

Impact of tumor cytorreduction in metastatic prostate cancer

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Objective: To assess the impact of tumor cytorreduction on cancer outcomes and patient survival in metastatic prostate cancer.

Patients and methods: It is a prospective study spanning a two-year period between October 1st 2015 and March 31st 2017. We enrolled 102 cases of metastatic hormone-sensitive prostate cancer. Fifty-seven (57) patients had exclusively androgen deprivation therapy (ADT) (group 1) and 45 had, in addition, an open prostatectomy or Transurethral resection of the Prostate (group 2). We compared both groups using the total PSA nadir, the time to PSA nadir, the overall survival (OS), and the progression-free survival (PFS).

Results: The average nadir PSA was lower for the tumor cytorreduction group (16.8 ± 1.6 ng/mL (0.01–193.5) versus 110.7 ± 17.9 ng/mL (0.01–1379)). Median time to PSA nadir was shorter in patients in the ADT only group (8 months vs 3 months ($p=0.025$)). The OS was shorter in patients treated with ADT only compared to the tumor cytorreduction group (median 14 months vs 24 months, respectively ($p=0.03$)). Similarly, tumor cytorreduction had a positive impact on patient progression (median PFS 20 months (group 1) vs 43 months (group 2)).

Conclusion: Tumor cytorreduction has a positive impact on the oncological results and the survival of patients under ADT.

Keywords: prostate cancer, cytorreduction, androgen suppression, TURP

Introduction

Prostate cancer is the most common cancer in elderly man. It is the third leading cause of cancer death in the male.¹ Androgen deprivation therapy (ADT) is the standard treatment for metastatic prostate cancer.

In developing countries, prostate cancer diagnosis is often made at a late stage where, low urinary tract symptoms or urinary retention occur.² These obstructive disorders must be taken into account in the management to improve the patients' quality of life. Transurethral resection of the prostate (TURP) is usually indicated in these cases.

Xiao-Jian and al,³ studied the impact of TURP on patients' survival as a cytorreduction method. They find a better response to ADT for patients who underwent TURP.

The objective of this study was to assess the impact of TURP or open prostatectomy as cytorreductive methods on oncological outcomes and patient survival in metastatic prostate cancer.

Patients and methods

We conducted a prospective study over a two-year period between October 1st 2015 and March 31st 2017. We evaluated the outcomes of 102 patients followed for

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Table 1 Therapeutic Protocols

Therapeutic protocols	Number of cases	Percentage %
ADT only (group 1)	57	55.9
Medical castration	09	8.8
Bilateral pulpectomy	48	47.1
Cytoreduction + ADT (group 2)	45	44.1
TURP + ADT	03	2.9
Open prostatectomy + ADT	42	4.1
Total	102	100

Abbreviations: ADT, androgen deprivation therapy; TURP, transurethral resection of the prostate.

metastatic hormone-sensitive prostate cancer (mHSPC). Of these patients, 57 are treated with ADT only (group 1) and 45 had, in addition to ADT, open prostatectomy or TURP, which we consider to be tumor cytorreduction (group 2). Patients were included in group 2 when they had bladder outlet obstruction indicating surgery for bladder unblocking. Those who did not need bladder outlet unblocking were included in group 1. ADT was performed by testicular pulpectomy or by LHRH analogs. Open prostatectomy was carried due to lack of endoscopic equipment. Therapeutic protocols are reported in Table 1.

The pretreatment patient characteristics were evaluated and compared between the two groups. Patients' general condition was appreciated by ECOG performance status.

Patients were reviewed every three months with total PSA control. Assessing results criteria were: total PSA nadir, time to reach nadir (the time from the start of treatment to the lowest PSA), overall survival (OS), and progression-free survival (PFS). The origin date was the date when ADT was initiated.

After progression, the evaluation criteria for second-line treatment were the PSA kinetics and OS. The second-line treatment included either estrogen therapy or chemotherapy.

Data processing is performed using SPSS 20.0 software. The comparative analysis of the data is carried out by the Student's *t*-test and chi-square to compare patient's pre and post-therapeutic features. OS and PFS were assessed using the Kaplan–Meier method and the log-rank method to determine survival differences between groups. Statistical tests were deemed significant at $p < 0.05$.

Results

Patients' average was 71.1 ± 8.6 years (54–88). The pre-therapeutic clinical characteristics of the patients are reported in Table 2. No difference was noted between the two groups.

The average PSA nadir was lower for the tumor cytorreduction group compared to the group ADT only (16.8 ± 1.6 ng/mL (0.01–193.5) vs 110.7 ± 17.9 ng/mL (0.01–1379) $p = 0.025$). Also, the median time to PSA nadir was longer in group 2 (8 months vs 3 months; $p = 0.025$).

