Long-Term Results in Three-Dimensional Conformal Radiotherapy of Localized Prostate Cancer at Moderate Dose (66 Gy)

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Purpose: Biochemical control (bNED), disease-specific survival (DSS), overall survival (OS), and late gastrointestinal (GI) and urogenital (UG) side effects (EORTC/RTOG) of patients with long-term follow-up were evaluated.
Patients and Methods: Three-dimensional radiotherapy up to 66 Gy with/without additional hormonal therapy was performed in 154 prostate cancer (T1–3 N0 M0) patients. According to T-stage, pretreatment prostate-specific antigen (PSA) and grading, patients were divided into a low-, intermediate-, and high-risk group. The 5-, 8-, and 10-year actuarial rates of bNED, DSS and OS and late side effects were calculated.
Results: Median follow-up was 80 months. Additional hormonal therapy was given in 57% of patients. Distribution concerning risk groups (low, intermediate, high) showed 15%, 49%, and 36% of patients, respectively. bNED 5-, 8-, and 10-year actuarial rates were 46%, 44%, and 44%. DSS 5-, 8- and 10-year rates amounted to 96%, 90%, and 82%. OS 5-, 8- and 10-year rates were 81%, 64%, and 56%. In uni- and multivariate analysis, only pretreatment PSA (< 10 vs. ≥ 10 ng/ml; $p < 0.05$) and PSA nadir (< 0.5 vs. ≥ 0.5 ng/ml; $p < 0.0001$) affected bNED significantly. Age, risk group, T-stage, grading, and hormonal therapy had no significant influence on bNED, DSS, and OS. Rates of late GI and UG side effects grade ≥ 2 at 5 years were 17% and 15%.
Conclusion: Current dose escalation studies with better bNED rates may be able to further increase long-term clinical outcome.

Key Words: Prostate cancer · Conformal radiotherapy · Long-term results · bNED · Survival

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Langzeitergebnisse bei dreidimensionaler konformaler Radiotherapie des lokalisierten Prostatakarzinoms mit moderater Dosis (66 Gy)

Ziel: Evaluierung der Langzeitergebnisse von biochemischer Rezidivfreiheit (bNED), krankheitsspezifischem Überleben (DSS) und Gesamtüberleben (OS) sowie später rektaler (GI) und urogenitaler (UG) Nebenwirkungen nach EORTC/RTOG.
Patienten und Methodik: 154 Patienten mit Prostatakarzinom (T1–3 N0 M0) erhielten eine dreidimensionale Radiotherapie bis 66 Gy mit/ohne Hormontherapie. Nach T-Stadium, prostataspezifischem Antigen (PSA) und Grading wurden die Patienten einer Niedrig-, Mittel- und Hochrisikogruppe zugeordnet. Die aktuarischen 5-, 8- und 10-Jahres-Daten von bNED, DSS und OS sowie Spätnebenwirkungen wurden ermittelt.
Ergebnisse: Der mittlere Nachbeobachtungszeitraum betrug 80 Monate. Eine Hormontherapie wurde bei 88/154 Patienten (57%) durchgeführt. In der Niedrig-, Mittel- und Hochrisikogruppe fanden sich 15%, 49% und 36% der Patienten. Die 5-, 8- und 10-Jahres-Daten bezüglich bNED ergaben 46%, 44% und 44%, bezüglich DSS 96%, 90% und 82% und bezüglich OS 81%, 64% und 56%. Bei uni- und multivariater Analyse zeigten prätherapeutisches PSA (< 10 ng/ml vs. ≥ 10 ng/ml; $p < 0,05$) und PSA-Nadir (< 0,5 ng/ml vs. ≥ 0,5 ng/ml; $p < 0,0001$) einen signifikanten Einfluss auf bNED. Alter, Risikogruppe, T-Stadium, histologisches Grading und Hormontherapie hatten keinen signifikanten Einfluss auf bNED, DSS und OS. GI und UG Spätnebenwirkungen Grad ≥ 2 nach 5 Jahren fanden sich bei 17% bzw. 15%.
Schlussfolgerung: Dosiseskalationsstudien mit besseren bNED-Raten sollten das Potential für eine weitere Verbesserung der klinischen Langzeitergebnisse haben.

