

Cytoreductive and Palliative Radical Prostatectomy, Extended Lymphadenectomy and Bilateral Orchiectomy in Advanced Prostate Cancer with Oligo and Widespread Bone Metastases: Result of Feasibility, Our Initial Experience

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Purpose: To evaluate the feasibility of cytoreductive radical prostatectomy (CRP), lymphadenectomy, and bilateral orchiectomy in patients with advanced prostate cancer with oligo- and poly-metastases. Furthermore, the functional and oncological outcomes of these patients in comparison with the control group that underwent treatment only with systemic therapy (ST group) is investigated in a well-selected, prospective cohort study.

Material and methods: A total of 26 patients were enrolled in CRP group and 23 patients in ST group. The patients have been followed (9 to 43 months (median: 19.5)) with PSA (prostate specific antigen), whole body bone scan and other necessary imaging and laboratory tests. Functional and oncological outcomes were compared between two groups.

Results: Biochemical relapse occurred in 9 patients (34.6%) in CRP group and in 17 patients (73.9%) in ST group ($P = 0.01$). Whole-body bone scans showed more reduced metastasis volume in CRP group ($P = 0.003$). There was no voiding dysfunction in 22 patients in CRP group post-operatively (84.6%), while in ST group trans-urethral resection of prostate or permanent Foley catheter was needed in 8 patients (34.7%) and bilateral percutaneous nephrostomy was done in one patient. Six patients in CRP group (23%) and eight patients in ST group (34.7%) died because of prostate cancer and there was no difference between cancer specific survival between the two groups ($P = 0.975$).

Conclusion: Although surgery doesn't improve cancer specific survival in patients with skeletal metastatic prostate cancer in the short term, but offers better local control, improves biochemical relapse-free survival, might

prevent excessive interventions, and reduce bone pain and metastasis.

Keywords: prostate neoplasms; metastasis; oligo and wide-spread metastasis; cyto-reductive radical prostatectomy; bilateral orchiectomy; functional and oncologic outcome

INTRODUCTION

Today, androgen deprivation therapy (ADT) is the gold standard treatment for advanced prostate cancer with bone metastases. Although radical prostatectomy (RP) is a choice treatment for localized PCa (prostate cancer) in men with a life expectancy of more than 10-15 years, there is not sufficient information that surgery could improve survival in patients with bone metastasis⁽¹⁻⁵⁾. For many years, it was believed that debulking surgery in metastatic cancer does not affect survival, because not all cancer cells can be eliminated by cytoreductive surgery. Now, however, the belief that the development of distant metastasis might be dependent on an intact primary focus has come about⁽⁶⁻⁸⁾. Some studies have demonstrated that cytoreductive cancer surgery can improve the response of the disease to adjuvant systemic therapy and finally improve cancer-specific survival. This hypothesis was proven by clinical trials and meta-analyses in some malignancies like renal cancer, colorectal cancer, and ovarian carcinoma⁽⁹⁻¹²⁾. The improvement may be because the production of tumor growth factors, immunosuppressive cytokines, and new metastases cells made by the pri-

mary tumor is reduced⁽¹³⁾. It is not yet clear whether or not this hypothesis is true for metastatic prostate cancer. The few studies that have been done in this regard have demonstrated that the role of RP is shifting from low-risk PCa to high-risk PCa and advanced disease. To achieve a better survival rate, RP with ADT may be a frontline treatment option for patients with mPCa (metastatic prostate cancer) in the future^(6,14,15).

On the other hand, because of prostate adhesion to the surrounding tissue in advanced PCa and difficult tissue dissection, the safety and feasibility of surgery are unclear. Excessive bleeding, rectal injury, sphincter damage, subsequent incontinence and other complications are predictable.

More than one third of these patients suffer from problems caused by the local progression of tumor-like urinary retention, bilateral hydronephrosis, and increased creatinine levels⁽¹⁶⁾. Permanent Foley catheter, bilateral nephrostomy tube placement, repeat channel trans-urethral resection of the prostate, and several other therapies may be needed to re-establish urine flow and prevent complications, but these actions affect quality of life.

The current study investigates the feasibility of cyto-

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Table 1. Patients' characteristics.

