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Original Article

The prognostic factors and clinical outcomes of prostate cancer patients who underwent long-term, continuous, and complete androgen blockade therapy

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Abstract: The prognostic factors for prostate cancer patients undergoing androgen deprivation therapy have been illustrated previously. However, there are few studies on the prognoses and prognostic predictors for patients undergoing a complete androgen blockade. Therefore, we conducted a retrospective study of patients with long-term, continuous, and complete androgen blockades to identify the prognostic factors for cancer-specific survival and cancer progression-free survival. The medical records of the patients who underwent long-term complete androgen blockades between 2005 and 2019 in our institution were reviewed retrospectively. The patients' ages, baseline PSAs before therapy, Gleason scores, clinical T stages, and bone and lymph node metastasis statuses before therapy were gathered. The Kaplan-Meier method was used to estimate the cancer progression-free survival times and the cancer-specific survival times, and log-rank tests were used to perform the comparisons between the groups. A Cox proportional hazards regression model was used to identify the independent prognostic factors for cancer specific survival and cancer progression-free survival. 168 patients were included according to preset criteria. The median follow-up time was 61 months. The median cancer specific survival time was 76 months. A baseline PSA > 30 ng/ml, bone metastasis, and a Gleason score ≥ 8 were independent prognostic predictors for cancer-specific survival. The median cancer progression-free survival time was 60 months. A multivariate analysis found that a PSA > 30 ng/ml, bone metastasis, and a Gleason score ≥ 8 were independent prognostic factors for the cancer progression-free survival times. Our analysis confirmed that bone metastasis, an increased baseline PSA > 30 ng/ml, and a Gleason score ≥ 8 were unfavorable independent prognostic factors for cancer progression-free survival and cancer specific survival.

Keywords: Prostate cancer, androgen deprivation therapy, combined androgen blockade, hormonal therapy, prognostic factors, castration-resistant prostate cancer

Introduction

Globally, prostate cancer is the second most common cancer among all male malignances [1]. Different therapeutical plans should be administrated according to each patient's clinical stage [2]. Hormonal therapy has been recommended as the standard treatment for metastatic prostate cancer. In addition, some patients with local disease may choose this therapy, because either their conditions make radical therapy or radiotherapy unsuitable or because of other undefined reasons. Hormonal therapy includes androgen deprivation therapy (castration) and anti-androgen therapy, and their combination, which is called complete androgen blockade (CAB). Hormonal therapy is effective at the early stage of its administration. Unfortunately, the development of castration-resistant prostate cancer (CRPC) is unavoidable once the therapy begins; consequently, other alternative therapies then become necessary. Currently, some researchers [3, 4] recommend abiraterone acetate or docetaxel in combination with androgen deprivation therapy to treat hormone-sensitive prostate cancer, with the aim of achieving better prognoses. These recommendations may bring more benefit in terms of longer survival, but on the other hand, the patients may suffer from more side-effects. Therefore, it is necessary to identify patients who could benefit from hormonal ther-

apy along with the goal of avoiding over-treatment and under-treatment. We retrospectively investigated the clinical outcomes and prognostic factors of prostate cancer patients receiving complete androgen blockade therapy in our institution, with the expectation of identifying the independent predictive variables for cancer-specific survival and progression-free survival, and providing support in selecting therapy plans.

Materials and methods

Study population

Patients diagnosed with prostate cancer between 1st January 2005 and 31st December 2019 in our institution were included according to the following criteria. Inclusion criteria: Patients who initially received hormonal therapy after their diagnoses were confirmed by biopsy, patients whose hormonal therapy was complete androgen blockade, and patients whose serum testosterone reached the castration level. Exclusion criteria: Patients whose therapy plans were changed before the CRPC developed, such as a combination of chemotherapy or radiotherapy, patients who died from any causes other than a cancer-specific reason, and patients who were lost to follow-up or whose records lacked complete survival data. The ethics committee of First Hospital of Tsinghua University approved this study and waived the informed consent requirement.

Study methods

The patients' ages, their last prostate-specific antigen (PSA) levels within two weeks before biopsy, their Gleason scores, clinical T stages, and their lymph node metastasis and bone metastasis statuses were gathered. The cancer progression-free survival time (CPFS) was defined as the survival time until the development of CRPC. The cancer-specific survival (CSS) time was defined as the survival time until the patient died from prostate cancer. The complete androgen blockade treatment was comprised of luteinizing-hormone-releasing hormone agonists (goserelin acetate or leuprorelin acetate) and bicalutamide. CRPC was confirmed in accordance with the following criteria: serum testosterone reached the castration level of < 50 ng/dl, PSA rose three times consecutively one week apart or more and increased 50% over the nadir two times consecutively, and a PSA level > 2 ng/ml.

