Patterns of Care in the Radiotherapy of Prostate Cancer in Northern Bavaria 1998–2000

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Purpose: A patterns-of-care study of radiotherapy (RT) in prostate cancer was performed in Northern Bavaria, Germany, to characterize patient selection, treatment strategies and outcome for the time period 1998–2000.
Material and Methods: Patients who received curative-intent radical or postoperative RT were identified from the databases of six centers (one university, five teaching/regional hospitals). Two centers treated < 20 patients and were excluded from further analysis. At the remaining four centers, 148 patients receiving radical RT and 134 undergoing postoperative RT were analyzed for pretreatment and RT characteristics and actuarial biochemical control (BC; ASTRO definition).
Results: All patients were treated with three-dimensional conformal external-beam techniques. In radical RT patients, cT- and cN-stages as well as the frequency of (neo)adjuvant hormonal therapy (53–91%) and RT to pelvic nodes (2–97%) and the mean total RT dose (64.8–71.0 Gy) varied significantly between centers. In postoperative RT, centers differed significantly in R-status, initial prostate-specific antigen (PSA) and nodal RT frequency (2–89%), whereas total RT doses were similar (62.3–64.8 Gy). After radical RT, 5-year BC was 68.6% and differed significantly between centers on univariate analysis. In a multivariate model, only total RT dose showed a trend toward an effect on BC. In postoperative RT patients, overall 5-year BC was 82.1%, and age and initial PSA were associated with BC on multivariate analysis.
Conclusion: From 1998 to 2000, radical RT for prostate cancer at the Northern Bavarian centers now studied was performed with three-dimensional conformal technique to conservative total doses and selection criteria for postoperative RT were highly variable.

Key Words: Prostate cancer · Radiotherapy · Patterns of care · Radical radiotherapy · Postoperative radiotherapy

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Versorgungsstrukturen in der Strahlentherapie des Prostatakarzinoms in Nordbayern 1998–2000

Ziel: Eine Untersuchung der Versorgungsstrukturen in der Strahlentherapie (RT) des Prostatakarzinoms in Nordbayern wurde durchgeführt, um für den Behandlungszeitraum 1998–2000 Patientenselektion, Behandlungskonzepte und Ergebnisse zu charakterisieren.
Material und Methodik: In kurativer Absicht primär oder postoperativ bestrahlte Patienten wurden aus den Datenbanken von sechs Zentren (eine universitäre Abteilung, fünf Lehr- oder regionale Krankenhäuser) ermittelt. Zwei Zentren behandelten < 20 Patienten und wurden in der weiteren Auswertung nicht berücksichtigt. In den restlichen vier Zentren waren 148 Patienten mit primärer RT und 134 mit postoperativer RT (Tabellen 1 und 2) bezüglich klinischer und therapeutischer Kriterien sowie der biochemischen Kontrolle (BC; ASTRO-Definition) auswertbar.
Ergebnisse: Alle Patienten wurden mit dreidimensionalen konformalen Techniken perkutan behandelt. In der primären RT waren die cT- und cN-Stadien sowie die Häufigkeit der (neo)adjuvanten Hormontherapie (53–91%), der RT der pelvinen Lymphknoten (2–97%) und die mittlere Gesamtdosis (64,8–71 Gy) zwischen den Zentren signifikant unterschiedlich (Tabelle 3, Abbildung 1). In der postoperativen Therapie bestanden signifikante Unterschiede zwischen den Zentren bezüglich R-Status, initialen prostataspezifischen Antigens (PSA) und Häufigkeit der nodalen RT (2–89%), während die Gesamtdosen (62,3–64,8 Gy) vergleichbar waren (Tabelle 4, Abbildung 2). Nach primärer RT betrug die 5-Jahres-BC 68,6%, bei signifikanten Unterschieden zwischen den Zentren in der univariaten Analyse (Tabelle 5, Abbildung 3). Im multivariaten Modell zeigte die Gesamtdosis einen Trend bezüglich eines Effekts auf die BC. Nach postoperativer RT betrug die 5-Jahres-BC 82,1% (Abbildung 4, Tabelle 6); diese war bei multivariater Analyse mit dem Alter und initialen PSA assoziiert.

