Erectile function after WST11 vascular-targeted photodynamic therapy for low-risk prostate cancer treatment

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Vascular-targeted photodynamic therapy (VTP) using padeliporfin is currently assessed as a low-risk prostate cancer (LRPCa) treatment. The aim of this study was to assess erectile function outcomes of VTP for LRPCa treatment. We prospectively included all patients treated with VTP for LRPCa. The primary endpoint was the post-treatment International Index of Erectile Function score (IIIEF5 score) evolution (at 6 months, 12 months, and then every year for 5 years). Secondary endpoints were the need of erectile dysfunction (ED) treatment and its efficacy. Eighty-two men were included. The median follow-up was 68 (range: 6–89) months. There was a 3-point significant decrease in the median IIIEF5 score between baseline and at 6 months post-VTP (23 [range: 1–25] vs 20 [range: 1–25], P = 0.005). There was a 1-point decrease at 1 year and 2 years post-VTP compared to baseline (22 [range: 2–25] and 22 [range: 0–25], P < 0.005). There was no significant difference at 3, 4, and 5 years compared to baseline. Twenty-seven (32.9%) patients received ED treatment: phosphodiesterase type-5 inhibitors (PDEI5; n = 18), intracavernous injections (ICI; n = 9), and intra-urethral gel (n = 1). The median IIIEF5 score statistically significantly increased after ED treatment (7 [range: 0–24] vs 21 [range: 1–25], P < 0.001). ED treatment was efficient for 75% of the patients. There was no statistically significant difference between IIIEF5 score at baseline and after ED treatment (P = 0.443). Forty-six patients were totally potent before VTP and among them, 13 needed ED treatment post-VTP with a success rate of 69.2%. VTP induced minimal changes in erectile function with a 3-point and a 1-point reduction in the IIIEF5 score at 6 months and at 1 year, respectively. When required, ED treatment was efficient.

We assume that VTP allows the treatment of the index lesion without exposing the neurovascular bundles to collateral damage. Thus, VTP might be a promising option for patients requiring an active treatment but eager to preserve their sexual function. Even if the data on oncological outcomes for FT are increasing, the available data on erectile functional outcomes remain sparse.

INTRODUCTION

Quality of life and functional outcomes are very important issues when it comes to prostate cancer management, especially for low-risk prostate cancer (LRPCa). Current treatment strategies lie between active surveillance (AS) and radical therapies (RT) with a risk of progression on one side and a risk of long-term morbidity on the other side. It has been shown that both radical prostatectomy (RP) and external beam radiotherapy (EBRT) might induce erectile dysfunction (ED). Focal therapies (FT) lie in the middle ground between RT and AS. FT might be an interesting mean to achieve cancer control with decreased treatment-related toxicity. Vascular-targeted photodynamic therapy (VTP) using padeliporfin is a FT that is currently being assessed for LRPCa treatment. Available oncological outcomes report a 6-month negative biopsy rate of 80.6% for patients treated by hemiablation and a decreased disease progression at 24 months when compared to AS (28% vs 58%, hazard ratio [HR] = 0.34, 95% confidence interval [95% CI]: 0.24–0.46; P < 0.0001). A prospective series of 82 patients with a median follow-up of 68 months reported a negative biopsy rate for clinically significant cancer of 82% of the treated lobes. In addition, 76% of patients avoided radical therapies after VTP.

Keywords: erectile function; focal therapy; padeliporfin; photodynamic therapy; prostatic neoplasms

PATIENTS AND METHODS

Patients

We included all patients treated by VTP in Angers University Hospital, Angers, France, between December 2008 and June 2013. Data were prospectively collected. All patients were initially included in one of the phase 2 or phase 3 European studies (NCT00707356 or NCT00975429 or NCT01310894), and were then followed up in the Department of Urology. All the studies were conducted according to the Good Clinical Practice (CPMP/ICH) regulations and the Declaration of Helsinki. The Committee for the Protection of Persons - CPP in France approved the protocols. All treatments were approved by the institutional review board.
patients gave their written informed consent to participate before any study-related activities were performed.

**Inclusion and exclusion criteria**

The main inclusion and exclusion criteria for the individual studies were the same as those reported in PCM201, PCM203, and PCM301 studies. All patients had LRPCa.

