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Functional Outcomes and Quality of Life After Radical Prostatectomy Only Versus a Combination of Prostatectomy with Radiation and Hormonal Therapy

Meike Adam [a,b,†], Pierre Tennstedt [a,†], Dominik Lanwehr [a], Derya Tilki [a,c], Thomas Steuber [a], Burkhard Beyer [a], Imke Thederan [a], Hans Heinzer [a], Alexander Haese [a], Georg Salomon [a], Lars Budäus [a], Uwe Michl [a], Dirk Pehrke [a], Pär Stattin [d,e], Jürgen Bernard [f], Bernd Klaus [g], Raisa S. Pompe [a], Cordula Petersen [g], Hartwig Huland [a], Markus Graefen [a], Rudolf Schwarz [g], Wolfgang Huber [h], Stacy Loeb [i], Thorsten Schlomm [a,c,]*

[a] *Martini-Klinik Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [b] *Department of Urology, University of Tuebingen, Tuebingen, Germany;* [c] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [d] *Department of Surgical Sciences, Uppsala University, Uppsala, Sweden;* [e] *Surgery and Perioperative Sciences, Urology and Andrology, Umeå University Hospital, Umeå, Sweden;* [f] *Fraunhofer-Institut für Grafische Datenverarbeitung, Darmstadt, Germany;* [g] *Department for Radiooncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [h] *Genome Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany;* [i] *Department of Urology, Population Health and Laura & Isaac Perlmutter Cancer Center, New York University, NY, USA*

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Abstract

Background: While the optimal use and timing of secondary therapy after radical prostatectomy (RP) remain controversial, there are limited data on patient-reported outcomes following multimodal therapy.
Objective: To assess the impact of additional radiation therapy (RT) and/or androgen deprivation therapy (ADT) on urinary continence, potency, and quality of life (QoL) after RP.
Design, setting, and participants: Among 13 150 men who underwent RP from 1992 to 2013, 905 received RP + RT, 407 RP + ADT and 688 RP + RT + ADT.
Outcome measurements and statistical analyses: Urinary function, sexual function, and overall QoL were evaluated annually using self-administered validated questionnaires. Propensity score–matched and bootstrap analyses were performed, and the distributions for all functional outcomes were analyzed as a function of time after RP.
Results and limitations: Patients who received RP + RT had a 4% higher overall incontinence rate 3 yr after surgery, and 1% higher rate for severe incontinence (>3 pads/24 h) compared to matched RP-only patients. ADT further increased the overall and severe incontinence rates by 4% and 3%, respectively, compared to matched RP + RT patients. RP + RT was associated with an 18% lower rate of potency compared to RP alone, while RP + RT + ADT was associated with a further 17% reduction compared to RP + RT. Additional RT reduced QoL by 10% and additional ADT by a further 12% compared to RP only and RP + RT, respectively. The timing of RT after RP had no influence on continence, but adjuvant compared to salvage RT was associated with significantly lower potency (37% vs 45%), but higher QoL (60% vs 56%). Limitations of

† These authors contributed equally to this study.
* Corresponding author. Martini Clinic, Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Tel. +49 40 741051300; Fax: +49 40 741051321.
E-mail address: tschlomm@uke.de (T. Schlomm).

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our study include the observational study design and potential for selection bias in the treatments received.
Conclusions: Secondary RT and ADT after RP have an additive negative influence on urinary function, potency, and QoL. Patients with high-risk disease should be counseled before RP on the potential net impairment of functional outcomes due to multimodal treatment.
Patient summary: Men with high-risk disease choosing surgery upfront should be counseled on the potential need for additional radiation and or androgen deprivation, and the potential net impairment of functional outcomes arising from multimodal treatment.

