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ORIGINAL ARTICLE

Early Functional Lesions and Complications after RPVE vs. Early Radiation-Induced Toxicity after EBRT for Localized Prostate Carcinoma. A Retrospective Observational Study from the Clinical Reality of the Daily Practice

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Abstract

Objective: Consecutive adverse events, responses to radiation, and early complications under real conditions in practice during the peri- and early post-therapeutic phase up to 6 months are described and assessed using the data of this observational study.

Patients and methods: Data from an open, cumulative, non-randomized, single-site study begun in 1996 and completed in 2016 is presented. Following a biopsy and staging, patients were divided into two different therapy arms-radical prostatectomy (RPVE/RARPE) and percutaneous radiation therapy (EBRT)-chronologically and based on patient preference. The base line showed no indications of urinary incontinence or ED for comorbidity relative to the therapy. The Clavien-Dindo classification, the Charlson-Comorbidity Index, the Erection Hardness Score, the Ingelheim-Sundberg incontinence score, and the RTOG/EORTC grading scale ere used to verify the results. Finally, a retrospective univariate/multivariate analysis was conducted.

Results: Included were 742 patients-493 (66.5%) from the RPVE arm, and 249 (33.6%) from the EBRT arm; the median age was 66.7 (SD 6.5) vs. 72.6 (SD 6.6) years. The 30-day mortality rate of this study was 0.0%. The dominant (early) complications of the RPVE arm were urinary incontinence. 39.2% of patients were continent, while 60.7% experienced gradual incontinence. The degree of incontinence correlated positively with age. Another adverse event included post-operative erectile dysfunction (ED): Penetrative intercourse was reported by only 3.25%, partial erectile ability in 31.9%, complete impotence in 63.6% of patients. This ED also correlated positively with age ($p < 0.0001$); no significant correlation with the selection-based low comorbidity (Charlson-Comorbidity Index, $p = 0.0428$). In 11.3%, rare lesions occurred as consecutive lymphoceles, 3.4% of which with interventional indications, and steno sing anastomosis in 4.6%, and reactive fatigue symptoms in 2.8% (3-mo. morbidity).

In the EBRT arm, the most common lesions were radiation-induced GI cystitis in 47.4% with the typical urgency, rarely with temporary urge incontinence. GI proctitis/diarrhea occurred in 8.4%, fatigue in 8.0%. Significantly rare early urethrastenosis in 4.4%, and consecutive bladder neck obstructions in 2.4% (6-mo. morbidity). Erectile dysfunction also bore a relevant morbidity (higher age, higher comorbidity, temporary ADT) in this therapy arm: EHGS of 4 in 16.9% with no ADT, EHGS of 3 in 16.0% with 7.5% ADT, and EHGS of 2, 1 or 0 with ADT in 67.1% of impotent patients.

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Conclusion: These results also reflect the findings of recent studies-including of patients under treatment. We therefore share the published conclusion that the quality of oncologic results may benefit from the introduction of new operative RARPE and advances in radiation technology, while the complications observed during therapy remain largely unchanged. Assessments of observed adverse events during follow-ups were not part of this analysis.

Keywords

Clinically localized prostate cancer, Adverse events, Early complications, Health care research

Abbreviations

ED: Erectile Dysfunction; EBRT: External Beam Radiotherapy; EHGS: Erection Hardness Grading Score; PCC: Prostate Cancer Center; GCP: Good Clinical Practice; RTOG: Radiation Toxicity Grading Scale; RARPE: Radical Retropubic and Robot-Assisted Prostatectomy; RPVE: Radical Retropubic Prostatovesiculectomy

Introduction

The ongoing, partly controversial discussion about differentiated therapeutic recommendations for locally confined prostate carcinoma, and the likelihood and management of adverse events raised the question of the extent to which the complex oncologic and non-oncologic outcome of patients can be described by an open cumulative observational study based on the treatment conditions of a urology office under the GCP standard.

Although direct comparisons between radical prostatectomies and percutaneous radiation therapy are rarely included in randomized prospective clinical studies (13 cited in [1]), they are important and relevant to us in practice.

The analysis of the patients, the allocation to each therapy arm, the overall survival, the tumor-specific and comorbidity-specific mortality, and the rates of recurrence and metastasis, were formulated as the primary points of this study, and we have already published these findings [2,3].

This analysis also offers a description and discussion of further study objectives, such as early side effects and early complications of the therapy, over a post-therapeutic period of up to 6 months.

