research article

Advancements in the radiooncological treatment of high-risk prostate cancer: a quarter century of achievements

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Background. The aim of the study was to evaluate the development of treatment of primary high-risk prostate cancer in regards to biochemical no evidence of disease (bNED), acute and late gastrointestinal (GI) and genitourinary (GU) side effects.

Patients and methods. Primary high-risk prostate cancer patients treated between 1994 and 2016 were included. Applied doses ranged from 60 to 80 Gy, with a dose of 1.8 or 2 Gy per fraction. Techniques were either 3D conformal or intensity modulated radiotherapy and volumetric intensity modulated arc therapy.

Results. 142 patients were treated with doses up to 70 Gy (median dose 66 Gy; 66 Gy group), 282 with doses between 70 and 76 Gy (median dose 74 Gy; 74 Gy group), and 141 with doses >76 Gy (median dose 78 Gy; 78 Gy group). The median follow-up was 48 months. The bNED rates were 50% after 5 years and 44% after 9 years in the 66 Gy group; 65% and 54%, respectively, in the 74 Gy group; and 83% and 66%, respectively, in the 78 Gy group ($p = 0.03$ *vs.* 74 Gy and $p < 0.0001$ *vs.* 66 Gy). We found a higher rate of acute GI side effects in the 78 Gy group compared to the other groups, but not in maximum acute GU side effects and late maximum GI and GU effects.

Conclusions. High-risk prostate cancer patients treated with doses of 78 Gy had significantly better bNED rates. Compared to the historical 66 Gy group, 50% more patients achieved bNED after a follow-up of 9 years.

Key words: biochemical control; gastrointestinal toxicity; genitourinary toxicity; dose escalation

Introduction

Prostate cancer is the most common cancer in men in the US and central Europe, accounting for 20–25% of all cases.[1-3] One in five of these cases is diagnosed with high-risk prostate cancer.[4] However, prostate cancer is only responsible for cancer mortality rates of 6–10%[3,5,6] and death from other reasons is much more likely after being diagnosed with prostate cancer[7] in study conditions.

In the last 25 years, many improvements have been introduced in the field of prostate cancer. In regards to diagnostics and staging, comprehensive PSA screening[1,2], use of ultrasound-guided biopsy[8], and computed tomography (CT)[9], magnetic resonance imagining (MRI)[10], and prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT[11] have found their way into clinical routine, especially for high-risk prostate cancer.

In addition, external beam radiotherapy (EBRT) has taken a leap forward within the last three decades. Starting with 3D conventional radiotherapy[12] and the use of lead blocks, and ending with volumetric intensity modulated arc therapy (VMAT)[13], new techniques allow dose escalation to 72 Gy with tolerable side effects[14], and even to ≥74 Gy[15-17], while also providing similar results as radical prostatectomy (RPE)[7,14] in localized prostate cancer. This dose escalation has significantly increased the curability

of prostate cancer and is, therefore, in our opinion, the most important advancement in the field of prostate cancer radiotherapy over the last quarter century.

Although a final conclusion has not yet been reached about the optimal duration[18-20], evidence-based androgen deprivation therapy (ADT)[2,19-22], especially in high-risk prostate cancer, has improved the outcome after radiotherapy.

With similar oncological results between RPE and EBRT, the focus of patient decision-making shifts more and more to side effects. Therefore, the goal of our study was not only to evaluate the development of high-risk prostate cancer treatment over the last 25 years and the resulting biochemical no evidence of disease (bNED), but also to compare the gastrointestinal (GI) and genitourinary (GU) side effects of radiotherapy.

Patients and methods

The study protocol was approved by the ethical review board of our medical university according to local laws and regulations (EK Nr: 1291/2020).

All patients included in this study were treated at our Department of Radiation Oncology between 1994 and 2016. The inclusion criteria were high-risk prostate cancer as defined by the NCCN classification[1] (PSA > 20 ng/ml, Gleason Score 8-10, or T stage ≥ T3). The required staging was localized cancer without evidence of locoregional or distant metastases. The lymph nodes of all patients were staged using CT. Bone scintigraphy and ADT were performed at the discretion of the treating urologist but were recommended for 3 years according to Bolla *et al*.[23] Patients were primarily treated locally with EBRT.