Schlüsselwörter: Prostatakarzinom · Konformale Strahlentherapie · Langzeitergebnisse · Biochemische Rezidivfreiheit · Überleben

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Introduction

In the beginning of three-dimensional conformal radiotherapy (3D-CRT) doses of ≤ 70 Gy were standard in localized prostate cancer radiotherapy. In a patterns-of-care survey, Zelefsky et al. [32] found only 3% of patients treated with doses ≥ 72 Gy in 1994 compared to 45% in 1999. Since 1996 multiple studies have illustrated a dose response [11, 18, 20, 21, 31] resulting in doses of ≥ 72 Gy in clinical routine nowadays. Furthermore, new technologies, such as computerized treatment plan optimization and intensity-modulated radiotherapy, offer new possibilities for dose escalation [2, 5–7, 9, 12, 14, 17, 23, 25].

All of these dose-escalating studies have more or less demonstrated an improvement in biochemical control. However, most reports have been based on series with a relatively short median follow-up. Due to the possibility of late failure and the long natural history of prostate cancer, long-term follow-up is, moreover, necessary to achieve appropriate data concerning survival. Furthermore, the ASTRO definition of biochemical control (bNED) may underestimate true failure due to backdating failure and inadequate follow-up [26]. Therefore, long-term follow-up is also required to achieve appropriate data about bNED.

Patients and Methods

Patients

154 prostate cancer patients (T1–3 N0 M0) treated between 02/1994 and 04/1999 were included. According to T-stage, grading (Gleason Score was determined only in a limited number during that time) and maximal pretreatment prostate-specific antigen (PSA), patients were classified into three risk groups. The low-risk group was defined as patients with a PSA < 10 ng/ml, T1/2 and G1/2. The intermediate-risk group was defined as a PSA of 10–20 ng/ml, T1/2 and G1–3, or patients with G3, T1/2 and a PSA < 10 ng/ml. The high-risk group included all patients with T-stage 3 and/or a PSA > 20 ng/ml. Additional hormonal treatment was recommended for intermediate- and high-risk patients.

Irradiation Technique

All patients were treated up to a total dose of 66 Gy (2 Gy/fraction) at the ICRU reference point. The clinical target volume included the prostate ± (base of) seminal vesicles. The planning target volume included a margin of 1.5–2.0 cm in the first 3 years and 0.5–1 cm thereafter [28, 29]. A rectal balloon catheter was placed before each treatment [8].

Follow-up

All measures of time were calculated from the last day of radiotherapy. During the first 4 years after radiotherapy, patients were seen every 3–6 months and at least once a year thereafter. Gastrointestinal (GI) and urogenital (UG) side effects were scored according to the EORTC/RTOG criteria. bNED was defined according to the ASTRO guidelines [1]. In addition, the start of hormonal therapy after irradiation was regarded as biochemical failure.

Statistical Analysis

Data were analyzed using SPSS® statistical software. A value of $p < 0.05$ was considered significant. Survival times were calculated by the Kaplan-Meier method using log-rank test for univariate analysis. The influence of T-stage, grading, PSA, risk group, hormonal therapy, PSA nadir and age on bNED, disease-specific survival (DSS) and overall survival (OS) was investigated by Cox regressions for multivariate analysis.

Results

Patients, Follow-up, and PSA Nadir

The median age was 70 years (54–86 years). The median follow-up for all 154 patients was 80 months (1–133 months) and 95 months (56–133 months) for the surviving patients, respectively.

Patient distribution concerning T-stage, grading, maximal pretreatment PSA, risk group, additional hormonal therapy, and duration of hormonal therapy is shown in detail in Table 1. One patient could not be classified to any risk group due to missing data. Radiotherapy alone was performed in 66 patients (43%), irradiation and hormonal therapy in 88 (57%). The median duration of hormonal treatment was 22 months

Table 1. Patients' characteristics (n = 154). PSA: prostate-specific antigen.

Tabelle 1. Patientencharakteristika (n = 154). PSA: prostataspezifisches Antigen.

n (%)	Patients
T-stage	
T1	24 (16)
T2	99 (64)
T3	28 (18)
Tx	3 (2)
Grading	
G1	60 (39)
G2	71 (46)
G3	14 (9)
Gx	9 (6)
Maximum PSA	
< 10 ng/ml	65 (42)
10–20 ng/ml	54 (35)
> 20 ng/ml	35 (23)
Risk group[a]	
Low	23 (15)
Intermediate	75 (49)
High	55 (36)
Hormonal therapy	
Yes	88 (57)
< 6 months	22 (25)
6–12 months	35 (40)
> 12 months	31 (35)

