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Cytoreductive Radical Prostatectomy in Men with Prostate Cancer and Skeletal Metastases

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Abstract

Background: Androgen deprivation therapy (ADT) represents the standard treatment for hormone-naïve prostate cancer with systemic metastases (mPCA). The role of radical prostatectomy (RP) in this setting is unclear.

Objective: To evaluate the oncological and functional outcomes of men with mPCA who underwent cytoreductive RP (CRP).

Design, setting, and participants: Retrospective, multi-institutional study of 113 patients with biopsy-proven mPCA who fulfilled the following selection criteria: (1) completely resectable PCA; (2) osseous metastases; (3) absence of gross retroperitoneal lymph node metastases; (4) absence of bulky pelvic lymph node metastases >3 cm; (5) no or minimal visceral metastases; (6) Eastern Cooperative Oncology Group performance status of 0–1; and (7) written informed consent.

Intervention: CRP with extended pelvic lymphadenectomy. Eighty patients (70.8%) received neoadjuvant ADT and 91 (86.5%) adjuvant ADT and/or radiation therapy.

Outcome measurements and statistical analysis: Cancer-specific survival, overall survival (OS), biochemical relapse-free survival (BRFS), and clinical relapse-free survival (CRFS) were evaluated using descriptive statistical analyses, the Kaplan-Meier method, and univariate and multivariate analyses. Treatment-associated complications were analysed according to the Clavien-Dindo classification.

Results and limitations: The mean patient age was 61 yr (range 42–69). The mean follow-up was 53.6 mo (range 13–96, median 45.7). The 3-yr and 5-yr OS was 99 (87.6%) and 90 (79.6%), respectively, and the mean CRFS was 72.3 mo. Preoperative prostate-specific antigen (PSA) < 1.0 ng/ml and PSA below the median of 8.0 ng/ml were significantly associated with BRFS ($p < 0.0004$). Pathohistology revealed viable PCA in all cases: 16 (14.2%) had pT4a, 21 (18.6%) had pT2a–c, and 76 (67.3%) had pT3a/b PCA. Positive lymph nodes were identified in 61.6% and positive surgical margins in 36.8% of the patients. Eleven men (9.7%) experienced Clavien Dindo grade IIIa–b complications. Low-volume disease, neoadjuvant ADT, and preoperative PSA were significantly associated with a lower risk of surgery-related complications ($p < 0.05$). No, mild (1–2 pads/d), and severe incontinence (>2 pads/d) was observed in 68.1%, 17.7%, and 14.1%, respectively. Limitations of the study are the retrospective nature and potential patient selection bias.

Conclusions: CRP results in 5-yr OS of 80%, a low rate of significant complications, and good functional outcome in well-selected patients. CRP might be an individualised treatment option in the multimodal management of mPCA.

Patient summary: We assessed oncological and functional outcomes associated with cytoreductive radical prostatectomy (CRP) in select men with prostate cancer and osseous metastases. We found that CRP might be associated with long overall and relapse-free survival in well-selected patients. CRP could become an additional treatment option in the multimodal therapy of metastatic prostate cancer; it should be performed in a clinical protocol setting and does not represent a standard therapeutic option.

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1. Introduction

Chemohormonal therapy or androgen deprivation therapy (ADT) represents the guideline-recommended treatment of choice for men with hormone-naïve metastatic prostate cancer (mPCA) [1]. Treatment of the primary tumor in the clinical setting of metastatic disease is usually ignored in decision-making on the most appropriate therapy because of the common belief that the biology of the disease is attributed to the metastatic spread and that it cannot be positively influenced by local treatment. However, it was recently demonstrated that lethal PCA clones persist intraprostatically despite extensive pretreatment with ADT and docetaxel-based chemotherapy [2]. Furthermore, preclinical studies demonstrated that prostatectomy results in a significant reduction in newly developed metastases in animals when compared to ADT alone [3].

A few retrospective and case-control studies demonstrated the feasibility of cytoreductive radical prostatectomy (CRP) and a benefit in terms of time to development of castration-resistant PCA, overall survival, and the frequency of locally progressing PCA with lower and upper urinary tract obstruction [4–10].

Here we report on oncological and functional outcomes of the largest cohort of men with PCA and skeletal metastases who underwent CRP.

2. Patients and methods

A total of 113 patients with biopsy-proven PCA and metastatic disease were scheduled for CRP and extended pelvic lymphadenectomy (PLND). Patients were treated at four different tertiary referral centres and the surgery was performed by experienced surgeons ($n = 38$ in centre A, $n = 32$ in centre B, $n = 25$ in centre C, $n = 18$ in centre D).