The definition of the clinical target volume was determined using CT and, from 1997 onwards, MRI for planning. The total prescribed dose ranged from 60 Gy to 80 Gy, with a dose of 1.8 to 2 Gy per fraction. Pelvic lymph nodes were irradiated with a dose of 1.8 or 2 Gy per fraction up to 45–50.4 Gy. Treatment groups were based on the median dose; 58% of patients in the 66 Gy group received 66 Gy, with a maximum of < 70 Gy, 63% in the 74 Gy group received 74 Gy, with doses between 70 and 76 Gy and 90% in the 78 Gy group received 78 Gy, with doses > 76 Gy. The dose was prescribed to 95% of the planning target volume (PTV) according to ICRU report 62.[24] Clinical target volumes (CTV) were defined as the prostate and the seminal vesicles. If pelvic lymph nodes were treated, the CTV also included the iliac vessels up to the aortic bifurcation. The safety margin around the clinical target volume was 5 mm in all directions with gold marker fiducials, 7 mm in all directions without fiducials for the 78 Gy group, and 10 mm in the 74 Gy group for the first 66 Gy and 5 mm dorsally for the last 8 Gy. For 66 Gy, the safety margin varied between 10 and 20 mm. Due to the broad time period of our study, safety margins varied over time. All patients received a rectal balloon[25] as internal immobilization. The irradiation was performed in supine position via either a 3D conformal 4-field box up until January 2013 or intensity-modulated radiation therapy (IMRT) or the VMAT technique from then on.

Follow-up was scheduled for 3 and 12 months after treatment, and then yearly thereafter. We defined bNED failure using the Phoenix criteria (nadir + 2 ng/ml).[26] Recent PSA values and late GI and GU side effects according to RTOG grading[27] were compiled by the physician during each follow-up. Survival data were retrieved from the population census (Statistik Austria).

Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software, San Diego, USA) and R version 3.6.1 (2019-07-05) with RStudio 1.2.1335 (packages: survival version 2.44-1.1, survminer version 0.4.6). A p-value < 0.05 was considered significant. The bNED and survival rates were estimated using the Kaplan-Meier method. The resulting curves were compared using the log-rank test. Multivariable Cox regression models were created including the initial PSA value (log2 transformed); Gleason score ≤ 6/Histograding 1, 7/Histograding 2, and 8-10/Histograding 3; applied dose in Gy; T stage 1a-c and 2a/X (reference), 2b/c and 3, or 4 according to the NCCN guidelines[1]; and pelvic irradiation. Side effects were analysed using the Mann-Whitney U test.

Results

Patient characteristics are provided in Table 1. As our observation period covers decades, irradiation techniques changed. Therefore, almost all patients in the 78 Gy group were treated using IMRT or VMAT. With the implementation of IMRT, we also introduced routine irradiation of the pelvic lymph nodes for high-risk prostate cancer patients. Thus, almost all patients in the 78 Gy group were also irradiated in the region of the pelvic lymph nodes. Exceptions were made for, for example, patients with earlier intestinal surgery.

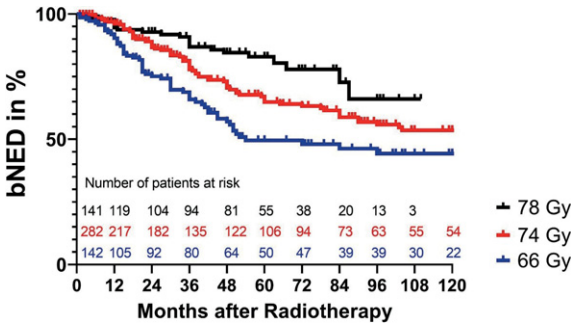

FIGURE 1. Biochemical no evidence of disease (bNED) rates in the 66 Gy, 74 Gy, and 78 Gy groups. The difference between the groups is highly significant ($p < 0.0001$).