1. Introduction

Recent guidelines recommend that patients with high-risk prostate cancer undergoing local therapy should be informed about multimodal therapy approaches, including radical prostatectomy (RP), radiation therapy (RT), and androgen deprivation therapy (ADT) [1]. Randomized clinical trials have been shown that adjuvant RT reduces the risk of biochemical recurrence (BCR) among men with adverse prostatectomy pathology [2–5]. However, this results in overtreatment of a proportion of men with adverse pathology features who were not destined to experience BCR. Recent studies from the USA have revealed a decline in the use of adjuvant RT over time [6]. An alternative option is early salvage RT at the time of BCR. Randomized data comparing adjuvant versus early salvage RT are not yet available. Briganti et al [7] reported 2-yr and 5-yr survival rates in a propensity-matched analysis [7].

ADT is frequently added to RT, although there is no randomized trial evaluating its oncologic effect [1]. Briganti and colleagues reported that RT plus ADT significantly improved cancer-specific survival of pT2–4 pN1 patients, regardless of the extent of nodal invasion, when compared to patients receiving ADT only [8].

Although additional RT with or without ADT may be efficacious in some patients, there are a few studies with inconsistent findings on quality of life (QoL) after RT + ADT [9–14]. Most of these studies were small with heterogeneous populations or lacked patient-reported outcomes. Longitudinal comparisons of individual patients before and after RT are also lacking, as are data on the functional implications of adding ADT to post-prostatectomy RT.

The objective of this study was to assess continence, potency, and QoL outcomes using annual questionnaires for a large cohort of men undergoing RP only or as part of a multimodal approach. We hypothesized that multimodal therapy would be associated with lower continence and potency rates and poorer QoL.

2. Patients and methods

2.1. Patient population

Overall, 17 918 consecutive patients who underwent RP at our institution between January 1992 and July 2013 were evaluated for this study. Of these, 4768 patients were excluded because of loss of follow-up (n = 1458) or no evaluable information from the QoL questionnaires (n = 3310). Patients were classified as RP only (RP group), RP with radiation therapy (RP + RT), RP with both RT and ADT (RP + RT + ADT), or RP with ADT (RP + ADT). Following exclusions, 13 150 patients were available for analysis.

All surgical procedures were performed using a standard technique as previously described [15–17]. Data were collected prospectively in a database approved by the institutional review board. Overall, 1593 patients underwent secondary RT after initial RP. Radiation was given in >60 different institutions using a three-dimensional conformal approach. The median radiation dose was 66.6 Gy (interquartile range [IQR] 64.8–68.4). Secondary RT was limited to the prostatic bed in 50% of the patients, was extended to the seminal vesicles in 26%, and was extended to the lymph node regions in 24%. Adjuvant RT was defined as secondary therapy before BCR and up to 6 mo after RP. RT was characterized as salvage for prostate-specific antigen ≥0.2 ng/ml or if RT initiation was at least 6 mo after surgery. The median time from surgery was 3.3 mo to adjuvant RT and 16.4 mo to salvage RT. All radiation treatments were delivered using conventional fractionation (1.8 or 2.0 Gy per fraction). Of the patients who received RT, 688 (43%) underwent adjuvant or salvage ADT. An additional 407 patients received ADT without RT at a median of 12 mo (IQR 4–45) after surgery.

Urinary function was assessed as the number of pads used per 24 h stratified as follows: 0 pads; 1 safety liner; 1–2 pads; 3–5 pads; and >5 pads. For this analysis, 3–5 pads and >5 pads were grouped as ≥3 pads. Patients whose response to the questionnaire before surgery was ≥1 pad/24 h (3%) were excluded from urinary function analyses. Sexual function and QoL were evaluated annually after surgery using self-administered validated questionnaires (International Index of Erectile Function [IIEF], and European Organization for Research and Treatment of Cancer [EORTC] QoL-C30). Potency was evaluated in terms of ability to achieve sexual intercourse using a scale from 1 to 5 points for IIEF question 2: "When you had erections with sexual stimulation, how often were your erections stiff enough for penetration?" Potency was defined as ≥3 points. Evaluation of potency was restricted to men with documented good preoperative erectile function (IIEF ≥19) who underwent unilateral or bilateral nerve-sparing RP. QoL was assessed using two questions on global health status/QoL from the QoL-C30 questionnaire with a range from 1 (very poor) to 7 (excellent). Linear transformation was then used to calculate a standardized score on the scale 0–100% using the following formula: (raw score − 1)/range × 100. The resulting scores were grouped as 83.3–100%, 58.3–75%, and ≤50%.