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Schlussfolgerung: Im Zeitraum 1998–2000 wurde die primäre RT an den untersuchten nordbayerischen Zentren mit dreidimensionalen konformalen Techniken und konservativen Gesamtdosen durchgeführt. Selektionskriterien für die postoperative RT variierten stark.

Schlüsselwörter: Prostatakarzinom · Strahlentherapie · Versorgungsstrukturen · Primäre Strahlentherapie · Postoperative Strahlentherapie

Introduction

Standards in radiotherapy (RT) of prostate cancer have changed dramatically during the last 10 years due to the increasing proportion of low-risk patients and the introduction of novel techniques [5]. Since the mid-1990s, the results obtained with advanced RT techniques, including three-dimensional conformal (3D-CRT) and intensity-modulated radiotherapy (IMRT) as well as brachytherapy, have been published with favorable biochemical control (BC) rates for different types of dose escalation in radical RT [6–9, 11, 14, 16, 19–24]. Several trials of the 1990s also provided guidelines on the combination of RT and androgen deprivation [3, 13]. Randomized trial results on postoperative RT of prostate cancer have only been published more recently [4].

Technical advances are not immediately transferred into day-to-day clinical routine. The purpose of the present study was to analyze patterns of RT in prostate cancer as provided by six radiation oncology departments in one geographic region of Germany, Northern Bavaria, during the time period from 1998 to 2000. This analysis focused on differences in patient selection and RT strategy between centers as well as center-specific treatment outcomes.

Material and Methods

Six RT centers in Northern Bavaria agreed to participate in this study of patterns of care in the RT of prostate cancer. These centers (one university department and five departments at teaching or regional hospitals) provide RT services for a population of approximately 2.3 million in Northern Bavaria, Germany [22]. Each center provided a database of patients with prostate cancer treated with curative intent between 1998 and 2000. In two of the centers, the total number of such patients was < 20 and these centers were not considered for further analysis. The numbers of the centers in this report do not correspond to the number indicated in the authors' affiliations.

In the remaining centers, RT charts were reviewed by two investigators (D.M. and S.W.) on site. Follow-up information was gathered from the patient charts as well as from treating urologist and general physicians. Survival status was determined by contacting local administrative offices.

Patient and treatment characteristics were compared between centers using the Kruskal-Wallis test. BC was studied as a primary endpoint. Actuarial BC rates were determined by the Kaplan-Meier method. For the latter, biochemical failure according to the 1996 ASTRO consensus definition (three consecutive rises with backdating) [2] was considered an event. BC was compared between subgroups of patients using the Wilcoxon test. Selected parameters were entered into a multivariate Cox model to assess their effect on BC.

Results

A total number of 148 patients receiving radical RT and 134 patients irradiated postoperatively were included in the analysis (Table 1). To characterize the data provided at each of the centers, follow-up times and the number of available prostate-specific antigen (PSA) values are given in Table 2. All patients received 3D-CRT.

Table 1. Distribution of prostate cancer patients by center and type of treatment.

Tabelle 1. Verteilung der Patienten mit Prostatakarzinom nach Zentren und Behandlungsindikationen.

Center	Radical radiotherapy	Postoperative radiotherapy	Total
Center 1	28	88	116
Center 2	47	18	65
Center 3	32	9	41
Center 4	41	19	60
Total	148	134	282

Table 2. Characteristics of data quality including follow-up intervals and number of available prostate-specific antigen (PSA) values by center and type of radiotherapy (RT).

