



Health-related quality of life and rates of toxicity after high-dose-rate brachytherapy in combination with external beam radiation therapy for high-risk prostate cancer

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Purpose: High-dose-rate brachytherapy (HDR-BT) with external beam radiation therapy (EBRT) is a common treatment option for locally advanced prostate cancer. Quality of life is an important factor when discussing therapy options for high-risk prostate cancer. This study evaluated adverse effects and health-related quality of life (HRQOL).

Materials and Methods: Ninety male patients (median age, 71 years; range, 50 to 79 years) with high-risk prostate cancer underwent HDR-BT after EBRT between December 2009 and January 2017 with a median follow-up of 43 months. A total of 57 patients (69.5%) answered the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients questionnaire (QLQ-C30; ver. 3.0), and 8 patients died during follow-up. In order to put the results of this study in context, we compared the results with reference data from the EORTC QLQ-C30 Scoring Manual. Correlations of prostate-specific antigen (PSA) values, International Prostate Symptom Score, and HRQOL measures were calculated.

Results: The study participants reported better physical functioning and better global health compared with the reference data, but worse social, role, and cognitive functioning. We found negative statistically significant correlations between the last-measured PSA value and social functioning ($p > 0.01$), cognitive functioning, pain, and constipation (all $p < 0.05$). Toxicity rates were 10.0% for gastrointestinal and 12.2% for genitourinary adverse effects. All reported complications for toxicity were Grade I.

Conclusions: The described therapy results in high biochemical control rates with minimal adverse effects. Compared with reference groups, the HRQOL of this study cohort was acceptable. PSA values during follow-up seem to be a possible indicator to influence HRQOL.

Keywords: Brachytherapy; Prostatic neoplasms; Quality of life; Radiotherapy

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INTRODUCTION

High-dose-rate brachytherapy (HDR-BT) with additional external beam radiation therapy (EBRT) is a possible therapy option for locally advanced high-risk prostate cancer (PCa) [1-3]. The European guidelines recommend radical prostatectomy (RP) or radiation therapy for the treatment of intermediate- and high-risk PCa in patients with a life expectancy of more than 10 years [4]. The expected health-related quality of life (HRQOL) is a crucial factor when patients and physicians decide on a treatment option. HRQOL is defined as the effects of the illness and the treatment on the patient's subjective psychological and physical well-being. All treatment modalities deleteriously affect sexual, urinary, and bowel function in many patients. In general, men who undergo RP report more urinary dysfunction, which can be defined as greater incontinence and can be measured as the need to use absorptive pads. Rates of sexual dysfunction, defined as reduced erectile capacity and decreased sexual desire, are higher after RP than after EBRT [5-8]. Bowel dysfunction (urgency and diarrhea) and irritative urinary dysfunction are reported more often by men treated with EBRT and BT than by men who undergo RP [6,8].

To date, no randomized clinical trials have compared oncologic and HRQOL outcomes of HDR-BT with those of RP [9]. Articles reporting the oncological outcomes of HDR-BT are also rare [10,11]. In particular, HDR-BT in combination with EBRT seems to be favorable compared with EBRT alone with respect to biochemical recurrence-free survival and aspects of quality of life [10,12]. PCa cells seem to have a low α/β ratio. This enables the use of HDR-BT in large doses per fraction and makes it one of the most efficient and convenient interventions of hypo-fractionated radiation. In combination with EBRT, reported series using HDR-BT boost describe impressive results for treatment of intermediate- and high-risk PCa [13,14].

In this study, we focused on high-risk patients with locally advanced diseases, treated with HDR-BT plus EBRT plus androgen-deprivation therapy (ADT) regarding toxicity rates, oncologic, and HRQOL outcomes. The aim of the following study was to determine toxicity rates as well as the frequency and severity of various physical and psychosocial adverse effects of HDR-BT in patients shortly after completing the treatment plan. Another question was to find out how prostate-specific antigen (PSA) influences clinical outcomes and/or HRQOL.