[a]one patient could not be classified due to missing data

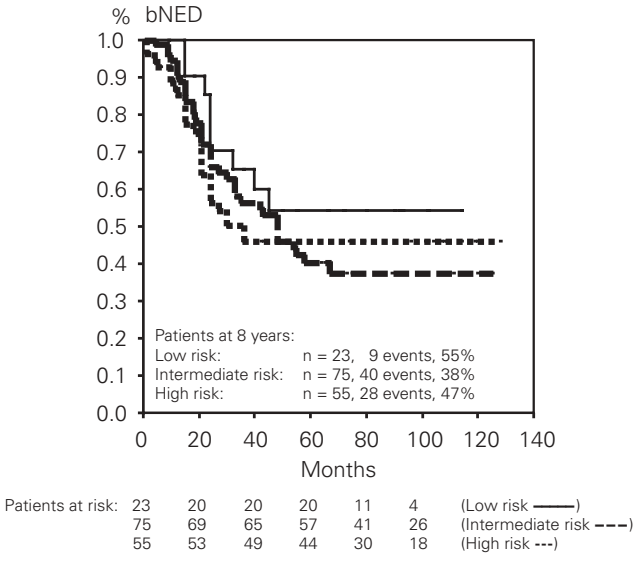

Figure 1a – Abbildung 1a

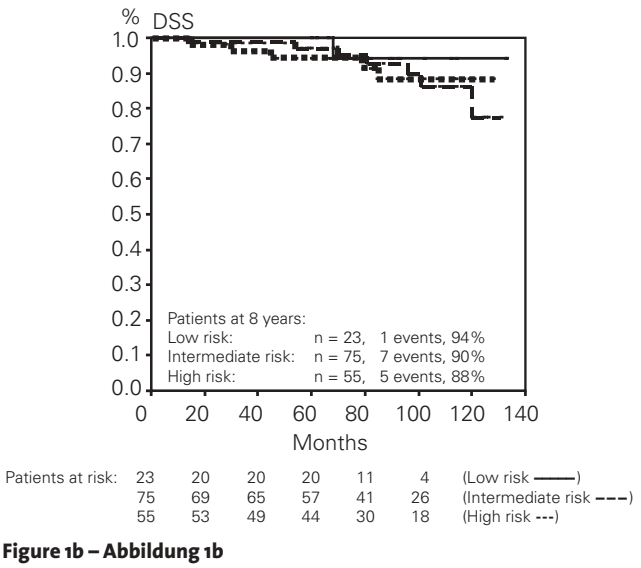

Figure 1b – Abbildung 1b

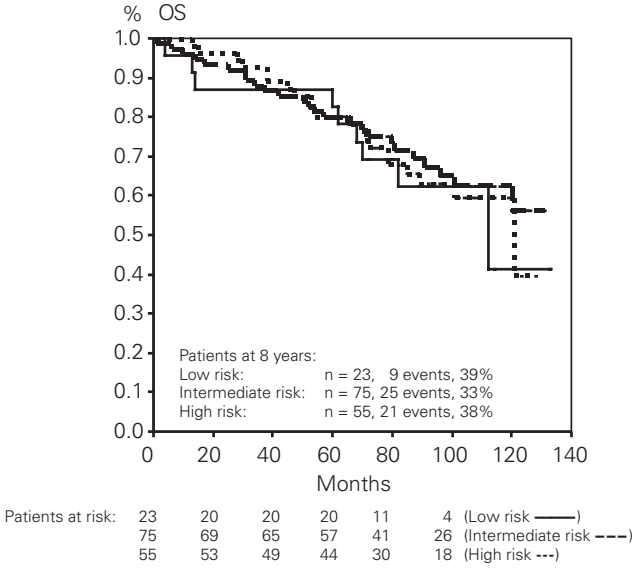

Figure 1c – Abbildung 1c

Figures 1a to 1c. a) bNED (biochemically no evidence of disease), b) DSS (disease-specific survival), and c) OS (overall survival) according to risk groups.

Abbildungen 1a bis 1c. a) bNED (biochemische Rezidivfreiheit), b) DSS (krankheitsspezifisches Überleben) und c) OS (Gesamtüberleben) entsprechend den Risikogruppen.

(1–120 months). The distribution of patients with versus without hormonal therapy concerning risk group was 48% versus 52% in the low-/intermediate-risk group and 72% versus 28% in the high-risk group, respectively.