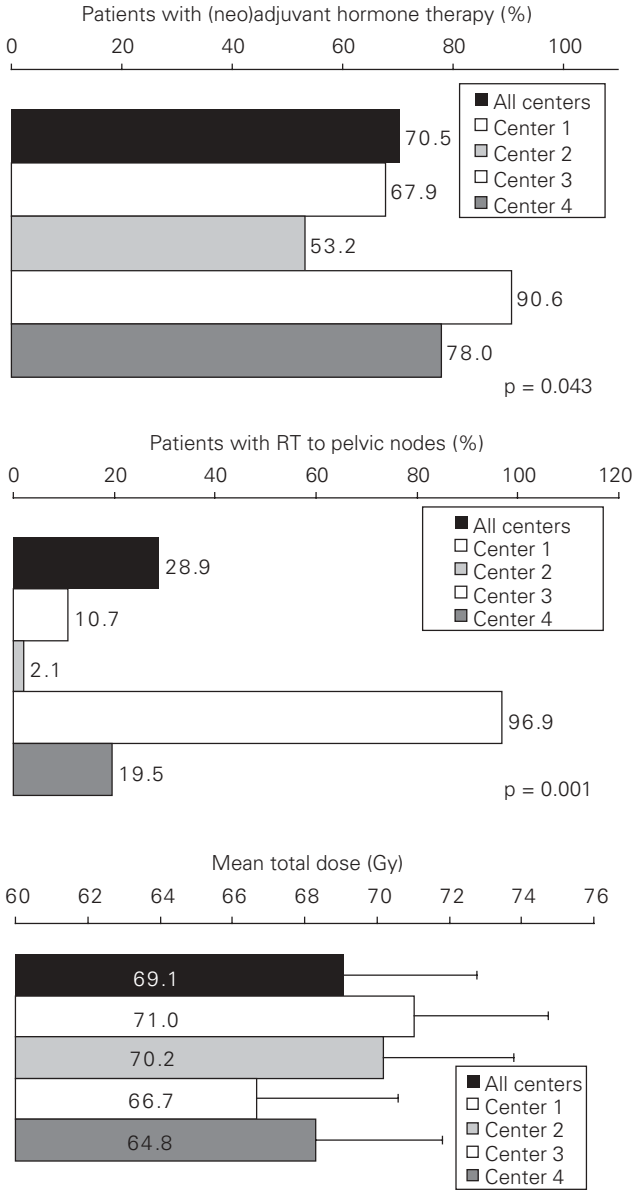
Tabelle 2. Beschreibung der Datenqualität nach Zentren und Bestrahlungsindikation anhand der Nachbeobachtungszeiten und Anzahl verfügbarer PSA-Werte (prostataspezifisches Antigen).

Center	Mean follow-up (radical RT)	Mean follow-up (postoperative RT)	Mean number of PSA values (radical RT)	Mean number of PSA values (postoperative RT)
Center 1	4.8	4.8	7.8	8.4
Center 2	4.3	3.9	6	5.2
Center 3	4.6	4.2	5.2	6.8
Center 4	5.4	5.0	7.7	9.1
Total	4.8	4.8	6.6	8

Table 3. Clinical characteristics of patients receiving radical radiotherapy by center. PSA: prostate-specific antigen; SD: standard deviation.
Tabelle 3. Klinische Eigenschaften der primär bestrahlten Patienten nach Zentren. PSA: prostataspezifisches Antigen; SD: Standardabweichung.

Parameter	Center 1 (n = 28)	Center 2 (n = 47)	Center 3 (n = 32)	Center 4 (n = 41)	All centers (n = 148)	p
Age, mean ± SD (years)	67 ± 5	70 ± 6	68 ± 8	69 ± 7	69 ± 7	0.17
cT-stage: T1/T2/T3/T4/unknown (%)	14/29/32/0/25	64/9/15/6/6	38/16/25/13/9	5/51/24/17/2	33/26/23/9/9	*0.0001*
cN+ (%)	7	6	34	7	13	*0.0002*
Mean/median initial PSA (mg/l)	42.3/8.4	20.7/11.3	40.7/17.3	32/11.8	32.1/11.3	0.40
Mean/median Gleason score	5.9/6	5.3/5	7/7	7.7/8	5.8/6	*0.0026*

In patients who underwent radical RT, significant differences between centers in clinical T- and N-stages as well as the biopsy Gleason score were detected (Table 3). The median initial PSA per center ranged from 8.4 to 17.3 mg/l, but this difference was not significant. Brachytherapy was not employed at any of the centers during the time period under investigation.



Patterns of treatment in radical RT were characterized by a significant variability of the use of (neo)adjuvant hormonal therapy, ranging from 53% to 91% of patients. Only in center 3, nearly all patients were also irradiated to the pelvic nodes during radical RT (Figure 1). This center also had by far the highest number of cN+ patients. Mean total RT doses in the centers varied significantly between 64.8 Gy and 71.0 Gy (Figure 1).