MATERIALS AND METHODS

1. Subjects

In this retrospective study, we report on 90 male patients (median age, 71 years; range, 50 to 79 years) who were treated between December 2009 and January 2017 at the Department of Urology and the Department of Radio-Oncology of HELIOS Hospital, Bad Saarow, Germany. All included patients were classified as intermediate- or high-risk PCa patients. The study was approved by the Institutional Review Board at the institution, and informed consent was obtained before therapy started.

To put the results in context, we compared our results regarding HRQOL with reference data from the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients questionnaire (QLQ-C30). Because the reference data are pretreatment values for patients, the results of the comparisons must be evaluated in light of this fact.

2. Study design

All patients (n=90) included in this study underwent HDR-BT. Diagnostic procedures before treatment included digital rectal examination (DRE), PSA measurement, computerized tomography, and a technetium-99 bone scan. Risk stratification was done as per the National Comprehensive Cancer Network (NCCN), and D'Amico risk stratification for PCa was documented for each patient. Exclusion criteria were surgically positive lymph node metastases, distant metastases, and prior pelvic radiotherapy. Additional exclusion criteria were patients with bladder outlet obstruction, patients who already had transurethral therapies before treatment, and prostate volume higher than 100 cm³. All patients had undergone neoadjuvant and adjuvant ADT for at least 2 years starting after laparoscopic pelvic lymphadenectomy.

HDR-BT was administered before EBRT, based on transrectal ultrasound imaging, using a planning system and the Ir192 treatment unit GammaMed Plus iX (by Varian, CClinac DHX, PaloAlto, CA, USA). HDR-BT was administered in two separate treatment sessions (1-wk interval) with 9 Gy per fraction. Overall, 18 Gy was applied to the prostate with a 2-mm margin. The procedure of HDR-BT was done under general anesthesia. The patient was placed in the lithotomy position. A square lightweight template having a 5-mm grid array was fixed on a stepper stand on which a transrectal ultrasound machine was mounted. Seven to 20 needles were inserted into the prostate. Then the trocars were removed and replaced by the 6 F ProGuide plastic needles in the same position. No needles were placed within 7

mm of the urethra to have control of the urethral dose. The needles were pushed beyond the prostate base. The posterior needles were placed 2 to 3 mm anterior to the anterior wall of the rectum to avoid overdosing the rectum. The planning target volume (PTV) was contoured by the radiation oncologist on each ultrasound slice and included the prostate with a 3-mm margin all around except posteriorly where no margin was given to avoid overdosing the anterior rectal wall. Superiorly, a margin of 5 to 7 mm was given to compensate for any post-implant edema and inadvertent caudal movement of the catheters in between the fractions. The PTV constraints were D90 (dose delivered to 90% of PTV) $\geq 97\%$, V95 $\geq 100\%$, and V150 $\leq 35\%$. The detailed procedure of HDR-BT and EBRT was described in detail in our previous publication [15].

Follow-up for all patients was organized 3, 6, and 9 months and 1, 3, and 5 years after radiation therapy in the department of Radio-Oncology to evaluate early and late toxicity adverse effects, metastases, local recurrence, and PSA value. At a mean time of 40.8 months after the end of therapy, all patients were sent an EORTC QLQ-C30 (ver. 3.0) questionnaire that was answered by 57 patients (69.5%). The questionnaire was answered by the patients after collection of all data included in this study.

3. Evaluated data

The evaluated data included patients' age, PSA value at time of diagnosis and during follow-up, PSA density, body mass index (BMI), Gleason score, D'Amico risk classification, DRE, time of follow-up, TNM classification, prostate volume, and early toxicity in follow-up. Pretreatment International Prostate Symptom Score (IPSS), uroflow, and residual urine after voiding were also documented. IPSS after treatment was also documented. All relevant dates were documented: date of birth, date of death, date of diagnosis, date of lymphadenectomy, date of ADT, date of HDR-BT, and date of follow-up after 1, 3, and 5 years.