**Padeliporfin VTP procedure**

A detailed description of the procedure has been reported in previous publications. The procedure was performed under general anesthesia. Patients had a single intravenous administration of padeliporfin (WST11, STEBA Biotech, Luxembourg) at a dose of 4 mg kg$^{-1}$, followed by local illumination of the targeted zone using a 753-nm laser light (Too-Diffuser, Laser Light & Life, Geneva, Switzerland) at a fixed power (150 mW cm$^{-2}$) and energy (200 J cm$^{-2}$) delivered through transperineal optical fibers positioned in the prostate. These fibers were inserted under ultrasound guidance according to a treatment plan. The treatment consisted of a hemiablation (treatment of only one lobe of the prostate) for patients with unilateral disease or in a conservative subtotal ablation (treatment of both lobes in the same procedure) in case of bilateral disease. The total duration of the procedure was 2 h. The patients were kept under medical surveillance under dimmed light for at least 6 h and could be discharged on the same day. The patients had to avoid direct exposure to sunlight for 48 h.

**Follow-up and end points**

We prospectively assessed all patients treated with VTP for LRPCa at our center. Assessment of erectile function was performed during clinic visits scheduled: at inclusion before VTP treatment, then at 6 months, 12 months, and every year for 5 years after VTP treatment. The primary endpoint was the International Index of Erectile Function score (IIEF5 score) evolution. The IIEF5 score is an abridged 5-item version of the 15-item International Index of Erectile Function, which is used to diagnose the presence and severity of ED. The secondary endpoints were the use of ED treatment and its efficacy. When patients required ED treatment, they could either receive phosphodiesterase type-5 inhibitors (PDEI5) and/or intracavernous injections (ICIs) and/or intra-urethral gel. The patients underwent a day-7 magnetic resonance imaging (MRI). In case of progression, the patients underwent a RT and subsequently were excluded from erectile function assessment once RT was performed ($n = 23$). Potency was defined by an IIEF5 score $\geq 22$. Mild ED was defined by an IIEF5 score of 17–21, moderate ED was defined by an IIEF5 score of 12–16, severe ED was defined by an IIEF5 score of 8–11, and very severe ED was defined by an IIEF5 score of 5–7. IIEF5 score $\leq 4$ was considered noninterpretable because of the absence of sexual activity. ED treatment success was defined as a recovery with $\leq 1$-point difference or an improvement of the IIEF5 score compared to baseline.

**Data analyses**

Statistical analysis was performed with the SPSS 15.0 software (IBM Corp., Armonk, NY, USA). Medians were compared with a Wilcoxon test; logistic regression was used for multivariable analyses. Associations with $P \leq 0.05$ were considered statistically significant.

**RESULTS**

A total of 82 men were treated by VTP and were all included in the study. The baseline characteristics are reported in Table 1. Sixty-one (74.4%) patients had initially unilateral treatment and 21 (25.6%) had bilateral treatment. Sixteen patients had repeated VTP: 5 on the same lobe and 11 on the contralateral lobe. The median follow-up was 68 (range: 6–89) months. Oncological outcomes were previously published.

Before VTP treatment, 46 (56.1%) had normal erectile function, 14 (17.1%) had mild ED, 8 (9.8%) had mild-to-moderate ED, 3 (3.7%) had moderate ED, 2 (2.4%) had severe ED, and 9 (11.0%) had non-interpretable IIEF5 score ($\leq 4$). The evolution of the IIEF5 score sorted by ED category is reported in Figure 1. The median IIEF5 score evolution is reported in Figure 2. There was a 3-point significant decrease in the median IIEF5 score between baseline and at 6 months post-VTP (23 [range: 1–25] vs 20 [range: 1–25], $P = 0.005$). There was a 1-point decrease at 1 year and 2 years post-VTP compared to baseline (22 [range: 2–25] and 22 [range: 0–25], respectively, $P < 0.005$). There was no statistically significant difference at 3, 4, and 5 years compared to baseline (23 [range: 1–25]; $P = 0.606$, 22 [range: 1–25], $P = 0.480$; and 22.5 [range: 0–25], $P = 0.968$, respectively). There was no significant difference in potency rate before and after VTP (Table 2). There were no cases of anejaculation or retrograde ejaculation.

