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ORIGINAL ARTICLE

Additional androgen deprivation makes the difference

Biochemical recurrence-free survival in prostate cancer patients after HDR brachytherapy and external beam radiotherapy

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Abstract
Background The role of additional androgen deprivation therapy (ADT) in prostate cancer (PCa) patients treated with combined HDR brachytherapy (HDR-BT) and external beam radiotherapy (EBRT) is still unknown.
Patients and methods Consecutive PCa patients classified as D'Amico intermediate and high-risk who underwent HDR-BT and EBRT treatment ± ADT at our institution between January 1999 and February 2009 were assessed. Multivariable Cox regression models predicting biochemical recurrence (BCR) were performed. BCR-free survival was assessed with Kaplan–Meier analyses.
Results Overall, 392 patients were assessable. Of these, 221 (56.4%) underwent trimodality (HDR-BT and EBRT and ADT) and 171 (43.6%) bimodality (HDR-BT and EBRT) treatment. Additional ADT administration reduced the risk of BCR (HR: 0.4, 95% CI: 0.3–0.7, $p<0.001$). D'Amico high-risk patients had superior BCR-free survival when additional ADT was administered (log-rank $p<0.001$). No significant difference for BCR-free survival was recorded when additional ADT was administered to D'Amico intermediate-risk patients (log-rank $p=0.2$).
Conclusions Additional ADT administration improves biochemical control in D'Amico high-risk patients when HDR-BT and EBRT are combined. Physicians should consider the oncological benefit of ADT administration for these patients during the decision-making process.

Keywords Androgen deprivation therapy · Biochemical recurrence · Brachytherapy · External beam radiotherapy · Prostate cancer

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Zusätzlicher Androgenentzug macht den Unterschied

Biochemisches rezidivfreies Überleben bei Prostatakarzinompatienten nach HDR-Brachytherapie und perkutaner Bestrahlung

Zusammenfassung
Hintergrund Der Nutzen einer zusätzlichen Hormonentzugstherapie (ADT, „androgen deprivation therapy") für Patienten mit Prostatakarzinom (PCa), welche mit einer Kombination aus HDR-Brachytherapie (HDR-BT) und perkutaner Bestrahlung (EBRT) behandelt werden, ist weiterhin ungeklärt.
Methodik Für diese Studie wurden konsekutive, nach der D'Amico-Risikoklassifizierung in „intermediate" und „high-risk" eingeteilte Patienten ausgewählt, die zwischen Januar 1999 und Februar 2009 in unserem Institut eine kombinierte Therapie aus HDR-BT, EBRT ± ADT erhalten haben. Eine multivariable Cox-Regressionsanalyse zur Vorhersage eines biochemischen Rezidivs (BCR) wurde durchgeführt. Zusätzlich wurde mit einer Kaplan-Meier-Analyse das BCR-freie Überleben in Abhängigkeit vom Status der Hormonentzugstherapie untersucht.

Ergebnisse Insgesamt wurden 221 von 392 Patienten (56,4 %) mit einer 3-fachen (HDR-BT und EBRT und ADT) und 171 (43,6 %) mit einer 2-fachen Therapie (HDR-BT und EBRT) behandelt. Die zusätzliche ADT hat das Risiko für ein BCR reduziert (HR 0,4; 95 %-KI 0,3–0,7; $p<0{,}001$). D'Amico high-risk-Patienten zeigten ein verbessertes BCR-freies Überleben, wenn eine zusätzliche Hormonentzugstherapie durchgeführt wurde (log-rank $p<0{,}001$). Bei D'Amico intermidiate-risk Patienten hatte die zusätzliche ADT keinen signifikanten Einfluss auf das BCR-freie Überleben (log-rank $p=0{,}2$).
Schlussfolgerung Die zusätzliche ADT führt bei „High-risk"-Patienten, die mit einer Kombination aus HDR-BT und EBRT behandelt werden, zu einem verbesserten BCR-freien Überleben. Der zusätzliche Nutzen einer ADT sollte in diesem Kontext bei der Therapieplanung erwogen werden.

