Permanent Prostate Brachytherapy for Localized High-risk Prostate Cancer Patients with Coronary Heart Disease: A 13-year Single-center Experience

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Abstract

Objective: To investigate whether permanent prostate brachytherapy (PPB) improves survival outcomes in localized high-risk prostate cancer (PCa) patients with coronary heart disease (CHD) via ameliorating prostate-specific antigen (PSA) kinetics.

Material and methods: We retrospectively reviewed the entire patient database regarding the survival and PSA kinetics of 216 consecutive localized PCa patients with clinical CHD who were treated from January 2001 to July 2012 at the Urology Department of the Beijing Anzhen Hospital. Kaplan-Meier analysis was used to calculate cause-specific survival (CSS) and overall survival (OS), and survival predictor was determined by log-rank and Cox-regression analyses. Differences in PSA kinetics and survival rate were compared between maximal androgen blockade (MAB)-treated cases and MAB + PPB-treated cases.

Results. The median follow-up time was 44 (range: 7-165) months. Brachytherapy, PSA nadir, and declining PSA were closely associated with survival. Compared with MAB monotherapy, combination therapy of MAB + PPB significantly ameliorated PSA kinetics. Additionally, MAB + PPB significantly improved the 13-year survival rate compared with MAB monotherapy (CSS: 56% vs. 13%; OS: 33% vs. 4%).

Conclusions: Combining PPB and MAB significantly increased the survival rates of localized high-risk PCa patients with CHD. PSA nadir ≤ 1 ng/mL and a >90% PSA decrease were independent prognostic factors for both CSS and OS.

Keywords: Prostate cancer, Brachytherapy, PSA kinetics, Maximal androgen blockade, Coronary heart disease

Introduction

Prostate cancer (PCA) is a common malignancy associated with high morbidity and mortality. Radical prostatectomy (RP), radical external beam radiation therapy (EBRT), and maximal androgen blockade (MAB) are always preferred approaches for localized high-risk PCa patients [1]. However, in patients suffering from severe coronary heart disease (CHD) who are not good candidates for RP or EBRT, MAB is a safer option, without possibilities of serious anesthesia complications. Although numerous studies demonstrated the utility of MAB, the survival outcome with MAB monotherapy is not entirely satisfactory. In recent years, it has become an important issue regarding how to establish recommended treatment schemes and improve survival outcomes in localized high-risk PCa patients with CHD.

Modern brachytherapy was first applied for PCa in the 1980s when transrectal ultrasound became available to plan and guide radioactive seed placement within the prostate. Because of excellent 15-year PSA outcomes [2], PPB has been routinely used either as monotherapy for patients with low-risk and low/intermediate-risk disease or in combination with EBRT for patients with higher risk disease [3]. A recent comprehensive literature reviewed screened 18,000 papers and included over 50,000 patients comparatively analyzed the PSA-free survival outcomes of localized PCa patients treated with different radical therapies [4], and the results suggested that PSA outcomes with brachytherapy are significantly superior to EBRT in low-risk patients and that brachytherapy monotherapy achieved equivalent PSA outcomes to a combination of EBRT and brachytherapy in patients with intermediate-risk disease. For high-risk patients, combination therapies involving EBRT and brachytherapy W/O androgen
deprivation therapy (ADT) appear superior to more localized monotherapies, including seed implantation, RP, or EBRT.

In view of the fact that most PCa patients, including those with high-risk disease, do not have metastatic disease at the time of treatment, local tumor eradication could produce excellent long-term PSA relapse-free outcomes [4-6]. Numerous researchers demonstrated that brachytherapy can achieve superior long-term PSA outcomes and is well tolerated by PCa patients over a long follow-up interval [7-10]. Unlike EBRT, high radiation doses delivered with brachytherapy produces much lower, usually undetectable PSA levels over long-term follow-up, suggesting an ablative effect of high radiation dose on prostate tissue [11,12].

Given the increasing incidence of cardiovascular disease, the number of PCa patients with comorbid severe CHD is also growing. Therefore, how to choose an appropriate treatment strategy for localized high-risk PCa patients with CHD and improve their survival prognosis became important challenges for urologists. In this study, we attempted to evaluate the clinical benefit of supplemental PPB by comparing the long-term survival outcomes and PSA kinetics in patients treated with MAB monotherapy, with a similar group of men who underwent combined MAB + PPB.