Twenty-seven (32.9%) patients have been treated for ED: 18 by PDEI5, 9 by ICI, and 1 by intra-urethral gel. The median time to treatment was 314 (range: 11–2480) days. The success rate was 75%. For these patients, the IIEF5 score significantly increased after ED treatment (7 [range: 0–24] vs 21 [range: 1–25], $P < 0.001$). There was no statistically significant difference between IIEF5 score at baseline and after ED treatment ($P = 0.443$). Six patients did not get any response to ED treatment. Among them, five had PDEI5 alone and one had an association of IPDE5 and ICI.

We analyzed the 46 patients who were totally potent before VTP (IIEF5 score $\geq 22$) as a subgroup. The median age was 63 (range: 51–75) years. Of these patients, 34 had initially unilateral treatment and 12 had bilateral treatment. Nine patients had repeated VTP: three on the same lobe and six on the contralateral lobe. Thirteen (28.3%) patients had undergone an ED treatment and 33 (71.7%) did not need any ED treatment. Nine (19.6%) patients in total required either ICI or remained impotent after VTP.

**Table 1: Baseline characteristics**

| Baseline characteristics | Median (range) | Patients (n) |
|--------------------------|---------------|-------------|
| Age (year)               | 63 (51–76)    | 46           |
| Weight (kg)              | 74 (60–119)   | 46           |
| Prostate volume (ml)     | 42 (22–147)   | 46           |
| PSA (ng ml$^{-1}$)       | 6.1 (1.3–10.0)| 46           |
| ISUP score 1             | 82            | 46           |
| T1c                      | 75            | 46           |
| T2a                      | 7             | 46           |

PSA: prostate-specific antigen; ISUP: International Society of Urological Pathology; T1c: the tumor is found during a needle biopsy, usually because the patient has an elevated PSA level; T2a: the tumor involves one-half of one side of the prostate

**Table 2: Potency rate through time compared to baseline**

| Time         | Potent patients, n/total (%) | OR  | 95% CI     | P     |
|--------------|-------------------------------|-----|------------|-------|
| Baseline     | 46/82 (56.1)                  |     |            |       |
| 6 months     | 27/63 (42.9)                  | 0.571 | 0.293–1.110 | 0.068 |
| 1 year       | 12/23 (52.2)                  | 0.83  | 0.328–2.101 | 0.436 |
| 2 years      | 22/43 (51.2)                  | 0.797 | 0.379–1.674 | 0.341 |
| 3 years      | 29/47 (67.4)                  | 1.226 | 0.588–2.555 | 0.361 |
| 4 years      | 21/41 (51.1)                  | 0.799 | 0.376–1.698 | 0.347 |
| 5 years      | 17/32 (53.1)                  | 0.862 | 0.379–1.961 | 0.442 |

$P < 0.05$ means statistically significant. OR: odds ratio; 95% CI: 95% confidence interval
The median time to treatment was 302 (range: 11–2137) days. Six patients had ICI and 11 had PDEI5 (among them, five had both treatments). The success rate of the treatment was 69.2% (efficient in nine patients and non-efficient in four patients). The median IIEF5 score before and after ED treatment instauration was 8 (range: 0–25) and 21 (range: 7–25), respectively ($P = 0.007$). There was a statistically significant difference between IIEF5 score at baseline and after ED treatment (25 [range: 22–25] vs 21 [range: 7–25], $P = 0.012$). We observed that in eight (61.5%) of these patients, there was extraprostatic necrosis on day-7 MRI (Figure 3). There was a negative correlation between ED treatment success and extraprostatic necrosis ($r = -0.527$, $P = 0.032$).

There were 35 patients who were not totally potent before VTP (IIEF5 score <22). They had a median age of 63 (52–76) years. Twenty patients had unilateral treatment and 15 had a bilateral treatment. In patients who initially had ED before VTP, 14 (40.0%) needed a post-VTP ED treatment. Three had ICI, 13 had PDEI5, and 1 had intra-urethral injections. The treatment efficacy rate was 64.3%. The ED treatment significantly increased the median IIEF5 score from 8 (range: 5–24) to 18 (range: 5–25) ($P = 0.028$). There was no statistically significant difference between IIEF5 score at baseline and after ED treatment (17 [range: 6–21] vs 18 [range: 5–25], $P = 0.858$). Among these patients, there were five patients who had severe and moderate ED before VTP (IIEF5 score 5–11). Only two among them had ED treatment with an improvement of the IIEF5 score from 7 to 16 under PDEI5 for one of them. Patients with a non-interpretable IIEF5 score (≤4) remained with a non-interpretable score after VTP.