The median OS of the patients in the series was 16 months (95% CI 12.9–19.1). It was shorter in group 1: 14 months vs 24 months; $p = 0.03$ (Figure 1).

The median PFS of the series was 36 months. It increased from 20 months for group 1 to 43 months for group 2 ($p = 0.025$). Tumor cytorreduction had a positive impact on delaying patient progression (Figure 2).

After a median follow-up period of 16 months, 61 patients (59.8%) had progression clinically or biologically (36 patients (35.3%) in group 1 and 25 patients (24.5%) in group 2).

The average total PSA level after progression of the patients in the series was 778.3 ng/mL (20–7889) and 985 ng/mL (20–7889) for the group 1 vs 480.5 ng/mL (98.3–1860 ng/mL) for the group 2 ($p = 0.08$).

After second-line treatment, the average total PSA level was 807.5 ng/mL (57.8–8923). It was lower in the group 2; 454.4 ng/mL (57.8–1389) vs 1052.7 ng/mL (88.2–8923) $p = 0.069$. The median OS was 6 months (95% CI 5.4–6.5) for the series, 6 months for group 1 and 8 months for group 2 (Figure 3). OS was similar for both groups at the castration resistance stage. Outcomes after cancer progression were not significantly different between the two groups. Table 3 summarizes the therapeutic results of the series and both groups.

Discussion

ADT has been the standard treatment for metastatic prostate cancer ever since the work of Huggins and Hodges, which helped understand the hormone-sensitivity of prostate cancer cells.⁴ ADT, can stop cancer progression. It was performed on both metastatic and N+ prostate cancer before it was expanded to locally advanced and localized forms.⁵ This ADT might be medical, using LHRH analogs or antagonists and/or anti-androgens. Also, it might be surgical (orchiectomy or bilateral pulpectomy).⁵

ADT is clinically and biologically effective in the majority of metastatic prostate cancers resulting in a

Table 2 Patients' pre-therapeutic characteristics

Parameters	Series	ADT only	Cytoreduction + ADT	p
Number of cases	102	57	45	0.9
Average age (years)	71.1	70.8	71.4	0.7
Performance status				
ECOG 1-2	26	12	14	0.4
ECOG 3-4	76	41	35	
Clinical stage				
≤T2	39	18	21	1
≥T3	63	29	34	
Total PSA average (ng/mL)	1,167.7	1,438.8	824.2	0.6
Average gleason	7 (4+3)	7 (4+3)	7 (4+3)	0.6
Metastatic' sites number				
1 site	52	33	19	0.3
≥2 sites	50	27	23	
Average follow-up duration	16 months	14 months	24 months	0.1

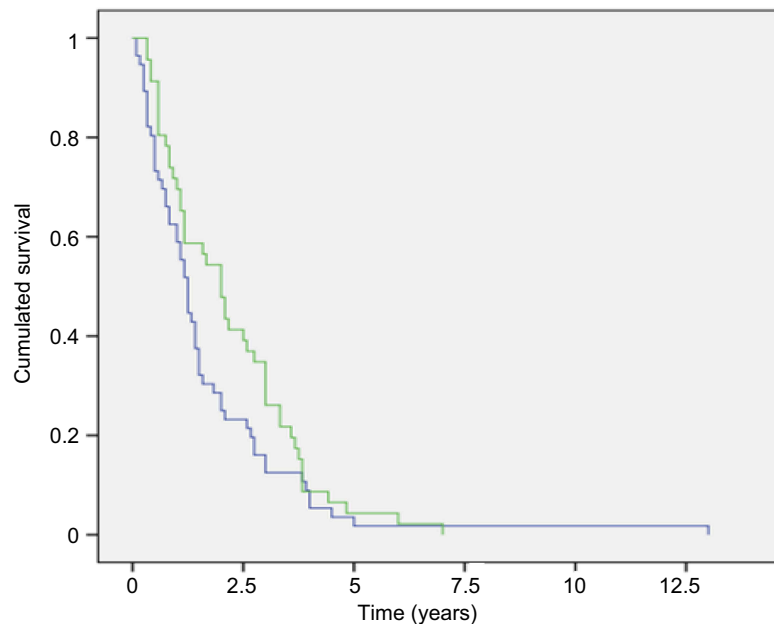


Figure 1 Overall survival curve of patients treated with ADT exclusively (group 1 in blue color) and that of patients treated with ADT and cytoreduction (group 2 in green color).
Abbreviation: ADT, androgen deprivation therapy

significant decrease in total PSA level and clinical symptoms. However, disease progression is expected within 18–24 months. It is hormone refractory prostate cancer stage.⁶

The time to progression depends on several factors. Prognostic factors of progression are the initial PSA, the tumor volume (extension and number of sites and volume of metastases), and the Gleason's score.⁶ During treatment, nadir PSA, time to nadir (TTN), and ratio TTN/Nadir are

powerful prognostic factors.^{6,7} Indeed a low PSA nadir and a long TTN, are associated with better survival.