Material and methods

Ethics statement

The study has been approved by the Committee on the Ethics of Clinical Experiments of the Capital Medical University, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all individuals. Details that might disclose the identity of the subjects under study have been omitted.

Subjects

Total 376 consecutive localized PCa patients with clinical CHD were treated at the Urology Department of Beijing Anzhen Hospital from January 1st 2001 to July 31st 2012. They were all previously diagnosed with CHD according to American Heart Association guidelines, with stenoses ≥70% in at least 1 major coronary artery, which was identified by coronary angiography and underwent successful PCI. Coronary artery stenting and postoperative treatment was performed according to the treatment guidelines for PCI. All the patients received one standardized drug treatment for at least 1 year which included aspirin (100 mg) and clopidogrel (75 mg), and statin lipid-lowering drugs were taken in the long-term. The CHD duration after PCI was 1.6 - 15 y (median: 5.8 y) for all these patients. For patients treated with brachytherapy additional to MAB, one month after seed implantation, pelvic CT scan were performed to detect the seed distribution within the prostate. If there is any unpredictable seed margin, a second implantation would be arranged. Follow-up for all the patients ended on December 31st, 2014. All patients were clinically diagnosed by concentration determination of serum PSA, transrectal prostate ultrasonography, pathological examination of puncture biopsy specimens or surgically removed specimens, radioisotope scan of bone, and computed tomography of the abdomen and pelvis.

Patient follow-up and data collection

Patients were monitored by serum PSA determinations every 3 months for the first year, every 6 months for the second year, and yearly thereafter. During follow-up intervals, we measured PSA kinetics, including PSA nadir, the time required for PSA to reach nadir, and the decrease in PSA. Additionally, PSA doubling time (PSADT) was calculated by natural log 2 divided by the slope of the relationship between the log of PSA and the time of PSA measurement for each patient [13]. The endpoints of the analysis were CSS and OS. The cause of death was determined for each deceased patient. Patients with metastatic PCa or castration-resistant disease without obvious metastases who died of any cause were classified as PCa-related death. All other deaths were attributed to the immediate cause of death.

Statistical analysis

Kaplan-Meier analysis was first performed to calculate the CSS and OS of the total cohort and by separate groups. Then treatment and PSA parameters were evaluated for their impact on CSS and OS by univariate log-rank analysis and multivariate Cox regression analysis. Furthermore, we compared PSA kinetics and survival rates between patients treated with MAB monotherapy and those who underwent MAB + PPB combination therapy. All PSA kinetics results are presented as mean±SD. PSA variables were compared using independent-sample t-tests. Categorical variables were compared with chi-square analyses. For all statistical tests, P<0.05 were considered statistically significant.

Results

Patients' characteristics

Among 376 patients, 216 presented with high-risk disease (PSA≥20 ng/ml or Gleason Score ≥8 or clinical stage ≥T2c). A total of 89(41.2%) men received MAB monotherapy (group A), and 127 (58.8%) men underwent combination therapy with MAB and PPB (group B). For combined therapeutic approaches, the minimum peripheral dose was 145 Gy for 1-125 exposure. And the median lengths of follow-up of the total cohort were 44 months (range: 7-165 months). Furthermore, Table 1 summarizes the detailed clinical characteristics of patients included in the analysis. The ages of patients in group A ranged from 54 to 83 years old (mean: 75.7 years old), while those in group B ranged from 51 to 83 years old (mean: 70.3 years old). The median lengths of follow-up were 38 months (range: 9-163 months) and 47 months (range: 7-165 months) in groups A and B, respectively.

