Neoadjuvant Hormonal Therapy and External-Beam Radiotherapy versus External-Beam Irradiation Alone for Prostate Cancer

A Quality-of-Life Analysis

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Purpose: To evaluate the impact of neoadjuvant hormonal therapy (NHT) on quality of life after external-beam radiotherapy (EBRT) for prostate cancer.
Patients and Methods: A group of 170 patients (85 with and 85 without NHT) has been surveyed prospectively before EBRT (70.2–72 Gy), at the last day of EBRT, a median time of 2 months and 15 months after EBRT using a validated questionnaire (Expanded Prostate Cancer Index Composite). Pairs with and without NHT (median treatment time of 3.5 months before EBRT) were matched according to the respective planning target volume and prostate volume.
Results: Before EBRT, significantly lower urinary function/bother, sexual function and hormonal function/bother scores were found for patients with NHT. More than 1 year after EBRT, only sexual function scores remained lower. In a multivariate analysis, NHT and adjuvant hormonal therapy (HT) versus NHT only (hazard ratio 14; 95% confidence interval 2.7–183; p = 0.02) and luteinizing hormone-releasing hormone (LHRH) agonists versus antiandrogens (hazard ratio 3.6; 95% confidence interval 1.1–12; p = 0.04) proved to be independent risk factors for long-term erectile dysfunction (no or very poor ability to have an erection).
Conclusion: With the exception of sexual function (additional adjuvant HT and application of LHRH analog independently adverse), short-term NHT was not found to decrease quality of life after EBRT for prostate cancer.

Key Words: Prostate neoplasm · Radiotherapy · Quality of life · Hormonal treatment

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Neoadjuvante Hormontherapie und perkutane Radiotherapie versus alleinige perkutane Radiotherapie beim Prostatakarzinom. Eine Lebensqualitätsanalyse

Ziel: Untersuchung des Einflusses einer neoadjuvanten Hormontherapie (NHT) auf die Lebensqualität nach perkutaner Radiotherapie (EBRT) beim Prostatakarzinom.
Patienten und Methodik: In einer Gruppe von 170 Patienten (85 mit und 85 ohne NHT) wurde die Lebensqualität prospektiv vor EBRT (70,2–72 Gy), am letzten Tag der EBRT, median 2 Monate und 15 Monate nach EBRT mittels eines validierten Fragebogens (Expanded Prostate Cancer Index Composite) erfasst. Paare mit und ohne NHT (median 3,5 Monate vor EBRT verabreicht) wurden entsprechend dem jeweiligen Planungszielvolumen und Prostatavolumen gematcht.
Ergebnisse: Vor EBRT zeigten sich bei Patienten mit NHT signifikant schlechtere Funktions- und Belastungswerte in den Domänen Wasserlassen, Sexualität und hormonelle Beschwerden. Über 1 Jahr nach Ende der EBRT blieb nur noch die sexuelle Funktion signifikant schlechter. In einer multivariaten Analyse zeigte sich der unabhängige Einfluss der NHT mit adjuvanter Hormontherapie (HT) versus alleiniger NHT (relatives Risiko 14; 95%-Konfidenzintervall 2,7–183; p = 0,02) und der Gonadotropin-releasing-Hormon-(GnRH-)Analoga versus Antiandrogene (relatives Risiko 3,6; 95%-Konfidenzintervall 1,1–12; p = 0,04) als Risikofaktoren für die längerfristige erektile Dysfunktion (keine oder sehr geringe Erektionsfähigkeit).
Schlussfolgerung: Mit Ausnahme des Einflusses auf die sexuellen Funktionswerte (zusätzliche adjuvante HT und Verwendung von GnRH-Analoga unabhängig voneinander nachteilig) zeigte die kurzzeitige NHT keine negativen Auswirkungen auf die Lebensqualität nach EBRT des Prostatakarzinoms.

