Original Article

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Treatment of Primary Tumor in Oligometastatic Prostate Cancer: An Observational Study of the Turkish Urooncology Association Prostate Diseases Working Group

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Abstract

Objective: To report the clinical results of patients who had metastatic prostate cancer (PC) at admission and underwent standard androgen deprivation therapy with radiotherapy (RT) and radical prostatectomy (RP) for the primary tumor.

Materials and Methods: This study used the PC database from the Turkish Urooncology Association, to which participating institutions submit online data. The following clinical, radiological, and pathological findings were retrieved from the database: age, total prostate-specific antigen, clinical TNM stage, number of metastases, International Society of Urological Pathology grade group of biopsy, time to castration-resistant disease, type of local treatment, type of staging method, status of survival, type of systemic treatment, and follow-up time.

Results: The median follow-up of the 18 included patients was 59.1 (19.9-180) months. RP and extended lymphadenectomy were performed in 12 patients. RT was performed in 6 patients. The median number of metastases was 2 (1-4) and 3 (1-4) in the RP and RT groups, respectively. In the RP group, 3 of 12 patients developed castration-resistant prostate cancer (CRPC) during the follow-up period. In the RT group, 2 of 6 patients developed CRPC in the follow-up period. The time to CRPC was 48.4 and 43.3 months, respectively.

Conclusion: While primary tumor-directed RT is effective in selected patients, the results of prospective randomized controlled studies are required to demonstrate the effectiveness of RP.

Keywords: Oligometastatic prostate cancer, radical prostatectomy, radiotherapy

Introduction

According to an analysis by the National Prostate Cancer Audit (1), approximately 13% of prostate cancer (PC) cases have distant metastases at the time of diagnosis. Although the incidence of distant metastatic PC has increased over the last decade, the 5-year survival rate has increased from 28.7% to 32.3% due to increased treatment options (2).

Androgen deprivation therapy (ADT) has long been the cornerstone of standard treatment for patients with PC presenting with systemic disease (3). Today, a more aggressive treatment approach is adopted in de novo metastatic disease in terms of both systemic treatment and localized treatment, including radical prostatectomy (RP), radiotherapy (RT) for primary tumors, and metastasis-directed therapy (MDT) for metastatic foci. Many systemic agents, which are used in the castration-resistant stage, have now had their survival advantage proven in hormone-sensitive disease (4-6). Data also suggest that treatments for primary tumors and metastatic foci provide survival advantage in selected patients (7). The term oligometastatic PC (OMPC) has been proposed to identify the patient group that will benefit from this survival advantage.

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Oligometastatic PC was first defined by Hellman and Weichselbaum (8) in 1995. They stated that the biology of oligometastatic disease differs from that of nonmetastatic and widespread metastatic disease, and that local therapies can affect the natural course of the disease and have curative effects. In other words, for a patient to be biologically oligometastatic, both the primary tumor and the metastatic foci must be locally treated with temporary hormonal therapy; thus, the patient can be cured without requiring systemic treatment. In the literature, the terms oligorecurrent disease (metastasis occurring without systemic therapy) and oligoprogressive disease (metastasis occurring under systemic therapy) are also used to describe castration-sensitive oligometastasis and castration-resistant oligometastasis after local treatment, respectively (7). The definition of OMPC, which is the subject of this article, includes de novo hormone-sensitive disease with synchronous metastases. However, one of the most critical shortcomings of OMPC is the lack of consensus in the literature regarding its definition. The definitions currently used are clinical quantitative definitions based on the site and number of metastases, as opposed to a biological definition. Although many definitions exist in the literature, having fewer than 5 metastases, no visceral metastases, and bone lesions in the axial skeleton can be said to be a widely accepted definition (9).

This study aimed to report the clinical results of patients who were metastatic at the time of admission and underwent standard ADT with RT and RP for the primary tumor.

Materials and Methods

Study Design

This study used the PC database from the Turkish Urooncology Association, to which participating institutions submit online data. All patient data were anonymized at the source center before being recorded in the database. For this study to be conducted using the PC database, approval was obtained from the Turkish Urooncology Association Prostate Diseases Working Group. The study was registered with the code TUO-PR-19-05. The study is structured as a database report, and therefore, ethical committee approval was unsought.

A total of 18 patients with PC who had bone or non-regional lymph node metastasis at the time of diagnosis and had undergone RT or RP for the primary tumor between 2005 and 2020 were included in the study. The follow-up data of the patients included in the study were updated by the relevant centers before the analysis.