Radiation oncologists and a urologist performed the follow-up evaluations, including DRE and PSA level during the follow-up scheme after initial therapy. PSA failure was defined in terms of the American Society for Therapeutic Radiology and Oncology Consensus Panel recommendations [16]. Acute toxicities were scored according to the Common Terminology Criteria for Adverse Events ver. 4.0 (CTCAE ver. 4.3), by the National Cancer Institute (CTCAE ver. 4.0). Acute toxicity was defined as symptoms that were observed during or after treatment and had been completely resolved 6 months after treatment.

4. EORTC QLQ-C30

HRQOL was assessed using the EORTC QLQ-C30 Core questionnaire (ver. 3.0). The EORTC QLQ-C30 is a cancer-specific 30-item questionnaire [17]. It includes five functional scales (physical, role, cognitive, emotional, and social), eight symptom scales (fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea), a financial scale, and a global health scale. All items have response categories with four levels, from "not at all" to "very much," except the two items of the global health scale (overall physical condition and for overall quality of life), which use seven-point items ranging from "very poor" to "excellent." High-scale scores present a high-response level, with high-functional scale scores representing high/healthy levels of functioning, and high scores for symptoms scales/items representing high levels of symptomatology/problems.

5. Statistical analysis

Bravais–Pearson correlation coefficients were estimated for pairs of variables. Odds ratios, 95% confidence intervals, and p-values of the Wald test were estimated using unadjusted logistic regression for local recurrence as a dependent variable. The level of significance was $p=0.05$. Tests and calculations were performed using the software R ver. 3.1.2 (R Development Core Team 2014) and IBM SPSS Statistics ver. 25.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Age, PSA (ng/mL) at time of diagnosis, PSA density, BMI, Gleason score, D'Amico risk classification for PCa, PSA value after 1 year of follow-up, and time of follow-up are shown in Table 1. The median follow-up time in our study was 43 months (range, 7 to 87 months). The frequencies of all important clinical parameters (PSA at time of diagnosis, Gleason score, T category, and D'Amico risk classification) are visible in Table 2. A total of 64.4% of the study cohort had an initial PSA value of more than 10 ng/mL. The Gleason score of 90% of the patients was ≥ 7 , and more than 80% of the patients had a clinical T category of 3 (positive DRE result and/or positive for tumor in transrectal ultrasound examination). According to the D'Amico risk classification for PCa, more than 95% were classified as risk group 3, meaning high risk.

Eight patients (8.9%) died during follow-up: two patients died of progressive disease of PCa, one of progressive pancreatic cancer, one of stroke, one of esophageal cancer, one of cardiac reasons, and two of other reasons. In total in three patients (3.3%) a local recurrence was detectable. But elevated PSA values during follow-up are not always caused by

Table 1. Main clinical parameters

| Parameter | Min. | 10% | 25% | Median | Mean | 75% | 90% | Max. | SD |
|--------------------------|-------|-------|--------|--------|-------|--------|--------|---------|-------|
| Age (y) | 50.00 | 60.00 | 66.000 | 71.000 | 69.39 | 74.000 | 76.000 | 79.000 | 6.44 |
| PSA diagnosis | 1.36 | 4.59 | 7.19 | 14.51 | 21.95 | 24.55 | 46.84 | 226.000 | 28.18 |
| PSA density | 0.05 | 0.13 | 0.25 | 0.47 | 0.75 | 0.82 | 1.71 | 4.97 | 0.89 |
| BMI (kg/m ²) | 20.76 | 23.40 | 25.07 | 27.08 | 27.60 | 28.73 | 32.08 | 44.38 | 4.04 |
| Gleason score | 6.00 | 6.90 | 7.00 | 7.00 | 7.41 | 8.00 | 9.00 | 9.00 | 0.90 |
| D'Amico | 2.00 | 3.00 | 3.00 | 3.00 | 2.96 | 3.00 | 3.00 | 3.00 | 0.19 |
| PSA FU 1a | 0.00 | 0.01 | 0.03 | 0.04 | 0.17 | 0.16 | 0.32 | 2.30 | 0.35 |
| Time FU | 7.00 | 19.00 | 31.00 | 43.00 | 46.98 | 64.00 | 81.00 | 87.00 | 22.03 |

Min., minimum; Max., maximum; SD, standard deviation; BMI, body mass index; PSA, prostate-specific antigen; FU, follow-up.