Schlüsselwörter Androgenentzugstherapie · Biochemisches Rezidiv · Brachytherapie · Externe Strahlentherapie · Prostatakarzinom

Introduction

Combining external beam radiotherapy (EBRT) [14] and high-dose-rate (HDR) brachytherapy (HDR-BT) [19] reduces the risk of recurrence and cancer-specific mortality compared with EBRT alone in prostate cancer (PCa) patients [15, 16, 27, 28].

The impact of androgen deprivation therapy (ADT) added to EBRT on prolonged cancer-specific and overall survival versus EBRT alone in high-risk and locally advanced PCa patients is well documented [3, 6, 11, 22, 23, 25]. Similarly, ADT added to HDR-BT for high-risk PCa patients resulted in promising biochemical control rates [31]. Although trimodality treatment (HDR-BT and EBRT and ADT) is feasible [18], the role of additional ADT in PCa patients treated with combined HDR-BT and EBRT is still under debate. Trimodality treatment in patients classified as high-risk according to D'Amico resulted in 9-year BCR-free and cancer-specific-free survival rates of 91.0 and 87.3 %, respectively [2, 20]. Despite these encouraging rates, it remained unclear to what extent the additional ADT contributes to these results [2, 20].

D'Amico et al. [7] were able to show a reduction in the risk of cancer-specific mortality in D'Amico high-risk patients undergoing trimodality treatment compared with those undergoing EBRT alone [hazard ratio (HR): 0.32, 95 % confidence interval (CI): 0.14–0.73, $p=0.006$]. However, no significant reduction in the risk of cancer-specific mortality was recorded when trimodality was compared with bimodality treatment of any type (HDR-BT and either EBRT or ADT; HR: 0.5, 95 % CI: 0.3–1.1, $p=0.08$) [7]. Other studies failed to show an improvement in failure rates when adding ADT to HDR-BT and EBRT [9, 10]. However, National Comprehensive Cancer Network guidelines suggest the trimodality treatment as primary option for intermediate- and high-risk PCa patients [21].

On the basis of contradictory results on the use of additional ADT administration in D'Amico high-risk patients treated with either EBRT [3, 6, 11, 22, 23] or a combination of HDR-BT and EBRT [9, 10], we decided to provide more evidence for the usage of additional ADT in D'Amico intermediate- and high-risk patients for whom HDR-BT and EBRT are contemplated. We hypothesized that trimodality treatment improves biochemical recurrence (BCR)-free survival compared with bimodality treatment (HDR-BT and EBRT) in D'Amico high-risk patients.

Patients and methods

Study population

We relied on our institutional database and included consecutive PCa patients who were treated with a combination of HDR-BT and EBRT between January 1999 and February 2009 ($n=843$). We excluded patients with a follow-up shorter than 12 months ($n=339$) and those who had D'Amico low-risk PCa ($n=112$). Overall, 392 patients were assessable. The study was approved by the local ethics committee.

Covariates

Patient age, PSA, biopsy Gleason score, clinical tumor stage, and D'Amico risk categories [5] were assessed. Since cardiovascular disease and hyperglycemia are possible side effects of ADT use [17], we additionally assessed baseline comorbidities such as any diagnosis of cardiovascular diseases and type 2 diabetes mellitus, which might affect the treatment choice. BCR was defined as a PSA level of 2 ng/ml over the nadir [26].

Treatment modalities

HDR-BT was administered prior to EBRT, based on transrectal ultrasound, using the planning system and the Ir192-treatment unit Gammamed 12i® (Sauerwein Company). HDR-BT was administered in two treatment sessions (1-week interval) with 9 Gy per fraction at the prostate capsule and 15 Gy to the peripheral zone of the prostate. Overall, 18 Gy was applied at the prostate capsule.

