrointestinal and urinary toxicity as well as dermatologic side effects. In general, the first routine follow-up was 2 weeks later, then every 3 months and once yearly thereafter, either at the ambulatory clinic for radiotherapy or at the patient's urologist/general practitioner. Residual side effects 3 months after treatment were classified as late toxicity, those healed prior to this were classified as acute toxicity. After 2 years, routine follow-up was often performed at the referring urologists.

Statistics

Kaplan-Meier statistics were used to generate survival curves. Multivariate analyses were performed using Cox proportional hazard regression. Statistical Package for Social Sciences (SPSS) was used for all analyses.

Results

306 patients, subjected to primary radiotherapy for prostate cancer between 1996 and 2001, fulfilled the criteria to be included in the analysis. The median observation period was 54.9 months, median age was 76 years. Median serum PSA level at time of diagnosis and Gleason score were 8.7 ng/ml and 6, respectively (Table 1). The preponderance of cT1c-staged can-

Table 1. Patients' characteristics. PSA: prostate-specific antigen.
Tabelle 1. Patientencharakteristika. PSA: prostataspezifisches Antigen.

Patients total	306
Age (median)	76
Comorbidity	59.8 %
Initial PSA (median)	8.7 ng/ml
Gleason score (median)	6
Observation period (median)	54.9 months
Biochemical failures	88 (28.8 %)
Total deaths	70 (22.9 %)
Deaths from cancer	15 (5.2 %)

cers is due to the lack of clinical staging information extractable from diagnostic imaging reports prior to 2000. Therefore, we did not include T-stage in analytic calculations to prevent a methodical error from falsifying our data (Table 2).

Survival Analyses

5-year overall survival rates for patients with and without PSA failure were 77% and 78%, respectively. The most significant parameters indicating a poorer outcome were comorbidity and Gleason score. Cause-specific survival was 95.20% at 5 years depending on whether biochemical failure had occurred (85.41% after failure vs. 100% otherwise). A total of 88 (29%) biochemical failures during the whole observation period were seen, resulting in 16 deaths from disease. Biochemical failure, PSA level at diagnosis and Gleason score were found to be of highest importance regarding cause-specific survival. 5-year disease-free survival rate was 71.54% with PSA level at the time of diagnosis and Gleason score being the only independent factors. Mostofi grading failed to prove significance in multivariate analysis (Figures 1 to 3, Tables 3 to 5).

Treatment Toxicity

Of all 306 patients included in the study, 60 (19.6%) felt no side effects at all, so some form of radiation-induced symptoms occurred in 246 men (80.40%) during and/or following therapy. There was insufficient data on impotence to include this aspect in the evaluation.

Urologic Toxicity

Mild symptoms (RTOG 1 and 2) related to bladder and urethra were reported by 190 men (62.1%) during therapy, nine patients (2.9%) had RTOG grade 3 toxicity. 107 men had no genitourinary symptoms (35%). 16 men (5.2%) still suffered from radiation-induced urologic side effects (RTOG ≤ 2) 90 days after treatment completion (Figure 4). Grade 3 or 4 toxicity was not reported.

Table 2. T-stage distribution.
Tabelle 2. T-Stadien-Verteilung.

T-stage	Frequency	%
cT1c	158	51,6
cT2	99	32,4
cT3	49	16,0

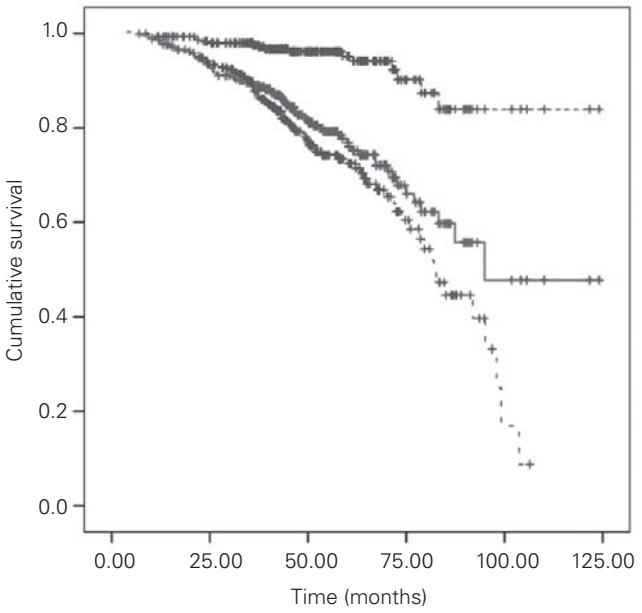

Figure 1. Actuarial overall (OS), cause-specific (CSS) and disease-free (DFS) survival rates. Due to a median observation of only 54.9 months, the curves are not representative after approximately 75 months. Longer observation is needed.