The median time of reaching a PSA nadir after radiotherapy was 17 months. The distribution of PSA nadirs showed 57% of patients reaching a level < 0.5 ng/ml.

bNED Control

77 patients (50%) were found to have biochemical failure. 35/77 patients showed signs of distant metastases (bone and/or lymph nodes). The actuarial bNED control rate for all 154 patients was 46% at 5 years and 44% each at 8 and 10 years. When bNED control rates were stratified by risk groups (low-, intermediate-, high-risk group), the 8-year actuarial rate was 55%, 38%, and 47% respectively (Figure 1a). When patients were stratified by pretreatment PSA (< 10 ng/ml vs. 10–20 ng/ml vs. > 20 ng/ml), the 8-year rate was 51% versus 38% versus 36%, finding a significant difference between < 10 ng/ml versus 10–20 ng/ml and > 20 ng/ml ($p < 0.05$) in univariate analysis. Comparing the 8-year bNED rate of patients with versus without additional hormonal therapy, a difference of 50% versus 36% was found. When bNED control rates were stratified by PSA nadir, the 8-year rate showed a significant difference ($p < 0.0001$) with 58% (nadir < 0.5 ng/ml) compared to 19% (nadir ≥ 0.5 ng/ml; Figure 2).

Disease-Specific Survival (DSS) and Overall Survival (OS)

At the time of evaluation, 99 patients (64%) were alive. Of the 55 nonsurvivors (36%), 42 died of intercurrent disease and 13 of prostate cancer (eight patients with bone and lymph node metastases, three patients with bone metastases, and two patients with lymph node metastases, Figure 3), resulting in an actuarial DSS rate at 5, 8, and 10 years of 96%, 90%, and 82%, respectively. When DSS was stratified by risk group (low-, intermediate-, high-risk group), the 8-year rates were 94%, 90%, and 88%, respectively (Figure 1b). When patients were stratified by PSA (< 10 ng/ml vs. 10–20 ng/ml vs. > 20 ng/ml), the 8-year DSS rates were 92% versus 91% versus 86%. Comparing patients with versus without additional hormonal therapy, the 8-year DSS rates were 93% versus 90%. When DSS

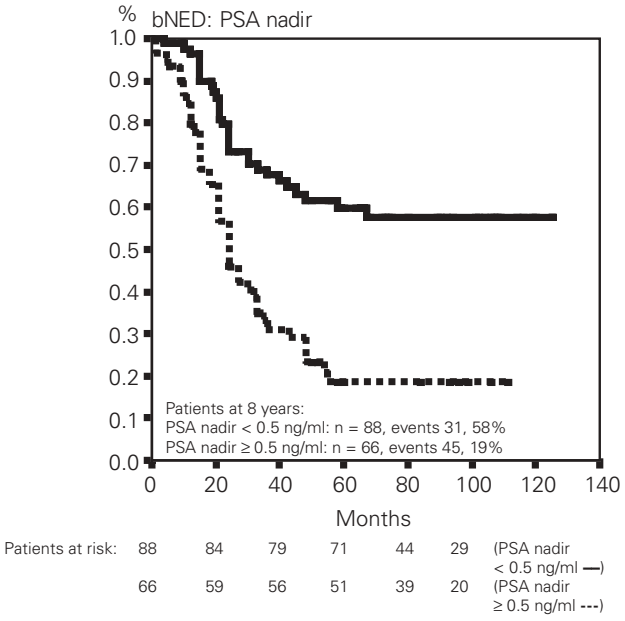

Figure 2. bNED (biochemically no evidence of disease): significant difference concerning PSA nadir ($p < 0.0001$) at 96 months: 58% vs. 19%.

Abbildung 2. bNED (biochemische Rezidivfreiheit): signifikanter Unterschied bezüglich PSA-Nadir ($p < 0{,}0001$) nach 96 Monaten: 58% vs. 19%.

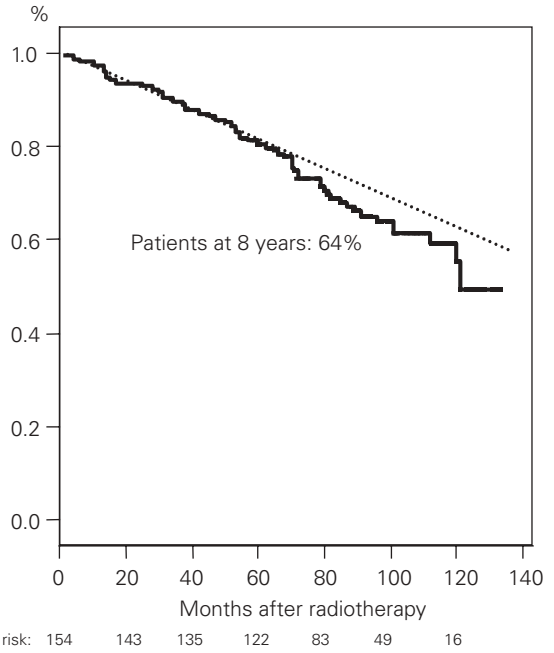

Figure 4. Overall survival compared to expected survival for an age-matched male Austrian population (dotted line).