EBRT started 1 week after HDR-BT using three-dimensional conformal radiotherapy with four to five fields

and individualized blocking. The target volume included the prostate and seminal vesicles with a safety margin of 1.5 cm. A total dose of 50.4 Gy, with 1.8 Gy per fraction and five fractions per week, was administered. Fifteen patients underwent extended EBRT including also locoregional lymphatic drainage in the small pelvis. The distribution of these patients was not significantly different between the bimodality and trimodality treatment groups ($n=4$ vs. 11, $p=0.1$).

Trimodality treatment was considered when additional ADT was administered concomitant to HDR-BT and EBRT. The duration of ADT administration was assessable in 124 (56.1 %) men who underwent the trimodality treatment. The median time of ADT administration was 3 months (IQR: 3–6) for these patients.

Statistical analyses

Baseline characteristics were compared using the χ^2 likelihood test for nominal variables and the nonparametric Wilcoxon test for continuous variables.

Additionally, multivariable Cox regression analyses for predicting BCR were performed. Comprising variables were patient age, PSA, biopsy Gleason score, clinical tumor stage, and ADT administration. Kaplan–Meier analyses for BCR-free survival were performed for all patients according to different treatment modalities (HDR-BT and EBRT and ADT vs. HDR-BT and EBRT) as well as stratified according to different D'Amico risk categories (intermediate-risk vs. high-risk).

Within subgroup analyses, we excluded patients with unknown duration of ADT ($n=97$). Statistical analyses were performed with the JMP software v. 9.0.2 (SAS Institute, Cary, N.C.) and R v.2.13.1 (R Project for Statistical Computing, http://www.R-project.org). All tests were two 2-sided with the significance level set at $p<0.05$.

Results

Overall, 392 intermediate- or high-risk PCa patients treated with combined HDR-BT and EBRT were assessable. Of these, 221 (56.4 %) men were assigned to trimodality and 171 (43.6 %) men to bimodality treatment.

Statistically significant differences between the two treatment groups were recorded for PSA, Gleason score, clinical tumor stage, and D'Amico risk categories. Specifically, patients with trimodality treatment had a higher median PSA (10.8 vs. 8.5 ng/ml, $p<0.001$) and comprised more patients with PSA >20 ng/ml (22.6 vs. 11.1 %, $p=0.003$) compared with bimodality treatment patients. Similarly, patients undergoing trimodality treatment more frequently had clinical tumor stage ≥cT3 compared with patients undergoing bimodality treatment (24.4 vs. 13.5 %, $p=0.007$). Trimodality-treated patients also more frequently harbored Gleason score ≥4+4 than bimodality-treated patients (20.5 vs. 7.6 %, $p=0.001$). Consequently, trimodality-treated patients more frequently harbored D'Amico high-risk PCa than bimodality-treated patients (62.0 vs. 43.3 %, $p<0.001$). The median follow-up was not significantly different between patients undergoing trimodality or bimodality treatment (51.0 vs. 48.0 months, respectively, $p=0.5$). No significant differences between treatment modality groups were recorded according to baseline comorbidities such as cardiovascular diseases or type 2 diabetes mellitus (all $p>0.05$; Table 1).

Multivariable Cox regression analyses predicting biochemical recurrence

In the second part of our analyses, we relied on multivariable Cox regression models to predict BCR after combined HDR-BT and EBRT. According to these analyses, two predictors achieved independent predictor status: ADT and Gleason score. Specifically, patients with additional ADT administration were less likely to experience BCR compared with their counterparts treated without additional ADT (HR: 0.4, 95 % CI: 0.3–0.7, $p<0.001$). Finally, patients with Gleason score ≥4+4 were more likely to experience BCR compared with their counterparts with Gleason score ≤3+3 (HR: 1.9, 95 % CI: 1.2–3.3, $p=0.01$; Table 2).