Abbildung 1. Aktuarisches Gesamt- (OS), tumorspezifisches (CSS) und krankheitsfreies (DFS) Überleben. Aufgrund des medianen Beobachtungszeitraums von lediglich 54,9 Monaten verlieren die Kurven nach ca. 75 Monaten ihre Aussagekraft. Ein längerer Beobachtungszeitraum ist erforderlich.

Gastrointestinal Toxicity

Grade 1 and 2 symptoms were reported by 96 patients (31.4%), eight men had grade 3 toxicity (2.6%). Ten patients (3.2%) had continuing side effects after 90 days. No grade 3 or 4 late toxicity was reported (Figure 5).

Dermatologic Toxicity

Mild erythema was found in 97 men (31.7%), mostly vanishing within 3 weeks after treatment. No skin-related late toxicity was reported.

Discussion

Overall Survival

On first glance, this collective's overall survival seems lower than that of other large meta-analyses. 78% actuarial 5-year overall survival stands in contrast to 88% and 85% as reported by Kwan et al. and Williams et al., respectively [11, 19]. In this context, the relatively high median age of our patients (76 years compared to 69 years for Williams et al.) as well as the

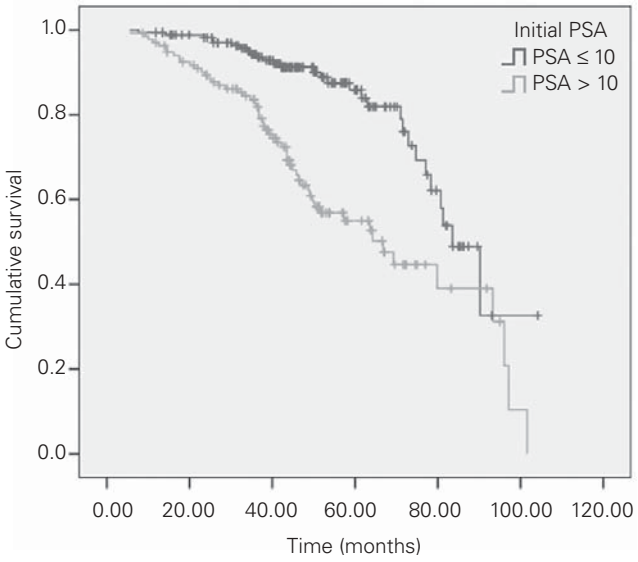

Figure 2. Disease-free survival depending upon initial PSA value.

Abbildung 2. Rezidivfreies Überleben in Abhängigkeit vom initialen PSA-Wert.

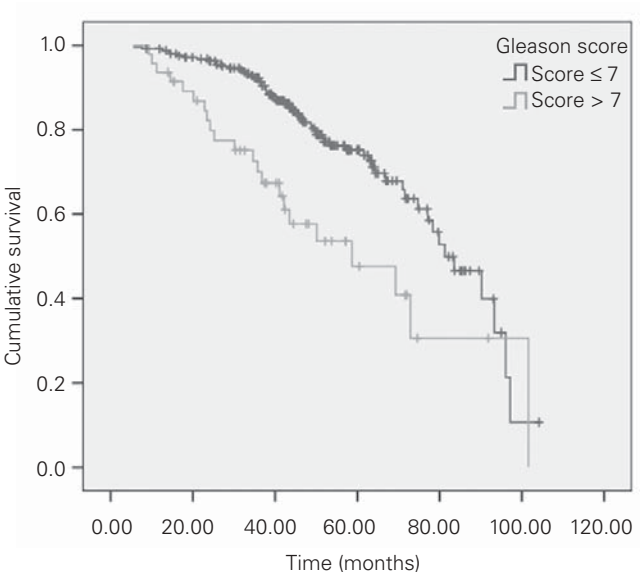

Figure 3. Disease-free survival depending upon initial Gleason score.

Abbildung 3. Rezidivfreies Überleben in Abhängigkeit vom initialen Gleason-Score.

Table 3. Overall survival. PSA: prostate-specific antigen.

Tabelle 3. Gesamtüberleben. PSA: prostataspezifisches Antigen.

Parameter	p-value
Age	0,034
Comorbidity	0,048
Initial PSA	0,233
Gleason score	0,233

Table 4. Cause-specific survival. PSA: prostate-specific antigen.

Tabelle 4. Tumorüberleben. PSA: prostataspezifisches Antigen.

Parameter	p-value
Age	0,041
Comorbidity	0,822
Initial PSA	0,017
Gleason score	0,016
Mostofi grading	0,331
Biochemical failure	< 0,001

Table 5. Disease-free survival. PSA: prostate-specific antigen.