Statistical analysis

Continuous variables with a normal distribution were reported as the mean and standard deviation (mean ± SD), or else as the median and quartiles (25th-75th percentiles). The categorical variables were reported as the frequency and percentage. The comparisons between groups were evaluated using chi-square tests for the category data and Wilcoxon rank tests for the continuous data. The cancer progression-free survival times and the cancer-specific survival times were estimated using the Kaplan-Meier method, and they were compared using log-rank tests between the groups. A Cox proportional hazards regression model was used to identify the independent prognostic factors for CPFS and CSS and to calculate the hazard ratio (HR) and 95% confidence intervals (CI). A P value < 0.05 was set as statistically significant. IBM SPSS version 26.0 statistical software was used to perform the statistical analysis.

Results

Patient characteristics

Until 31st December 2019, 182 patients had undergone continuous CAB in our hospital. 14 patients had visceral metastasis, but only two of them met the inclusion criteria, so we excluded visceral metastasis from our analysis of the prognosis. According to the inclusion and exclusion criteria mentioned above, 168 patients were included. The demographic characteristics of all the patients are listed in **Table 1**. The median follow-up time (25th-75th percentile) was 61 (27.0-83.5) months. At the end of the follow-up, 106 (63.1%) patients died and 62 (36.9%) patients survived. The mean age was 75.9±7.9 years, the median baseline PSA was 34.84 (14.43-165) ng/ml/. 51 (30.4%), and 48 (28.6%) patients had bone and lymph node metastases respectively. 90 (53.6%) patients had a Gleason score ≥ 8, and 66 (39.3%) patients had a clinical T stage > T2.

Cancer specific survival

The median survival time was 76 months. The baseline PSAs, the ages, bone metastasis, ly-

Table 1. Demographic characteristics of the patients

Variables	N (%)
Baseline PSA (ng/ml) (median, 25th-75th percentile)	34.84 (14.43, 165.00)
Follow-up times (months) (median, 25th-75th percentile)	61 (27.0, 83.5)
Age (years) (mean ± SD)	75.9±7.9
Bone metastasis	
No	117 (69.6)
Yes	51 (30.4)
Lymph node metastasis	
No	120 (71.4)
Yes	48 (28.6)
Gleason score	
≤ 6	28 (16.7)
7	50 (29.8)
8	44 (26.2)
≥ 9	46 (27.4)
Clinical T stage	
T1	37 (22.0)
T2	65 (38.7)
T3	44 (26.2)
T4	22 (13.1)

mph node metastasis, Gleason scores, and clinical T stages were included in the univariate analysis, and the results are shown in **Table 2**. Except for age (P=0.468), the baseline PSAs, Gleason scores, bone metastasis, lymph node metastasis, and clinical T stages were prognostic factors for the cancer-specific survival times. All the significant variables were included in the multivariate analysis (**Table 2**). A baseline PSA > 30 ng/ml, bone metastasis, and a Gleason score ≥ 8 were independent prognostic predictors for CSS. The comparisons between groups for the PSA levels, the Gleason scores, and the bone metastases are shown in **Figures 1A** and **2**.

Cancer progression-free survival

Based on the development of CRPC, all the patients were stratified into a cancer progression-free (CPF) group and a cancer progression (CP) group. 82 (48.8%) patients were in the CPF group, and 86 (51.2%) in were in the CP group. The median CPFS time was 60 months. The patients in the CP group had higher proportions of bone (76.5%) and lymph node (64.6%) metastases, Gleason scores ≥ 8 (66.7%), and clinical T stages > T2 (69.7%) than the patients in CPF group (P < 0.05). The results of the Cox regression analysis of these variables are listed in **Table 3**. Our univariate analysis found that a baseline PSA > 30 ng/ml, bone and lymph node metastasis, a Gleason score ≥ 8, and a clinical T stage > T2 were associated with CPFS (P < 0.001). A multivariate analysis confirmed that a PSA > 30 ng/ml, bone metastasis, and a Gleason score ≥ 8 were independent prognostic factors for CPFS. A Kaplan-Meier description and the log-rank tests of CPFS for PSA, the Gleason scores, and the bone metastasis between groups are presented in **Figures 1B** and **3**. Patients with increased baseline PSA levels, bone metastasis, and Gleason scores ≥ 8 were more likely to develop CRPC and had shorter cancer progression-free survival times.