Kaplan–Meier analyses for biochemical recurrence-free survival

In the third part of our analyses, we relied on Kaplan–Meier analyses for BCR-free survival. In the overall population, Kaplan–Meier analysis revealed superior BCR-free survival in patients undergoing trimodality vs. bimodality treatment (Fig. 1a, log-rank $p=0.003$). The BCR-free survival rates for men undergoing trimodality vs. those undergoing bimodality treatment at 1, 5, and 10 years after treatment were 90.0 (95 % CI: 85.3–93.4) vs. 76.0 (95 % CI: 69.1–81.8), 77.3 (95 % CI: 70.2–83.1) vs. 65.7 (95 % CI: 57.8–72.8), and 53.8 (95 % CI: 38.7–68.2) vs. 57.0 % (95 % CI: 46.3–67.1), respectively.

Regarding D'Amico high-risk patients, Kaplan–Meier analysis revealed superior BCR-free survival in patients undergoing trimodality treatment than in those undergoing bimodality treatment (Fig. 1b, log-rank $p<0.001$). The BCR-free survival rates for D'Amico high-risk patients undergoing trimodality treatment vs. those undergoing bimodality treatment at 1, 5, and 10 years after treatment were 91.2 (95 % CI: 85.2–95.0) vs. 71.6 (95 % CI: 60.4–80.7), 76.9 (95 % CI: 67.8–84.1) vs. 56.3 (95 % CI: 44.1–67.8), and 49.6 (95 % CI: 32.3–67.0) vs. 39.4 % (95 % CI: 22.6–59.0), respectively.

Table 1 Baseline characteristics of 392 D'Amico intermediate- or high-risk prostate cancer patients treated with combined HDR brachytherapy and external beam radiotherapy ± androgen deprivation therapy between 1999 and February 2009 at the University Medical Center Hamburg-Eppendorf

Parameter	Overall	Trimodality	Bimodality	*p*
Patients, *n* (%)	392	221 (56.4)	171 (43.6)	–
Patient age (years), median (IQR)	69.0 (65.0–72.0)	69.0 (65.0–71.5)	69.0 (65.0–72.0)	0.3
Patient age (years), categories, n (%)				
<65	90 (23.0)	52 (23.5)	38 (22.2)	0.5
65–68	96 (24.5)	56 (25.3)	40 (23.4)	
69–71	97 (24.7)	58 (26.2)	39 (22.8)	
≥72	109 (27.8)	55 (24.9)	54 (31.6)	
PSA (ng/ml) at diagnosis, median (IQR)	9.6 (6.1–16.8)	10.8 (7.2–19.3)	8.5 (5.8–13.7)	<0.001
PSA (ng/ml) categories, n (%)				
≤10	201 (51.3)	99 (44.8)	102 (59.6)	0.003
>10–20	122 (31.1)	72 (32.6)	50 (29.2)	
>20	69 (17.6)	50 (22.6)	19 (11.1)	
Biopsy Gleason score, n (%)				
≤3+3	146 (37.3)	69 (31.4)	77 (45.0)	0.001
3+4	120 (30.7)	64 (29.1)	56 (32.7)	
4+3	67 (17.1)	42 (19.1)	25 (14.6)	
≥4+4	58 (14.8)	45 (20.5)	13 (7.6)	
Clinical tumor stage, n (%)				
≤ cT2	315 (80.4)	167 (75.6)	148 (86.5)	0.007
≥ cT3	77 (19.6)	54 (24.4)	23 (13.5)	
D'Amico risk groups, n (%)				
Intermediate	181 (46.2)	84 (38.0)	97 (56.7)	<0.001
High	211 (53.8)	137 (62.0)	74 (43.3)	
Cardiovascular disease, *n* (%)	213 (54.3)	120 (54.3)	93 (54.4)	0.9
Type 2 diabetes mellitus, *n* (%)	31 (7.9)	16 (7.2)	15 (8.8)	0.6
Biochemical recurrence, *n* (%)	114 (29.1)	54 (24.4)	60 (35.1)	0.02
Follow-up (months), median (IQR)	49.0 (24.0–85.0)	51.0 (24.0–88.0)	48.0 (24.0–80.0)	0.5

