

Longitudinal Analysis of Quality of Life in Patients Receiving Conformal Radiation Therapy for Prostate Cancer

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Purpose: To prospectively assess quality of life (QoL) in patients receiving conformal radiation therapy (CRT) for prostate cancer.

Patients and Methods: 78 men with definitive CRT for prostate cancer were entered into the study. Patients were assessed before CRT, at 40 and 60 Gy, and 2, 12 and 24 months after the end of treatment. QoL was assessed using the EORTC Quality of Life Questionnaire C30 and the prostate module PR25. Changes in mean QoL scores with time of ≥ 10 points were considered clinically relevant.

Results: Global QoL did not change statistically significant during CRT and was slightly above baseline levels during follow-up. CRT had a statistically significant negative short-term impact on role functioning, fatigue, and PR25 urinary symptoms. The scores recovered within 2 months to 1 year after CRT. Emotional functioning and social functioning scores slightly increased during and after CRT. Role functioning decreased by > 10 points at 60 Gy and urinary symptoms decreased by > 10 points at 40 and 60 Gy. All other differences were < 10 points. A high number of concomitant diseases and having no children were negative pretreatment predictors for long-term global QoL.

Conclusion: Definitive CRT for prostate cancer does not compromise global QoL during therapy and up to 2 years after treatment. It has a limited negative effect on role functioning, urinary symptoms and, to a lesser extent, on fatigue with restitution within 2 months to 1 year after treatment.

Key Words: Prostate cancer · Conformal radiation therapy · Quality of life · Fatigue

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Longitudinale Untersuchung der Lebensqualität bei Patienten mit konformaler Strahlentherapie des Prostatakarzinoms

Ziel: Prospektive Untersuchung der gesundheitsassoziierten Lebensqualität bei Patienten mit konformaler Strahlentherapie des Prostatakarzinoms.

Patienten und Methodik: 78 Patienten mit definitiver konformaler Strahlentherapie eines Prostatakarzinoms wurden vor, während (40 Gy, 60 Gy) sowie 2, 12 und 24 Monate nach Therapie untersucht. Zur Evaluation der Lebensqualität wurden der EORTC Quality of Life Questionnaire C30 und das Prostatamodul PR25 verwendet. Veränderungen ≥ 10 Scorepunkte wurden als klinisch signifikant eingestuft.

Ergebnisse: Die globale Lebensqualität änderte sich während der Strahlentherapie nicht statistisch signifikant und lag im Beobachtungszeitraum nach Behandlung etwas oberhalb der Ausgangswerte. Es fand sich ein kurzfristiger, statistisch signifikanter negativer Effekt auf Rollenfunktion, Fatigue und urologische Symptome. Die betroffenen Scores erholten sich innerhalb von 8 Wochen bis 1 Jahr nach der Strahlentherapie. Der emotionale und der soziale Funktionsscore stiegen während und nach Therapie etwas an. Bei 60 Gy lag die Rollenfunktion um > 10 Punkte unterhalb des Ausgangswerts, und bei 40 und 60 Gy stieg der Score für urologische Symptome um > 10 Punkte über den Ausgangswert an. Alle anderen Veränderungen waren < 10 Scorepunkte. Eine höhere Anzahl an Begleiterkrankungen und Kinderlosigkeit waren negative prätherapeutische Prädiktoren für die globale Lebensqualität nach 2 Jahren.

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Schlussfolgerung: Eine definitive konformale Strahlentherapie des Prostatakarzinoms wirkt sich nicht negativ auf die globale Lebensqualität während und bis zu 2 Jahren nach Behandlung aus. Sie hat einen zeitlich limitierten negativen Effekt auf die Rollenfunktion und die urologischen Symptome und in einem geringeren Ausmaß auf die Fatigue.