Observed bNED rates for the 66 Gy group were 50% after 5 years and 44% after 9 years. For the 74 Gy group, these values were 65% and 54%, respectively, and for the 78 Gy group, 83% and 66%, respectively. A significant difference was found when comparing all groups at once ($p < 0.0001$; Figure 1).

Regarding survival, we detected 7 disease-specific deaths and 40 other causes of death in the 66 Gy group, 11 and 44, respectively, in the 74 Gy group, and 0 and 7, respectively, in the 78 Gy group, respectively.

Disease-specific survival rates after 5 years were 95% in the 66 Gy group, 97% in the 74 Gy group, and 100% in the 78 Gy group ($p = 0.11$). The overall survival rates after 5 years were 74%, 82%, and 96% ($p = 0.0002$), respectively.

The results of the multivariable analysis are displayed in Table 2. The log2-transformed PSA value has to be interpreted as a twice as high initial PSA value leading to a 19% increased risk of bNED failure when comparing two patients.

Maximum acute GI and GU side effects are provided in Table 3. Significantly more acute GI side effects occurred in the 78 Gy group compared to the 74 Gy and 66 Gy groups ($p < 0.001$ and $p = 0.02$, respectively). No significant differences were observed for acute GU side effects ($p = 0.19$ for 78 *vs.* 66 Gy, and $p = 0.88$ 78 *vs.* 74 Gy).

Table 4 provides the maximum late GI and GU side effects. No significant differences were found (GI side effects: $p = 0.40$ for 78 *vs.* 66 Gy, and $p = 0.74$ for 78 *vs.* 66 Gy; GU side effects: $p = 0.13$ and 0.37, respectively).

The onset of RTOG grade 2 or higher is shown in Figure 2 for late GI side effects and Figure 3 for late GU side effects. No significant difference was found for late GI side effects ($p = 0.96$). For late GU side effects, we detected a significant difference ($p = 0.006$).

TABLE 1. Patient characteristics

Median Dose	78 Gy	N = 141	74 Gy	N = 282	66 Gy	N = 142
Dose distribution in Gy						
Min	76		70.4		60	
Max	80		75		70	
N with median dose	127	90%	178	63%	83	58%
T category						
T1	43	30%	48	17%	21	15%
T2	61	43%	108	38%	53	37%
T3	36	26%	121	43%	60	42%
T4	1	1%	5	2%	8	6%
Gleason score						
≤6 or histological grading 1	20	14%	94	31%	40	11%
7 or histological grading 2	29	21%	66	20%	52	4%
8–10 or histol. grading 3	92	65%	118	42%	42	30%
X	0	0%	4	1%	8	6%
iPSA in ng/ml						
Median	15.7		20.6		21	
Technique						
3D-conformal	11	8%	281	100%	142	100%
IMRT or VMAT	130	92%	1	0%	0	0%
Inclusion of LN	133	94%	105	37%	15	11%
ADT	126	89%	259	92%	113	80%
Mean in months	21		16		23	
Follow-up in months						
Min	3		2		3	
Max	116		240		240	
Median	48		47		59	
Age in years						
Min	49		51		53	
Max	84		86		93	
Median	75		73		71	
Gold marker fiducials	53%		1%		0%	

ADT = androgen deprivation therapy; iPSA = initial prostate specific antigen, IMRT = intensity modulated radiotherapy, T = Tumour extension; VMAT = volumetric intensity modulated arc therapy; LN = lymph nodes; X = no Gleason score or histological grading available

We also performed a subgroup analysis and compared the onset of late GU toxicity in patients with irradiated lymph nodes. No significant differences were found when comparing all dose groups at once and 78 Gy with 74 Gy ($p = 0.15$ and 0.17, respectively).