Patients underwent a routine transrectal ultrasound-guided 12- to 18-core biopsy of the prostate to assess the number of positive biopsy cores, the localisation and Gleason score for positive biopsy cores, the length of biopsy core involvement, the percentage biopsy core involved with cancer, and the presence of vascular, lymphatic, or perineural invasion.

Patients underwent routine pretreatment imaging staging procedures, including abdominal/pelvic computed tomography, chest X-ray, and skeletal scintigraphy. Magnetic resonance imaging was only performed for unequivocal skeletal findings on bone scintigraphy or computed tomography.

Patients were eligible for CRP if they fulfilled the following selection criteria: (1) completely resectable PCA; (2) osseous metastases; (3) absence of gross retroperitoneal lymph node metastases; (4) absence of bulky pelvic lymph node metastases >3 cm; (5) no visceral metastases; (6) Eastern Cooperative Oncology Group performance status of 0–1; and (7) written informed consent. The extent of skeletal metastases was defined according to the CHAARTED study [13].

Neoadjuvant ADT was administered according to the discretion of the treating physician. If neoadjuvant ADT was delivered, patients underwent flare-up prophylaxis with bicalutamide 50 mg/d followed by ADT with luteinising hormone–releasing hormone (LHRH) analogues. Bicalutamide was discontinued 1–3 d later. Prostate-specific antigen (PSA) and serum testosterone concentrations were measured at 4 wk and 3 mo and then quarterly. Patients with decreasing PSA, remission of or stable osseous metastases, and no development of new lymph node or visceral metastases were considered candidates for CRP.

Open retropubic CRP or robot-assisted CRP with extended PLND was performed as previously described [11,12]. In general, patients were recommended to continue with ADT for another 2 yr before treatment was discontinued if serum PSA concentrations were < 1.0 ng/ml and if there was no PSA progression. Some patients with M1a disease received a minimum of 6 mo of ADT and patients with M1b disease received a minimum of 6 mo of ADT and metastasis-directed therapy in the form of external beam radiation therapy or cryoablation.

Prostatectomy specimens were stained and routinely processed as previously described [4,11,12].

2.1. Follow-up

Patients were followed at 3-mo intervals for the first 2 yr, at 6-mo intervals during postoperative years 3 and 4, and yearly thereafter. Follow-up examinations included measurement of serum concentrations of PSA, testosterone, glucose, cholesterol, triglycerides, lactate dehydrogenase, alkaline phosphatase, and C-reactive protein, as well as digital rectal examination (DRE). Continence status was evaluated using the classic pad test and the International Continence Society short-form questionnaire at 3 and 12 mo. No routine imaging studies were performed in patients with serum PSA < 5 ng/ml.

2.2. Definition of progression

Biochemical progression was defined as a PSA increase to 0.2 ng/ml validated by two consecutive increases at 2-wk intervals if PSA decreased to undetectable serum levels postoperatively. If PSA was still detectable postoperatively, biochemical progression was defined as two consecutive increases above the first postoperative PSA, 1 wk apart, resulting in two 50% increases over the nadir. No routine imaging studies were performed unless serum PSA increased to >5 ng/ml or if it was associated with clinical symptoms.

Clinical progression was defined as the onset of new symptoms due to local progression or lymphonodular or systemic metastases. The time to castration-resistant PCA was measured as the time from ADT initiation until documentation of confirmed biochemical progression in the presence of castrate serum testosterone levels, defined as ≤50 ng/dl.

Progression-free survival (PFS) was defined as the time from ADT initiation to the first evidence of biochemical or clinical progression. Cancer-specific survival (CSS) was defined as the time from diagnosis to death from prostate cancer. Overall survival (OS) was defined as the time from initial PCA diagnosis to death from any noncancer-related cause.

2.3. Statistical analysis

Patient characteristics were summarised using descriptive statistics and exploratory data analysis. Continuous variables were summarised using descriptive statistical measures (mean and standard deviation) and categorical data were described using contingency tables. Fisher's exact test was used to assess the association between categorical variables, and a two-sample t test was used to assess mean between-group differences for continuous variables. Survival curves were estimated using the Kaplan-Meier method. All p-value determinations were two-sided at a significance level of 0.05. Bonferroni correction was applied to adjust for multiple comparisons. Analyses were performed using SAS for Windows (1999–2000, version 8.1) and S-PLUS 2000 software.

3. Results

A total of 113 patients with mPCA underwent CRP. The patient characteristics are summarised in Table 1.