Schlüsselwörter: Prostatakarzinom · Konformale Strahlentherapie · Lebensqualität · Fatigue

Introduction

Since prostate cancer is often a slowly growing disease causing little or no symptoms, treatment toxicity and quality of life (QoL) are of major concern [5, 7, 8, 10, 13, 23, 24]. QoL might be directly influenced by the anticancer treatment or indirectly via the onset of treatment-related side effects. Since the prevalence of treatment-related side effects varies with time, it is expected that also QoL changes during and after anticancer treatment. To describe the time course of QoL in patients with conformal radiation therapy (CRT) for prostate cancer, we undertook a prospective longitudinal study where patients were assessed at different time points before, during, and after CRT.

One of the major disadvantages of longitudinal studies in cancer patients is the fact that it is almost impossible to acquire true baseline values. With the moment of getting notified the cancer diagnosis the reference frame of the patients shifts, thus QoL evaluation does no longer reflect the patients' normal state of well-being. In addition, patients might receive various therapies before being referred to the radiation oncology department. The aim of the present study was, therefore, to assess the "net" effect of CRT on QoL as compared to baseline values acquired within 2 weeks prior to treatment.

Patients and Methods

Eligibility Criteria

This study was carried out in a single center, all patients received radiation treatment at the Department of Radiation Oncology of the Technische Universität in Munich, Germany. Participants for this prospective study were recruited between December 2001 and February 2003. Patients who received CRT for localized (cN0 cM0) prostate cancer either as a definitive treatment or in the adjuvant setting were eligible. Herein, we report only on patients receiving definitive CRT. Participants had to have a sufficient command of the German language and they had to give written informed consent. The study was approved by the local ethics committee.

Treatment

Conformal treatment was carried out throughout the whole course of radiation therapy. None of the patients received treatment of the pelvic lymphatics. All patients were treated with 6- to 15-MeV photons from a linear accelerator via four to five individually shaped treatment fields. Dose was prescribed according to the ICRU 50 guidelines. The 95% isodose encompassed the planning target volume (PTV) and the maximum dose did not exceed 107% of the prescribed dose. Patients were advised to be irradiated with a moderately filled

bladder. A rectal balloon catheter for internal immobilization of the prostate was used in 69 patients (89%) during CRT [29]. Planning constraints: no more than 25% of the rectum (outer contour) should received ≥ 70 Gy. Dose per fraction was 2.0 Gy. Three-dimensional planning was carried out using the HELAX TMS planning system (Nucletron, Veenendaal, The Netherlands). Dose prescription and clinical target volumes were defined according to risk groups. Low-risk patients (T1/T2a and G1 or G2 [Gleason Scores 2–6] and pretreatment prostate-specific antigen [PSA] ≤ 10 ng/ml) were treated with 70 Gy to the prostate. Intermediate-risk patients (T1/T2 and G3 [Gleason Scores 7–10] and/or pretreatment PSA > 10 ng/ml and ≤ 20 ng/ml) were treated with 70 Gy to the prostate and the base of the seminal vesicles. High-risk patients (T3/T4 or pretreatment PSA > 20 ng/ml and < 50 ng/ml) were treated with 74 Gy to the prostate and base of the seminal vesicles. Intermediate- and high-risk patients were offered neoadjuvant hormonal therapy for 3–6 months before and 3 months during radiotherapy. Additional adjuvant hormonal therapy was recommended in patients with high-risk prostate cancer. The safety margins for the PTV were 1 cm in all directions except for patients who received 74 Gy, where the safety margins in the dorsal direction were 0.5 cm for the first 8 Gy.

Of the entire patient population, 73 (94%) received neoadjuvant hormonal therapy for a median duration of 3 months before the onset of radiotherapy (Table 1). Treatment was discontinued either at the end of radiotherapy ($n = 41$) or it was continued adjuvantly for a median of another 2 months ($n = 32$). The majority of the patients ($n = 65$, 84%) were treated with a gonadotropin-releasing hormone (GnRH) agonist and 32 (43%) received a peripheral antiandrogen either in addition to the GnRH agonist ($n = 24$) or as the sole hormonal treatment ($n = 8$).

Patient Assessment and Instruments

Patients were evaluated within 2 weeks before the onset of CRT, at the end of treatment weeks 4 and 6, and 2, 12 and 24 months after the end of CRT. At the first evaluation the patients were instructed on how to fill out the questionnaires, during the further time points they usually filled in the questionnaires on their own. If assistance was needed, the patients could contact one of the authors or the hospital staff.