Factors influencing the prescription of ED treatment were assessed by univariate and multivariate analyses (Table 3). Extraprostatic necrosis identified on the day-7 MRI was an independent risk factor for ED treatment prescription (odds ratio [OR] = 3.657; 95% CI: 1.247–10.724; $P = 0.018$). Age, number of treated lobes, repeated VTP, and cancer progression were not associated with ED treatment prescription.

**DISCUSSION**

Patients who underwent VTP for LRPCa did experience a transient 3-point median decrease of the IIEF5 score 6 months after treatment. After 1 year, the median IIEF5 score improved with only a 1-point decrease from baseline. After 2 years, the difference was not significant anymore. One-third of the patients required an ED treatment after 6 months post-VTP, which corresponds to the IIEF5 score nadir we reported at 6 months. The efficacy rate of the ED treatment was 75%, which explained an increase of the median IIEF5 score after 1 year.

We focused on patients who were potent before VTP, and we found a significant decrease of 1–1.5 point in the median IIEF5 score through time. Even if statistical significance was met, the median variation had no clinical significance because the median IIEF5 score still remained
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Table 3: Factors influencing erectile dysfunction treatment instauration using univariate and multivariate analyses

| Factors                      | Univariate analysis | Multivariate analysis |
|------------------------------|---------------------|-----------------------|
|                              | Odds ratio (95% CI) | P         | Odds ratio (95% CI) | P         |
| Age                          | 1.013 (0.923–1.112) | 0.779   | 1.043 (0.937–1.162) | 0.438   |
| Pre-VTP IIEF5 score           | 0.977 (0.920–1.037) | 0.436   | 0.976 (0.913–1.043) | 0.976   |
| Cancer progression            | 0.587 (0.202–1.709) | 0.237   | 0.416 (0.129–1.338) | 0.141   |
| Repeated VTP                 | 0.234 (0.049–1.118) | 0.045   | 0.210 (0.037–1.189) | 0.078   |
| Bilateral treatment          | 1.360 (0.484–3.826) | 0.371   | 1.301 (0.442–4.014) | 0.647   |
| Extraprostatic necrosis      | 3.221 (1.235–8.401) | 0.014   | 3.657 (1.247–10.724) | 0.018   |

p<0.05 means statistically significant; CI: confidence interval; pre-VTP IIEF5 score: prevascular-targeted photodynamic International Index of Erectile Function score; repeated VTP: repeated vascular-targeted photodynamic; OR: odds ratio

over the potency threshold. We also showed that the rate of potent men before and after treatment did not vary. This shows that potent patients are likely to stay potent after VTP treatment without any need of ED treatment for 71.7% of them. We also looked at patients who had ED before VTP and showed that ED treatments were also efficient in restoring potency after VTP.

We tried to identify factors that may have influenced the erectile function prognosis. None of the following factors was associated with ED treatment prescription: age, number of treated lobes, repeated VTP, or cancer progression. The only independent factor we could identify was the extraprostatic necrosis on the MRI performed on day-7 post-VTP. We also found a negative correlation between the presence of extraprostatic necrosis and the efficacy of ED treatment in initially potent men. Extraprostatic necrosis was observed exclusively in the early cases. A better targeting of the area to treat was obtained in the second half of the series with no necrosis outside the prostate. We suppose that extraprostatic necrosis might have been responsible for a nerve bundle damage that might have induced ED. One can assume that once the learning curve is passed through, the operator can perform VTP with a higher accuracy in targeting of the area to treat. This eventually translates into a decreased risk of extraprostatic damage, which might result in better erectile function preservation.

It appears that VTP, as a focal therapy, is more likely to preserve erectile function than radical therapies such as RP, EBRT, and brachytherapy (BT). According to a systematic review by Burnett et al., RP, EBRT, and BT induce an ED rate of 26%–100%, 8%–85%, and 14%–61%, respectively. These data are confirmed by the ProtecT study’s functional outcomes: it is reported that 67% of the patients were potent at inclusion and only 12% and 22% remained potent 6 months post-RP and post-EBRT, respectively. On the contrary, 52% remained potent in the AS group. Six years after treatment, the potency rate was 17% and 27% for RP and EBRT, respectively. In our study, the potency rate remained stable at 53% even after 5 years post-VTP. It has been reported that 49% of patients on AS had at least moderate ED. It seems that older age, time on AS, increased baseline PSA, and diabetes were all associated with declining sexual function over time.