Tabelle 5. Rezidivfreies Überleben. PSA: prostataspezifisches Antigen.

Parameter	p-value
Age	0,653
Comorbidity	0,757
Initial PSA	< 0,001
Gleason score	0,017
Mostofi grading	0,153

high incidence of various internistic comorbidity (65%) are likely to be held responsible.

Additionally, Gleason score of the tissue specimen was found to be significant as already stated by Kwan et al. and others. By contrast, an influence of initial serum PSA level could not be demonstrated. Unfortunately, the relevance of tumor stage could not be investigated due to the lack of clinical staging information prior to the year 2000. For the same reason, the value of neoadjuvant hormone deprivation therapy also remains unclear in this retrospective evaluation.

Cause-Specific Survival

As the actual data shows, there is a slight but not significant advantage in terms of actuarial cause-specific survival for our patients (95%) compared to the analyses of Kwan et al. (84.4%) and Williams et al. (94.4%), at least for a period of 5 years [11, 19]. Both groups reported initial PSA and Gleason score as well as biochemical failure being highly significant prognostic factors, which are findings our data fully confirms. It is to be mentioned that the prescribed total dose to the target volume does not seem to alter the outcome. Neither Williams et al. who had a dose range between 52.5 and 66.0 Gy (2 Gy per fraction) nor Kwan et al. with a dose range between 66.0 and 72.0 Gy (2 Gy per fraction) nor Mayer et al. [12] with doses ranging from 50.0 to 72.0 Gy (1.8 Gy per fraction) were able to demonstrate a significant advantage in survival compared to our own data. However, a definite conclusion should not be drawn at this point of time, as possibly only long-term observation might be able to show the value of higher doses on survival.

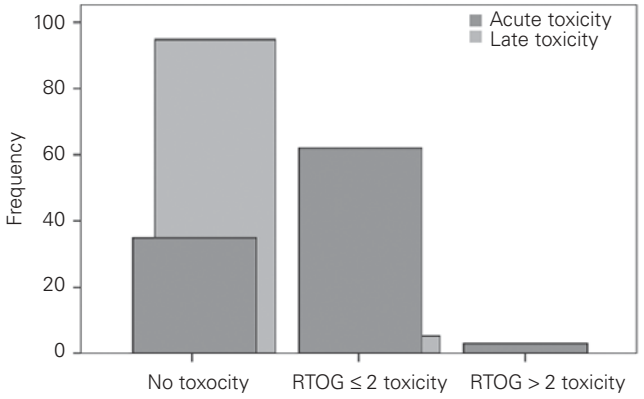

Figure 4. Urologic acute and late toxicity.

Abbildung 4. Urologische Akut- und Spätnebenwirkungen.

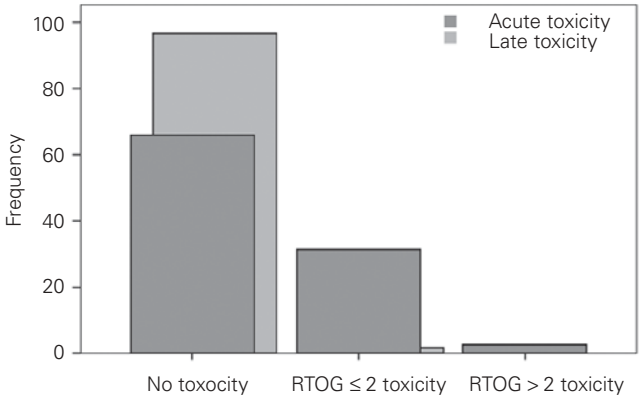

Figure 5. Acute and late gastrointestinal toxicity.

Abbildung 5. Gastrointestinale Akut- und Spätnebenwirkungen.

Biochemical Failure

In absolute numbers, 28% of our patients suffered biochemical failure within the whole observation period. The actuarial 5-year relapse-free rate (71.54%) compares favorably with other series (Kwan et al.: 62.7%, Williams et al.: 33.9%). Mayer et al. found pretreatment PSA level, Gleason score and tumor stage to be predictive for the risk of biochemical failure (20.3%) in patients following primary irradiation which can also be said for our own collective (T-stage which was not included in the evaluation) [11, 12, 19]. Kupelian et al. reported 5-year disease-free survival rates between 51% and 83% after evaluating the outcome of 2,991 patients treated with different dose schemes. They concluded that low radiation doses < 72 Gy should be avoided due to poor results and found initial PSA, Gleason score and total dose to be independent prognostic factors [10]. Although our own collective performs much better than reported by Kupelian et al. at a dose of 70.2 Gy (51% vs. 72%), the above-mentioned findings of Kwan et al. (66–72 Gy) and Williams et al. (52.5–66 Gy) indirectly support the data of Kupelian et al. and higher radiation doses might be favorable. However, longer observation is needed to draw a conclusion on the value of dose escalation, a statement that is also supported by Goldner et al. [6]. Other factors possibly influencing outcome such as PSA dynamics after treatment were not investigated. For example, Geinitz et al. reported PSA nadir and time to PSA nadir being predictive for biochemical failure in their trial on 180 patients [4].