Data Collection and Definitions

Clinical, radiological, and pathological findings [age, total prostate-specific antigen (PSA), clinical TNM stage, number of metastases, International Society of Urological Pathology (ISUP) grade group] of biopsy, time to castration-resistant disease, type of local treatment, type of staging method, survival status, type of systemic treatment, and follow-up time were retrieved from the PC database. The ISUP grading system revised at the 2014 ISUP consensus conference was used (10). Castration-resistant PC (CRPC) was defined as a biochemical or radiological progression with a serum testosterone level of less than 50 ng/dL or 1.7 nmol/L. Biochemical progression was determined by 3 consecutive rises in PSA at least 1 week apart, resulting in 2 increases of 50% over the nadir and a PSA >2 ng/mL. Furthermore, radiological progression was determined by the presence of 2 or more new bone lesions in a bone scan or of a soft tissue lesion using the Response Evaluation Criteria in Solid Tumors (11).

Statistical Analysis

The normal distribution of continuous variables was evaluated by analytical methods. In the descriptive findings, categorical variables are given as numbers (percentage), and continuous variables are median (minimum-maximum) for normal non-scattering data. Time to CRPC was defined as the time from the date of RP/RT to the date of CRPC. All statistical analyses were performed in R version 4.0.4 through R Studio version 1.4.1106.

Results

The median follow-up of the 18 patients included in the study was 59.1 (19.9-180) months. Their median age was 66 years (48-75) and their median total PSA was 12.3 (4.2-324). Whole-body bone scintigraphy (WBBS) in 10 patients, computed tomography (CT)/magnetic resonance imaging (MRI) in 11 patients, and Gallium-68 prostate-specific membrane antigen positron emission tomography/CT (^{68}Ga-PSMA PET) in 5 patients were used for the systemic staging of PC.

RP was performed along with the extended lymph node dissection in 12 patients. Open RP was performed in 9 patients, and robotic RP was performed in 3 patients. In the RP group, the median operative time was 165 (120-309) minutes and the median time to urethral catheter removal was 14 (8-15) days. Two patients received postoperative adjuvant RT, while 3 patients underwent metastasis-directed stereotactic RT. After diagnosis, all patients were prescribed luteinizing hormone-releasing hormone (LHRH) analog treatment before surgery, which was continued as standard therapy after surgical intervention.

RT was performed in 6 patients. Pelvic RT to the lymph nodes was also applied to all patients. Two patients received conventional external beam RT, while 4 patients received intensity-modulated RT. All patients received a simultaneous LHRH analog therapy, while 1 patient received additional docetaxel chemotherapy. Three patients underwent metastasis-directed stereotactic RT.

The clinical stages and pathological findings are summarized in Table 1. The median number of metastases was 2 (1-4) and 3 (1-4) in the RP and RT groups, respectively. Non-axial skeletal and visceral metastases were not detected in any patient.

In the RP group, 3 of 12 patients developed CRPC during their follow-up, whereas in the RT group, 2 of 6 patients developed CRPC during their follow-up. The time to CRPC was 48.4 and 43.3 months, respectively, while no deaths were observed in the RP group, death due to PC was reported in 2 patients in the RT group who developed CRPC.

Discussion

We report the outcome data of 18 patients who received systemic treatment with ADT with or without docetaxel and underwent RT or RP for the prostatic disease site. There were no restrictions on the number and location of distant metastases in our study. We found that the median number of metastases was 2 (1-4) in the RP group and 3 (1-4) in the RT group. The majority of the patients were in stage M1b. Castration-resistant disease developed in 5 patients during follow-up. The time to castration resistance was 48.4 and 43.3 months in the RP and RT groups, respectively. In the RT group, 2 patients died due to PC during follow-up.

At the time of our patients' initial diagnosis, the standard treatment for hormone-sensitive metastatic PC was ADT. Therefore, the majority of our patients received only LHRH therapy as systemic treatment. However, the current guidelines strongly recommend a combination of ADT with agents such as docetaxel, enzalutamide, and abiraterone acetate, which have been proven to have a survival advantage both in the castration naïve and resistant stages as the first-line treatment for primary metastatic PC (11). In a Cochrane review conducted in 2019, taxane-based chemotherapy given with ADT significantly increases cancer-specific survival (CSS) and overall survival (OS) as well as delays disease progression in the hormone-sensitive stage (12). Furthermore, the STAMPEDE, LATITUDE, ENZAMET, and TITAN studies have demonstrated that abiraterone acetate plus prednisone, enzalutamide, and apalutamide significantly increase OS in metastatic hormone-sensitive PC (mHSPC) with ADT, respectively (13-16). The PEACE-1 study published in 2022 added abiraterone acetate plus prednisone as a third agent to the standard treatments of ADT + docetaxel for de novo mHSPC. It was found that this "triple" treatment significantly increased OS and radiological progression-free survival compared with the standard treatment. Although the study included patients who received and did not receive RT for the primary tumor, no subgroup analysis was performed on this topic (17).