In our center, a progression rate of 20.2% with a median PFS of 10.5 months (6–25) and an OS of 52.3% at 2 years were noticed in an earlier study assessing bilateral pulpectomy outcomes.²

Tumor cytoreduction in metastatic cancers corresponds to treatments aimed at local tumor control or a decrease in

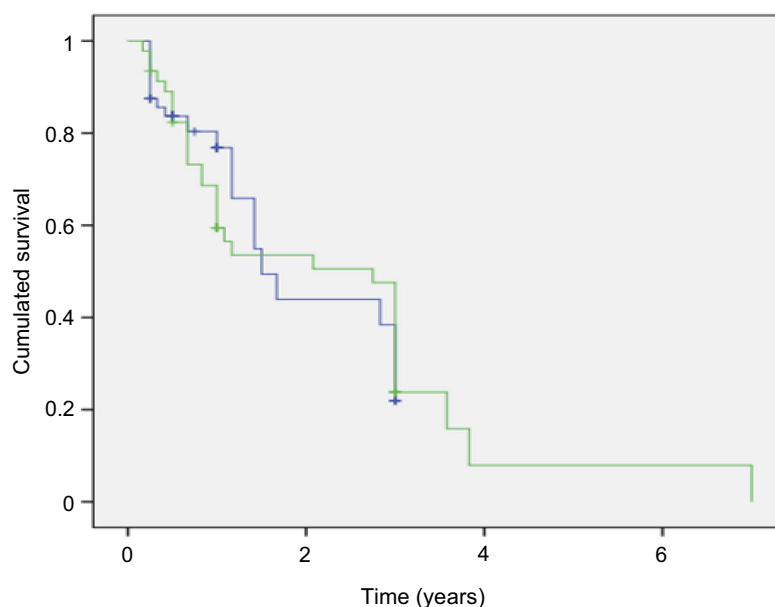


Figure 2 Progression-free survival curve of patients treated with ADT exclusively (group 1 in blue color) and that of patients treated with ADT + cytotoreduction (group 2 in green color).
Abbreviation: ADT, androgen deprivation therapy.

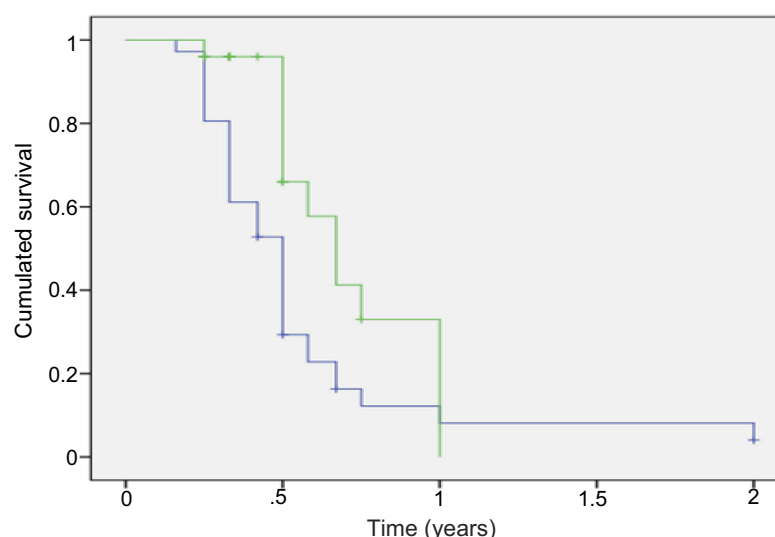


Figure 3 Overall survival curve of group 1 and 2 patients after disease progression.

tumor volume with the aim of improving survival and/or treating local complications in patients undergoing systemic treatment. We used in our series open prostatectomy or TURP to decrease tumor volume.