One case of RTOG grade 4 acute GU toxicity was observed in a patient treated with 74 Gy without irradiation of the pelvic lymph nodes. That patient

TABLE 2. Multivariate analysis of potential predictors of biochemical no evidence of disease (bNED)

Variable	HR	95% CI	p-value
iPSA (log2 transformed)	1.193	1.058–1.345	0.004
Gleason ≤ 6 or Histograding 1	reference		
Gleason 7 or Histograding 2	1.254	0.797–1.890	0.280
Gleason 8-10 or Histograding 3	1.687	1.132–2.515	0.010
Pelvic irradiation	0.783	0.540–1.135	0.196
T stage ≤ 2a	reference		
T stage 2b/c	1.466	0.950-2.262	0.084
T stage 3/4	1.517	1.054-2.181	0.025
Dose (Gy)	0.928	0.890-0.969	< 0.001

CI =confidence interval; HR = hazard ratio; iPSA = initial PSA; T stage low = T1a-c and 2a/X; intermediate = 2b/c; high = 3 or 4

TABLE 3. Maximum acute side effects

GI acute	0	1	2	3	GU acute	0	1	2	3
78 Gy	11%	50%	39%	1%	**78 Gy**	13%	54%	32%	1%
74 Gy	35%	35%	29%	1%	**74 Gy**	19%	45%	34%	1%
66 Gy	38%	22%	40%	0%	**66 Gy**	25%	44%	30%	1%

GI = gastrointestinal; GU = genitourinary

TABLE 4. Maximum late side effects

GI late	0	1	2	3	GU late	0	1	2	3
78 Gy	62%	21%	13%	4%	**78 Gy**	49%	23%	23%	5%
74 Gy	63%	22%	13%	1%	**74 Gy**	53%	21%	22%	3%
66 Gy	66%	22%	12%	0%	**66 Gy**	54%	29%	15%	2%

GI = gastrointestinal; GU = genitourinary

developed overflow incontinence and required surgery. No other grade 4 side effects were observed.

Discussion

The goal of our study was to evaluate the development of high-risk prostate cancer treatment over more than two decades in our department. As surgery and radiotherapy are comparable treatment alternatives, side effects are an important factor in choosing a therapy based on informed decision-making.[1,2,7]

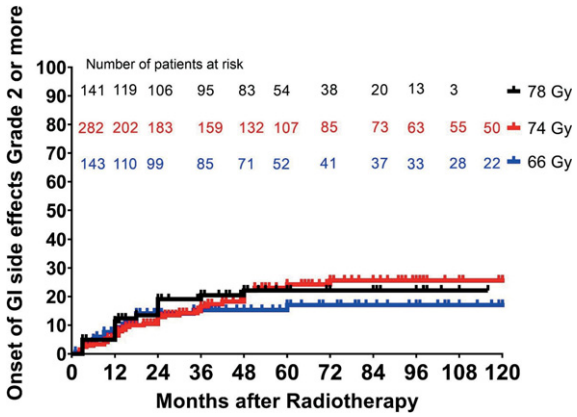

FIGURE 2. Onset of RTOG grade ≥2 gastrointestinal (GI) side effects after treatment over a follow-up period of 120 months.

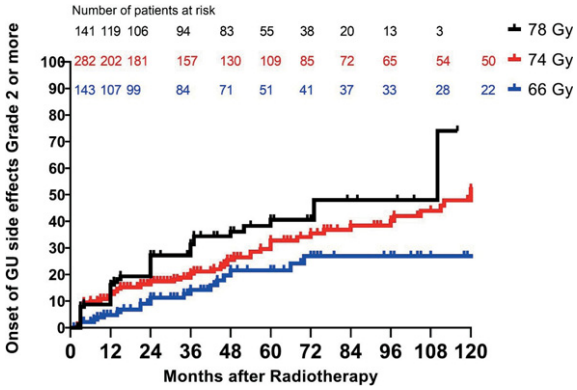

FIGURE 3. Onset of RTOG grade ≥ 2 genitourinary (GU) side effects after treatment over a follow-up period of 120 months.

Starting in the late 1990s, several important studies regarding dose escalation were initiated. Dearnaley *et al.*[16] showed a 10-year bNED rate of 55% in patients treated with 74 Gy compared to 43% after treatment with 64 Gy. Even higher rates were reported in the M.D. Anderson trial[15] and by Peeters *et al.*[17], who escalated the dose from 70 Gy or 68 Gy to 78 Gy. Peeters *et al*. reported a 5-year bNED rate of approximately 70%, and the M.D. Anderson trial reported 75% after 10 years in high-risk patients.