Table 2. Frequency of important clinical parameters for the study cohort and early toxicity rates after radiation therapy

| Clinical parameter | n (%) |
|---------------------------|-----------|
| PSA value (ng/mL) | |
| <10 | 32 (35.6) |
| 10–19 | 27 (30.0) |
| ≥20 | 31 (34.4) |
| Gleason score | |
| 6 | 9 (10.0) |
| 7a | 27 (30.0) |
| 7b | 24 (26.7) |
| 8 | 14 (15.6) |
| 9 | 16 (17.8) |
| Clinical T classification | |
| 2a | 2 (2.2) |
| 2b | 5 (5.6) |
| 2c | 10 (11.1) |
| 3 | 73 (81.1) |
| D'Amico classification | |
| 1 | 0 (0.0) |
| 2 | 3 (3.3) |
| 3 | 87 (96.7) |
| Adverse effects | |
| None | 67 (74.4) |
| Intestinal | |
| Pain | 5 (5.6) |
| Proctitis | 2 (2.2) |
| Diarrhea | 2 (2.2) |
| Hemorrhage | 0 (0.0) |
| Genitourinary | |
| Frequency | 6 (6.7) |
| Urgency | 3 (3.3) |
| Incontinence | 0 (0.0) |
| Hematuria | 0 (0.0) |
| Retention | 1 (1.1) |
| Pain | 1 (1.1) |

PSA, prostate-specific antigen.

the detection of metastases or local recurrences.

The next interesting point of the study is the description of adverse effects regarding toxicity rates of the demonstrated treatment. In 74.4% of the patients, no adverse effects were reported. All documented complications in toxicity were Grade I. Most reported adverse effects were anal pain (5.6%), symptomatic proctitis (2.2%), and diarrhea (2.2%) for the gastrointestinal tract; high urinary frequency (6.7%), retention (1.1%), pain (1.1%), and urgency (3.3%) were the most cited adverse effects for the urinary tract. All complications are shown in Table 2.

Table 3 shows the comparison of the reference data from the EORTC QLQ-C30 Scoring Manual [17] with the study patients. The most salient results were that the study patients reported worse social, role, and cognitive functioning compared with all other groups, but similar emotional functioning compared with all other groups. For physical functioning, the patients of this study were functioning better than reference patients of stages III to IV but worse than reference patients of stages I to II. Compared with all reference patients, the patients of this study reported having more diarrhea and insomnia. Their global health status was significantly better only in comparison with reference patients in stages I to II and stages III to IV at the p<0.1 level. Total scoring for the EORTC dimensions is shown in Fig. 1.

Concerning concurrent validity, a minimum prerequisite for a valid and specific QoL measure is that there should be a relation to global health (Table 4). Most functions correlated with global health. Data for global health are visible in Fig. 2.

Correlations between HRQOL and clinical parameters were analyzed (Table 5). Cognitive functioning (r=-0.276; p=0.042), social functioning (r=-0.357; p=0.008), pain (r=0.319; p=0.018), and constipation (r=0.305; p=0.024) showed negative, medium-sized, statistically significant correlations with the last-measured PSA value. Role functioning (r=-0.334; p=0.014), global health (r=-0.327; p=0.015), and constipation (r=0.347;