Quality of Life

QoL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30, version 3.0) [1]. The QLQ-C30

consists of five functional scales, three symptom scales, a global health status/quality of life scale, and six single items. Scales and items of the questionnaire range in score from 0 to 100. For the current evaluation, only the functional scales, the global QoL and the fatigue scale were considered, data on the remainder of the QLQ-C30 scales will be reported elsewhere. A change of 10% of the scale breadth or 10 points was considered clinically relevant [19, 21]. Since determining a “clinically relevant change” in QoL scores is a matter of debate [21, 26], all statistically significant changes are displayed in addition.

Prostate Cancer Module QLQ-PR25

The prostate cancer module was developed as a supplementary questionnaire to be employed in conjunction with the QLQ-C30 for the assessment of prostate cancer-related symptoms and disease-affected additional QoL domains. It consists of 25 items in four subscales assessing urinary symptoms (nine items), bowel symptoms (four items), treatment-related symptoms (six items), and sexual functioning (six items). The field testing of the prostate cancer module by the EORTC is currently under way. Since most patients were not sexually active during the study period, sexual functioning was not analyzed for the current evaluation (the score could only be created for patients who were sexually active).

Concomitant Disease

All patients were interviewed for the occurrence of concomitant disease before the onset of radiation therapy and 12 and 24 months after therapy.

PSA Values and Biochemical Recurrence

A biochemical recurrence was defined according to the RTOG-ASTRO Phoenix definition [25] as an increase of > 2 ng/ml above the nadir PSA. Furthermore, the start of hormonal therapy after radiotherapy was regarded as a biochemical failure.

Statistical Analysis

The Friedman test was employed to detect changes in QoL and fatigue over time. When significant, the Wilcoxon test was performed to determine the differences to pretreatment values. Bivariate correlations were calculated using the Spearman correlation coefficient. Stepwise linear regression analysis was carried out to determine independent predictors for long-term global QoL (multivariate analysis). Significance was set to 5%. All tests were carried out two-sided.

Results

Recruitment

From December 2001 to February 2003, 105 patients who were to receive definitive radiotherapy were addressed for the study. Of those, 85 (81%) agreed to take part in the study: twelve (12%) denied participation, six (6%) had insufficient command of the German language, and two (2%) were unable

Table 1. Sociodemographics and clinical characteristics. CRT: conformal radiotherapy; PSA: prostate-specific antigen; WHO: World Health Organization.

Tabelle 1. Patientencharakteristika. CRT: konformale Strahlentherapie; PSA: prostataspezifisches Antigen; WHO: Weltgesundheitsorganisation.

Patients (n)	78
Median age [years (range)]	70 (51–86)
Educational level [n (%)]	
Low	1 (1)
Intermediate	43 (55)
High	31 (40)
Unknown	3 (4)
Marital status [n (%)]	
Single	9 (12)
Married/partner	64 (82)
Unknown	5 (6)
Disease stage [n (%)]	
T1	6 (8)
T2	49 (63)
T3	22 (28)
T4	1 (1)
Risk group^a [n (%)]	
Low	31 (40)
Intermediate	19 (24)
High	28 (36)
Median prostate dose [Gy (range)]	70.0 (64.0–74.0)
Neoadjuvant hormonal therapy [n (%)]	73 (94)
Median duration [months (range)]	3 (1–19)
Adjuvant hormonal therapy [n (%)]	32 (41)
Median duration [months (range)]	2 (1–26)
Disease status 2 years after CRT [n (%)]	
Biochemical relapse (Phoenix criteria)	5 (7)
Distant metastasis	2 (3)
Deceased	1 (1)
Hormonal therapy for biochemical recurrence [n (%)]	2 (3)
Concomitant disease	
Total number [mean (range)]	1.5 (0–6)
Cardiovascular disease [n (%)]	48 (62)
Gastrointestinal disease [n (%)]	14 (18)
Second tumor [n (%)]	9 (12)
Diabetes mellitus [n (%)]	17 (22)
Pulmonary disease [n (%)]	9 (12)
Depression [n (%)]	3 (4)