Toxicity

The prognosis of prostate cancer patients seems to be favorable in terms of survival as shown above. However, the high rate of men surviving ≥ 5 years emphasizes quality-of-life considerations. Long-term toxicity following irradiation can severely impede a patient's quality of life. After performing a search through published peer-reviewed literature dealing with this aspect, it can be observed that patients of nearly all large studies were consistently 3-D-CT-planned and treated with daily doses of 2.0–2.5 Gy up to a total dose of 50.0–80.0 Gy. Using such treatment setup, Beckendorf et al. reported acute toxicity of up to 88% and long-term toxicity (2 months after therapy) in up to 25% of the cases in a total of 306 men observed. A difference between a 70-Gy and an 80-Gy arm could not be found [2]. Similar data was reported by Peeters et al. having up to 29.7% gastrointestinal (RTOG ≥ 2) and 28.5% urogenital (RTOG ≥ 2) long-term toxicity rates with no significant difference between total doses of 68 Gy versus 78 Gy [14]. Comparing our own data to this, incidences of side effects (especially long-term) seem to be favorable (5.2% urologic, 3.2% gastrointestinal late toxicity, no RTOG grade 3 or 4). Therapy-induced impotence as a part of the toxicity profile was not considered in our trial, first, because the exact point of onset could not be evaluated retrospectively, second, due to the fact that applied hormone deprivation therapy is an independent influence, and, third, because this symptom is not covered by the RTOG criteria. Without performing an in-depth discussion about a possible correlation between toxicity and planning target volumes (not evaluated in our own study), two additional aspects should be taken into account which are hardly mentioned in the reviewed literature. As stated above, our own patients were treated with a single fractionation dose of 1.8 Gy per day, planned via MR projection. The common method of using a rectal balloon for sparing the rectal wall was never exercised at our institution and does not seem to be necessary in view of our disease-free survival and toxicity results, especially as it is causing substantial discomfort in most patients [5, 7]. As already mentioned, the total target volume dose was not found to significantly alter toxicity rates in different trials, a fact which was additionally affirmed by Valicenti et al. who failed to show differences between 68 and 79 Gy [16]. Possibly, the fractionation scheme is the key to lowering toxicity. Therefore, it remains unclear to the authors why there are no intentions to use 1.8 Gy a day as gold standard, especially when taking into account that survival rates seem uninfluenced. Of course it must be mentioned that long-term

results (8 or 10 years) are not yet available. Unfortunately, due to the lack of a control group in our own institution (i.e., patients receiving ≥ 2.0 Gy) we cannot draw a definite conclusion on this subject. However, as stated above, there is a second point that may influence the favorable toxicity profile being the consistent use of MR-projected treatment planning. Wachter et al. were able to show that MR delivers anatomic detail information that is far superior to CT, thus optimizing normal tissue sparing [17]. Finally, it is to be mentioned that the introduction of new treatment schemes will much likely lead to a further decline in toxicity: intensity-modulated radiotherapy and proton-based radiotherapy [3, 13].

Conclusion

In our study, we retrospectively analyzed data of 306 patients suffering from prostate cancer, homogeneously treated with conformal external-beam radiation between 1996 and 2001 at a single institution. Toxicity rates were found to be substantially lower for our patients compared to other published series, most notably the absence of grade 3–4 toxicity. Possible explanations for this might be the used fractionation of 1.8 Gy and careful MR-based treatment volume definition. Our cause-specific and disease-free survival confirm previously published results. 5-year rates for overall, cause-specific and disease-free survival were 78%, 95.20% and 71.54%, respectively. Pretreatment PSA and Gleason score were found to be of great importance in predicting therapy outcome and biochemical failure was the most important negative prognostic factor for cancer-specific death. Due to the relatively short median follow-up of 54.9 months, no sensible 8- or 10-year survival rate prediction could be made. Hence, further observation is needed.

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Address for Correspondence
Dr. Wolfgang Weiss
Department of Radiotherapy
University Hospital of Innsbruck
Anichstraße 35
6020 Innsbruck
Austria
Phone (+43/512) 504-22801, Fax -22812
e-mail: wolfgang.weiss@uibk.ac.at