Schlüsselwörter: Prostatakarzinom · Radiotherapie · Lebensqualität · Hormontherapie

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Introduction

Alternatively to radical prostatectomy, external-beam radiotherapy is a well-established standard treatment of prostate cancer [9, 11, 15, 20, 33, 35, 36]. Several prospective randomized trials have shown a local and distant tumor control benefit, as well as a disease-free survival or overall survival advantage with the addition of a neoadjuvant hormonal therapy (NHT) for patients with specific risk factors [1, 3, 7, 12, 23, 30]. However, the indications for NHT are not always evidence-based and vary widely in clinical practice. The percentage of patients with NHT ranges between 30% and 91% in different German radiotherapy centers [24, 33].

Though a downsizing effect on the prostate volume with an associated normal-tissue sparing is well known [17, 39], an actual quality-of-life improvement has not been shown in the past. On the contrary, several authors found a negative effect of NHT on urinary [2, 10, 24, 31] gastrointestinal [12, 16, 31] and sexual [8] symptoms. Similar adverse effects of NHT have been observed after interstitial prostate brachytherapy [4, 19, 25, 29].

The aim of this study was to prospectively evaluate the effects of NHT on health-related quality of life (HRQoL) in the urinary, bowel, sexual and hormonal domains from the patients' perspective. Matched pairs have been selected, ensuring the same prostate volumes and planning target volumes (PTVs) for patients with and without NHT.

Patients and Methods

The study population was selected from patients with cT1–3 N0 M0 prostate cancer, who received external conformal radiotherapy (EBRT) with 1.8- to 2.0-Gy fractions up to a total dose of 70.2–72.0 Gy in the years 2003–2006. EBRT was based on a treatment-planning computed tomography (CT) scan in supine position with a slice thickness of 5 mm. Patients were asked to have a full bladder for the planning CT scan and each radiotherapy fraction. In all scans PTV, bladder and rectum were delineated by identifying the external contours. The rectum enclosed the region from the anal canal to the rectosigmoid flexure. The same individual (M.P.) performed all prostate volume contouring. A prior study involving the same radiation oncologist demonstrated no overestimation of CT-defined compared to transrectal ultrasound-defined prostate volumes [28]. Treatment plans were calculated using a four-field-box technique with 15-MeV photons and a multileaf collimator. The PTV was required to be enclosed by the 90% isodose relative to the ICRU reference point [14] with a margin of 1.5 cm in the anterior/lateral and 1 cm in the craniocaudal and dorsal directions to the clinical target volume (CTV = prostate with or without seminal vesicles; prostate only after 66.0 or 66.6 Gy for all patients).

Patients have been surveyed prospectively before EBRT (time A), at the last day of EBRT (time B), and a median time of 2 months (range 6 weeks to 6 months; time C) and 15 months (range 1–2 years; time D) after EBRT using a validated questionnaire (Expanded Prostate Cancer Index Composite [EPIC]) [26, 34]. The EPIC questionnaire comprises 50 items concerning the urinary, bowel, sexual and hormonal domains for function and bother. The multi-item scale scores were transformed lineary to a 0–100 scale, with higher scores representing better HRQoL. Questions in the urinary domain were classified into incontinence and irritation/obstruction subscales [18, 34]. Mean change in scores of about 5–10 can be interpreted as of "little", 10–20 as of "moderate", and > 20 as of "very much" clinical significance [21, 26].

The questionnaires were handed over to the patients personally by one of the physicians at times A, B, and C. Missed questionnaires at time C and all questionnaires at time D were sent to the patients with a return envelope. If a questionnaire was not returned within 4 weeks, patients were contacted by telephone and urged to complete it.

A response to the questionnaires at times A and D was required for inclusion in this analysis, resulting in a group of 85 patients with and 177 patients without NHT. No difference resulted for the response rate at time D for initially responding patients with and without NHT (93% in both groups). To evaluate the impact of an additional NHT, matched pairs were selected for the patient group with NHT with the aim to achieve two comparable groups concerning EBRT-associated parameters. Pairs (n = 85) were matched according to the PTV (first criterion: ± 10%; second criterion: prostate ± seminal vesicles) and prostate volume (± 10 cm^3). A total number of 170/120/151/170 questionnaires resulted at times A/B/C/D for this analysis. Number of questionnaires was lowest at the end of EBRT (time B) because this point in time was limited to a single day (last radiotherapy fraction) and no second opportunity existed for a missed questionnaire.

