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Original Article

Cytoreductive cryosurgery in patients with bone metastatic prostate cancer: A retrospective analysis

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Abstract The current study is a retrospective analysis of 49 patients with bone metastatic prostate cancer: 26 receiving androgen deprivation therapy (ADT) alone versus 23 receiving cytoreductive cryosurgery of the primary tumor plus ADT treatment. Progression-free survival (PFS) was the primary outcome variable, and Cox proportional hazards regression analysis was used to identify predictors for PFS. The baseline characteristics were generally comparable between the 2 groups. Median follow-up time was 41 months (range 24–56) and 37 months (range 19–53) in ADT alone group and cryosurgery groups, respectively. Patients receiving cryosurgery had significantly longer PFS (35 vs 25 months, P = 0.0027) and time to castration resistance (36 vs 25 months, P = 0.0011). Cox multivariate analysis associated longer PFS with the following factors: cryosurgery (HR0.207, 95% CI 0.094–0.456), lower prostate specific antigen at diagnosis (≤100 ng/ml, HR0.235, 95% CI 0.072–0.763) and lower Gleason score (≤7, HR0.195, 95% CI 0.077–0.496). Cryosurgery reduced the risk of progression by 79.3%. In conclusion, cytoreductive cryosurgery of the primary tumor in patients with bone metastatic prostate cancer could reduce the risk of progression and delay time to castration-resistant prostate cancer.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Androgen deprivation therapy (ADT) is the recommended treatment for patient with metastatic prostate cancer (mPCa) [1]. Unfortunately, many patients eventually develop castration-resistant prostate cancer (CRPC) within two to three years [1]. And more than one third of patients without local treatment to the primary tumors will experience local complications due to local progression of prostate cancer (PCa) [2,3]. Recent studies have suggested patients with mPCa would benefit from local treatment to the primary tumor [4—6]. Fossati et al. found that the benefits of local treatment of the primary tumor in mPCa patients (either with radical prostatectomy or radiation therapy) depend on tumor characteristics [4]. Heidenreich et al. showed that cytoreductive radical prostatectomy could reduce the risk of locally recurrent PCa and local complications in mPCa patients who respond well to neoadjuvant ADT [3]. Traditionally, local treatments to the primary tumor in mPCa included radical prostatectomy or external beam radiation therapy [2]. There are limited available data on the outcomes of cryosurgery for mPCa. Cryosurgery has been increasingly used for localized prostate cancer [6], mostly due to less blood loss and minimal invasion [7]. We speculate that cryosurgery could reduce local complications and/or improve progression-free survival (PFS) in patients with mPCa. In this study, we retrospectively analyzed a group of patients with bone mPCa receiving cytoreductive cryosurgery on a background of ADT vs. a group of patients receiving ADT only. Cox proportional hazards regression analysis was used to identify predictors for PFS. Prostate specific antigen (PSA) kinetics after the surgery was also examined.

Methods

Study design and patients

The current retrospective study was approved by the Ethics Committee. A total of 49 mPCa subjects receiving ADT, with or without cytoreductive cryosurgery, during a period from September 2010 to July 2014 were included in the analysis. 23 patients received cytoreductive cryosurgery plus ADT (the cryosurgery group); the remaining 26 patients received ADT alone (the control). The following set of criteria was used to identify these cases: 1. A diagnosis of PCa based on transperiaeum prostate needle biopsy under transrectal ultrasound (TRUS) guidance; 2. Metastasis to the bone, as confirmed by radionuclide bone scan; 3. Absence of visceral metastases; 4. Clinical stage $\leq$cT3a; 5. Prostate volume $\leq$50 ml; 6. PSA decrease to $\leq$1.0 ng/ml within 6 months of ADT; 7. Written informed consents. Cases with severe comorbid diseases and expected survival at $<$1 year were excluded.

Project of cryosurgery plus ADT

Neoadjuvant and adjuvant ADT

Upon a definitive diagnosis, bicalutamide (50 mg/d, p.o.) was initiated. Leuprolide (3.75 mg, s.c.; once every month) was added 2 weeks later. PSA and serum testosterone were measured at 4 weeks, 3 and 6 months. Radiographic assessment was made at 6 months to evaluate the treatment response. Patients with a PSA decrease to less than 1.0 ng/ml within 6 months, remission or stable disease of osseous metastases and without the development of new lymph node or visceral metastases were considered candidates for cryosurgery. The patients received cryosurgery at 6 months after ADT. Adjuvant ADT after cytoreductive cryosurgery was identical to the neoadjuvant treatment.

Cryosurgery

Cryosurgery was carried out by the same surgeon using a CRYO care system (Endocare, USA) in all cases. Thirty minutes after administration of pethidine (75—100 mg) and phenergan (25 mg), patients were placed in the dorsal lithotomy position and received local infiltration anesthesia with 10-ml 1% lidocaine. A warming catheter was inserted into the bladder to protect the urethra. A real-time biplanar TRUS probe was used to visualize the insertion of cryoprobes and temperature probes and monitor the freeze—thaw cycles. 17-G cryoprobes were inserted under TRUS guidance and spaced approximately 1.0 cm apart. The needles were placed according to prostate size and shape. Warm saline irrigation was started through the warming unit in a continuous-flow manner to avoid urethral freezing. Two freeze—thaw cycles were performed. After surgery, the urethral warming unit was kept in place for 5 min. Bladder irrigation continued for 24 h. The Foley catheter was removed 1—2 weeks later.

Project of ADT alone

The patients in the control received ADT alone. Upon a definitive diagnosis, bicalutamide (50 mg/d, p.o.) was initiated. Leuprolide (3.75 mg, s.c.; once every month) was added 2 weeks later.

Follow-up

Patients were followed up at 1-month interval in the first year, at 3-month interval during the next 2 years, and once every year thereafter. Follow-up examinations included serum PSA, testosterone, creatinine, alanine aminotransferase and alkaline phosphatase, as well as digital rectal examination. Prostate magnetic resonance imaging (MRI) and radionuclide bone scan were performed every 6 months.

Outcomes

Biochemical progression was defined as 3 consecutive PSA increases, 1 week apart, resulting in 50% increases over the nadir. Clinical progression was defined as the onset of new symptoms due to local progression, lymphonodular or systemic metastases. PFS was defined as the time from the initiation of ADT to the first evidence of biochemical or clinical progression. Time to CRPC was defined as the time from the initiation of ADT to confirmed biochemical progression in the presence of castrate serum testosterone levels ($\leqq$50 ng/dl). Nadir PSA after cryosurgery was defined as PSA decreased to nadir level firstly after cryosurgery. In subjects receiving cryosurgery, time to nadir PSA and time to PSA progression was calculated from the time of cryosurgery.