Concerning biochemical control, we are able to reproduce the increased bNED rates by escalating the dose as in the above studies.[15-17] Our bNED rates of 54% and 66% after 9 years for 74 Gy and 78 Gy, respectively, are comparable to the 55% bNED for 74 Gy after 10 years[16] and 70% after 5 years[17] and to the 75% after 10 years for 78 Gy.[15] Notably, our mean ADT duration was higher in the 78 Gy group than in the 74 Gy group, possibly shifting

the bNED rates additionally in favour of the 78 Gy group.[19] Regarding our 78 Gy group, the bNED rate of 83% after 5 years is similar to the 78% described by Ozyigit *et al*.[28] However, the mean ADT duration was 21 months in the 78 Gy group, which is lower than the suggested 24 to 36 months of ADT[2] after Bolla *et al*.[20] showed inferior survival after only 6 months of ADT compared to 36 months. Evidence indicates that 18 months leads to no worse outcomes than 36 months[18], possibly reducing the recommended duration of ADT in the future. Regarding pelvic lymph node irradiation, we were able to detect a tendency of increased bNED rates in our multivariable analysis but no significance, leaving this question unanswered.

Regarding follow-up and survival, as our department has a large catchment area, it is difficult to gather reliable data concerning disease-specific and overall survival, as patients often die in another hospital not associated with our digital infrastructure. Therefore, with a median follow-up of 48 to 59 months, we decided to report only 5-year disease-specific and overall survival rates. However, the similar follow-up does not harm the comparability between groups.

That said, our data suggest great success of high-risk prostate cancer treatment, as 78 Gy provides a 50% increase in bNED rates after 9 years compared to 66 Gy. With absolute bNED rates in the 78 Gy group of 83% and 66% after 5 and 9 years, respectively, and a median age of 75 years in that treatment group, life-long curation of high-risk prostate cancer can be achieved in many cases.

A direct comparison of side effects between our groups is hampered by the fact that our 78 Gy group was almost completely treated using VMAT with reduced margins. Therefore, as IMRT leads to lower GI toxicity[29], caution in making comparisons is advised. However, almost all patients in this group received pelvic lymph node irradiation, which increases toxicity[30], though only by a small amount. Over time, we were able to detect significantly more late GU side effects with increased dose while seeing no difference in late GI side effects. This is possibly due to smaller safety margins, especially when gold markers were implanted, as well as broader use of the IMRT and VMAT technique. Maximum late GI and GU side effects were not significantly different when comparing the 78 Gy group to the other groups. However, when defining the onset of late GU side effects ≥ grade 2 as an event, we detected a significant difference. As the subgroup analysis including only patients with irradiated lymph nodes did not show a significant difference, the cause for this is more likely in the dose escalation to the prostatic urethra and the bottom of the bladder.

A limitation of this study is its retrospective nature. In addition, due to the broad time period of the study, not only doses, but also irradiation technique and irradiated volume, varied over the 25-year observation period. Furthermore, our groups varied in regards to the percentage of patients with lymph node irradiation.

A strength of our study is that it is monocentric with systematic recording of GI/GU side effects. Thus, it provides consistent acquisition of side effects. This is especially important because of the large difference in reported toxicity by patients and physicians.[31] Moreover, we include a large collective of only one risk group for which we are able to present the development of daily routine without any bias due to study conditions.

Over the last quarter century, long-term bNED rates of patients treated with EBRT have increased by 50%. If such success could be achieved by a new drug, it would be all over the news. Sadly, our discipline fails to market this great success accordingly compared to developments in the areas of surgery and systemic treatments, especially with new, promising developments in high-risk prostate cancer treatment, such as simultaneously integrated boosts, as displayed in the FLAME-trial.[32]

Conclusions

Great progress has been made in the treatment of high-risk prostate cancer. Doses of 78 Gy result in significantly higher biochemical control rates and acceptable side effects. Therefore, dose escalation in EBRT for high-risk prostate cancer patients is an appropriate standard of care.

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