2.2. Statistical analyses

To assess the impact of additional RT and/or ADT on urinary function, sexual function, and QoL, propensity score–matched analyses were performed in regression models using variables known to be predictive of urinary function (age, extent of nerve-sparing, prostate volume, year of surgery), sexual function (age, extent of nerve-sparing, IIEF score before RP, prostate volume, year of surgery), and QoL (age, extent of nerve-sparing, prostate volume, year of surgery) as covariates. On the basis of estimated propensity scores, patients were matched 1:1 via

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caliper matching using the R package *matching* (Supplementary Table 1) [18,19]. We repeated additional propensity score–matched analyses by adding the number of questionnaires answered and body mass index (BMI) as possible confounding factors (Supplementary Table 2). A curve-fitting procedure was used to plot the relative frequency (0–100%) for each treatment group and time, and this was repeated 1000 times. A one-sided Student *t*-test was performed to test for significant differences between treatment groups for the highest functional status (continence, 0/1 safety liner/24 h; potency, ≥3 points; QoL, 83.3–100%) at 3 yr (Supplementary material). Finally, multivariable logistic regression analyses were performed to predict the risk of incontinence (≥1 pad/24 h), impotence (<3 points), and a QoL score <83.3%.

Baseline characteristics between patients subgroups were compared using the χ^2 (likelihood ratio) test and the Wilcoxon log-rank or Welch test for categorical or continuous variables. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using JMP software, version 9.0.2 (SAS Institute, Cary, NC, USA) and R [20]

3. Results

Clinicopathologic data for all patients are described in Table 1. Patients treated with additional RT and/or ADT had significantly more adverse tumor features. The median follow-up was 49 mo. The median number of questionnaires answered per patient was two (range 1–5). The median time from surgery to the last questionnaire was 36 mo (range 11–246 mo).

3.1. Continence

Propensity score matching resulted in a cohort of 688 matched pairs for RP versus RP + RT, 371 for RP versus RP + RT + ADT, and 335 for RP + RT versus RP + RT + ADT (Supplementary Table 1). At 3 yr after surgery, patients treated with RP alone had a 91% probability of being continent (0 pads or 1 safety liner) compared to 87% for matched patients who had RP + RT ($p < 0.001$; Table 2); severe incontinence (≥3 pads) was 2% for RP and 4% for RP + RT. For patients who had RP + RT + ADT, the probability of being continent was 80%, compared to 87% for matched patients who received RP alone ($p < 0.001$); severe incontinence was 6% for RP + RT + ADT and 2% for RP. In patients with RP + RT + ADT compared to matched patients with