Patients treated postoperatively exhibited significantly different R-status and initial PSA, but not T-stage or Gleason score, between centers (Table 4). Whereas center 3 routinely treated the pelvic nodes also in this patient group, the total doses in postoperative RT varied between centers only within a narrow range with mean doses between 62.3 and 64.8 Gy (Figure 2).

The 5-year BC rates were 68.6% for all patients receiving radical RT and 82.1% after postoperative RT.

On univariate analysis, the total RT dose and the center were significantly associated with BC after radical RT (Table 5). BC by center is displayed in Figure 3. In a multivariate model containing only these two parameters, the influence of the center lost its significance ($p = 0.81$) whereas a trend toward an influence of total RT dose remained ($p = 0.10$). When initial PSA and Gleason score were added to the model, as known prognostic factors, the p-value for total RT dose was 0.13, the other parameters were not significantly associated with BC.

In postoperative RT, patient age (younger age better) and initial PSA were significantly associated with BC, with a trend for total RT dose (higher dose worse; Table 6). The BC by center is shown in Figure 4. In a multivariate model containing these three parameters with $p < 0.1$, the effect of dose lost significance ($p =$

Figure 1. Treatment characteristics of patients receiving radical radiotherapy (RT) by center.

Abbildung 1. Therapiecharakteristika der Patienten mit primärer Strahlentherapie nach Zentren.

Table 4. Clinical characteristics of patients receiving postoperative radiotherapy by center. PSA: prostate-specific antigen; SD: standard deviation.
Tabelle 4. Klinische Eigenschaften der postoperativ bestrahlten Patienten nach Zentren. PSA: prostataspezifisches Antigen; SD: Standardabweichung.

Parameter	Center 1 (n = 88)	Center 2 (n = 18)	Center 3 (n = 9)	Center 4 (n = 19)	All centers (n = 134)	p
Age, mean ± SD (years)	63 ± 6	64 ± 6	65 ± 5	63 ± 6	63 ± 6	0.79
pT-stage: T1/T2/T3/T4 (%)	0/13/73/15	0/0/72/28	9/0/67/33	0/11/84/5	0/10/74/16	0.63
pN+ (%)	0	0	0	0	0	–
R-status: R0/R1/R2/unknown (%)	28/65/0/7	39/33/0/28	22/56/11/11	5/74/21/0	26/61/4/9	*0.0015*
Mean/median initial PSA (mg/l)	19.4/10.4	14.2/6.1	7.7/7.9	25.6/15.3	18.8/9.8	*0.044*
Mean/median Gleason score	6.9/7	6.5/6.5	6.7/7	7/7	6.8/7	0.51

0.28) whereas age (p = 0.087) and initial PSA (p = 0.076) still exhibited a trend toward significant influence on BC. In a model where pT-stage, R-status and Gleason score were added as known prognostic factors, age (p = 0.03) and initial PSA (p = 0.04) had a significant effect with a trend for R-status (p = 0.07). Gleason score and pT-stage had no significant influence.

Discussion

In the present analysis, a rather low total number of prostate cancer cases receiving curative-intent RT during a 3-year period was detected. Considering the number of new prostate cancer cases reported by the German cancer registries for Germany in the year 2000, approximately 40,000 [1], and the population of the area under investigation, approximately 2.3 million, one could estimate roughly 1,000 new prostate cancer patients per year in the respective area. Thus, of approximately 3,000 new cases in the 3-year period, about 10% received RT as part of their initial treatment. All cases were treated with modern RT technique (3D-CRT), but brachytherapy was not yet in use and dose escalation > 70 Gy was rarely and cautiously applied. All centers have experienced increases in prostate cancer patient numbers since the end of the study period (data not shown). For instance, the radiation oncology department at the University of Wuerzburg alone treated 290 prostate cancer patients with curative intent during the 3-year period 2003–2005.