In metastatic kidney cancer, it has been shown that cytoreductive nephrectomy provides a benefit in survival in selected patients in combination with systemic therapy.⁸ In metastatic prostate cancer, cytotoreduction is a new area of exploration.⁹ It can be performed for local tumor control: radical prostatectomy (RP) or radiotherapy (RT) or to

treat local complications (TURP). Several studies have reported a benefit on the survival of metastatic patients with cytotoreduction by local treatment.^{10,11}

Like TURP or open prostatectomy, other tumor local treatments offer beneficial effect to the patients by improving oncological outcomes. The other local treatments studied were RP, RT, and cryotherapy.

Heidenreich and al,¹² investigated the feasibility of RP in patients with metastatic prostate cancer associated with ADT by comparing them to a control group of metastatic

Table 3 Outcomes according to the different parameters studied

Parameters	Series	ADT only	Cytoreduction + ADT	p
Average PSA nadir (ng/mL)	66.9	110.7	16.8	0.025
Median time to nadir (months)	6	3	6	0.025
Median OS (months)	16	14	24	0.03
Median PFS (months)	36	20	43	0.025
Castration resistance (number of cases)	61	36	25	0.09
PSA <4 ng/mL (number of cases)	45	15	30	0.0001
Mean PSA after progression (ng/mL)	778.3	985	480.5	0.08
Mean PSA after second-line treatment (ng/mL)	807.5	1,052.7	454.4	0.069
Median OS after progression (months)	6	6	8	0.08

Abbreviations: OS, overall survival; PFS, progression-free survival.

patients on ADT only. RP significantly improved both the time to progression (40 months vs 29 months, $p=0.04$), and the median PFS (38.6 vs 26.5 months, $p=0.032$). On the other hand, global survivals were similar.

Previously, Culp et al,¹³ report overall and specific survival rates of 67.4% and 75.8%, respectively, for metastatic patients with RP vs 22.5% and 48.7% for those without local treatment. Similarly, Fossati and al,¹⁴ after an analysis of the SEER data (Surveillance Epidemiology and End Results), noted that the local treatment (RP or brachytherapy) offered a higher specific survival rate in metastatic patients in whom specific mortality by cancer (SMC) predicted was less than 40%. On the other hand, no benefit was noted when the predicted SMC was greater than 50%.

Cytoreduction by RP, in addition to improving the survival of metastatic patients, provides a better comfort by reducing the risk of local complications such as urinary retentions, hematuria, rectal invasion, ureteral obstruction and risk of renal failure, and pains related to pelvic nerve

infiltration.⁹ Cytoreductive RP was associated with greater blood loss, longer intervention time, and higher incontinence rate compared to RP in patients with localized cancer.¹⁵ However, Kateralis and al,⁹ report a good rate of continence after cytoreduction by RP-assisted robot.

Other methods of tumor cytoreduction such as RT and cryotherapy are also studied in mHSPC. Local RT or brachytherapy treatment improves patient survival compared to patients without local treatment.^{10,11,13} This benefit of RT was lower than that of cytoreduction RP.¹⁰

Ming-Xiong and al,¹⁶ reported a reduction in the risk of progression of 79.3% and an increase in the time to castration resistance after cryosurgery of the prostate in metastatic patients compared to patients without local treatment.

Regarding TURP, the study of Xiao-Jian et al³ is the only one we know that assesses the impact of TURP on patient survival by considering it as a cytoreduction method. These authors reported a better response to ADT for the group with TURP with a lower median PSA nadir (0.15 ng/mL vs 0.82 ng/mL $p=0.015$) and a longer time to reach PSA nadir. The rate of progression was higher for the group without TURP. There is also a positive influence on overall and specific survival, however, without statistical significance.

Our study confirms the benefit of tumor cytoreduction on both PSA kinetics and patient survival. Compared to ADT alone, TURP or open prostatectomy cytoreduction offered lower PSA nadir and longer time to PSA nadir. It also significantly improves PFS and OS.

This study, although prospective, has some limits including the smaller number of patient, the short patient follow-up time and patients selection that depended on the need for bladder outlet unblocking and not randomly. Further randomized studies with larger numbers are needed to confirm the benefit noted in order to allow routine use of TURP as a cytoreduction method.

Conclusion

Tumor cytoreduction (TURP or open prostatectomy) performed in our practice for bladder outlet unblocking has a positive impact on the oncological results of patients with mHSPC. The cytoreduction offers more beneficial effect to the patients, with lower PSA nadir, longer time to PSA nadir, and longer PFS. However, after cancer progression outcomes were not significantly different between the two groups.

Ethics statement

Our Institutional Review Board (the urology pedagogical committee of the Cheikh Anta Diop University of Dakar) approved this study. This study was carried out in accordance with the principles of the Declaration of Helsinki. All patients got information about the study and gave their written informed consent.

Disclosure

The authors report no conflicts of interest in this work.

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