Table 1 – Patient characteristics

Parameter	Overall	RP	RP + RT	RP + RT + ADT	RP + ADT	*p* value
Patients, *n* (%)	13150	11150 (84.8)	905 (6.9)	688 (5.2)	407 (3.1)	
Age at surgery (yr)						
Median	65	64	65	65	66	<0.001
Interquartile range	60–69	60–68	60–69	60–68	61–70	
Body mass index (kg/m^2)						
Median	26.1	26	26.3	26.2	26.2	0.007
Interquartile range	24.3–28.4	24.3–28.3	24.4–28.7	24.5–28.6	24.3–28.4	
Prostate volume (ml)						
Median	40	40	39	40	40	0.036
Interquartile range	30–53	30–54	30–52	32–52	30–53	
Preoperative PSA (ng/ml)						
Median	6.6	6.3	9	10.2	10.1	<0.001
Interquartile range	4.8–9.9	4.7–9.1	5.9–14.4	6.2–17.5	6.5–19.0	
Follow-up (mo)						
Median	48.6	48.5	48.2	60.6	60.7	<0.001
Interquartile range	24.7–84.3	24.6–84.2	26.7–72.9	36.6–96.2	36.1–108.4	
Year of surgery, *n* (%)						
1992–1999	560	462 (4.1)	22 (2.4)	35 (5.1)	41 (10.1)	<0.001
2000–2005	2624	2217 (19.9)	144 (15.9)	171 (24.9)	92 (22.6)	
2006–2013	9966	8471 (76.0)	739 (81.7)	482 (70.1)	274 (67.3)	
Nerve sparing, *n* (%)						
Bilateral	8564	7901 (70.9)	404 (44.6)	165 (24)	94 (23.2)	<0.001
Unilateral	3297	2523 (22.6)	350 (38.7)	265 (38.6)	159 (39.2)	
No	1284	723 (6.5)	151 (16.7)	257 (37.4)	153 (37.7)	
pT stage, *n* (%)						
pT2	9049	8577 (76.9)	272 (30.1)	106 (15.4)	94 (23.1)	<0.001
pT3a	2650	1991 (17.9)	328 (36.2)	209 (30.4)	122 (30)	
pT3b/4	1450	581 (5.2)	305 (33.7)	373 (54.2)	191 (46.9)	
pN status, *n* (%)						
Nx	4876	4533 (40.7)	192 (21.2)	90 (13.1)	61 (15)	<0.001
N0	7491	6379 (57.3)	564 (62.4)	338 (49.2)	210 (51.7)	
N+	755	213 (1.9)	148 (16.4)	259 (37.7)	135 (33.3)	
Gleason score, *n* (%)						
3 + 3	3346	3243 (29.1)	65 (7.2)	19 (2.8)	19 (4.7)	<0.001
3 + 4	7202	6472 (58.1)	420 (46.4)	183 (26.7)	127 (31.3)	
4 + 3	1950	1218 (10.9)	302 (33.4)	274 (39.9)	156 (38.4)	
≥4 + 4	635	203 (1.8)	118 (13)	210 (30.6)	104 (25.6)	
Surgical margins, *n* (%)						
R0	10798	9826 (88.1)	390 (43.1)	309 (44.9)	273 (67.2)	<0.001
R1	2348	1321 (11.9)	515 (56.9)	379 (55.1)	133 (32.8)	

RP = radical prostatectomy; RT = radiation therapy; ADT = androgen deprivation therapy; PSA = prostate-specific antigen.

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Table 2 – Continence, potency, and quality-of-life outcome probability for propensity score–matched patients after bootstrap analyses at 3 yr after surgery

Outcome	Probability, % (95% confidence interval)					
	Matched cohort 1		Matched cohort 2		Matched cohort 3	
	RP	RP + RT	RP	RP + RT + ADT	RP + RT	RP + RT + ADT
Continence						
0/1 safety liner/24 h	90.9 (89.0–93.3)	87.0 (84.2–89.8)*	87.2 (84.4–90.3)	80.2 (76.4–84.1)*	85.7 (82.4–88.9)	81.3 (77.2–85.5)*
1–2 pads/24 h	6.6 (4.5–8.4)	9.3 (6.8–11.7)	10.6 (8.0–13.0)	13.9 (10.8–16.9)	11.0 (8.2–13.8)	12.3 (9.2–15.6)
≥3 pads/24 h	2.4 (1.3–3.5)	3.8 (2.1–5.2)	2.2 (1.0–3.2)	5.8 (3.4–8.0)	3.4 (1.8–4.6)	6.4 (3.4–8.9)
Sexual function score						
3–5 points	57.9 (53.4–62.3)	40.3 (35.8–44.5)*	54.8 (47.3–63.4)	23.9 (16.5–31.5)*	41.3 (33.5–48.8)	24.1 (15.6–31.8)*
0–2 points	42.1 (37.7–46.7)	59.7 (55.5–64.2)	45.2 (36.6–52.7)	76.1 (68.5–83.5)	58.7 (51.2–66.5)	75.9 (68.2–84.4)
Quality of life score						
83.3–100%	67.9 (64.9–70.7)	57.4 (54.4–60.9)*	59.3 (54.6–63.7)	48.2 (44.0–52.9)*	59.7 (55.7–64.6)	47.2 (42.2–51.7)*
58.3–75.0%	22.6 (20.0–25.2)	29.9 (26.8–32.5)	27.9 (23.6–31.7)	30.6 (26.5–34.4)	25.6 (21.5–29.3)	30.8 (26.6–35.1)
≤50.0%	9.6 (7.9–11.3)	12.7 (10.8–14.7)	12.8 (9.9–15.9)	21.1 (17.2–24.8)	14.7 (11.2–17.8)	22.0 (17.9–26.2)