The referring urologist decided about the indication for NHT due to prognostic risk factors or to offer an immediate treatment before the decision for a definitive curative method. As a consequence, several different agents have been used: luteinizing hormone-releasing hormone (LHRH) agonists (3-monthly depot preparations) in 42 cases (49%), antiandrogens in 35 cases (41%), and a combination of LHRH agonists and antiandrogens in eight cases (9%). The median time of NHT before the beginning of EBRT was 3.5 months (range 2 weeks to 11 years). Hormonal therapy (HT) was continued after EBRT in 27 cases (32%) – always until the time of the last questionnaire at time D.

Statistical analysis was performed using the SPSS 14.0 software (SPSS, Chicago, IL, USA). Wilcoxon's matched-pairs test was applied to determine differences between the treatment groups and longitudinal changes in a specific subgroup. To explore statistical HRQoL score differences between different subgroups, the Mann-Whitney U-test was used. Contingency table analysis with the χ^2-test was performed to compare treatment groups with respect to categorical variables. In a forward stepwise multivariate analysis, different factors (NHT only or NHT in combination with adjuvant HT; LHRH analog vs. antiandrogen; treatment duration) were tested for

their independent impact on specific problems. All p-values reported are two-sided, $p < 0.05$ is considered significant.

Results

With the exception of the Gleason Score, T-stage, bladder volume in the treatment-planning CT and the area under the curve of the dose-volume histogram (AUC) for the bladder, patient groups treated with EBRT alone and EBRT + NHT were well balanced considering baseline characteristics (Table 1).

The largest HRQoL score differences were found before EBRT (Table 2). Apart from sexual function and hormonal function/bother scores, significantly lower urinary function and urinary obstructive/irritative bother scores were found for patients receiving NHT. Lower urinary obstructive/irritative bother scores are well explaining a smaller bladder volume in the treatment-planning CT: scores of ≥ 90 versus < 90 were associated with a mean bladder volume of 261 cm^3 versus 200 cm^3 ($p < 0.01$).

At times C and D after EBRT, sexual function was the only domain with significantly lower scores for patients after EBRT and NHT versus EBRT alone. While sexual function scores decreased significantly after EBRT alone ($p < 0.01$), comparable scores were found at times A and D for patients with NHT. The results of the quality-of-life score analysis are well supported by the percentage of patients reporting specific problems Table 3).

Several different treatment regimens were involved in the patient group with NHT. Differences were based on NHT only or NHT in combination with adjuvant HT, the applied substance and treatment duration. Focusing on the subgroup of patients without adjuvant HT (n = 58 with the respective matched pairs), no significant quality-of-life differences were found in the urinary and bowel domains at any time with the exception of significantly lower urinary obstructive/irritative scores before EBRT for patients with NHT versus those without NHT. Sexual function scores were found to be significantly lower with NHT only at time A. However, the percentage of patients with erections firm enough for sexual intercourse was still lower at time D (9% with vs. 25% without NHT; $p < 0.01$). A significant negative effect of NHT on hormonal function and bother scores was detectable at times A–C.

Table 4 demonstrates the impact of HT variations on sexual function scores. Patients with NHT only, shorter treatment duration and the application of an antiandrogen (in comparison to LHRH analog) reached significantly higher sexual function scores. Sexual function scores of patients after antiandrogen treatment were comparable to patients without NHT at times C and D. In a multivariate analysis including these three factors, NHT and adjuvant HT versus NHT only (hazard ratio 14; 95% confidence interval 2.7–183; $p = 0.02$) and LHRH analog versus antiandrogen (hazard ratio 3.6; 95% confidence interval 1.1–12; $p = 0.04$) proved to be independent risk factors for "no or poor ability to have an erection" (in contrast to the treatment duration) at time D.