Abbildung 4. Gesamtüberleben im Vergleich zu altersentsprechenden österreichischen Männern (gepunktete Linie).

rates were stratified by PSA nadir, the 8-year rate showed a significant difference ($p < 0.005$) with 97% (nadir < 0.5 ng/ml) compared to 83% (nadir ≥ 0.5 ng/ml), respectively.

The actuarial OS rate at 5, 8, and 10 years after radiotherapy was 81%, 64%, and 56%, respectively. Figure 1c shows the OS curves according to risk groups. When OS rates were stratified by risk group, pretreatment PSA, hormonal therapy or PSA nadir, no significant difference was found. The OS for the study patients compared with the expected survival for an age-matched male Austrian population [24] is shown in Figure 4.

Pretreatment PSA ($p = 0.04$) and PSA nadir ($p < 0.0001$) were the only significant factors in regard of bNED outcome performing multivariate analysis.

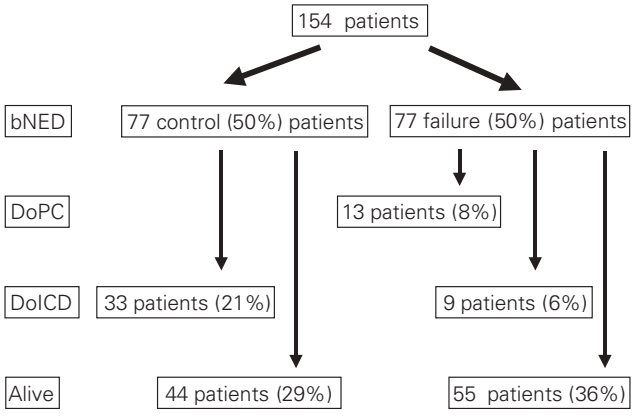

Figure 3. Overview of clinical outcome. bNED: biochemically no evidence of disease; DoPC: death of prostate cancer; DoICD: death of intercurrent disease.

Abbildung 3. Überblick der klinischen Ergebnisse. bNED: biochemische Rezidivfreiheit; DoPC: Tod Prostatakarzinom; DoICD: Tod andere Ursache.

Late Gastrointestinal (GI) and Urogenital (UG) Side Effects

The actuarial 5-year rates of late GI and UG side effects ≥ grade 2 (EORTC/RTOG) were 17% and 15%, respectively. The 8- and 10-year rates of late GI and UG side effects ≥ grade 2 amounted to 17% and 21%, respectively.

Discussion

Due to the long natural history of prostate cancer and the possibility of late failure, long-term follow-up is necessary to achieve appropriate data concerning survival. Vicini et al. [26] concluded that an approximate 2-year gap may be required between the time at which actuarial bNED rates are examined and the median follow-up period for accurately reporting data. This results in about 84 months follow-up to achieve proper 5-year bNED data. This analysis describes the long-term results with a median follow-up of 95 months of the surviving patients.

Clinical Outcome (bNED, DSS, OS; Table 2)

In a phase III randomized trial of 301 patients receiving between 70 and 78 Gy, Pollack et al. [21] reported a 5-year actuarial bNED rate of 68% (70-Gy arm) as compared to 46% in our study (66 Gy). In contrast to our study, patients were treated with larger fields and a higher dose. The percentage of patients with a pretreatment PSA ≤ 10 ng/ml was 64% versus 40% in our analysis. Follow-up was only 57 months compared to 80 months in our study. In an additional study, Pollack et al. [19] reported on 67% of patients in the 70-Gy arm reaching a PSA nadir ≤ 0.5 ng/ml compared to 80% of patients in the 78-Gy arm. The PSA nadir significantly correlated with FFF (freedom from failure) only in univariate analysis. In our study, the PSA nadir was found to be a significant factor also in multivariate analysis concerning bNED. Various studies showed the predictive accuracy of PSA nadir in regard to outcome. Nevertheless, the cutpoint used has varied among investigators [3, 4, 15, 27]. The 6-year actuarial OS rate of 83% (70-Gy arm) in the study by Pollack et al. [21] was similar to our results with 81% OS at 5 years.