Discussion

CRPC is an unavoidable consequence of hormonal therapy. The most important mechanism for the development of CRPC is the continuous activation of the androgen receptors in the prostate cancer cells [5]. Other mechanisms, including the amplification of the androgen receptors, receptor hyper-sensitivity, the mutation of the coactivators, and the presence of androgen receptor variants, also contribute to the development of CRPC [6]. Hörnberg [7] found higher expressions of the androgen receptor variants in bone samples collected from prostate cancer patients with bone metastasis than from patients without bone metastasis. He concluded that this kind of variant was associated with the development of CRPC and resulted in poor prognoses. With the progression of CRPC, the survival time will shorten gradually. Therefore, it is necessary to identify independent prognostic factors for cancer specific survival and the development of CRPC for the sake of making appropriate therapeutic plans.

Table 2. Results of the Cox regression analysis of prognostic factors for cancer specific survival

Variables		Univariate				Multivariate			
		P value	HR	95% CI		*P* value	HR	95% CI	
				Lower	Upper			Lower	Upper
PSA (ng/ml)	≤ 30 vs. > 30	.000	2.300	1.551	3.411	.006	1.801	1.185	2.736
Age (y)		.468	1.010	.983	1.037				
Bone metastasis	Yes vs. no	.000	2.375	1.588	3.553	.034	1.619	1.037	2.528
Lymph nodes metastasis	Yes vs. no	.000	2.347	1.569	3.511	.520	1.190	.700	2.025
Gleason score	≤ 7 vs. ≥ 8	.000	2.316	1.570	3.418	.020	1.673	1.084	2.583
T stage	≤ T2 vs. > T2	.000	2.205	1.504	3.232	.199	1.344	.856	2.108

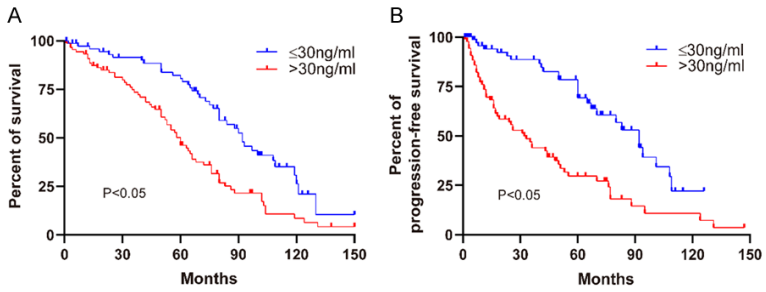

Figure 1. Kaplan-Meier description and log-rank comparisons of cancer specific survival (A) and cancer progression-free survival (B) between the groups for PSA.

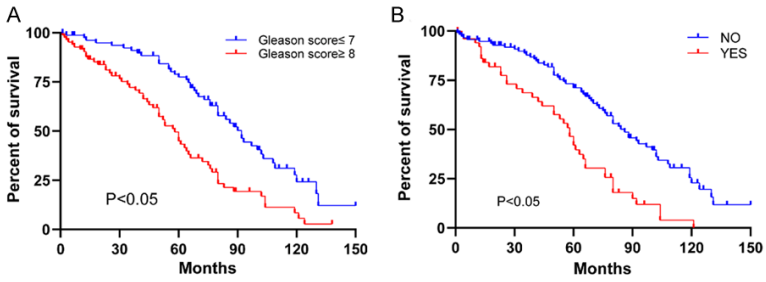

Figure 2. Kaplan-Meier description and log-rank comparison of the cancer specific survival between the groups for Gleason scores (A) and bone metastasis statuses (B).

We retrospectively evaluated the clinical outcomes and prognostic factors in patients undergoing long-term CAB. Androgen deprivation therapy is the most-discussed hormonal therapy plan in recently published studies [8-11], with drug castration as the most common choice. Combined ADT and anti-androgen therapy is rarely researched [12]. In order to investigate the prognostic factors of survival in patients with CAB, our work confined the therapy plan to CAB. Published studies presume that different hormonal therapy plans have different influences on prognosis [13-15]. Consequently, we excluded patients receiving intermittent CAB at inclusion to avoid the influence of this confounding factor on the results of our analysis. Also, in order to accurately estimate the overall survival, only patients who died of prostate cancer were included. The median follow-up time was 61 months, and the longest follow-up time was 150 months, and longer follow-up times were beneficial to deriving a more accurate conclusion.