These aspect shave only been treated cautiously in literature. This specific and complex treatment remains challenging for patients, urologists providing outpatient care, and rehabilitation facilities [4,5].

We have intentionally omitted additional data on side effects and complications during follow-ups after 1 or 2 years, as the literature fully covers comparisons between RARPE and RPE, and the spectrum of long-term changes [6-10].

Material und Methodology

From 1996-2016, following the explanation/biopsy/grading/staging of 1166 prostate cancer patients who sought initial consultation at the doctor's office, locally-confined tumors were detected in 742 patients (63.96%). These patients were selected for the therapy arms of this observational study in the outpatient setting of the doctor's office-strictly in compliance with current guidelines, GCP requirements, and especially in consideration of age, oncologic risk, comorbidity, and patient preference.

493 patients were assigned to the RPVE arm, and 249 patients to the EBRT arm of this two-arm observational study. The patient characteristics are summarized in Table 1. As expected, in the operative study arm, at 77.8%, retropubic extraperitoneal RPVE exceeded robot-assisted modification introduced later.

Table 1: Study characteristics following pretherapeutic allocation.

Variable	RPVE Mean, (SD), resp.%	EBRT Mean, (SD), resp.%	P
Study participants	493	249	
Age	66.70 (6.52)	72.55 (6.56)	< 0.0001
Proportion positive biopsies	0.40 (0.27)	0.36 (0.14)	0.4612
Gleason-score	5.79 (1.61)	6,68 (1.14)	< 0.0001
D'Amico-score	2.88 (1.44)	2.52 (1.43)	0.0004
Charlson Comorbidity -Index	0.68 (0.90)	1.14 (1.09)	< 0.0001
Prostate volume	42.95 (20.22)	30.07 (17.57)	< 0.0001
PSA	11.14 (12.64)	12.62 (15.20)	0.4339
Stage			
cT1a-cT1c	60.8%	39.2%	< 0.0001
cT2a-cT2b	67.7%	32.3%	< 0.0001
cT2c	78.1%	21.9%	< 0.0001
cT3a-cT3b	35.7%	64.3%	< 0.0001

90.3% of these procedures were performed at a high case volume center. The assessed variables were peri procedural complications classified according to Clavien-Dindo [11,12], erectile function after 8 weeks based on the EHGS [13,14], the rate of positive resection margins (R1), periprostatic nerve sparing, and urinary in continence after 4 weeks, as defined by the Ingelheim-Sundberg score [15]. Own study data on nerve sparing appeared indispensable to us for the interpretation of the postoperative erection status in comparison to the published data of the annual quality reports of the PCCs.

The primary intended ***percutaneous radiation therapy*** was performed at two centers with total dosages of 70-78 Gy in individual dosages of 1.8-2.0 Gy-through CT exactly: planning, first using a 3D-conformal multiple-field technique, then adding intensity-modulated radiation therapy (IMRT).

4% of patients of the low-risk group (24.1%), according to the D'Amico classification, received neoadjuvant treatment with flutamide, a nonsteroidal antiandrogen, for 3 months, while 47.2% of the intermediate-risk group (33.7%) and all patients of the high-risk group (42.2%) received adjuvant treatment with leuprorelin, a GnRH analogue, regularly, i.e., for 2 years. The specific toxicity for the EBRT arm was determined based on the RTOG scale [16]. Specific points of this study were matched with age, the Charlson-Comorbidity Index [17], and androgen deprivation status.

Periprocedural and early postoperative side effects were assessed separately after 1, 2, or 6 months. All diagnostics data was assessed face-to-face during the consultation at the follow-ups and added to the structured study registry. We performed the chi-squared test to process the results statistically.

Results

Early side effects and complications in the RPVE arm

The assessed intra- and postoperative early complications are listed in Table 2. Of 493 operations during the observation period, we registered a rate of complications of 22.3% of various kinds under the Clavien-Dindo classification. Clinically-irrelevant Grade I components (packed red blood cell transfusions, indwelling catheter insertion period) were excluded-and not cited in the medical case history. For G II (4.4%), G III (8.6%), G IV (1.2%), and G V (0.0%) lesions, we recorded fewer complications than other authors. However, these findings are based on the individual subtleties of the researcher [12]. Clinical stages pT1-pT3b had a rate of histologically confirmed R1 resections of 15.6% (Table 3).

Table 2: Radical Prostatovesiculectomy-(early) complications during the clinical phase.