Additionally, NHT with adjuvant HT versus NHT alone and LHRH analog versus antiandrogen led to significantly lower hormonal function and hormonal bother scores more than 1 year after EBRT (Table 5). In a multivariate analysis, both factors proved to be important: NHT and adjuvant HT versus NHT only was independently associated with a big/moderate problem with hot flushes (hazard ratio 15; 95% confidence interval 2.7–78; $p < 0.01$); LHRH analog versus antiandrogen was independently associated with a big/moderate problem with lack of energy

Table 1. Patient characteristics.
AUC: area under the dose-volume histogram curve; COPD: chronic obstructive pulmonary disease; NHT: neoadjuvant hormonal therapy; PSA: prostate-specific antigen; PTV: planning target volume; EBRT: external-beam radiotherapy.

Tabelle 1. Patientencharakteristika.
AUC: Fläche unter der Dosis-Volumen-Histogramm-Kurve; COPD: chronisch-obstruktive Lungenerkrankung; NHT: neoadjuvante Hormontherapie; PSA: prostataspezifisches Antigen; PTV: Planungszielvolumen; EBRT: perkutane Radiotherapie.

		EBRT (n = 85)	EBRT + NHT (n = 85)
Patient age [years; median (range)]		72 (51–82)	72 (48–82)
Prostate volume [cm^3; median (range)]		35 (14–96)	34 (11–97)
PTV [cm^3; median (range)]		328 (169–494)	322 (179–529)
Bladder volume [cm^3; median (range)]*		199 (40–806)	175 (30–657)
Rectum volume [cm^3; median (range)]		96 (28–301)	94 (28–295)
AUC – bladder [%; median (range)]*		40 (11–98)	44 (7–87)
AUC – rectum [%; median (range)]		50 (19–75)	53 (19–77)
PSA [ng/ml; median (range)]		9 (1.5–29)	9 (1.0–66)
Biopsy Gleason Score < 7 [n (%)]**		59 (69)	41 (48)
Clinical T stage ≤ 2a [n (%)]*		74 (87)	61 (72)
Comorbidities [n (%)]		50 (59)	54 (64)
Comorbidities with incidence > 5%	Hypertension [n (%)]	23 (27)	22 (26)
	Coronary heart disease [n (%)]	25 (29)	24 (28)
	Diabetes [n (%)]	5 (6)	10 (12)
	COPD [n (%)]	7 (8)	6 (7)

*$p < 0.05$
**$p < 0.01$

Table 2. Mean function and bother scores (quartiles in brackets).
NHT: neoadjuvant hormonal therapy; EBRT: external-beam radiotherapy.

Tabelle 2. Durchschnittliche Funktions- und Belastungswerte (Quartile in Klammern).
NHT: neoadjuvante Hormontherapie; EBRT: perkutane Radiotherapie.