The primary rationale for local treatment in oligometastatic disease is to reduce the volume of cancer cells and interrupt the crosstalk between disseminated tumor cells and primary lesions. As long as this crosstalk continues, the release of inflammatory cytokines can lead to the formation of metastatic foci in disseminated cells as well as aggressive local growth due to increased angiogenesis in primary tumor. The removal of the primary tumor can also result in the regression of distant metastases, similar to the abscopal effect observed in patients treated with RT. In addition, local treatment can eliminate potential lethal cell clones that are responsible for the persistence and progression of the disease after systemic therapy (7). Another benefit of removing as much of the tumor burden as possible in oligometastatic disease is that it may increase the success of targeted therapies (e.g., radionuclide lutetium) that may be given in the future. In a study conducted in 2022 by Gafita et al., (18) which investigated the tumor sink effect, the authors found that GA68 PSMA biodistribution in normal organs was significantly lower in patients with high tumor burden

Table 1. Baseline characteristics

	Radical prostatectomy (n=12)	**Radiotherapy (n=6)**	**Overall (n=18)**
Age [(year) median (range)]	66.0 (48.9-75.0)	68.0 (53.0-73.2)	66.2 (48.9-75.0)
Total PSA [(ng/mL) median (range)]	12.2 (4.2-85.0)	16.0 (4.8-324)	12.3 (4.2-324)
Biopsy ISUP GG n (%)			
1	1 (8.3)	0 (0.0)	1 (5.6)
2	0 (0.0)	2 (33.3)	2 (11.1)
3	4 (33.3)	1 (16.7)	5 (27.8)
4	3 (25.0)	0 (0.0)	3 (16.7)
5	4 (33.3)	3 (50.0)	7 (38.9)
Clinical T stage n (%)			
T2	6 (50.0)	2 (33.3)	8 (44.4)
T3a	3 (25.0)	1 (16.7)	4 (22.2)
T3b	3 (25.0)	2 (33.3)	5 (27.8)
T4	0 (0.0)	1 (16.7)	1 (5.6)
Clinical N stage n (%)			
N0	4 (33.3)	2 (33.3)	6 (33.3)
N1	8 (66.7)	4 (66.7)	12 (66.7)
Clinical M stage n (%)			
M1a	4 (33.3)	1 (16.7)	5 (27.8)
M1b	8 (66.7)	5 (83.3)	13 (72.2)
The number of metastases [(n) median (range)]	2 (1-4)	3 (1-4)	2 (1-4)

ISUP GG: International Society of Urological Pathology grade group

compared with those with low tumor burden. This may be due to the reduction of tumor burden in metastatic disease which allows for higher doses of radionuclides to reach the remaining tumors (18).

The most critical factor to consider when deciding on treatment for primary tumors in mHSPC is disease burden. This concept first appeared in the CHAARTED study, which demonstrated that the administration of ADT along with docetaxel in patients with high-volume mHSPC provided survival advantage. In the study, high-volume disease (HVD) was defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis. However, these definitions are based on CT and WBBS findings (19). Similarly, definitions of OMPC in the literature are based on the location and number of metastases. In our data, PSMA was used to stage only 5 patients, while 13 patients were staged using BT/MRI and WBBS. Currently, promising studies suggest that Ga-68 PSMA PET, which is now routinely used in staging due to its high sensitivity and specificity, can also be used to accurately determine disease burden. The semiautomatic calculation of tumor burden in bone metastases using PSMA PET CT was first described by Bieth et al. (20) in 2017. Subsequently, in 2019, Gafita et al. (21) developed a software-based "qPSMA" to determine the semiautomatic tumor burden in the whole body, including skeletal, visceral, and lymph node metastases, and stated that its use is feasible. In 2021, Barbato et al. (22) designed a study to determine PSMA PET disease volume criteria in patients with mHSPC compatible with CT-based CHAARTED criteria. According to this study, more lesions were found in 62% of patients with Ga68 PSMA PET/CT, and 40% of patients were upgraded from low-volume disease (LVD) to HVD according to the CHAARTED criteria. When ROC analysis was performed to predict the CT-based CHAARTED HVD criteria, the estimated PSMA PET disease volume was 38.8 cm^3. Therefore, the PSMA disease volume criteria were defined as LVD for unifocal disease or tumor burden <40 cm^3 and as HVD for multifocal disease with a tumor burden ≥40 cm^3 (22).