HDR high dose rate, *Trimodality* HDR brachytherapy and external beam radiotherapy and androgen deprivation therapy, *Bimodality* HDR brachytherapy and external beam radiotherapy, *IQR* interquartile range, *PSA* prostate-specific antigen

Table 2 Multivariable Cox regression model predicting biochemical recurrence in 392 D'Amico intermediate- or high-risk prostate cancer patients treated with HDR brachytherapy and external beam radiotherapy between 1999 and February 2009 at the University Medical Center Hamburg-Eppendorf

	Univariable analyses		Multivariable analyses	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Androgen deprivation therapy				
No	1 (ref.)		1 (ref.)	
Yes	0.6 (0.4–0.8)	0.004	0.4 (0.3–0.7)	<0.001
Biopsy Gleason score				
≤3+3	1 (ref.)		1 (ref.)	
3+4	0.9 (0.6–1.4)	0.6	0.9 (0.6–1.5)	0.7
4+3	0.9 (0.5–1.6)	0.7	0.9 (0.5–1.6)	0.7
≥4+4	1.7 (1.1–2.8)	0.03	1.9 (1.2–3.3)	0.01
Clinical tumor stage				
≤cT2	1 (ref.)		1 (ref.)	
≥cT3	1.3 (0.9–2.0)	0.2	1.5 (0.98–2.4)	0.059
PSA	1.0 (0.99–1.02)	0.07	1.01 (0.99–1.03)	0.09
Patient age	0.99 (0.96–1.03)	0.6	0.99 (0.96–1.03)	0.7

HDR high dose rate, *HR* hazard ratio, *CI* confidence interval, *PSA* prostate-specific antigen

Regarding D'Amico intermediate-risk patients, Kaplan–Meier analysis recorded no significant differences for BCR-free survival between patients undergoing trimodality treatment than for those undergoing bimodality treatment (Fig. 1c, log-rank $p=0.2$). The BCR-free survival rates for D'Amico intermediate-risk patients undergoing trimodality vs. those undergoing bimodality treatment at 1, 5, and 10 years after treatment were 88.1 (95% CI: 79.3–93.5) vs. 79.4 (95% CI: 70.2–86.3), 78.1 (95% CI: 65.7–86.9) vs. 72.9 (95% CI: 62.7–81.1), and 68.7 (95% CI: 51.6–81.9) vs. 69.0% (95% CI: 56.6–79.2), respectively.

Subgroup analyses

In the fourth part of our assessments we relied on subgroup ($n=295$) analyses (patients with unknown duration of ADT administration were excluded). The median time of ADT administration was 3 months (IQR: 3–6). The mean follow-up of these patients was 58 months (median: 48; IQR: 23–85; range: 12–156). In this subgroup, 90 (30.5%) men experienced BCR.

In the multivariable Cox regression analyses predicting BCR, one predictor achieved independent predictor status. Specifically, patients undergoing trimodality treatment were less likely to experience BCR than those undergoing bimodality treatment (Table 3, HR: 0.5, 95% CI: 0.3–0.7, $p=0.001$). Additionally, Kaplan–Meier analyses recorded improved BCR-free survival when ADT was administered in the overall subgroup population (log-rank $p=0.008$). Similarly, improved BCR-free survival was recorded in D'Amico high-risk patients when trimodality treatment was administered (log-rank $p<0.001$). Finally, no benefit on BCR-free survival was recorded in D'Amico intermediate-risk patients stratified according to trimodality or bimodality treatment (log-rank $p=0.6$).