Complications	Cases (n)	Percentage (%)	Clavien-Dindo-Classification
Vesicourethral anastomotic stricture	23	4.6	IIIa
Lymphocele with intervention	17	3.4	IIIb
Lymphocele, conservatively treated	39	7.9	I
Rectum Lesions	1	0.2	IIIb
Septic pneumonia	1	0.2	II
Secondary suturing	2	0.4	IIIb
Deep vein thrombosis	6	1.2	II
Pulmonary embolism	5	1.2	IV
Fatigue, temporary depressive Episode	14	2.8	II
Delir	1	0.2	II
Ureteral Lesions	1	0.2	IIIb
Mortality	0	0.0	0
All	110	22.3	

RPVE: Radical Prostatovesiculectomy; EBRT: External Beam Radiotherapy

Table 3: Cut edge characteristics (pT1- pT3b).

Variable	Cases (n)	Percentage (%)
Surgical margins R0 (negative)	405	82.2
R1 (positive - Histology)	77	15.6
R2 (positive - Macroscopy)	3	0.6
All	485	98.4
Missing/no Data	8	1.6
In total	493	100.0

*R-Status, TNM-Classification, 8.ed. 2017

Table 4: RPVE/EBRT-consecutive urinary incontinence vs. age (1-month morbidity).

Variable	Therapy	Incontinence*	Cases (n)	(%)	Age/median	SD	Min (a)	Max (a)
Age	RPVE	0	190	39.2	66	6.9	48	80
		1	134	27.6	66	6.4	42	79
		2	143	29.4	67	6.2	51	79
		3	18	3.7	70	5.4	60	79
		Missing	8	1.6	66	8.1	51	77
		In Total	493	100.0	67		42	80
Age	EBRT	0	231	95.5	72	6.7	50	90
		1	7	2.9	73	6.5	63	80
		2	4	1.6	72	2.2	71	76
		Missing	7	2.8	64	5.5	57	71
		In Total	249	100.0	70	6.7	50	90

RPVE Radical Prostatovesiculectomy, EBRT External Beam Radiotherapy *Severity levels according to Stamey and Ingelmann-Sundberg

Table 5: RPVE-Surgery and Nerve sparing.

Variable			Surgical procedures				Nerve Sparing			
Study			RPE		RARPE		Yes		no/no data	
	n	%	n	%	n	%	n	%	n	%
University PCC*	445	90.3	1263**	77.8	62	22.3	1038**	63.9	587**	36.1
Other certified PCC*	48	9.7	40	83.3	8	16.7	16	33.3	24	50.0
In total	493	100.0								

*PCC certified Prostate Cancer Centers **Arithmetic average, Qm-reports for 2012-2013-2014-2015, RPE Open Radical Prostatovesiculectomy, RARPE Robotic-assisted Radical Prostatovesiculectomy

Table 6: RPVE-Erectile Function vs. Age (2-month morbidity).

Variable	EHGS*	n	%	Mean	SD	Min	Max	p -value
Age	All	493	100.0	66	6.6	42	80	< 0.0001
	Score 4	16	3.25	66	4.1	60	74	
	Score 3	72	14.63	63	6.6	48	79	
	Score 2	70	14.22	65	7.0	42	79	
	Score 1	15	3.05	64	6.6	53	79	
	Score 0	313	63.62	67	6.3	49	80	
	Missing	7						

*Erection Hardness Grading Scale: G4 complete and hard erection, G0 noerection.

Urinary incontinence: Our data finds a primary continence rate of 39.2%. None of the study participants experienced incontinence preoperatively. The differentiated distribution of incontinent patients based on their Ingelheim-Sundberg score [15] shows a positive correlation with age when compared directly (Table 4).

Erectile dysfunction: In this context, the studied patients' age of 66.5 (RPVE arm) and 72.5 (EBRT arm) years, which tends to be advanced when receiving such treatment, should be noted. No patient reported an EHS of 0-2 requiring therapy during the preoperative exploration.

Controlled, preferably bilateral nerve sparing is necessary for an erection to achieve the firmness needed for penetration. Our data indicates implementation in prostate cancerous regions in 63.9%-33.3% (Table 5).

The Erection Hardness Score proved to be the preferred variant for direct exploration of functional sexual status under these treatment conditions [13,14]. The assessment of the data revealed a highly significant correlation between a decline in erectile function and the age of patients who had undergone surgery (Table 6). Table 7 shows the coincidence between erectile function and comorbidity to be only weakly significant. This is due to the design of the study for which patients with a higher Charlson, Comorbidity Index were preferred for the EBRT arm. Nonetheless, the data demonstrates that-in addition to the risk factor ages, and relative intraoperative traumatization of neurovascular structures, metabolic comorbidity represents another causal component of the quality of erectile function.