^alow: T1/T2a and WHO grading 1 or 2 (Gleason Scores 2–6) and initial PSA ≤ 10 ng/ml; intermediate: T1/T2 and G3 (Gleason Scores 7–10) and/or PSA > 10 ng/ml and ≤ 20 ng/ml; high: T3/T4 or PSA > 20 ng/ml

to respond to questionnaires because of psychiatric disorders. Of these 85 patients seven failed to return their questionnaires before the start of therapy. Thus, 78 patients were evaluable. The response rate was high with > 90% of the patients responding to the questionnaires at 1 and 2 years after treatment (n = 72 and 71, respectively).

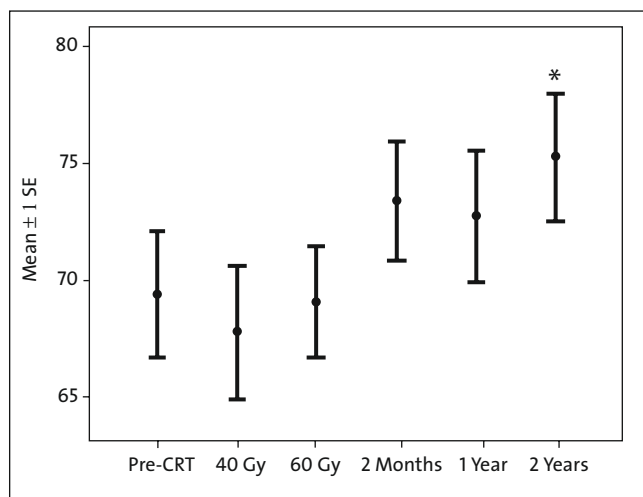


Figure 1. Time course of global quality of life (QLQ-C30). Mean score values \pm 1 standard error (SE) of the mean. A higher value indicates a better global quality of life. * $p < 0.05$.

Abbildung 1. Zeitverlauf der globalen Lebensqualität (QLQ-C30). Mittlerer Score \pm einfacher Standardfehler (SE) des Mittelwerts. Höhere Werte entsprechen einer besseren globalen Lebensqualität. * $p < 0,05$.

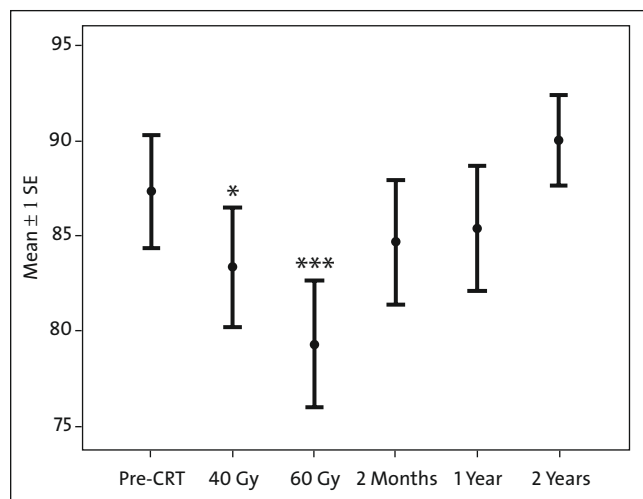


Figure 2. Time course of role functioning (QLQ-C30). Mean score values \pm 1 standard error (SE) of the mean. A higher value indicates a better role functioning. * $p < 0.05$; *** $p < 0.001$.

Abbildung 2. Zeitverlauf der Rollenfunktion (QLQ-C30). Mittlerer Score \pm einfacher Standardfehler (SE) des Mittelwerts. Höhere Werte entsprechen einer besseren Rollenfunktion. * $p < 0,05$; *** $p < 0,001$.

Patient and Treatment Characteristics

Sociodemographics and clinical characteristics are shown in Table 1. Within the 2-year follow-up, one patient died due to prostate cancer and two patients developed distant metastasis. Five patients experienced a biochemical recurrence according to the Phoenix criteria, and in two patients, hormonal therapy was (re)initiated due to rising PSA values.