RP = radical prostatectomy; RT = radiation therapy; ADT = androgen deprivation therapy.
* Statistically significant (one-sided Student *t*-test).

RP + RT, continence was 81% and 86%, and severe incontinence was 6% and 3%, respectively ($p < 0.001$; Table 2). Figure 1A–C compares urinary function over time among the groups.

3.2. Potency

Propensity score matching resulted in 420 matched pairs for RP versus RP + RT, 142 for RP versus RP + RT + ADT, and 138 for RP + RT versus RP + RT + ADT (Supplementary Table 1). At 3 yr after surgery, 58% of patients treated with RP alone were potent, compared to 40% among matched patients who had RP + RT ($p < 0.001$; Table 2). Comparing matched patients treated with RP alone and RP + RT + ADT, the probability of being potent was 55% and 24%, respectively ($p < 0.001$). For patients with RP + RT + ADT, the probability of being potent was 24%, compared to 41% among matched patients with RP + RT ($p < 0.001$). Figure 1D–F compares potency among the groups over time.

3.3. Quality of life

Propensity score matching resulted in 747 matched pairs for RP versus RP + RT, 371 for RP versus RP + RT + ADT, and 336 for RP + RT versus RP + RT + ADT (Supplementary Table 1). At 3 yr after surgery, the probability of a QoL score ≥83.3% was 68% for RP alone compared to 57% for RP + RT among matched patients ($p < 0.001$; Table 2). For patients with RP + RT + ADT, this probability was 48%, compared to 59% for patients treated with RP alone ($p < 0.001$). Comparing patients with RP + RT + ADT to RP + RT, the probability of a QoL score ≥83.3% was 47% and 60%, respectively ($p < 0.001$). Figure 1G–I compares QoL among the treatment groups over time.

3.4. Additional comparisons

We performed additional comparisons among all other possible treatment groups (RP vs RP + ADT and RP + RT vs RP + ADT; Supplementary Table 1). Supplementary Figure 1 and Supplementary Table 3 show comparisons of the functional outcomes among these groups. Furthermore, an alternative propensity matching was performed with addition of BMI and the number of questionnaires, which yielded similar results (Supplementary Fig. 2 and Supplementary Tables 2 and 4). In addition, multivariable logistic regression analyses predicting incontinence (≥1 pad/24 h), impotence (<3 points out of 5), and a QoL score <83.3% support the data (Supplementary Tables 5–7).

3.5. Impact of secondary RT timing on continence, sexual function, and QoL

Some 285 patient (31.5%) with adjuvant RT and 620 (68.5%) with salvage RT without hormonal treatment were available for analysis. Propensity score matching resulted in 234, 118, and 248 matched patients (Supplementary Table 8). There was no significant difference in continence at 3 yr after radical prostatectomy (88% vs 85%). Patients undergoing adjuvant RT did have a significantly lower rate of potency (37% vs 45%) but a significantly higher overall QoL (60% vs 56%) 3 yr after surgery (Supplementary Table 9 and Fig. 2A–C).