Table 7: RPVE-Erectile Function vs. Comorbidity (2-month morbidity).

Variable	EHGS*	n	%	Mean	SD	Min	Max	p - value
Charlson-Score	All	493	100.0	0.70	0.92	0	4	0.0428
	Score 4	16	3.2	0.63	0.96	0	3	
	Score 1-3	158	32.0	0.57	0.87	0	4	
	Score 0	313	63.0	0.77	0.94	0	4	
	Missing	0						

*Erection Hardness Grading Scale

Table 8: EBRT-Adverse event pattern (6-month morbidity).

Variable*		Cases (n)	Percentage (%)
249 patients (study arm EBRT)			100.0
Asymptomatic events		122	49.0
Symptomatic events		127	51.0
Fatigue, temporary depressive episode		20	8.0
Radiogenic temporary cystitis	Grade I**	118	47.4
Radiogenic temporary proctitis	Grade I**	21	8.4
Urethral stricture	Grade IV**	11	4.4
Bladder outlet obstruction	Grade IV**	6	2.4
All		176	

*Multiple entries included, **RTOG / EORTC Radiation Toxicity Grading Scale, Grad IV modify.

Table 9: EBRT-Erectile function vs. androgen deprivation (6-month morbidity).

Variable	Erectile Function		ADT	
	post therapeutic		adjuvant treatment	
	n	%	n	%
*EHGS 4	41	16.9	0	0.0
EHGS 3	39	16.0	11	7.5
EHGS 2	25	10.2	16	11.0
EHGS 1	14	5.7	10	6.8
EHSG 0	125	51.2	109	74.7
All	244	100.0	146	100.0
Missing	5			
In total	249			

*Erection Hardness Grading Scale, ADT Temporary Androgen Deprivation

Early side effects and early complications in the EBRT arm

The RTOG/EORTC Grade IV complications in Table 8 after percutaneous radiation therapy required-sometimes after temporary catheter insertion-operative intervention (internal urethrotomy, TUR-P/BA) within 3-6 months of EBRT. The temporary psychological dysregulation in the form of fatigue reported by 8.03% of the EBRT arm was significantly more frequent than the 2.8% reported by the RPVE arm. The urinary incontinence of the urge type following the initial and partially per acute radiation-induced cystitis experienced by 8.2% in the EBRT arm was mostly episodic. According to our data, this reaction to radiation is the most registered temporary side effect of the therapy. These specific symptoms are not correlated with age (Table 4).

The seemingly causal momentum of comorbidity, including in the context of the discussion about post-therapeutic erectile dysfunction, becomes even more evident when juxtaposing the variables erectile function with androgen status of the EBRT therapy arm. There is a direct correlation between EHGS and the adjuvant application of the LHRH analogue leuprorelin. This becomes clear when comparing EHGS 4 (no ADT) and EHGS 0 (74.7% ADT). For EHGS 4, our data shows erectile dysfunction in only 16.9% of patients, as opposed to 51.2% of patients with EHGS 0 (Table 9).

Discussion

Systematic registration of lesions, side effects, and long-term problems caused by therapy constitutes an indispensable element of good clinical practice for strengthening own internal procedures to verifiably ensure recognized quality standards [8,18-20]. For this, Begg, et al. specifically notes the importance of the Romano-Charlson index, according to which we achieved a mortality rate of 0.3% (Index 0), or 1.6% (Index > 2). The same applies to our data on side effects caused by clinical therapy in 28% or 43% of patients. The dispersion of the complication rates depends significantly on the case index [21].

In 2021, a systemic review of an international panel of experts also demonstrated a direct correlation between the number of cases, experience of surgeons, and oncologic and non-oncologic outcomes. In this

evaluation, the rate of hospital mortality was between 0.02% and 0.6% [20]. Our data shows a comparable hospital mortality rate of 0.0% and a perioperative/ early complication rate of 22.3% for a median age of 66.3 years (Table 1 and Table 2).

Individual tumor characteristics, such as clinical stages cT2c and cT3, a Gleason grade ≥ 8, but also operative nerve sparing can increase the risk of R1 resection. In our study, this rate was 15.6% for 493 patients who underwent surgery in the clinical tumor stages of pT1-pT3b pN0-pN1. For tumor stage pT2pN0, data of the PCC of the collaborating high case volume center was used to determine a mean value of 7.87% for 2012-2015 (Table 3).