Table 2. Long-term results in prostate cancer radiotherapy: values of bNED (biochemically no evidence of disease), DSS (disease-specific survival), and OS (overall survival) in percent; n: number of patients.

Tabelle 2. Langzeitergebnisse bei Prostatabestrahlung: Werte für bNED (biochemische Rezidivfreiheit), DSS (krankheitsspezifisches Überleben) und OS (Gesamtüberleben) in Prozent; n: Anzahl der Patienten.

Authors	n	Follow-up (months) all patients (surviving patients)	Dose (Gy)	bNED (years)	DSS (years)	OS (years)
Pollack et al. [21][a]	150	57 (–)	70	64 (6)	–	83 (6)
Hanks et al. [10]	229	– (110)	67–81	48 (10)	–	56[c] (10)
Pilepich et al. [16][b]	477	91 (132)	65–70	37 (10)	85[c] (10)	49 (10)
Wiegel et al. [30]	169	98 (–)	60–65	–	72 (10)	37 (10)
Own study	154	80 (95)	66	44 (10)	82 (10)	56 (10)

[a]only 70-Gy patients; [b]only radiotherapy and hormonal therapy patients; [c]values out of figure

Long-term results of the dose escalation study by Hanks et al. [10] included 229 patients treated with 68–79 Gy. The actuarial bNED was 55% at 5 years and 48% at 10 years, comparable to 46% and 44% in our study. The difference in outcome of bNED, regarding PSA groups of 10–20 ng/ml and > 20 ng/ml with 38% and 36% in our study compared to 19% and 8% in the study by Hanks et al., may be caused by the additional hormonal therapy in 66% of our patients. Hanks et al. reported a total of 42% deaths and 7% disease-specific deaths, comparable to 36% and 8%, respectively, in our study.

The phase III RTOG 85-31 study by Pilepich et al. [16] included unfavorable patients with T3 or with regional lymphatic involvement and 15% of patients after radical prostatectomy staged T3. Patients were randomized to either irradiation and hormonal therapy (arm 1) or radiotherapy alone (arm 2). A total dose of 60 Gy (postoperatively) and 65–70 Gy (primary radiotherapy) was given. DSS rates at 10 years were 84% (arm 1) and 78% (arm 2) and 10-year OS rates 49% and 39%, respectively, comparable to our study with 10-year DSS and OS rates in the high-risk group of 88% and 40%. Pilepich et al. found a significant improvement in DSS and OS in the irradiation and hormonal therapy arm. In our study, the intermediate-group showed 8-year bNED rates of 38% compared to 47% in the high-risk group. This benefit in bNED for the high-risk group patients might be caused by the fact that the amount of patients with additional hormonal therapy was only 48% in the intermediate-risk group versus 72% in the high-risk group.

Wiegel et al. [30] reported on 169 patients with clinical stage C treated with 60–65 Gy. The 5-, 8- and 10-year OS rate was 73%, 51%, and 37% and the corresponding DSS rate 92%, 78%, and 72%. Histological grading had a significant influence on OS and DSS. In our study, we also found such a trend concerning OS with a p-value of 0.06 in regard to histological grading.

After 10 years, the OS curve in our patients showed a difference of about 9% in comparison to a "normal" age-matched Austrian male population. The OS curves published by Hanks et al. [10] showed a difference of < 5% and those by Wiegel et al. [30] a difference of about 14% after 10 years each.

Late Gastrointestinal (GI) and Urogenital (UG) Side Effects

Radiotherapy was well tolerated with 86% of patients reporting maximal cumulative grade 0/1 GI and UG side effects. Our actuarial 5-year rates of late GI and UG side effects grade ≥ 2 with 17% and 15% are comparable to those in the literature. In the randomized trial by Pollack et al. [21], grade ≥ 2 rectal and bladder toxicities at 6 years were 12% and 10% in the 70-Gy arm. Hanks et al. [10] found a 5-year rate of late GI and UG morbidity grade ≥ 2 in 16% and 12%, when patients were treated with a total dose < 71 Gy. The RTOG 9406 dose escalation study found 22% of grade 2 late side effects in patients treated with a dose level of 68.4 Gy [22].

Conclusion

All patients were treated with a total prostate dose of 66 Gy. Our data concerning late side effects and clinical outcome are in good agreement with the literature [10, 13, 16, 19, 21, 30]. DSS rate at 10 years is 82% showing excellent OS rates, which

are only slightly reduced in comparison to an age-matched population.

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