Table 3. Comparison of reference data from EORTC QLQ-C30 Scoring Manual (Aaronson) with own patient group

| Functioning scales | Reference PCa | | | Own results (n=57) | Significance |
|------------------------|----------------------|--------------------|------------------------|--------------------|---|
| | All stages (n=3,361) | Stage I–II (n=959) | Stage III–IV (n=1,511) | | |
| Functioning scales | | | | | |
| Physical functioning | 80.2±25.6 | 93.0±12 | 53.2±28.8 | 81.51±21.22 | Stage I–II and stage III–IV differ significantly from own results on p<0.001 level. |
| Role functioning | 82.7±28.2 | 90.6±20.3 | 81.4±29.3 | 70.27±30.13 | All stages, stage I–II differ significantly from own results on p<0.001 level. Stage III–IV differs significantly from own results on p<0.05 level. |
| Cognitive functioning | 83.2±20.8 | 86.1±19.3 | 82.8±31.3 | 73.30±24.29 | All stages and stage I–II differ significantly from own results on p<0.001 level. Stage III–IV differs significantly from own results on p<0.05 level. |
| Emotional functioning | 76.6±23 | 78.0±22.8 | 77.7±22.5 | 78.67±24.07 | No significant differences. |
| Social functioning | 80.2±27.2 | 83.9±25 | 81.5±26.5 | 71.75±26.37 | All stages differs significantly from own results on p<0.05 level. Stage I–II differs significantly from own results on p<0.001 level. Stage III–IV differs significantly from own results on p<0.01 level. |
| Symptoms scales | | | | | |
| Fatigue | 26.9±26.6 | 18.9±22.7 | 26.2±26.5 | 31.79±25.20 | Stage I–II differs significantly from own results on p<0.001 level. |
| Nausea and vomiting | 5.1±14.2 | 2.4±9.1 | 4.7±13.8 | 3.53±10.80 | No significant differences. |
| Pain | 23.3±30.3 | 14.6±24.5 | 20.4±29.1 | 24.30±29.54 | Stage I–II differs significantly from own results on p<0.01 level. |
| Dyspnea | 16.8±25.7 | 12.2±22.6 | 17.6±26.7 | 18.45±27.71 | Stage I–II differs significantly from own results on p<0.05 level. |
| Insomnia | 24.5±30.5 | 20.9±28.8 | 23.0±29.6 | 39.89±36.28 | All stages, stage I–II and stage III–IV differ significantly from own results on p<0.001 level. |
| Appetite loss | 10.4±23.6 | 4.9±16.3 | 8.8±22 | 8.19±20.26 | No significant differences. |
| Constipation | 14.6±27.2 | 8.8±20.3 | 13.0±26 | 14.04±25.99 | No significant differences. |
| Diarrhea | 8.4±19.4 | 8.5±20.2 | 7.8±18.5 | 15.77±23.61 | All stages, stage I–II and stage III–IV differ significantly from own results on p<0.01 level. |
| Financial difficulties | 9.0±21.5 | 8.5±21.2 | 8.3±20.5 | 11.11±23.89 | No significant differences. |
| Global health status | 68.4±22.2 | 70.8±20.5 | 68.3±22.4 | 61.82±20.92 | All stages and stage III–IV differ significantly from own results on p<0.05 level. Stage I–II and stage III–IV differ significantly from own results on p<0.01 level. |

Values are presented as mean±standard deviation.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients questionnaire; PCa, prostate cancer.

p=0.009) showed negative, medium-sized, statistically significant correlations with IPSS after treatment assessment.

DISCUSSION

HDR brachytherapy is a minimally invasive technique of delivering conformal hypo-fractionated radiotherapy with a steep fall-off of dose beyond the prostate gland. The prostate gland lies very close to critical normal tissues, the ante-

rior rectum wall, urethra, and bladder neck. Because of that biological fact, HDR-BT is ideal for the treatment of PCa [18].