Although retrospective data exist on primary tumor-directed treatment for metastatic PC, there are limited prospective randomized controlled trials (RCTs). The first RCT designed to evaluate primary tumor-directed treatment for metastatic PC was the HORRAD study by Boevé et al. (23). The control group received only ADT, whereas the experimental group received ADT and RT targeted to the prostate. Pelvic lymph nodes and areas of metastasis were not treated with RT. The study participants were divided into groups based on the number of bone metastases on WBBS as follows: <5, 5-15, and more than 15. At a median follow-up of 47 months, no significant difference existed in OS between the control and experimental groups either in the entire cohort or in the subgroups (23). The STAMPEDE study, another RCT published in 2018, used both WBBS and CT for staging and divided the participants into LVD and HVD groups based on the metastatic burden using the CHAARTED criteria. Unlike the HORRAD study, docetaxel was also given as part of the standard systemic therapy to participants enrolled after 2015. In this study, there was also no significant difference in OS between the control and experimental groups in the general group at a median follow-up of 37 months; however, a statistically significant OS advantage was found in the LVD group of the RT group (p=0.007; 3-year survival 73% with control vs 81% with RT) (24). In our study, time to CRPC in the RT group was 43.3 months; however, in the HORRAD study, the time to PSA progression was 15 months, while the failure-free survival was 26.2 months in the STAMPEDE study. The STOPCAP meta-analysis, which included these 2 studies, demonstrated a 7% 3-year survival advantage in those with fewer than 5 bone metastases (25). The current 2022 EAU guidelines strongly recommend local radiation therapy targeted at the prostate with ADT in low-volume metastatic disease due to survival advantage (11).

Currently, ongoing RCTs (g-RAAMP, TRoMbone, and SWOG S1802) are evaluating the effectiveness of RP in metastatic PC, but all available data in the literature are retrospective (26). Surgical treatment of the primary tumor and local treatment of metastasis are not recommended outside well-designed clinical studies (11). In a meta-analysis published in 2022, Shemshaki et al. (27) included retrospective data and found that in metastatic patients, compared with systemic therapy, cytoreductive RP (cRP) led to statistically significantly higher CSS and OS. However, no difference existed in survival between cRP and RT (27). In a prospective case–control study of 83 patients, Steuber et al. (28) found that although no differences existed in OS and CRPC-free survival, locoregional complications were significantly lower in the cytoreductive RP group (7.0% vs 35%; p<0.01).

In our study, 6 patients from each group were given stereotactic RT as MDT. In a retrospective series, data indicate that MDT along with primary tumor treatment increases CSS and CRPC-free survival in de novo OMPC (7). However, no RCT data are available on MDT for de novo OMPC. In a limited number of RCTs in oligorecurrent disease, MDT statistically significantly increases progression- and ADT-free survival; however, no data indicate that it increases OS (29,30).

Study Limitations

This study had some limitations. First, it was designed as a retrospective database study, and no control group received standard systemic treatment. Second, the number of patients was relatively small because the standard treatment approach for the prostatic disease site is yet to be defined within the context of metastatic disease. Third, staging in most of our patients was performed by conventional methods such as WBBS and BT-MRI. The relatively longer time to castration in patients in our study compared to the literature suggests that there may be false positive results in staging with conventional methods in terms of metastasis in these patients. Fourth, patients were not standardized according to the site and the number of metastases. Furthermore, the techniques and doses used for radiation therapy for primary tumors and metastatic foci are not standardized, and data on complications related to local treatments are incomplete.

Conclusion

It is crucial to objectively determine tumor burden using newer generation imaging methods to achieve satisfactory results in determining treatment approaches for OMPC. This is because tumor burden is critical for determining treatment approaches.

While primary tumor-directed RT is effective in selected patients, our results raise the possibility of similar efficacy with RP. However, the awaited results of ongoing prospective randomized controlled clinical trials will further define the actual role of surgery in this patient population.

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Ethics

Ethics Committee Approval: The study is structured as a database report and therefore, ethical committee approval was not sought.

Informed Consent: Database report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.S.S., G.A., S.B., L.T., Concept: T.S.S., G.A., S.B., L.T., Design: T.S.S., G.A., S.B., L.T., Data Collection or Processing: M.Y.K., G.A., S.B., O.E., Analysis or Interpretation: M.Y.K., O.E., Literature Search: M.Y.K., O.E., Writing: M.Y.K., T.S.S., L.T.

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