	Group CRP	Group ST	P value
Number of patients	26	23	
Mean age (SD); years	61.5 (7.67)	64.6 (6.18)	0.16
Median F/U (range); months	18 (9-42)	21 (14-43)	0.14
Mean Pre-op PSA (SD); ng/dL	108 (73)	84 (61)	0.21
Median (IQR)	100(79-113)	69(47-100)	
Mean PSA after 6 month (SD)	8.14 (21.3)	38.6 (59.2)	0.003
Median (IQR)	0.1(0.05-1.5)	5.4 (0.1-67)	
Mean PSA in last F/U (SD)	19.2 (44.5)	75.3 (97.7)	0.003
Median(IQR)	0.2(0.05-10.1)	27(0.8-100)	
Type of metastasis; N(%)			0.962
Poly-metastasis	16 (61.5%)	14 (60.9%)	
Oligo-metastasis	10 (38.5%)	9 (39.1%)	
Chief complaint; N(%)			1.00
No symptom	8 (30.8%)	7 (30.4%)	
Hematuria	1 (3.8%)	0	
Obstructive LUTS	17 (65.4%)	16 (69.6%)	

ductive RP (CRP), lymphadenectomy, and bilateral orchiectomy in patients with advanced PCa with oligo- and poly-metastases. Furthermore, the functional and oncological outcomes of these patients in comparison with the control group that underwent treatment only with systemic therapy is investigated in a well-selected, prospective cohort study.

Case 1

A 52 years old man presented with urinary retention, bilateral severe hydronephrosis and serum creatinine 5 mg/dl and PSA 220 ng/dl. Trans rectal biopsy of prostate showed adenocarcinoma of prostate. Whole body bone scan revealed 3 foci of metastasis in right iliac, right ischium and right pubis. He underwent cyto-reductive radical prostatectomy, extended lymphadenectomy and bilateral orchiectomy (**Figure1**).

After 43 months follow up, serum PSA is 0.02 ng/dl, hydronephrosis disappeared, creatinine came down to normal range, all the metastases points disappeared in follow up bone scans and the patient is currently continent and voiding well.



Figure 1. Radical prostatectomy, extended lymphadenectomy and bilateral orchiectomy.

Case 2

A 54 years old man presented with history of obstructive urinary symptoms that was not improved with standard medical treatment. He had bone pain in his back. Post-voiding residual urine was 100cc, the serum PSA was more than 100 ng/dl. Whole body bone scan showed wide-spread bone metastases. Trans rectal biopsy of prostate revealed adenocarcinoma of prostate. He underwent RP, extended LND and bilateral orchiectomy like the previous case. After 30 months follow up, metastatic points decreased significantly in subsequent bone scan and no new metastases appeared. (fig2), the serum PSA level is 0.1 ng/dl and the patients has no complaints of bone pain any more.

MATERIALS AND METHODS

A total of 49 patients with mPCa and skeletal metastasis were enrolled in the current study from 2014 to 2017. The patients were referred to the surgery and oncology clinic and after consideration of inclusion criteria, the advantages and disadvantages of each type of treatment were described by the surgeon and the oncologist. After discussion and consultation, the patients decided on the treatment method. Written informed consent was obtained from all the patients after approval from our institutional review board. Twenty-six patients underwent cytoreductive RP, lymphadenectomy, and bilateral orchiectomy (CRP group) (Figure 1) and were compared with similar patients treated non-surgically with systemic therapy (ST group). Prostate adenocarcinoma in all these patients was diagnosed by transrectal ultrasound-guided biopsy (12 cores) after an abnormal digital rectal exam or elevated serum prostate-specific antigen (PSA). Routine pre-treatment laboratory tests and imaging staging procedures, including chest X-ray, abdominal-pelvic computerized tomography (CT scan), magnetic resonance imaging (MRI), and whole-body bone scan, were done to evaluate lymphadenopathy, distant metastases, and staging. Prostate specific membrane antigen scans (PSMA scan) were performed in suspicious cases to confirm the diagnosis.

Inclusion criteria in this study were 1) newly diagnosed prostate cancer with oligometastases and also wide-spread bone metastases with any elevated PSA levels and lymph nodes of any size; 2) imaging and DRE (digital rectal exam) confirmation of entirely resectable PCa; 3) the absence of visceral metastasis; 4) lack of

Table 2. Peri-operative and post-operative data.