Our multivariate analysis showed that a baseline PSA > 30 ng/ml, a Gleason score ≥ 8, and bone metastasis were independent prognostic factors for both cancer-specific survival and cancer progression-free survival. Shintaro Narita [16] conducted a retrospective multicenter research study to identify the independent hazard factors of overall survival. He found that a Gleason score ≥ 9 and a baseline PSA ≥ 301 ng/ml are associated with shortened survival time. Shusuke Akamatsu [17] implemented a retrospective study on hormone-sensitive metastatic prostate cancer patients and reported that a baseline PSA > 100 ng/ml and a primary Gleason score of 5 are prognostic factors for overall survival. Because of the different settings of the cut-off values for baseline PSA, Different studies [13, 18, 19] presented varied baseline PSA levels as the prognostic factor. It is difficult to define a reasonable cut-

Table 3. Results of the Cox regression analysis of prognostic factors for progression-free survival

Variables		Univariate				Multivariate			
		P value	HR	95% CI		*P* value	HR	95% CI	
				Lower	Upper			Lower	Upper
PSA (ng/ml)	≤ 30 vs. > 30	.000	3.114	1.978	4.902	.003	2.094	1.292	3.393
Age (y)		.737	.995	.965	1.026				
Bone metastasis	Yes vs. no	.000	4.321	2.747	6.798	.000	2.858	1.753	4.659
Lymph nodes metastasis	Yes vs. no	.000	3.053	1.943	4.797	.896	1.037	.599	1.798
Gleason score	≤ 7 vs. ≥ 8	.000	4.114	2.565	6.597	.000	2.592	1.569	4.282
T stage	≤ T2 vs. > T2	.000	3.012	1.958	4.632	.057	1.572	.987	2.503

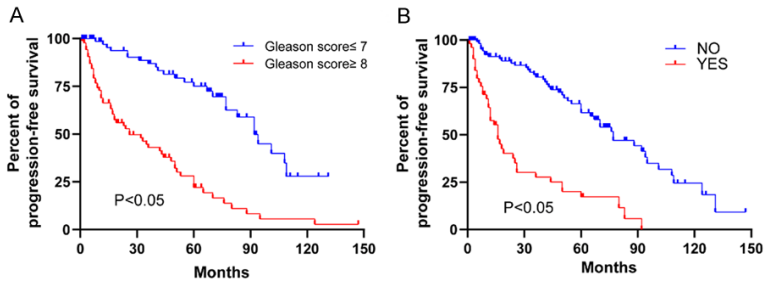

Figure 3. Kaplan-Meier description and log-rank comparison of cancer progression-free survival between the groups for Gleason score (A) and bone metastasis (B).

off value of the baseline PSA to predict the prognosis. However, it is appropriate to conclude that the prognosis worsens along with an increased baseline PSA. David D Yang [10] investigated the influence of androgen deprivation therapy on overall survival in patients with Gleason scores of 8 and 9-10 respectively. His results indicated that higher Gleason scores are related to a worse prognosis. Together with our retrospective results, it can be considered that the baseline PSA levels and the Gleason scores are independent prognostic factors for prostate cancer patient survival.

The relevance between the time to CRPC and the overall survival time was found in a retrospective study by Frees [20]. However, no relevance was found between the groups in their survival times after CRPC. Therefore, the authors suggested that the time to CRPC should be prolonged as far as possible. Hideaki Miyake [21] also reached the same conclusion. Hence, prolonging cancer progression-free survival time is beneficial to overall survival. The independent prognostic factors for CPFS are helpful in the identification of high-risk patients.

As with the results for cancer-specific survival derived using a multivariate analysis, the baseline PSA levels, the Gleason scores, and bone metastasis were also independent prognostic factors for CPFS in our study. Kyo Chul Koo [22] compared the influence of different metastasis sites on overall survival and non-CRPC survival, and he concluded that bone metastasis before therapy is related to short overall survival times and non-CRPC survival times. The predictive significance of bone metastasis for the development of CRPC was equally demonstrated in other studies [22, 23]. Consequently, patients with bone metastasis before primary therapy develop CRPC more quickly than those who don't have bone metastasis. With regard to those patients, other kinds of therapy, such as radiotherapy, or a combination with abiraterone acetate or docetaxel should be considered in order to reach a better prognosis.

This study was retrospective, so no intervention could be administrated to the therapy after CRPC, thus the interference of the different subsequent therapy plans on overall survival couldn't be avoided. The number of patients was relatively small, so a larger patient sample should be recruited in future research.

In conclusion, the baseline PSA levels, the Gleason scores, and bone metastasis are prognostic factors for cancer progression-free survival and cancer-specific survival. Patients with bone metastasis before therapy, increased baseline PSA levels > 30 ng/ml, and Gleason scores ≥ 8 are associated with a poor prognosis. With a cautious selection, long-term, complete androgen blockade can be administrated to the patients without the above-mentioned

factors. Conversely, patients with those hazard factors should consider the incorporation of other kinds of therapy plans other than monohormonal therapy.

Disclosure of conflict of interest

None.

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