A national 14-center study from Norway examined the correlation between individual experience of the surgeons and the outcome for localized tumors and found an R1 rate of 26% as the median with a range of 18%-44%-comparable to our low-level zone results [19]. In a study of the American Vattikuti Institute, this rate was 23% out of 1151 cases [7].

The assessed complications-both early and late lesions-may be weighed using the Clavien-Dindo classification, which was validated for the RPVE arm [11,12]. Whether this instrument can establish itself for assessments of clinical complications in future examinations seems doubtful, considering the clinical and methodical heterogeneity of internal quality definitions [10,7,22-26].

The data of Steinsvik, et al. from 2022 showed a rate of *postoperative urinary incontinence* of 40% even after 12 months [19]. Donovan JL, Hamdy FC, et al. presented the complex data of the Protec T Study which reported an *EPIC Urinary Incontinence Sub. Score* of 67.4 (RPVE) and 88.7 (EBRT) after 6 months for a baseline of 92.8. The median age of the total cohort was 62 years [22].

New data of the HAROW observational study shows that 25% of those who have undergone surgery required a subsequent procedure to improve continence [6]. Briel, et al. presented data of 1393 patients of a rehabilitation facility from 2009 and 2016.

Surprisingly, the authors found a significant increase in consecutive stress incontinence from 23% (2009) to 33.9% (2016) for 30-day morbidity. According to their findings (p = 0.078), the operation (RPVE vs. RARPE) did not influence the results with certainty [4].

Following the introduction of a quality assurance program by the National Health Service in England, RPVE could only be performed by a certified and strictly monitored center for 3 years. The urinary in continence rate improved from 43% to 36% [18]. Our study had an early 30-day morbidity rate of 29.4% (Grade 2) and 3.7% (Grade 3) of patients with clinically relevant symptoms under the Ingelheim-Sundberg grading scale (Table 4).

In 2013, M. Resnick's group was prevented from reporting a post-therapeutic in continence rate of just 10.6% after RPVE (24-mo. morbidity!) [9].

M Menon, et al. published a postoperative continence rate of 96% without any pads application after only 6 months [7].

Intact *erectile function* is seen as an indication of postoperative quality of life after RPVE/EBRT. The protection of periprostatic neurovascular structures during an operation is considered evidence based. Studies describe bilateral nerve sparing (bNS) as a consistent procedure [9,18,27]. In their prospective and randomized three-arm study, JL Donovan, et al. report realistic nerve sparing in 48.8% (bNS 75.9%, nNS 19.7%, xNS 4.4%) after 553 RPVEs [22]. Studies should reflect the real procedures of everyday hospital life-and this is how we treat the retrospective findings of our study. For our patients, we identified a mean nerve sparing rate of 33.3%-63.9% from 2012-2015 at collaborating centers (Table 4). According to valid German data, the German-Cancer-Society' target of ≥ 80% could only be met for a very small group of patients (low-risk, IIEF ≥ 22/25) [23].

The higher median age of the participants in our study implies the risk of population-based preference expectations for comorbid erectile dysfunction with vascular-metabolic-endocrine causes [22,28,29]. Epidemiologic studies suggest a global incidence of erectile dysfunction of 17%-34% [30]. The "Cologne Male Survey" identified an ED preference of 15.7% (aged 50-59), 34.4% (aged 60-65), and 53.4% (aged 70-80) [28] in a normal population of over 4000 participants in the year 2000. These findings have been confirmed by other working groups [29]. The Protec T Study cited an EPIC (erection firm enough for intercourse) score of only 65.77% among G4 erections in the pre therapeutic base line-with a 6-month morbidity of merely 12.0% [22].

Claims of post-therapeutic erection rates of more 80% should therefore be questioned. For example, in a single-site study, 94% of patients interviewed 6-18 months after an operation stated to successfully have had intercourse, despite an average SHIM score of 18/25-astounding results, even for a highly-selected cohort [13]. In 2015, P Cathart, et al. published that, under strict external monitoring, the rate of intact erections had improved from 21% to 61% after 12 months at a single site with consistent bilateral nerve sparing [18].