Factors influencing survival prognosis

Table 2 shows the univariate and multivariate analyses for predictors of CSS and OS. The number of coronary stents, brachytherapy, PSA nadir, the time for PSA to decrease to nadir, and the decline in PSA were independent prognostic factors of CSS(P<0.05). Although the traditional prognostic factor of prostate volume was significant on univariate analysis, it was not significant on multivariate analysis (P=0.691). Age, MAB pattern, and PSADT were not significantly associated with CSS (P>0.05). Additionally, univariate analysis indicated that age, the number of coronary stents, brachytherapy, PSA nadir, PSADT, and the decline in PSA were all predictors for OS in localized high-risk PCa patients (P<0.05). Multivariate Cox regression analysis further identified brachytherapy, PSA nadir and decline in PSA as independent prognostic indicators for OS (P<0.05).
Effect of additional PPB on the PSA kinetics of MAB-treated high-risk patients

Several recent studies reported that PSA kinetics are closely related to long-term survival outcomes of PCa patients [14-16]. In this study, we summarized that characteristics of PSA kinetics were influenced by PPB in localized high-risk PCa patients with CHD. The mean PSA nadir of patients treated with MAB monotherapy (group A) was 2.85 ± 1.37 ng/mL (range: 0.03-16.00 ng/mL), whereas the mean PSA nadir of patients treated with MAB+PPB combination therapy (group B) was 0.11 ± 0.05 ng/mL (range: 0.00-1.78 ng/mL). The mean time of PSA decrease to nadir in groups A and B were 7.12 ± 1.48 months (range: 3-15 months) and 3.66 ± 1.29 months (range: 1-9 months), respectively. Additionally, mean PSADTs were 10.48 ± 3.17 months [range: 0.87-21.56 months] in group A and 16.72 ± 5.43 months [range: 3.46-39.52 months] in group B. Finally, mean decreases in PSA were 82.29 ± 1.21% (range: 73.61-88.25%) in group A and 97.86 ± 0.65% (range: 91.31-99.89%) in group B. Our results demonstrated that PPB significantly improved PSA kinetics as shown in Figure 1. Specifically, PSA nadir and the decrease in PSA, both of which are important independent indicators for CSS and OS, were notably ameliorated by additional PPB.

Effect of additional PPB on the survival curves of MAB-treated high-risk patients

As shown in Figure 2A, the OS of all patients rapidly decreased...
from 92% to 34% during the 6 years after treatment, then slowly declined to 21% during the last 7 years. Overall, the downward trend in group A was much swifter than that in group B. During the first 6 years of the follow-up period, the OS in group A fell from 92% to 12%, whereas the OS in group B decreased more gradually from 94% to 52%. At the end of follow-up, the OS in group A finally decreased to 4%, whereas the OS in group B still maintained around 33% (P < 0.01). Median survival was 12% in group A and 43% in group B (P < 0.01), respectively. Figure 2B shows that the CSS of all patients progressively decreased from 98% to 43%, and the CSS curve of group A dropped sharply from 98% to 13%, while that of group B declined from 98% to 56%. And the 13-year cumulative CSS is significantly different between these two groups (13% vs 56%, P < 0.01). Median survival was 38% in group A and 74% in group B (P < 0.01), respectively.

Based on these data, we concluded that the addition of PPB could significantly improve the OS and CSS of patients treated with MAB.

**Discussion**

As it is known that MAB is a safe option for PCa patients with comorbidities that make them poor candidates for RP or EBRT [1]. But for patients suffering from severe coronary heart disease (CHD), the survival outcome with MAB monotherapy is not extensively investigated. In the other hand, permanent prostate brachytherapy (PPB) has recently emerged as a definitive treatment option in men with clinically localized prostate cancer. While some groups believe that all patients should receive adjuvant EBRT, it appears that those at low and intermediate
risk may be treated successfully with an implant as monotherapy [7]. Therefore, in this single-center study, we investigate and present a 13-year follow-up outcomes from a complete data set of consecutively treated patients who have undergone MAB monotherapy, as compared with combined MAB + PPB, in order to evaluate whether the addition of PPB to an MAB regimen improved survival in PCa patients with CHD.

MAB is widely used as a monotherapy or as an adjuvant to EBRT, RP, or brachytherapy. In advanced PCa, MAB was found to significantly improve 5-year survival by about 2.9% compared to androgen deprivation therapy (ADT) alone, and there was no significant heterogeneity in treatment effect (MAB vs. ADT) with respect to age or disease stage [17].