		Time A	Time B	Time C	Time D
Urinary function score	EBRT	93*	76	89	92
		(89;100;100)	(65;80;94)	(80;100;100)	(89;95;100)
	EBRT + NHT	*89**	*80*	*89*	*91*
		(80;94;100)	*(65;84;100)*	*(85;94;100)*	*(89;94;100)*
Urinary incontinence score	EBRT	92	85	90	94
		(92;100;100)	(67;100;100)	(83;100;100)	(100;100;100)
	EBRT + NHT	*90*	*85*	*91*	*92*
		(89;100;100)	*(67;100;100)*	*(89;100;100)*	*(100;100;100)*
Urinary obstructive/irritative score	EBRT	98	76	94	96
		(100;100;100)	(50;75;100)	(100;100;100)	(100;100;100)
	EBRT + NHT	*96*	*84*	*95*	*98*
		(100;100;100)	*(63;100;100)*	*(100;100;100)*	*(100;100;100)*
Urinary bother score	EBRT	84	59	78	82
		(77;90;100)	(39;57;81)	(64;83;96)	(68;89;96)
	EBRT + NHT	*79*	*63*	*78*	*78*
		(68;86;96)	*(43;68;82)*	*(61;86;96)*	*(61;86;96)*
Urinary incontinence bother score	EBRT	91	79	86	86
		(100;100;100)	(50;100;100)	(75;100;100)	(75;100;100)
	EBRT + NHT	*87*	*75*	*82*	*86*
		(88;100;100)	*(50;100;100)*	*(64;85;96)*	*(75;100;100)*
Urinary obstructive/irritative bother score	EBRT	84*	58	78	82
		(75;90;100)	(40;55;80)	(65;80;95)	(70;90;95)
	EBRT + NHT	*79**	*63*	*78*	*77*
		(65;85;95)	*(45;63;80)*	*(64;85;96)*	*(64;80;95)*
Bowel function score	EBRT	93	75	85	89
		(89;96;100)	(64;79;93)	(79;91;96)	(86;93;100)
	EBRT + NHT	*91*	*79*	*88*	*89*
		(86;93;96)	*(69;86;93)*	*(81;93;96)*	*(86;93;96)*
Bowel bother score	EBRT	94	72	83	86
		(93;100;100)	(50;73;96)	(71;93;100)	(79;96;100)
	EBRT + NHT	*91*	*74*	*82*	*85*
		(89;100;100)	*(51;82;96)*	*(68;93;100)*	*(79;93;100)*
Sexual function score	EBRT	39*	28*	30*	26*
		(26;42;55)	(16;27;39)	(11;30;44)	(6;20;45)
	EBRT + NHT	*19**	*13**	*17**	*18**
		(0;14;34)	*(0;5;22)*	*(0;6;30)*	*(0;6;31)*
Sexual bother score	EBRT	60	49	48	48
		(25;63;94)	(13;47;83)	(13;41;87)	(25;44;84)
	EBRT + NHT	*55*	*43*	*46*	*42*
		(13;50;100)	*(0;25;87)*	*(0;31;97)*	*(0;38;75)*
Hormonal function score	EBRT	91*	86*	86	87
		(85;95;100)	(80;90;100)	(80;90;100)	(80;90;100)
	EBRT + NHT	*81**	*77**	*80*	*84*
		(70;85;95)	*(70;80;90)*	*(70;85;96)*	*(80;90;100)*
Hormonal bother score	EBRT	91*	89	88	88
		(83;100;100)	(79;96;100)	(83;96;100)	(79;96;100)
	EBRT + NHT	*84**	*82*	*81*	*84*
		(75;92;100)	*(75;88;94)*	*(70;88;100)*	*(75;92;100)*

*$p < 0.05$

Table 3. Selected answers.
NHT: neoadjuvant hormonal therapy; EBRT: external-beam radiotherapy.

Tabelle 3. Ausgewählte Antworten.
NHT: neoadjuvante Hormontherapie; EBRT: perkutane Radiotherapie.

		Time A (%)	Time B (%)	Time C (%)	Time D (%)
No total urinary control	EBRT	22**	47	34	38
	EBRT + NHT	*51***	*57*	*47*	*46*
Pain with urination at least once a day	EBRT	1*	43	8	4
	EBRT + NHT	*7**	*27*	*8*	*0*
Moderate/big problem from dripping or leaking urine	EBRT	6	22	9	8
	EBRT + NHT	*10*	*21*	*15*	*10*
Moderate/big problem from waking up to urinate	EBRT	18*	64	28	21
	EBRT + NHT	*32**	*54*	*27*	*34*
Moderate/big problem from urinary dysfunction	EBRT	13	51	18	13
	EBRT + NHT	*20*	*40*	*22*	*14*
Uncontrolled leakage of stool at least rarely	EBRT	2	30	21	17
	EBRT + NHT	*9*	*19*	*16*	*14*
Rectal urgency at least once a day	EBRT	18	47	20	12
	EBRT + NHT	*22*	*42*	*20*	*18*
Bloody stools at least rarely	EBRT	5	13	9	15
	EBRT + NHT	*6*	*14*	*8*	*7*
Moderate/big problem from bowel dysfunction	EBRT	5	32	15	14
	EBRT + NHT	*9*	*32*	*18*	*13*
Poor or no ability to have an erection	EBRT	17**	33**	27**	42*
	EBRT + NHT	*56***	*67***	*60***	*61**
No erections firm enough for intercourse	EBRT	51**	82	69*	75*
	EBRT + NHT	*79***	*91*	*89**	*91**
Moderate/big problem from sexual dysfunction	EBRT	29	48	48	51
	EBRT + NHT	*44*	*53*	*55*	*52*
Hot flushes at least once a day	EBRT	3**	7**	7**	5
	EBRT + NHT	*30***	*37***	*23***	*12*
Lack of energy at least once a day	EBRT	6*	9	14	16
	EBRT + NHT	*17**	*22*	*12*	*21*
Change in weight ≥ 5 kg	EBRT	15*	33	39	30
	EBRT + NHT	*29**	*37*	*43*	*33*