4. Discussion

Our data demonstrate an additive impact of secondary RT and ADT on functional outcomes and QoL after RP. While RT was associated with a small but statistically significant impact on continence, addition of ADT was associated with a greater decrement. Similarly, each additional therapy had a large impact on erectile function.

These data are important in light of the recent trend towards reverse stage migration to higher-risk disease [21]. An increasing number of patients with high-risk disease undergo initial RP as part of a multimodal approach, with the potential for subsequent secondary RT and/or hormonal therapy. Despite a large body of evidence on the

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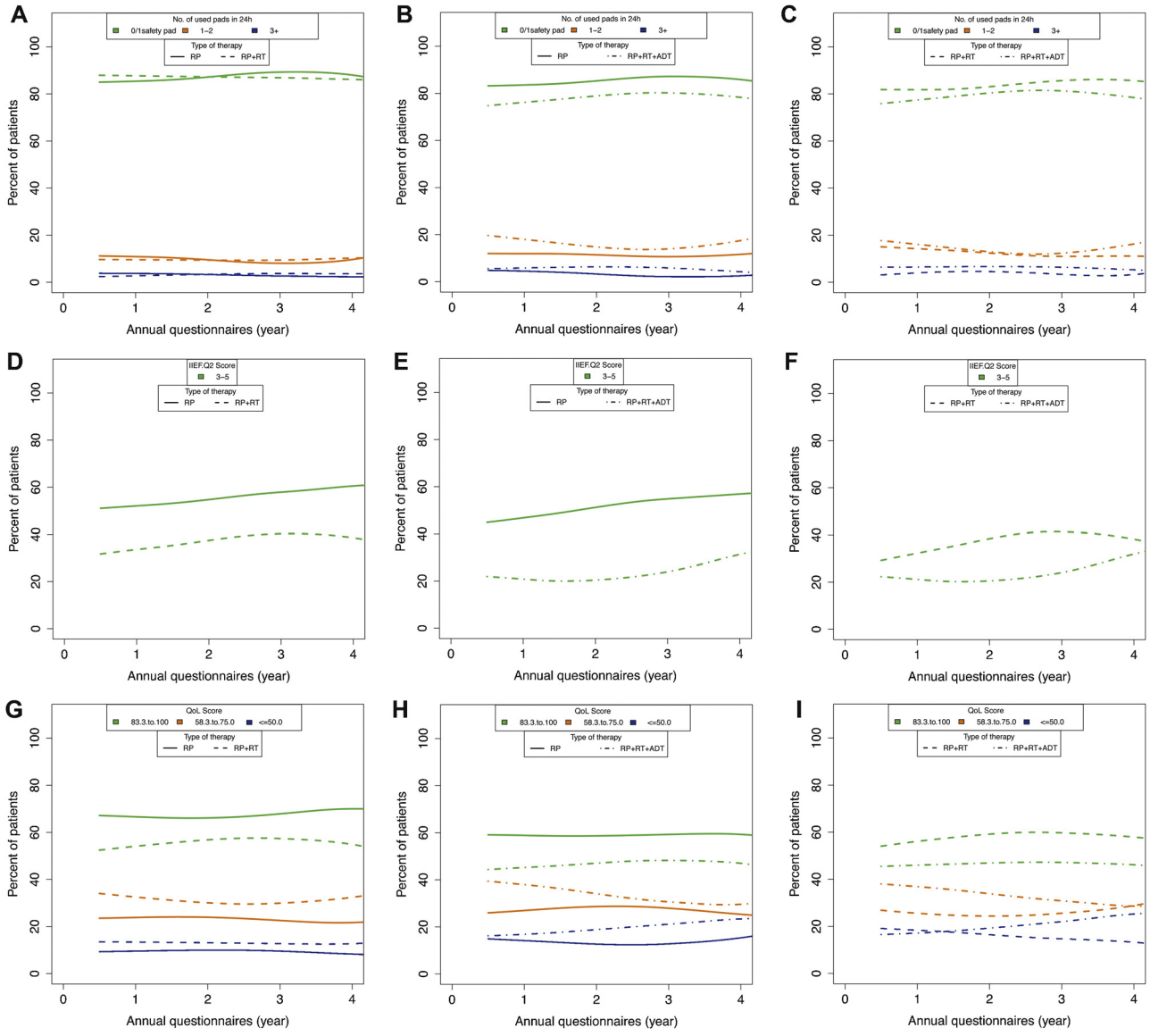