Discussion

Our hypothesis stated that additional ADT administration might improve BCR-free survival in D'Amico high-risk patients, when combined HDR-BT and EBRT are contemplated. To test this hypothesis we relied on our institutional database and investigated 392 D'Amico intermediate- or high-risk patients treated with HDR-BT and EBRT ± ADT.

Our analyses yielded several important results. First, we recorded significant differences between patients in whom additional ADT was administered and those in whom it was not. Specifically, men with additional ADT more frequently harbored D'Amico high-risk disease (62.0 vs. 43.3%, $p<0.001$). This observation suggests that additional ADT administration is more frequently considered in patients with unfavorable clinical tumor characteristics.

Second, in our multivariable Cox regression model predicting BCR, additional ADT administration achieved independent predictor status. Specifically, patients with additional ADT administration were less likely to experience BCR compared with those without additional ADT administration (HR: 0.4, 95% CI: 0.3–0.7, $p<0.001$). The protective effect of ADT was also recorded in our subgroup analyses (HR: 0.5, 95% CI: 0.3–0.7, $p=0.001$), which

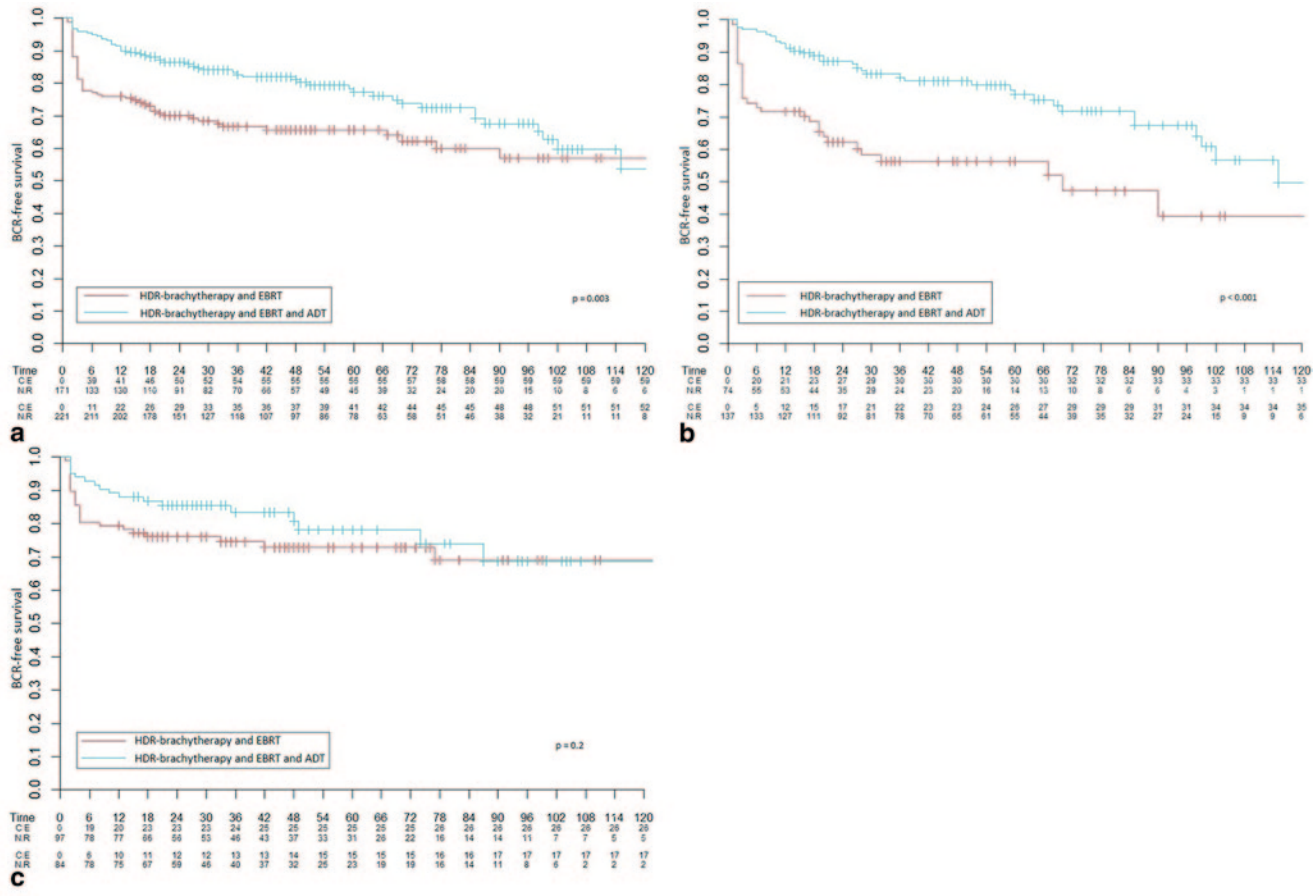

Fig. 1 **a**–**c** Kaplan–Meier analyses for biochemical recurrence (*BCR*)-free survival over time (months) of 392 D'Amico intermediate- and high-risk prostate cancer patients treated with either high-dose-rate (*HDR*) brachytherapy and external beam radiotherapy (*EBRT*) and androgen deprivation therapy (*ADT*) or HDR brachytherapy and EBRT alone. Patients were stratified according to **a** overall, **b** D'Amico high-risk, and **c** D'Amico intermediate-risk. *C.E.* cumulative events, *NR* number of risk