The present analysis documents distinct patterns of patient referral and selection at the specific RT centers. This is exemplified by the considerable variation between centers in the proportions of patients treated radically or postoperatively (Table 1). Although the significant differences in cT- and cN-stages in radical RT patients may be related to the local data quality or staging procedures, the difference in biopsy Gleason scores can be considered an indicator of a center-specific prognostic profile in these patients (Table 3).

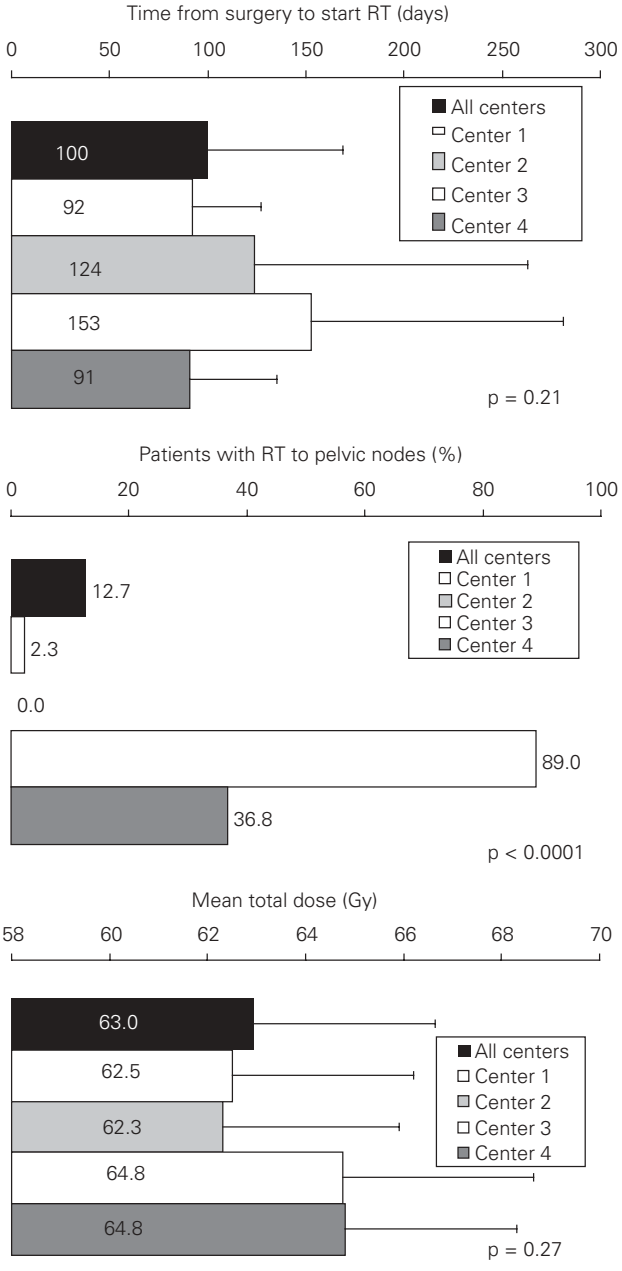


Figure 2. Treatment characteristics of patients receiving postoperative radiotherapy (RT) by center.

Abbildung 2. Therapiecharakteristika der Patienten mit postoperativer Strahlentherapie nach Zentren.

Table 5. Effect of patient and treatment characteristics on biochemical control after radical radiotherapy (univariate analysis). PSA: prostate-specific antigen; RT: radiotherapy.

Tabelle 5. Einfluss von Patienten- und Therapiecharakteristika auf die biochemische Kontrolle nach primärer Strahlentherapie (univariate Analyse). PSA: prostataspezifisches Antigen; RT: Radiotherapie.

Parameter		5-year biochemical control (%)	p
Age	> 69 years	70	0.22
	≤ 69 years	66.8	
cT-stage	T1–2	65.9	0.62
	T3–4	65	
Initial PSA	> 10 µg/l	64.1	0.18
	≤ 10 µg/l	73.3	
Gleason score	≤ 6	70.3	0.13
	> 6	70.2	
(Neo)adjuvant hormones	Yes	70.3	0.37
	No	63.8	
RT to pelvic nodes	Yes	68.5	0.49
	No	67.6	
Total RT dose	< 70 Gy	61.3	*0.02*
	≥ 70 Gy	72.4	
Center	1	59.2	*0.009*
	2	81.3	
	3	69.7	
	4	53.1	