Brachytherapy has previously been shown to profoundly affect patients' quality of life [19,20]. Hoskin et al. [21] reported that the incidence of early grade 3 or higher genitourinary and gastrointestinal morbidity was 3% to 7% and 0%, respectively, in patients with localized prostate adenocarcinoma treated with HDR-BT alone. In another study, Barkati et al. [22] reported 3-year and 5-year biochemical control rates

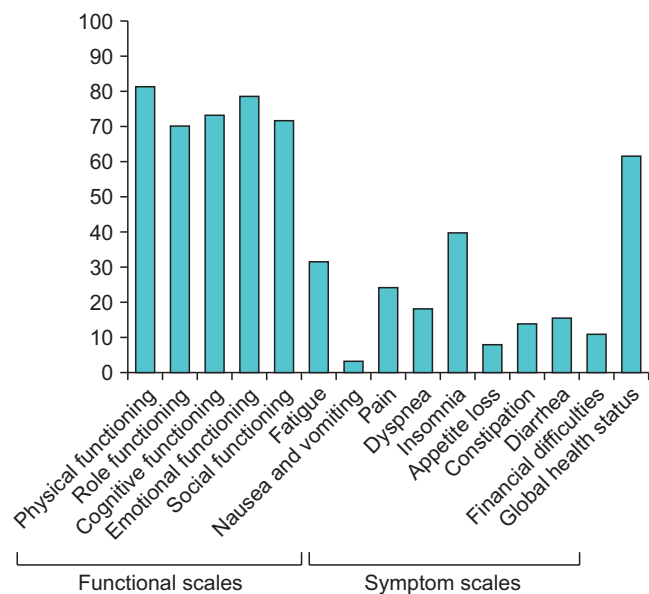


Fig. 1. Mean values for functional and symptom scales.

of 88% and 85%, respectively. They reported all acute genitourinary toxicity as grade 1. Chronic grade 3 urinary toxicity was <10%, but no grade 4 toxicity was seen.

Deger et al. [23] presented data for 422 patients with localized PCa treated between 1992 and 2001 with HDR-BT. As also reported in our therapy protocol, all of those patients underwent laparoscopic pelvic lymph node dissection for exact pathological lymph node staging and to be sure to exclude patients with lymphatic metastases. Patients were classified according to the D'Amico classification as having low-risk, intermediate-risk, and high-risk PCa. The biological nonevidence of disease (bNED) according to risk group was 100% for low-risk, 75% for intermediate-risk, and 60% for high-risk cancer at 5 years. Five-year bNED was 81% in the low-risk, 65% in the intermediate-risk, and 59% in the high-risk group. Five-year overall survival and bNED were 87% and 94%, respectively. The authors also observed that initial PSA value, risk group, and age were significantly related to bNED.

Ferenc et al. [24] reported on physical and psychosocial adverse effects of brachytherapy in different tumors. A high percentage of treated patients reported that brachytherapy decreased their life satisfaction (54.3%), sense of security (41.4%), and self-esteem (34.3%). The highest frequency of gastroenterologic and urologic symptoms was reported by PCa patients.

Contreras et al. [25] used the Expanded Prostate Cancer Index Composite (EPIC) in their study to assess QoL after HDR-BT. Six months after treatment, they found a significant decrease ($p < 0.05$) in urinary, bowel, and sexual scores,

including urinary overall, urinary function, urinary bother, urinary irritative, bowel overall, bowel bother, sexual overall, and sexual bother scores. By 1 year after treatment, EPIC urinary, bowel, and sexual scores had increased and only the bowel overall and bowel bother scores remained significantly below baseline values.

Morton et al. [26] reported HRQOL changes in intermediate-risk PCa patients who received EBRT and an HDR brachytherapy boost without ADT. Patients experienced clinically significant decreases in EPIC urinary, bowel, and sexual overall scores 12 months and 24 months after treatment. In contrast, the EPIC hormonal overall score did not change significantly due to radiotherapy.

In the study of Conaglen et al. [27], they concluded that urinary, bowel, and sexual problems in these men are becoming worse after HDR-BT and will not return to baseline levels once therapy is completed. This was documented 2 years after therapy was completed. In our study we also found severe changes in patients who completed the questionnaire a longer time after finishing the therapy. In a bigger cohort of 347 patients, Hjälm-Eriksson et al. [28] showed in a comparative study between RP and HDR-BT no real difference in HRQOL. But all included patients were patients with localized PCa. In our study, nearly all included patients had high-risk PCa.