In 2002, J Noldus, et al. presented the results of the Martini-Clinic's Hamburg 12-month study of erection-protective RPVE. The median age of the 366 studied patients was 62.5 years and, therefore, four years younger than our cohort. The unilateral procedure resulted in sufficient, unassisted erections in 19% of the group aged under 60, and in 13% of those over 60. Following bilateral nerve sparing, the results improved to 45% and 38% [31].

In 2019, P Capogrosso's group published the data of high case volume university center about how to regain erectile function during the observation period from 2008-2015. Despite great advances in technical operative and perioperative management, the outcome of the last decade did not improve-not even after 12 or 24 months [32]. These results only confirm the conclusion of I Schauer, et al. whose analysis of 11 excellent RCTs found that the rate of intact erections can be assumed to be no higher than 20-25% after ns RPVE [10].

A representative study of LMU Munich on the status of erectile function after RPVE which surveyed both urologists and their patients found a large discrepancy. While urologists claimed intact postoperative erections of 9.1%, patients reported merely 4.7%. Although 73.9% of urologists believed in erection-protecting long-term therapy, this was only confirmed by 30.3% of patients. Just 28.9% of patients were satisfied with their sexual performance, but their urologists raised this figure as high as 46.2% [5].

Finally, in an editorial about further discrepancies between clinical results after elective intervention, D Tilki, et al. asked if accelerating the further development of high case volume centers wasn't an ethical obligation [33].

In the baseline of our study, the *Charlson-Comorbidity Index* showed significant discrepancies (Table 1) between the 0.68 (SD 0.90) for the RPVE arm and the 1.14 (SD 1.09) for the RTx arm. Our data on gradual postoperative urinary incontinence (Ingelheim-Sundberg score) and on consecutive erectile dysfunction (EHS) was therefore able to demonstrate that weighted functional lesions depended directly on age and the comorbidity index for both therapy arms (Table 4, Table 6 and Table 7). Comorbidity is therefore also of clinical importance as a predictor of individualized radiation therapy for localized prostate cancer [26].

Meerleer, et al. published their data on *early toxicity after intensity-modulated radiation therapy* for a localized prostate cancer. They found GI toxicity of 39%, of 27% in G2, and GU toxicity of 17% in G1 and 36% in G2; only 10% of their patients reported no symptoms [34]. Our data shows a different distribution. We found GI toxicity of merely 8.4% in G1, GU toxicity of 47% in G1, and GU toxicity of 6.8% in G4. In our control cohort, 49% of patients completed therapy asymptomatically (Table 8). According to PL Nguyen's working group, only EBRT is associated with increased mortality for prostate cancer among the intermediary risk group (HR 3.0 [95%CI 1.3-7.2], p = 0.01). However, only patients with low comorbidity benefited from adjuvant 6-month ADT. This increased likelihood of survival could not be demonstrated for patients with medium to high comorbidity since the higher comorbidity-specific mortality became the determining factor [27]. Our group made very similar findings in the past [3].

Due to more recent data, the clinical benefits of adjuvant ADT for heterogenous intermediary risk tumors can be assessed in a more differentiated manner. Especially for the lower intermediary risk status (Gleason 3 + 4 = 7, < 50% positive biopsies), the authors recommend a sole dosage-based EBRT with consecutive lower tumor-specific mortality. The relevant toxicity of the ADT is also referred to explicitly [35,36]. In this context, the lower rate of intact post-therapeutic erectile function of 16.9% (EHS 4) can also be explained by our data (Table 9). The Protec T Study cited analogous EPIC data of merely 22.2% for a baseline of 68.4 (6-month morbidity) [22].

Conclusions

The systematic assessment of early side effects and lesions resulting from complications during the reality of post-therapeutic assistance continues to be of clinical interest. The data reflects the objective indication spectrum of differential diagnostic/therapeutic requirements in clinical practice. In addition to complex medicinal, physiotherapeutic, and invasive intervention, psychosomatic exploration should also be given clinical relevance to support patients effectively in an outpatient home setting. Such coordinated procedure is necessary for meaningful progress on non-oncological outcomes.

Disclosure Statement

The authors declare that they have no conflicts of interest.

Adherence to Ethical Guidelines

No further experimental studies on humans and animals were carried out for these investigations. The required ethical guidelines applied to the collection of data and its processing.

Author Contributions

W-DUB has full access to all the data in this study and take responsibility for the integrity of the accuracy of the data analysis. Study concept and design: W-DUB, StZ, MPW. Acquisition of data: W-DUB, AN, TH. Critical revision of the manuscript for important intellectual content: MPW, StZ, TH. Supervision: WDUB, MPW.

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