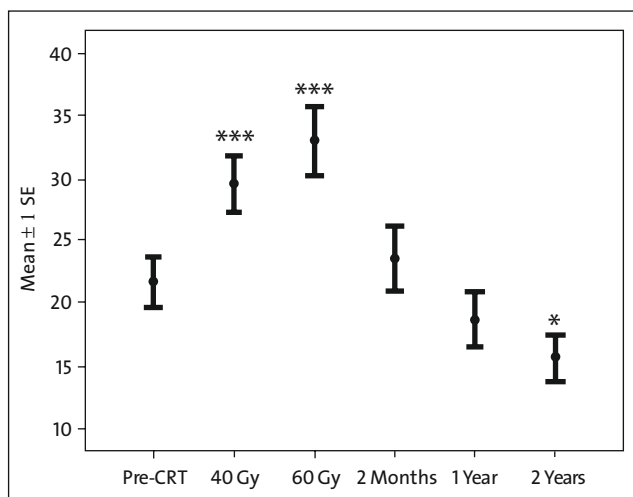


Figure 3. Time course of urinary symptoms (QLQ-PR25). Mean score values \pm 1 standard error (SE) of the mean. A higher value indicates more urinary symptoms. * $p < 0.05$; *** $p < 0.001$.

Abbildung 3. Zeitverlauf urologischer Symptome (QLQ-PR25). Mittlerer Score \pm einfacher Standardfehler (SE) des Mittelwerts. Höhere Werte entsprechen mehr Symptomen. * $p < 0,05$; *** $p < 0,001$.

Quality of Life

Global QoL did not decrease statistically significant during therapy, after treatment levels were slightly above pretreatment values, reaching statistical significance at 2 years after CRT (Wilcoxon test: $p = 0.019$; Figure 1, Table 2). Emotional functioning and social function increased slightly during and after CRT (Friedman test: $p < 0.001$ and $p = 0.044$; Table 2). Role functioning deteriorated significantly during CRT, but recovered as soon as 8 weeks after treatment and stayed within baseline levels throughout further follow-up (Friedman test: $p = 0.001$; Figure 2, Table 2). Fatigue did increase during CRT but reached baseline levels within 8 weeks after CRT (Friedman test: $p < 0.001$; Table 2). Physical functioning and cognitive functioning were not affected by CRT and did not change significantly during or after CRT.

PR25 urinary symptoms significantly increased during CRT but reached baseline levels within 8 weeks after therapy (Friedman test: $p < 0.001$; Figure 3, Table 2). PR25 treatment symptoms did not change significantly during treatment but were below baseline values 2 years after CRT (Wilcoxon test: $p < 0.001$; Table 2). PR25 bowel symptoms did not change significantly during or after CRT. Clinically significant changes in score values of > 10 points were recorded only for role functioning and urinary symptoms: the mean score for role functioning decreased by 11.0 points at 60 Gy and the mean score for urinary symptoms increased by 12.5 points at 40 Gy and 14.0 points by 60 Gy. All other differences were < 10 points. Fatigue increased by 8.5 points at 60 Gy.

Table 2. Quality of life (QoL) before conformal radiotherapy (CRT), at 6o Gy, and 2 years after CRT. SD: standard deviation.**Tabelle 2.** Lebensqualität (QoL) vor konformaler Strahlentherapie (CRT), bei 6o Gy und 2 Jahre nach CRT. SD: Standardabweichung.