Fig. 1 – Graphical visualization of the within-group frequency of (A–C) the number of pads used in 24 h, (D–F), potency (ability to achieve sexual intercourse), and (G–I) quality of life score annually after propensity score matching and bootstrap analysis. RP = radical prostaectomy; RT = radiation therapy; ADT = androgen deprivation therapy. IIEF = International Index of Erectile Function.

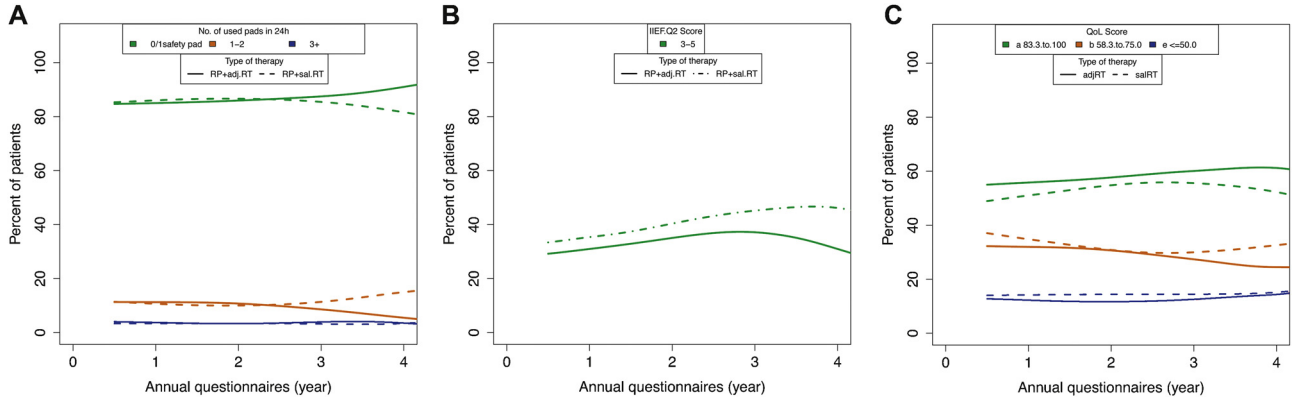

Fig. 2 – Graphical visualization of the within-group frequency of (A) the number of pads used in 24 h, (B) potency (ability to achieve sexual intercourse), and (C) quality of life (QoL) score annually after propensity score matching and bootstrap analysis for patients treated with adjuvant radiation therapy (adjRT) and salvage RT (salRT) after radical prostatectomy (RP). IIEF = International Index of Erectile Function.

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long-term side effects of single-modality treatment, there are scarce data on functional outcomes and QoL after multimodal treatment. The risks of all three modalities are an important component of patient counseling, even before the initial RP.

A previous smaller study by Suardi et al [14] revealed a significant negative impact of adjuvant RT on continence among 361 patients treated with RP (hazard ratio 0.57, 95% confidence interval 0.43–0.76). However, none of the patients in this study received ADT.

Among men in the National Prostate Cancer Register of Sweden, patients who underwent multimodal therapy with prostatectomy followed by RT and ADT had a significant increase in the risk of erectile dysfunction (odds ratio [OR] 3.74), urinary incontinence (OR 3.22). and bowel dysfunction (OR 2.29) [22]. However, this study was cross-sectional in nature and did not include data on functional status before treatment.