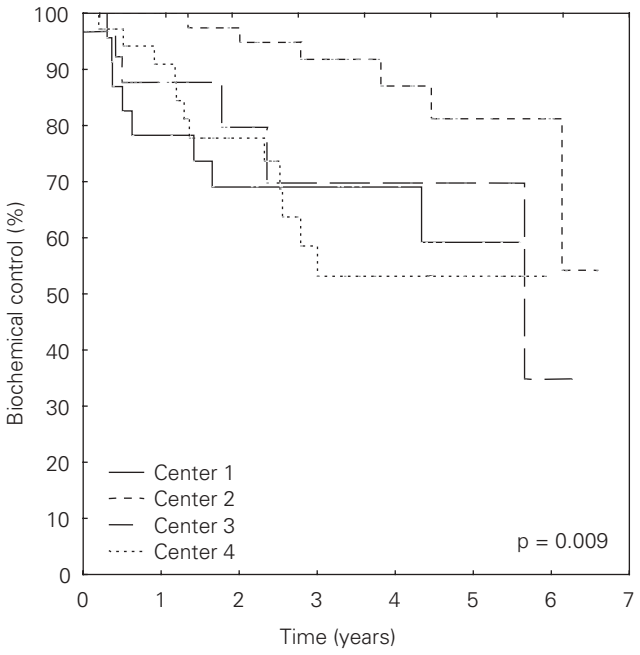


Figure 3. Biochemical control by center in patients who received radical radiotherapy.

Abbildung 3. Biochemische Kontrolle nach primärer Strahlentherapie nach Zentrum.

In patients treated postoperatively, those with positive margins were represented to significantly different percentages, from 33% to 95% (Table 4). This is likely a mixed effect of patient selection for radical prostatectomy, as the center with the highest rate of positive margins also had the highest mean and median initial PSA, and local criteria for RT indication.

Analysis of major treatment factors in curative RT revealed a frequent use of neoadjuvant or adjuvant hormonal therapy, the rare application (with the exception of one center) of RT to pelvic nodes and, in particular, significant differences in total RT dose (Figure 1). At only two centers was the mean total dose (slightly) > 70 Gy.

In postoperative RT, similar patterns as in radical treatment were observed regarding the center-specific use of pelvic node RT (Figure 2). Mean total doses varied only between 62 and 65 Gy and a time interval of well above 3 months between surgery and the initiation of RT was typically respected.

Analysis of treatment outcome was affected by the strong differences in patient and treatment parameters between centers. A lower initial PSA (≤ 10 µg/l) was associated with a 9% improvement in 5-year BC after radical therapy but not significantly so. The lack of any effect of the biopsy Gleason score suggests that these scores may be poorly comparable in this setting of decentralized pathologic evaluation. Whereas the four centers exhibited significantly different BC rates (Figure 3), this effect was lost when other prognostic factors

Table 6. Effect of patient and treatment characteristics on biochemical control after postoperative radiotherapy (univariate analysis). PSA: prostate-specific antigen; RT: radiotherapy.

Tabelle 6. Einfluss von Patienten- und Therapiecharakteristika auf die biochemische Kontrolle nach postoperativer Strahlentherapie (univariate Analyse). PSA: prostataspezifisches Antigen; RT: Radiotherapie.

Parameter		5-year biochemical control (%)	p
Age	> 63 years	72.1	*0.047*
	≤ 63 years	88.8	
pT-stage	T2	90	0.6
	T3–4	79	
R-status	R0	79.6	0.44
	R1–2	78.1	
Initial PSA	> 10 µg/l	69.8	*0.018*
	≤ 10 µg/l	88.5	
Gleason score	≤ 6	94.4	0.94
	> 6	92.5	
Time surgery to RT	< 100 days	83.5	0.13
	≥ 100 days	73.7	
RT to pelvic nodes	Yes	80.2	0.81
	No	80.4	
Total RT dose	< 63 Gy	87.1	*0.088*
	≥ 63 Gy	72.3	
Center	1	80.4	0.31
	2	82.6	
	3	100	
	4	63.8	