Table 3 Multivariable Cox regression model predicting biochemical recurrence in a subgroup of 295 D'Amico intermediate- or high-risk prostate cancer patients treated with HDR brachytherapy and external beam radiotherapy between 1999 and February 2009 at the University Medical Center Hamburg-Eppendorf

	Univariable analyses		Multivariable analyses	
	HR (95 % CI)	*p*	HR (95 % CI)	*p*
Androgen deprivation therapy				
No	1 (ref.)		1 (ref.)	
Yes	0.6 (0.4–0.9)	0.01	0.5 (0.3–0.7)	0.001
Biopsy Gleason score				
≤3+3	1 (ref.)		1 (ref.)	
3+4	0.8 (0.5–1.3)	0.4	0.8 (0.5–1.4)	0.4
4+3	0.9 (0.5–1.8)	0.8	0.9 (0.5–1.8)	0.8
≥4+4	1.4 (0.8–2.5)	0.3	1.5 (0.8–2.7)	0.2
Clinical tumor stage				
≤cT2	1 (ref.)		1 (ref.)	
≥cT3	1.2 (0.7–2.0)	0.5	1.4 (0.8–2.4)	0.2
PSA	1.0 (0.99–1.02)	0.2	1.01 (0.99–1.03)	0.1

HDR high dose rate, *HR* hazard ratio, *CI* confidence interval, *PSA* prostate-specific antigen

relied exclusively on patients with known duration of ADT administration (median: 3 months; $n=295$).

Third, Kaplan–Meier analyses recorded superior BCR-free survival in D'Amico high-risk patients undergoing trimodality treatment. The latter was recorded in the overall (log-rank $p<0.001$) as well as in the subgroup population (log-rank $p<0.001$). Conversely, additional ADT administration does not affect BCR-free survival in D'Amico intermediate-risk patients, neither in the overall (log-rank $p=0.2$) nor the subgroup population (log-rank $p=0.6$).

Taken together, our results confirm our hypothesis. Additional ADT administration improved BCR-free survival in D'Amico high-risk patients treated with combined HDR-BT and EBRT. The missing effect in D'Amico intermediate-risk patients emphasizes that ADT administration should be considered especially in those patients with D'Amico high-risk disease, when combined HDR-BT and EBRT is contemplated.