Mean operation time	85 mins (75-110)
Mean blood loss	700 ml (500-1600)
Mean hospitalization	2.7 days (2-10)
Mean catheterization	10 days
Pathology Stage	
PT2b	1 (3.8%)
PT2c	1 (3.8%)
PT3a	1 (3.8%)
PT3b	22 (84.6%)
PT4	1 (3.8%)
Gleason's score	
7	1 (3.8%)
8	2 (7.6%)
9	18 (69.2%)
10	5 (19.2%)
Margin of surgery	
Positive	26 (100%)
negative	-
Metastatic lymph node1	
Yes	24 (92.3%)
No	1 (3.8%)

1) Lymphadenectomy in one patient was impossible because of adhesion to vessels

significant comorbidities; 5) age under 75 years; and 6) no prior radiation therapy.

Radical prostatectomy was done in open retro-pubic incision method with an antegrade approach. Extended pelvic lymph node dissection (ePLND) was done as excision of fibro-fatty tissue along the external and internal iliac vessels and obturator fossa and common iliac artery bilaterally^(17,18). A bilateral orchiectomy was done through a midline incision of the scrotum using the epididymal sparing technique (**Figure 1**).

Beside the CRP group, 23 patients with the same inclusion criteria received the best systemic therapy (ADT with antiandrogen drugs) as the standard and traditional treatment group (ST group).⁽¹⁹⁾ All data for the CRP and ST groups was collected prospectively.

Data collection

All pre-operative, peri-operative, and post-operative data, i.e. age, PSA, Gleason score, tumor stage according to the TNM system, margin status, number of lymph nodes removed, operative time, amount of bleeding, hospitalization duration, catheterization duration, state of continence, and voiding pattern, and any complication that occurred were recorded. All patients were regularly followed every month for the first three months and then every three months. Serum PSA and other markers that were needed were measured in each visit. Patient symptoms and functional outcome, such as urine continence, bone pain, and lower urinary tract symptoms, were evaluated. A whole-body bone scan

was done every six months to detect changes in the metastases burden. All other imaging studies were performed if necessary.

Oligometastatic PCa was defined as 5 or fewer metastatic lesions diagnosed by a whole-body bone scan. Patients with more than 5 bone metastases were categorized as poly-metastatic (widespread) PCa⁽²⁰⁻²²⁾. Time to castration resistance was defined as the time of surgery until the documented confirmation of biochemical progression. Cancer-specific survival (CSS) was defined as the time of diagnosis until death due to PCa. Overall survival (OS) was described as the time of diagnosis until death for any reason⁽¹³⁾.

Complications were evaluated according to Clavien grade system^(23,24). The independent sample T test and Mann-Whitney were used to compare normal and non-normal quantitative variables, respectively, in two groups. Normality of variables was checked with Shapiro Wilk test. Chi-square test was used to explore the relationship between qualitative variables. Survival were explored using Log Rank test and Kaplan-Meier plots.

RESULTS

Presenting cases

Characteristics and surgery data

A total of 26 patients (CRP group) underwent RP, lymphadenectomy, and bilateral orchiectomy. All peri-operative, post-operative and the histopathologic findings are shown in **Table 2**. Lymphadenectomy was impossible in one patient because of severe adhesion to the vessels. On average, 16.06 lymph nodes were removed from each patient (range = 6 to 49), of which an average of 8.1 of them showed metastatic cancer (range = 0 to 30).

Complications and functional outcomes of CRP group: Recto-vesical fistula occurred in 2 patients because of tumor adhesion to the rectum, and the condition was managed conservatively. One patient needed palliative cystectomy and the placement of bilateral ureterostomy because of a very small, thick, contracted bladder. Deep vein thrombosis (DVT) developed in two patients that underwent medical treatment. Injury of the external iliac artery during lymphadenectomy occurred in one patient because of adhesive LN, and it was repaired at the same time. One patient developed a significant hematoma in his pelvis and underwent re-exploration to remove hematoma and establish hemostasis. No Clavien grade 4 or 5 complication occurred⁽²⁴⁾. A total of 22 patients voided entirely with continence, and 3 patients used pads because of some degrees of stress incontinence. The patient with a bilateral ureterostomy used

Table 3. outcomes based on the number of metastases.