The currently available data on functional outcomes post-FT are limited; most of the studies are either small or retrospective or with a short follow-up. Li et al. reported a series of 47 patients treated by focal cryotherapy with an initial IIEF15 score of 27.8. They observed a significant decrease to 9.8 at 6 months posttreatment. Subsequently, the IIEF15 progressively increased with no more significant difference from baseline 3 years after treatment. They also reported a series of 55 patients who were treated by high-intensity focused ultrasound (HIFU). The pretreatment IIEF15 score was 27.3. The patients experienced a significant decrease to 15.5 at 6 months posttreatment with a progressive increase to 22.3 after 2 years. In a study by Ahmed et al. that included 41 patients treated by HIFU, the IIEF15 score did not differ from baseline 1 year after treatment, however they observed a significant decrease in the “erectile function” domain (24.0 [13.0–29.0] vs 21.0 [10.3–27.3], P = 0.042). In a series of 118 patients reported by Yap et al., there was a significant decrease of the erectile function 3 months post-HIFU with recovery at 6 months. Our results are very similar to those reported for HIFU and cryotherapy with an initial decrease during the first 6 months after treatment and a subsequent recovery after 1 year. Our results go even further by showing stability of the erectile function with a longer follow-up (median prospective follow-up of 68 months).

Our study has several limitations such as its single-arm design and its population size. In addition, we did not use any control group, and randomizing VTP versus AS or RT would have provided more solid conclusions. Moreover, the use of the IIEF15 score would have been more informative with a more detailed analysis of the sexual disorders. Furthermore, the IIEF5 score might have underestimated erectile function in men who do not have sexual intercourse. In addition, using a self-reporting score in order to assess a functional outcome might also be a limitation because it relies on a subjective assessment of the patient himself. One could suppose that some patients might have been reluctant to report an erectile dysfunction, which might be a risk of having overestimated favorable outcomes. Nevertheless, the IIEF5 score remains a validated and informative tool. The missing data due to the self-reporting approach of the IIEF5 score might also be a limitation; however, a paired analysis was performed in order to increase the statistical power and reduce the effects of confounders. Other limitations might have been an “attrition bias” (with patients leaving the study) or a “follow-up bias” (with patients not sending back their questionnaires); both biases lead unfortunately to missing data, which might weaken the statistical power. Finally, we did not assess cardiovascular risk factors during the follow-up. However, no patients with heavy cardiovascular condition were included in our study due to the study’s design. As a matter of fact, cardiovascular diseases and antiplatelet and anticoagulant treatments were the noninclusion criteria. This may have limited the cardiovascular bias risk. Furthermore, this also might explain the higher median IIEF5 baseline score in our study compared to that of the general population. Finally, patients treated in this study had low-risk prostate cancer, who were eligible for active surveillance. The challenge in the years to come is to assess the efficacy and the functional outcomes of VTP for intermediate-risk prostate cancer as an alternative to radical treatments. A study is currently taking place at the Memorial Sloan Kettering Cancer Center (MSKCC) assessing the oncological and functional outcomes of VTP for the International Society of Urological Pathology (ISUP) 2 PCa treatment and will hopefully provide precious data (NCT03315754).

Despite the limitations, this is the largest reported data assessing erectile function post-VTP for LRPCa treatment.
CONCLUSION
Focal therapy such as VTP is an emerging option for LRPCa treatment, while potentially maintaining erectile function. To date, this is the largest reported data assessing erectile function post-VTP. We highlighted a minimal impact on erectile function with a 3-point reduction in the IIEF5 score after 6 months, followed by a recovery with only a 1-point difference after 1 year. When required, ED treatment was efficient. VTP may represent an interesting alternative option for men wishing an active treatment and maintaining erectile function.

AUTHOR CONTRIBUTIONS
SC, SL, and ARA carried out experiments. SC and SL drafted the manuscript and performed the data analysis. SC, SL, and PM participated in the data collection. PB and ARA performed the manuscript reviewing. All authors read and approved the final manuscript.

COMPETING INTERESTS
ARA is an investigator and proctor for Steba Biotech. All other authors declared no competing interests.

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