*$p < 0.05$
**$p < 0.01$

(hazard ratio 3.7; 95% confidence interval 1.1–13; $p = 0.04$). Finally, patients treated with an LHRH analog versus antiandrogen presented with significantly lower urinary bother (median 80 vs. 89; $p = 0.05$) and bowel bother scores (median 89 vs. 96; $p = 0.01$) at time D.

Discussion

This study has evaluated the effects on HRQoL in a patient group treated with EBRT alone in comparison to a second group, treated with EBRT and NHT. The aim was to find potential adverse effects, demonstrated in several studies before [2, 8, 10, 12, 16, 24, 31]. A special aspect of this analysis was the application of a quality-of-life questionnaire, ensuring function and bother documentation from the patients' perspective. Furthermore, as never before, two groups with the same EBRT concerning the PTV and prostate volume have been compared. In a second step, the impact of a combination of NHT with adjuvant HT, the applied agent (LHRH analogs vs. antiandrogens) and the treatment duration were analyzed.

Hot flushes, nausea, diarrhea, hepatotoxicity, weight gain, gynecomastia, loss of libido, anemia, osteoporosis, and cardiovascular toxicity are known side effects of androgen suppression [13, 32, 38]. These changes can persist after discontinuing androgen suppression, especially in men of advanced age [3]. A meta-analysis of randomized trials shows that 6 months of

Table 4. Mean sexual function scores (quartiles in brackets) in dependence on treatment concept.
HT: hormonal therapy; LHRH: luteinizing hormone-releasing hormone; NHT: neoadjuvant hormonal therapy.

Tabelle 4. Durchschnittliche sexuelle Funtionswerte (Quartile in Klammern) in Abhängigkeit vom Behandlungskonzept.
HT: Hormontherapie; LHRH: luteinisierendes Hormon-releasing-Hormon; NHT: neoadjuvante Hormontherapie.

	Time A	Time B	Time C	Time D
Without NHT	39	28	30	26
	(26;42;55)	(16;27;39)	(11;30;44)	(6;20;45)
NHT only	23**	16*	22**	22**
	(3;23;35)	(3;10;25)	(0;18;40)	(3;22;33)
NHT and adjuvant HT	*11***	*8**	*7***	*8***
	(0;0;25)	*(0;3;6)*	*(0;0;6)*	*(0;0;5)*
NHT < 6 months	24*	16	19	21*
	(0;24;38)	(0;7;26)	(0;12;33)	(3;14;31)
NHT ≥ 6 months	*10**	*7*	*11*	*12**
	(0;3;21)	*(0;4;10)*	*(0;0;23)*	*(0;3;24)*
Antiandrogen	30**	19*	28**	29**
	(14;28;46)	(4;8;30)	(5;27;49)	(6;28;39)
LHRH analog	*10***	*9**	*9***	*12***
	(0;3;24)	(0;2;12)	(0;0;16)	(0;4;20)

*p < 0.05
**p < 0.01

Table 5. Mean hormonal function scores (quartiles in brackets) in dependence on treatment concept.
HT: hormonal therapy; NHT: neoadjuvant hormonal therapy.

Tabelle 5. Durchschnittliche hormonelle Funtionswerte (Quartile in Klammern) in Abhängigkeit vom Behandlungskonzept.
HT: Hormontherapie; NHT: neoadjuvante Hormontherapie.