	CRP Group		ST Group	
	Oligo	Poly	Oligo	Poly
Biochemical relapse	3/10 (30.%)	6/16 (37.5%)	5/9 (55.6%)	12/14 (85.7%)
Bone pain				
Decrease	2 (20%)	12 (75%)	2 (22.2%)	1 (7.1%)
Increase	0	1 (6.3%)	4 (44.4%)	7 (50%)
No change	8 (80%)	3 (18.8%)	3 (33.3%)	6 (42.9%)
Metastasis in bone scan				
Decrease	3 (30%)	10 (62.5%)	2 (22.2%)	1 (7.1%)
Increase	1 (10%)	1 (6.3%)	4 (44.4%)	6 (42.9%)
No change	6 (60%)	5 (31.3%)	3 (33.3%)	7 (50%)
Mortality	1/10 (16.7 %)	5/16 (31.3%)	2/9 (22.2%)	6/14 (42.9%)

two urine bags on his abdomen to collect urine.

Oncologic outcomes of CRP group

In the mean follow up of 19.2 months (range = 9 to 42 months), 20/26 patients (76.9%) were alive. The six deceased patients had died from cancer. Biochemical relapse occurred in 9 patients (34.6%).

Sixteen patients complained of bone pain before surgery; bone pain was increased in only one patient during the follow-up period. In 14 patients (53.8%), bone pain decreased significantly. Serial whole-body bone scans showed an increased burden of metastasis in two (7.7%) patients and a reduced burden in 13 (50%) patients; no changes were seen in the other 11 (42.3%) patients. (Table 3)

Characteristics and oncologic outcomes of ST group:

In a concurrent evaluation, 23 patients with the same inclusion criteria as the control group (ST group) underwent standard systemic therapy (Table 1). In the mean follow-up period of 22.8 months (range = 14 to 43 months), 15 patients (65.2%) remained alive. The eight deceased patients died from cancer. Biochemical relapse occurred in 17 patients (73.9%).

Pre-treatment bone pain was found in 4 patients. Bone pain occurred or intensified in 11 patients (47.8%) and decreased in only 3 patients. Serial whole-body bone scans showed an increased burden of metastasis in 10 (43.5%) patients, a reduced burden in 3 (13%) patients, and no change in the other 10 (43.5%).

Complications and functional outcomes of ST group:

Because of local progression of the tumor, 4 patients (17.3%) underwent channel transurethral resection of the prostate to resolve signs and symptoms, one (4.3%) patient needed bilateral percutaneous nephrostomy, and 4 (17.3%) patients required the placement of a permanent Foley catheter, because their physical condition was too poor to undergo intervention.

As mentioned, the data showed a significant decrease

in bone pain in patients who underwent surgery, while patients who underwent systemic therapy complained of increasing pain ($P < 0.001$). Whole-body bone scans showed reduced metastasis volume occurred more in CRP group ($P = 0.003$). Biochemical relapse occurred in ST group significantly higher than in the CRP group ($P = 0.01$). Six patients in CRP group (23%) and eight patients in ST group (34.7%) died because of prostate cancer. Kaplan-meier curves are shown in Figure 3 to compare the survival between two groups. Log rank test shows no difference between cancer specific survival between two groups ($P = 0.975$).

DISCUSSION

The first aim of this study was to demonstrate the feasibility of RP in patients with oligo- and widespread skeletal-metastatic PCa. Based on the results, RP not only has no major complications, but it also has many advantages. No Clavien grade 4 or 5 and no major complication occurred because of surgery. All patients except one were discharged from hospital in good condition after 2 to 5 days.

The mortality rate in group CRP was 23% (6/26 patients), which was higher than the mortality in similar studies. This difference may be explained by the broad inclusion criteria^(13,25). Table 3 shows that the mortality rate was higher in patients with more than five metastases (poly-metastatic prostate cancer). To the best of the authors' knowledge, this is the first prospective cohort study to evaluate cytoreductive RP in patients with both oligo- and poly-metastasis in bones, prospectively. Only one patient in group CRP and two in group ST with oligometastasis died because of cancer, as shown in Table 3.