	Before CRT			At 60 Gy			2 years after CRT		
	Mean	Median	1 SD	Mean	Median	1 SD	Mean	Median	1 SD
Global QoL	68.3	66.7	23.1	66.1	66.7	18.0	75.6	83.3	19.2*
Physical functioning	89.4	93.3	14.9	86.4	86.7	14.2	88.9	93.3	13.4
Role functioning	87.4	100.0	20.5	76.4	83.3	25.0***	89.0	100.0	17.4
Emotional functioning	74.9	83.3	24.4	78.1	83.3	21.5	82.2	83.3	19.5**
Cognitive functioning	84.4	100.0	22.5	86.3	100.0	17.2	84.3	83.3	19.1
Social functioning	84.2	100.0	21.8	79.7	83.3	24.4	86.6	100.0	18.7
Fatigue	24.1	22.2	23.7	32.6	33.3	22.8**	23.4	22.2	21.7
PR25 urinary symptoms	21.7	20.8	16.1	35.7	33.3	22.2***	19.1	12.5	16.9*
PR25 bowel symptoms	6.1	0.0	9.0	10.4	8.3	11.1	9.7	8.3	12.6
PR25 treatment symptoms	17.9	16.7	15.0	18.7	16.7	14.2	12.1	11.1	11.3***

p-values for the entire distribution compared with pre-CRT values (Wilcoxon's signed rank test; the test was performed only when the Friedman test was significant).

*p < 0,05; **p < 0,01; ***p < 0,001

Pretreatment Predictors for Long-Term Global Quality of Life

The following variables were tested for their association with 2-year global QoL: age at start of CRT, partner (yes/no), children (yes/no), educational level, number of concomitant diseases, risk group, and duration of neoadjuvant hormonal therapy. Negative predictors in multivariate analysis were: no children ($p = 0.031$) and high number of concomitant diseases ($p = 0.031$).

Discussion

In this longitudinal study, we did not find evidence that CRT for prostate cancer has a long-lasting negative effect on global QoL and a variety of functional QoL scores. Nevertheless, CRT exerted significant short-term effects on role functioning, fatigue, and urinary symptoms. The affected scores recovered, however, within 8 weeks to 1 year after treatment. Clinically relevant changes defined as changes in mean scores of ≥ 10 points were observed only for role functioning and urinary symptoms.

Longitudinal studies on QoL in patients with CRT for prostate cancer are rare [2, 14, 16, 18, 19, 27, 30], and mostly have a follow-up of ≤ 1 year [2, 14, 16, 18, 27, 30]. In concordance with our results, these studies demonstrate that QoL is not profoundly impaired by CRT and that there is only a temporary deterioration of a limited number of QoL domains during or shortly after therapy [14, 18, 27]. Janda et al. analyzed QoL (Medical Outcomes Study Group Short Form Health Survey [SF-36] and QLQ-C30) in 43 men receiving CRT for prostate cancer [14]. They observed a temporary decline of role functioning and a temporary increase of fatigue during CRT. Emotional functioning displayed a significant improvement 6 weeks after therapy. 30 weeks after CRT, no significant difference from the baseline values was observed for any

of the QoL domains. Staff et al. presented QoL data (SF-36) on 60 patients with prostate cancer before, during, and up to 10 months after CRT [27]. They found a decline in physical composite scores, physical functioning, the role physical score, and the vitality score. Lips et al. analyzed QoL (RAND-36 generic health survey, EORTC QLQ-C30, and PR25) in 78 patients treated with CRT and 92 men with intensity-modulated radiotherapy (IMRT) for prostate cancer before, and 1 and 6 months after therapy [18]. Patients in the CRT group (70 Gy) revealed temporary deterioration in pain, role functioning, and urinary symptoms. Men in the IMRT group (76 Gy) demonstrated a better QoL as compared to the CRT patients in terms of change in health 1 and 6 months after therapy. In both groups, a temporary deterioration in physical role restriction and an improvement in emotional role restriction occurred. A recent publication of this study group disclosed a significant improvement of emotional role restriction and functioning, change in health, mental health, and insomnia 3 years after IMRT with 76 Gy for 95 patients as compared with baseline levels before treatment [19]. Sexual activity was significantly decreased at 3 years.

The threshold for clinically significant changes of QoL scores still is a matter of debate [21, 26]. Osoba et al., in an article that summarizes the approach of the National Cancer Institute of the Canada Clinical Trials Group, state that "A change of from 5% to 10% (or in general, 0.5 of a standard deviation) of the scale breadth is perceptible to patients as a meaningful change", but that "10% of the scale breadth appears to be a more reasonable number to use as a cut-off point when classifying patients into 'improved', 'stable' and 'worsened' QoL categories" [21]. These statements already show that there are some uncertainties on how to define a clinically relevant change in QoL scores. For the present study we chose 10% or 10 points on the scale of 0–100 as a cutoff point, since

it is widely accepted as a threshold for clinically relevant QoL changes amongst clinicians and researchers and it is comparable to other studies on QoL in prostate cancer [19].