Another cross-sectional study from Japan involving 160 men who had ADT after RP found a significant decreases in sexual function and hormonal function [23]. In our study, ADT was associated with a decrement not only in sexual function but also in continence. Notably, a previous study of 67 men showed a 4.5% decrease in urinary function scores before and 6 mo after ADT, although this did not reach statistical significance [24]. The mechanism underlying the impact of ADT on continence requires further study.

The combined findings in all these studies highlight the substantial impact of multimodal therapy on QoL, and thus the importance of identifying patients who will benefit from additional therapy to justify these risks. However, it should be noted that only a small minority of patients in our cohort (5.2%) ultimately received all three therapies, and even in the D'Amico high-risk group, this was only 18%. Other studies have similarly shown that a substantial proportion of patients with high-risk disease achieve long-term progression-free survival with surgery and selective use of secondary RT or ADT [25,26]. In a series of patients with high-risk disease managed with upfront RP at Johns Hopkins, 71% remained free from hormonal therapy at 10 yr.

Another interesting finding in our study is the improved potency in men undergoing salvage compared to adjuvant RT. These data provide additional support for initial observation with selective early salvage RT to allow recovery of function, since we observed substantial spontaneous recovery of potency among men who received RP alone. Our observation of an association between a longer time interval from RP to additional RT and better recovery of sexual function is confirmed by a recent study by von Stam et al [27], who compared health-related QoL between patients treated with RP only and patients treated with RP and salvage RT.

The advantages of our study include the large sample size of 17 918 consecutive patients treated using a highly standardized surgical technique. Men received RT at diverse centers, which increases the generalizability. We used propensity score adjustment to better isolate the impact of additional RT and ADT on urinary continence, erectile function, and QoL. In addition, not all patients responded to the survey at each time point. However, we used statistical methods to account for this, and the overall response rate was high at ~90%.

The limitations of our study include the observational study design and the potential for selection bias in the treatments received, since the indication for multimodal treatment cannot be completely separated from the effect of the treatments. However, all the outcome data were collected prospectively, and propensity score analysis including key prognostic factors was conducted for multiple variable combinations with similar results. It is possible that requiring additional therapy and an awareness that the cancer may not be cured could itself have an impact on QoL. Nevertheless, it is important that patients recognize that a potential need for additional therapy can further impact QoL.

To avoid >30 statistical comparisons, analyses of QoL and potency were limited to the most easily comparable and clinically meaningful questions from the global health status/QoL of the QoL-C30 questionnaire, and question two (ability to achieve sexual intercourse) of the IIEF questionnaire.

5. Conclusions

Prostatectomy followed by RT and hormonal therapy had the greatest impact on urinary control, sexual function, and QoL. For patients who ultimately required all three forms of therapy, there was an additional 1% rate of severe incontinence on addition of RT, plus an additional 3% for ADT. The rate of erectile dysfunction was increased by 18% on addition of secondary RT plus an additional 17% for ADT. QoL was reduced by 11% by RT plus an additional 13% by ADT. Although only a minority of patients received all three therapies, patients with high-risk disease should be counseled before RP on the potential net impairment of functional outcomes arising from multimodal treatment. These data may be used to inform decisions regarding the optimal timing of secondary therapy.

Author contributions: Thorsten Schlomm had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Schlomm.
Acquisition of data: Adam, Tennstedt, Lanwehr, Steuber, Beyer, Thederan, Heinzer, Haese, Salomon, Budäus, Michl, Pehrke, Pompe, Huland, Graefen, Schlomm.
Analysis and interpretation of data: Adam, Tennstedt, Huber, Loeb, Schlomm.
Drafting of the manuscript: Adam, Tennstedt, Huber, Loeb, Schlomm.
Critical revision of the manuscript for important intellectual content: Tilki, Steuber, Beyer, Heinzer, Haese, Salomon, Budäus, Michl, Stattin, Bernard, Klaus, Pompe, Petersen, Huland, Graefen, Schwarz.
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Appendix A. Supplementary data

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