Heidenreich evaluated the data of 23 patients with oligometastatic prostate cancer who underwent cytoreductive RP (group 1) and 38 patients with the same criteria who underwent systemic therapy (group 2), retrospectively⁽¹³⁾. Patients in group 1 received neoadjuvant ADT to decrease the PSA to less than 1 ng/dL; otherwise, they were not entered into the study. Heidenreich found improvement in the cancer-specific survival rate and time to castration resistance, but no difference was seen in overall survival. The time to castration resistance was increased in the current study, but no improvement was observed in cancer-specific survival or overall survival. Although surgery could improve biochemical relapse-free survival (BRFS), the overall survival rate was similar between the two groups. Another difference between the current study and that of Heidenreich was that surgery was performed immediately after diagnosis with any amount of pre-op PSA without waiting for neoadjuvant ADT. It is speculated that waiting six months before radical surgery might cause the disease to progress. In further contrast with the Heidenreich study, those patients in whom PSA was not decreased to 1 ng/ml before surgery were not excluded; surgery was performed on patients with PSA over 100 ng/mL.

A Surveillance, Epidemiology, and End Results (SEER)-based study showed the role of local therapy in the improvement of CSS and OS in patients with metastatic prostate cancer^(16,26). Further evaluation, however, showed that patients who had undergone surgery were younger, were in better physical condition, and were more likely to have a lower Gleason score and clinical stage. This selection bias indicates the importance of



Figure 2. Significant decrease in bone metastasis during follow up whole body bone scan after surgery (almost disappeared)

using a prospective study with proper case selection. Concerns about functional outcomes are growing, because many patients are diagnosed at earlier ages. Quality of life is very important in malignancies⁽²⁷⁾. Despite using drug agents to control LUTS (lower urinary tract syndrome), 17 patients (65.4%) in the CRP group of the current study developed obstructive LUTS that caused a rise in creatinine levels in some cases. Bilateral hydronephrosis occurred in one patient and urinary retention occurred in 4 patients. After surgery, all patients (except one who needed cystectomy) were voiding without difficulty. The bilateral hydronephrosis disappeared, creatinine decreased to within normal range, and 85% of patients were continent. In the ST group, 16 patients (69.6%) presented with obstructive LUTS that caused retention in 3 patients and bilateral hydronephrosis and rise in creatinine in one patient. Nine patients required intervention or permanent catheterization to resolve these signs and symptoms. The data shows that even if surgery does not lead to more cancer-specific survival in the short term, it might eliminate problems caused by local progression and increase the quality of life for the patient's remaining days.

As mentioned, the effects of surgery on improving bone pain and metastasis were previously reported; however, the current study did not reveal the same results as reported in the literature. **Figure 2** reveals the near disappearance of bone metastasis in a follow-up whole-body bone scan after surgery.

Despite the many benefits that surgery has for such patients, it should be noted that surgery in these patients is more difficult and complicated than a usual radical prostatectomy because of the adhesion of the advanced tumor to neighboring organs like the rectum, the difficulty of dissection, and the risk of bleeding. In contrast with the Heidenreich study, patients were included in the CRP group of the current study even if their lymph nodes were larger than 3 cm. In such cases, they may be attached entirely to the iliac vessels, and there is a possibility of harm being done to them during lymphadenopathy. This was experienced in one patient of the current study. The external iliac artery was repaired with 6-0 nylon sutures, and the patient had no problems after surgery. It is very important that such surgeries be performed by a surgeon who is very experienced in vascular and pelvic surgery. It is important to note that all operations done during this evaluation were performed by one surgeon; this is one of the positive points of this study.

Despite the fact that in similar studies a medical agent was used for ADT, surgical castration was preferred in the present study. Many studies have shown a lower risk of orchiectomy in bone fractures, peripheral arterial disease, cardiac-related complications, and venous thromboembolism in comparison to LHRH agonists^{28,29}. For such patients, permanent castration is required, and apart from the above-mentioned complications, orchiectomy is easy, less expensive, and does not require the patient to take medications continuously.

Limitations of this study are low sample size and short follow-up period. Another limitation was that patients were not selected in a randomized trial. After receiving a complete explanation of the project, the patients decided how to continue their treatment. To evaluate the advantages and disadvantages of cytoreductive surgery in patients with skeletal oligo and widespread mPCa,

randomized clinical studies with higher numbers of patients and longer follow-up times are necessary.

CONCLUSIONS

Although surgery does not seem to improve cancer specific survival rates in patients with skeletal-metastatic prostate cancer in the short term, it does offer better local control, improves biochemical relapse-free survival, might prevent excessive interventions, and reduces bone pain and metastasis volume. The role of RP in advanced PCa is increasing, and it may be considered as a standard method instead of systemic therapy in metastatic prostate cancer patients, even in those with skeletal metastasis.

CONFLICTS OF INTEREST

None declared.

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