It is worth pointing out that ADT has a risk of adverse side effects [1, 17] and might also affect quality of life [4, 8]. Consequently, ADT administration should be considered individually and possible side effects should be balanced with possible superior oncological outcome.

Our results differ from those of previous reports. For example, Dattoli et al. [9] investigated 321 D'Amico intermediate- and high-risk patients who were treated between 1992 and 1997 with brachytherapy and EBRT ± ADT. In this patient group, Dattoli and coworkers were not able to show significant differences for BCR-free survival according to additional ADT administration within a univariable model ($p=0.4$). However, the authors failed to present a multivariable model that might have adjusted for possible bias.

Demanes et al. [10] investigated 411 PCa patients treated with HDR-BT and EBRT ± ADT. This study failed to demonstrate a superior BCR-free survival in patients who had additional ADT administration. However, since the group of patients who were treated with ADT comprised more subjects with D'Amico high-risk disease (58 vs. 42 %) and a lower percentage of D'Amico low-risk disease (36 vs. 64 %), a non-negligible selection bias might be at play when interpreting these data.

Galalae et al. [13] examined 611 PCa patients treated with HDR-BT and EBRT ± ADT between 1986 and 2000. They were not able to demonstrate ADT as an independent predictor for BCR within a multivariable Cox regression model 5 years after treatment ($p=0.6$). Although these data argue against the possible benefit of additional ADT administration when HDR-BT and EBRT are contemplated, they should be reproducible in more contemporary patient cohorts.

D'Amico et al. [7] were able to show a reduction in the risk of cancer-specific mortality within D'Amico high-risk patients undergoing trimodality treatment compared with those undergoing EBRT alone (HR: 0.32, 95 % CI: 0.14–0.73, $p=0.006$). However, no significant reduction in the risk of cancer-specific mortality was recorded when trimodality was compared with bimodality treatment of any type (HDR-BT and EBRT or ADT; HR: 0.5, 95 % CI: 0.3–1.1, $p=0.08$) [7].

Although the question of whether or not additional ADT should be administered represents an important clinical topic, the available evidence for this issue is suboptimal. Previous studies that questioned the benefit of additional ADT administration might have had insufficient statistical approaches [9, 10], did not comprise a clear control group [7], or represent more or less historical data from partially the pre-PSA area [13], respectively.

Although our data might not represent the final answer, they point out that trimodality treatment may offer superior biochemical control than bimodality treatment for D'Amico high-risk patients. Further studies are needed to contribute to the debate on the additional usage of ADT when HDR-BT and EBRT are at play. Especially, more evidence is needed to define the most efficient duration of ADT administration regarding the balance of minimizing side effects and beneficial oncological outcome. Additionally, more evidence on complication rates [12, 30] and quality of life [29] is warranted when comparing bimodality vs. trimodality treatment.

Despite its strengths, our study has limitations. First, the retrospective study design limits the quality of the data. Second, detailed information on the duration of ADT administration was not available in all cases. However, focusing on ADT patients with detailed information on the duration of ADT administration did not change the results. Third,

due to the small patient numbers, a meaningful propensity-matched cohort was not available. However, in the detailed analyses of different D'Amico risk categories we were able to roughly control for the most important clinical tumor characteristics. Finally, our data lack information on metastases-free and cancer-specific survival. However, biochemical recurrence most likely represents the first sign of progression [24] and subsequently we endeavor to reduce BCR rates.

Conclusion

Additional ADT administration improves biochemical control when HDR-BT and EBRT are combined in D'Amico high-risk patients. Physicians should consider the oncological benefit of ADT administration for these patients during the decision-making process.

Compliance with ethical guidelines

Conflict of interest J. Schiffmann, H. Lesmana, P. Tennstedt, B. Beyer, K. Boehm, V. Platz, D. Tilki, G. Salomon, C. Petersen, A. Krüll, M. Graefen, and R. Schwarz state that there are no conflicts of interest.

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