Interstitial radiation therapy has always been used to treat clinically localized PCa, and most researchers believe that the 5-year PSA outcome of brachytherapy in low-risk patients is not statistically different with those who undergo RP or EBRT. In addition, intermediate- and high-risk patients treated with RP or EBRT may respond better than those treated by brachytherapy [18]. However, this view remains controversial. Polascik et al. reported that 7-year actuarial PSA progression-free survival following RP was remarkably higher than that of patients who underwent 1-125 brachytherapy (97.8% vs 79%) [19,20] in patients with localized PCa. Therefore, Polascik et al. pointed out that brachytherapy should be cautiously recommended to patients with localized PCa. Sharkey and colleagues analyzed data from 1,707 PCa patients with T1 or T2 staging who were treated by either brachytherapy or RP. They concluded that the time to PSA-indicated recurrence was better controlled by brachytherapy than RP in intermediate (9% vs. 58%, P < 0.05) and high-risk (80% vs. 43%, P < 0.05) groups, but not in low-risk groups (99% vs. 94%, P = 0.174) [21]. Moreover, Taira et al. reported data from 329 cases of high-risk PCa treated with brachytherapy + EBRT with a 10-year follow-up, which indicated that CSS in patients of Gleason 5 is significantly lower than that in non-Gleason 5 patients (90.3% vs. 98.1%, P = 0.011). However, there is no remarkable difference in biochemical relapse-free survival and OS between these two groups of patients [22].

In addition, Demanes et al. also reviewed data from 209 cases treated with brachytherapy + EBRT with a 10-year follow-up and observed that the OS and CSS rates were 79% and 97%, respectively. The PSA progression-free survival rates were 90%, 87%, and 69% for the low-, intermediate-, and high-risk groups, respectively [23]. Another study reported that compared to brachytherapy monotherapy, the combination strategy of brachytherapy + EBRT conferred a significant advantage in the 5-year biochemical relapse-free survival rate (80% vs 59%, P < 0.01) despite the greater proportion of adverse disease factors in the EBRT group [24]. Collectively, the existing clinical research supports brachytherapy + EBRT as a proven treatment for all stages of localized PCa [25].

When additional hormonal therapy to brachytherapy, the 5-year actuarial freedom from biochemical relapse rate of PCa patients (stage T1b-T3b) improved from 54% to 79%. In intermediate-risk patients, the 4-year actuarial freedom from biochemical relapse rate was 94%. The addition of hormonal therapy could noticeably improve outcome in intermediate- to high-risk PCa patients treated with brachytherapy [26]. However, after retrospectively analyzing data from 1,668 cases, Ciezki et al. concluded that addition of ADT did not improve the 5-year biochemical relapse-free survival in low- and intermediate-risk patients treated by brachytherapy [27].

In the past, it was controversial whether PPB + hormonal therapy was an effective and safe option for PCa patients with CHD. Nanda and colleagues conducted series of studies about the relationship between the additions of neoadjuvant hormonal therapy to brachytherapy in PCa patients with comorbidities. They concluded that there was a significantly increased risk of all-cause mortality in men with congestive heart failure, myocardial infarction, diabetes mellitus, or hypertension compared with men without comorbidities. In contrast, men with hypercholesterolemia had a similar risk of all-cause mortality when compared with men with no comorbidity [28]. Similarly, neoadjuvant hormonal therapy was not associated with an increased risk of all-cause mortality in radiation therapy-treated men with a single CHD risk factor after a median follow-up of 4.4 years. However, for radiation therapy-treated men with CHD-induced congestive heart failure or myocardial infarction, neoadjuvant hormonal therapy was significantly associated with increased risk of all-cause mortality after 5.1 years of follow-up [29]. Subsequently, they accurately summarized that for men with no risk factors or at least a single risk factor for CHD, neoadjuvant hormonal therapy is associated with an increased risk of all-cause mortality in the setting of low-risk but not intermediate- or high-risk PCa. Given the widespread use of neoadjuvant hormonal therapy for prostate downsizing prior to brachytherapy, these findings warrant additional validation [30].

As to the limitation, patients in this study were treated at a single center; so the results may not be generalized to more diverse populations. In addition, patients were not stratified by CHD severity. A large, randomized, multi-center study that assesses PCa patients with different levels of CHD severity would provide additional evidence regarding the outcomes for this group of patients.

In conclusion, combination MAB + PPB treatment is a preferred option for high-risk PCa patients with CHD, because it achieves excellent survival outcomes and favorable PSA kinetics. Our results indicate that PSA nadir ≤ 1 ng/mL and a PSA decrease >90% are two independent prognostic factors for both CSS and OS.

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Interest Statement

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