One of the most prominent acute side effects of radiotherapy is fatigue [6, 9]. The exact pathophysiology of this symptom remains unclear. In our patients, fatigue increased up to the 6th treatment week and returned to baseline levels within 8 weeks after CRT. This time course is in concordance with other studies evaluating radiation-induced fatigue during and shortly after external-beam radiotherapy [4, 6, 12, 32, 33]. During further follow-up (1 and 2 years after CRT), fatigue stayed within pretreatment values, indicating that radiation-induced fatigue in patients with CRT for prostate cancer is primarily an acute toxicity without evidence of a second “chronic” fatigue peak.

PR25 urinary symptoms increased clinically significant in our patients during CRT and reached baseline levels within 1 year after CRT. This is in line with clinical evidence and reports on acute urinary toxicity [7, 22]. On the other hand, PR25 bowel symptoms did not increase significantly during CRT and were not elevated during follow-up which is not in accordance with clinical evidence and published reports on acute and chronic intestinal toxicity [3, 8, 10, 11, 13, 17, 20, 22, 31]. A reason for this discrepancy could lie in the four questions of the PR25 addressing bowel symptoms (“Have your daily activities been limited by bowel problems?”, “Have you had any unintentional release (leakage) of stools?”, “Have you had blood in your stools?”, “Did you have a bloated feeling in your abdomen?”), that might not be sensitive and/or specific enough to reflect alterations in bowel habits during or after CRT for prostate cancer. In particular, questions addressing increased stool frequency, stool urge, defecation pain or mucus in stool are completely lacking, although these are rather frequent (acute) side effects of pelvic radiation therapy.

One limitation of our study is the fact that we did not assess QoL before the onset of neoadjuvant hormonal therapy, due to the fact, that most of the patients already were on antiandrogen treatment when visiting our department. This situation probably reflects a common circumstance in many radiooncology departments in Germany. Almost all patients with neoadjuvant hormonal therapy (n = 73) received that therapy until the end of CRT. The short-term effects on QoL during CRT are therefore most likely not influenced by hormonal therapy (since its prevalence did not change during that time span). The number of patients with antiandrogen therapy then declined to ten and nine at 1 and 2 years after CRT, respectively. Therefore, one cannot rule out that QoL at 1 and 2 years after radiotherapy might appear better in relation to pre-CRT values due to the fact that a lower number of patients received hormonal therapy at these times as compared to prior to radiotherapy. On the other hand, neither the duration of neoadjuvant/adjuvant hormonal therapy nor the prevalence of hormonal therapy at 1 and 2 years correlated with global QoL, functional QoL scores, fatigue, or PR25 urinary and bowel symptoms. The only correlation with hormonal therapy

was found for PR25 treatment symptoms which were higher in those patients who received hormonal therapy at 1 and 2 years after CRT (p = 0.041). In addition, other published studies did not disclose a major effect of neoadjuvant hormonal therapy on QoL except for sexual functioning [15, 24, 28].

In summary, our study discloses that CRT with doses of 70–74 Gy has only a small and limited negative impact on QoL in patients with prostate cancer. The data might serve to guide future radiooncologic treatment strategies applying higher doses with recent techniques like IMRT, IGRT (image-guided radiotherapy), or tomotherapy.

Conclusion

The effects of prostate cancer CRT on QoL are limited and mostly temporary. Especially global QoL of life is not compromised by CRT for prostate cancer during and up to 2 years after radiotherapy. Role functioning, urinary symptoms and, to a lesser extent, fatigue were negatively affected but recovered within 8 weeks to 1 year after radiotherapy. Owing to its small detrimental impact on QoL definitive CRT for prostate cancer seems to be an excellent treatment choice for this generally slowly growing disease with a small burden of symptoms.

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