In our study nearly all patients had high-risk PCa, and all of them received ADT and laparoscopic lymphadenectomy. The worse results for HRQOL of our study cohort in the social, role, and cognitive functioning dimensions may be because of their advanced PCa. Another study has reported patient-assessed HRQOL changes in PCa patients treated with HDR-BT as a single therapy. Barkati et al. [22] treated a similar number of patients: 79 low- and intermediate-risk PCa patients with HDR brachytherapy monotherapy. Seven patients also received neoadjuvant ADT. They observed a decline in EPIC scores across all four domains as early as 1 month after treatment. Urinary, bowel, and hormonal scores recovered 3 months after HDR brachytherapy monotherapy. The patients' ages were similar to our study. However, baseline sexual overall scores were lower in this report. Regarding physical functioning, the patients of this study were functioning better than reference patients of stages III to IV and also had better global health status.

The negative correlations of elevated PSA values with some dimensions of HRQOL may be caused by two possible facts: on the one hand, patients respond very sensitively to any change of their PSA values, and an increase often leads to heightened anxiety, which could influence HRQOL parameters. On the other hand, an elevated PSA value in a

Table 4. Correlation between functional and symptom scales of the EORTC

| Scales | Physical functioning | Role functioning | Cognitive functioning | Emotional functioning | Social functioning | Fatigue | Nausea and vomiting | Pain | Dyspnea | Insomnia | Appetite loss | Constipation | Diarrhea | Financial difficulties |
|------------------------|----------------------|------------------|-----------------------|-----------------------|--------------------|----------|---------------------|----------|----------|----------|---------------|--------------|----------|------------------------|
| Role functioning | 0.738** | | | | | | | | | | | | | |
| Cognitive functioning | 0.431** | 0.490** | | | | | | | | | | | | |
| Emotional functioning | 0.399** | 0.333* | 0.540** | | | | | | | | | | | |
| Social functioning | 0.512** | 0.611** | 0.585** | 0.310* | | | | | | | | | | |
| Fatigue | -0.743** | -0.720** | -0.653** | -0.470** | -0.519** | | | | | | | | | |
| Nausea and vomiting | -0.250 | -0.410** | -0.393** | -0.372** | -0.420** | 0.421** | | | | | | | | |
| Pain | -0.419** | -0.508** | -0.514** | -0.442** | -0.499** | 0.522** | 0.287* | | | | | | | |
| Dyspnea | -0.553** | -0.543** | -0.250 | -0.314* | -0.393** | 0.537** | 0.481** | 0.222 | | | | | | |
| Insomnia | -0.164 | -0.255 | -0.448** | -0.374** | -0.104 | 0.493** | 0.300* | 0.443** | 0.170 | | | | | |
| Appetite loss | -0.380** | -0.330* | -0.557** | -0.411** | -0.326* | 0.542** | 0.412** | 0.443** | 0.152 | 0.254 | | | | |
| Constipation | -0.182 | -0.168 | -0.288* | -0.082 | -0.153 | 0.366** | 0.212 | 0.168 | 0.246 | 0.199 | 0.155 | | | |
| Diarrhea | -0.102 | -0.096 | -0.014 | -0.128 | -0.003 | 0.247 | 0.244 | 0.112 | 0.061 | 0.358** | 0.054 | -0.048 | | |
| Financial difficulties | -0.128 | -0.210 | -0.470** | -0.219 | -0.458** | 0.281* | 0.388** | 0.412** | 0.044 | 0.333* | 0.346** | 0.225 | 0.174 | |
| Global Health | 0.630** | 0.699** | 0.469** | 0.424** | 0.656** | -0.560** | -0.350** | -0.486** | -0.466** | -0.198 | -0.315* | -0.127 | -0.067 | -0.239 |

EORTC, European Organisation for Research and Treatment of Cancer.