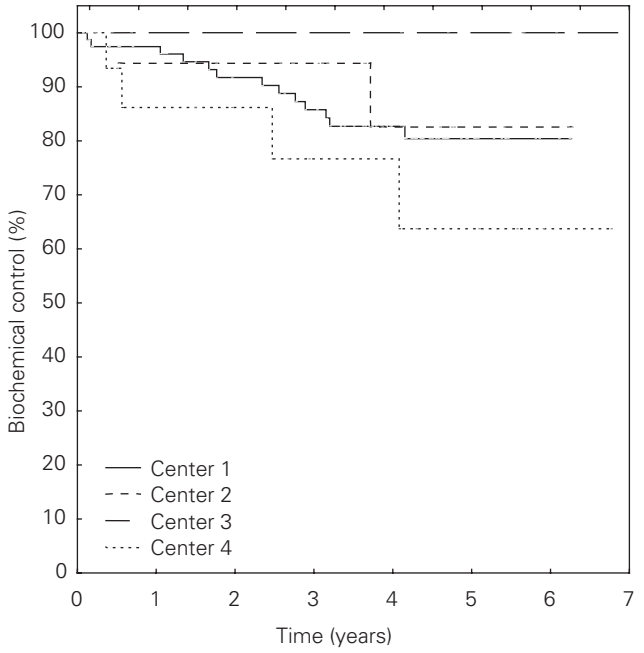


Figure 4. Biochemical control by center in patients who received postoperative radiotherapy.

Abbildung 4. Biochemische Kontrolle nach postoperativer Strahlentherapie nach Zentrum.

were considered in the statistical model suggesting a predominant patient selection effect. In this limited dataset, total radiation dose was significant on univariate analysis, but lost significance when other prognostic factors were considered.

After postoperative RT, BC was not different between centers (Figure 4), with a low number of cases and events at some centers. Interestingly, not only lower initial PSA but also younger patient age were associated with better BC on uni- and multivariate analysis.

Study groups from Europe, North America and Japan previously addressed the patterns of care in RT of prostate cancer in the late 1990s.

In the 1999 United States patterns-of-care survey for prostate cancer, already 36% of patients with clinically localized prostate cancer received brachytherapy [10, 25]. Among patients undergoing external-beam radiotherapy (EBRT), CT-based planning was used in 95% and 51% received additional androgen deprivation treatment. The total dose prescribed was ≥ 72 Gy already in 45% of patients. The respective proportion in the radical RT patients now studied was 15%. Mean initial PSA was 13.3 in the United States compared to 32 in the Northern Bavaria group.

Another study using registry data documented the following changes in the management of low-risk prostate cancer in the USA from 1989 to 2001: increase in the use of brachytherapy (from 3% to 12%) and androgen deprivation monotherapy (from 3% to 22%), and decrease in the rates of prostatectomy (from 64% to 52%) and EBRT (from 16% to 7%) [5].

A regional analysis of the Rotterdam Cancer Registry, The Netherlands, found that from 1989 to 1995, the incidence of prostate cancer doubled from 62 to 125 per 100,000 men and that the number of patients receiving RT increased from 80 to 258 per year [18]. In another Dutch region, the frequency of prostatectomy and of radical RT doubled from the 1991–93 to the 1994–96 time period [15].

In a national survey in Japan, a decrease in preoperative stage cT3/4 patients and in initial PSA from the 1996–98 to the 1999–2001 time period was described for patients eventually undergoing postoperative RT whereas median RT dose remained unchanged at 60 Gy [17]. The same study group compared radical EBRT in Japan (1999–2001) to the patterns of care in the USA in 1999 and found significantly more advanced disease, according to T-stage, Gleason score and initial PSA, in Japan as well as significantly higher total doses in the USA [12].

Conclusion

The situation in the region of Northern Bavaria now studied in the time period from 1998 to 2000 is characterized by rather low patient numbers, referral of patients with unfavorable tumors, as compared to the 1999 status in the USA, general application of 3D-CRT techniques with conservative total doses, the absence of prostate brachytherapy, and highly variable selection criteria for postoperative RT. Follow-up studies will be necessary to determine the impact of more widespread application of dose escalation into clinical practice.

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