	Time A	Time B	Time C	Time D
Without NHT	91	86	86	87
	(85;95;100)	(80;90;100)	(80;90;100)	(80;90;100)
NHT only	81	75	80	87*
	(70;85;100)	(60;80;90)	(70;80;100)	(80;90;100)
NHT and adjuvant HT	*81*	*82*	*82*	*78**
	(70;85;100)	*(80;85;98)*	*(65;90;95)*	*(68;80;91)*
NHT < 6 months	83	78	81	87
	(80;85;95)	(71;83;90)	(75;85;95)	(80;90;100)
NHT ≥ 6 months	*77*	*74*	*77*	*79*
	(60;80;95)	*(46;80;100)*	*(58;80;100)*	*(64;80;100)*
Antiandrogen	86**	82	87**	89**
	(80;90;100)	(80;85;91)	(80;90;100)	(88;95;100)
LHRH analog	*76***	*75*	*74***	*81***
	(60;80;90)	*(50;80;90)*	*(60;80;90)*	*(75;80;95)*

*p < 0.05
**p < 0.01

androgen suppression shortens the time to a fatal myocardial infarction in men of advanced age [6].

Accordingly, lower sexual function scores and lower hormonal function/bother scores were found in this study for patients who received NHT before EBRT (time A). Lower urinary function and urinary obstructive/irritative scores indicate persisting symptoms after downsizing the prostate volume as an effect of NHT. The association of larger prostate volume (in this study: patient group with NHT before starting NHT) with lower urinary obstructive/irritative scores has been demonstrated earlier [24].

In our patient population, receiving predominantly a short-term NHT, no adverse effects of NHT have been found after completion of EBRT with the exception of still lower hormonal function scores at the end of EBRT and lower sexual function scores at all intervals. Focusing on sexual function and different aspects of NHT (Table 4), we have found the additional adjuvant HT (vs. NHT alone) and the administration of LHRH analogs (vs. antiandrogens) to be independent risk factors for long-term erectile dysfunction (no or very poor ability to have an erection). Additionally to lower sexual function scores, lower hormonal function and hormonal bother scores were found after additional adjuvant HT and the application of LHRH analogs. In both situations, testosterone effects and/or testosterone levels are still suppressed several months after EBRT. After administration of LHRH analogs, testosterone levels may need 2 years or longer to normalize, particularly after a long-term androgen suppression [22, 37]. Prostate-specific antigen (PSA) levels can be expected to rise during this period [27]. In contrast to LHRH analogs, antiandrogens do not suppress testosterone levels. Sexual and hormonal function is preserved better, with similar scores more than 1 year after EBRT as for patients treated with EBRT alone.

A significantly adverse effect on long-term urinary and bowel bother scores was only found in the specific subgroup of patients treated with LHRH analogs versus anitandrogens. As reported by Feigenberg et al. [10], the treatment duration may be an important aspect for the association of genitourinary and gastrointestinal morbi-

dity with androgen suppression. Increased genitourinary and gastrointestinal morbidity was only found in the patient group with long-term (> 6 months; n = 140) androgen suppression, as opposed to short-term (≤ 6 months; n = 119) androgen suppression. The effect of treatment duration was only found for sexual function in our study (Table 4), possibly due to smaller patient numbers with long-term androgen suppression.

In view of potential additional toxicity, it is important to well consider the administration of NHT in accordance with the results of the available randomized trials [1, 3, 7, 12, 23, 30]. In particular, a prognostic advantage of NHT for patients without any prognostic risk factors (PSA < 10 ng/ml, Gleason Score < 7, cT-stage < 2b) has never been shown – while patients with locally advanced tumors or patients with high Gleason Scores (especially 8–10) clearly benefit from androgen suppression. The optimal treatment duration is still not known [5]. Administration of NHT for downsizing the prostate volume is questionable in view of missing clinical data for a quality-of-life improvement in the genitourinary and gastrointestinal domains.

Conclusion

With the exception of sexual function (additional adjuvant HT and application of LHRH analogs independently adverse), short-term NHT was not found to decrease quality of life after EBRT for prostate cancer. The indication for the administration of NHT should be based on the results of available randomized trials.

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