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

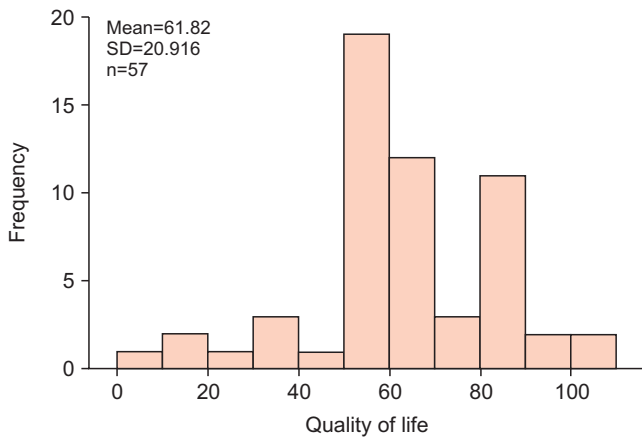


Fig. 2. Frequency for quality of life. SD, standard deviation.

PCa patient is an indicator of illness, which is significantly correlated with pain, and is thereby directly associated with health status. We focused on the parameters that showed statistical significance in correlation with PSA level; these parameters were cognitive functioning (p=0.042), social functioning (p=0.008), pain (p=0.018), and constipation (p=0.024). An elevated PSA at the last documented follow-up could influence all these parameters negatively.

In our study, 57/82 patients (69.5%) completed the EORTC questionnaire. This rate is acceptable and comparable to Contreras et al. [25], who reported 64/84 (76.2%) and others with reported compliance rates of 36% to 78% [22,29].

Most studies about radiotherapy in PCa focus on two points: the effectiveness of the treatment and its tolerance. Due to different classifications of radiation reactions, it is difficult to compare the toxicity rates.

The main limitation of this study was the small number of patients, although the number was acceptable for a single-center study. The follow-up time regarding the influence on cancer-specific survival, overall survival, and biochemical relapse could be longer. Our study adds to the already existing evidence for the effectiveness of HDR-BT in combination with EBRT. Other limitations of the present study are that no information was obtained on pretreatment function, so no firm conclusions can be drawn about treatment-related changes. Additionally, the HRQOL comparisons we conducted were calculated with pretreatment reference data, as no post-treatment reference data were available. Future studies are needed that are prospective, longitudinal, and long-term. Assessing patients at baseline before treatment and following them over time will provide important insights into treatment-related differences in HRQOL.

Table 5. Selected correlations between scales of the EORTC and clinical parameters

| Parameter | Pearson correlation (p) |
|--------------------------------|-------------------------|
| Role functioning×IPSS post | -0.334 (0.014) |
| Cognitive functioning×last PSA | -0.276 (0.042) |
| Social functioning×last PSA | -0.357 (0.008) |
| Quality of life×IPSS post | -0.327 (0.015) |
| Pain×last PSA | 0.319 (0.018) |
| Constipation×last PSA | 0.305 (0.024) |
| Constipation×IPSS post | 0.347 (0.009) |

EORTC, European Organisation for Research and Treatment of Cancer; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.

CONCLUSIONS

HDR-BT in combination with additional EBRT in the present design for high-risk PCa results in high biochemical control rates with minimal side effects. Compared to reference groups and literature results, the HRQOL of this study cohort is acceptable. The PSA value during follow-up seems to be a possible indicator of the patients' HRQOL.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Hui-Juan Huang-Tiel was involved in collecting data and writing the manuscript. Klaus Golka, Silvia Selinski, and Isabella Otto were mainly involved in performance of statistics. Stephan Koswig and Kathrin Bathe were involved in performing the treatment as radio-oncologists and collecting the data. Steffen Hallmann was involved in writing the manuscript and making treatment decisions. Thorsten H. Ecke was mainly involved in collecting data, writing the manuscript, and performing the treatment as a urologist and the supervisor of the study.

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