ORIGINAL

Long-term outcomes of the Japanese hemodialysis patients with prostate cancer detected by prostate-specific antigen screening

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Abstract : We investigated the long-term outcomes of the Japanese hemodialysis patients with prostate cancer detected by prostate-specific antigen (PSA) screening. Clinical data of 646 male hemodialysis patients aged 55 years or older who started yearly PSA testing in the period from January 1, 2004 to December 31, 2012 and were followed until December 31, 2017 were analyzed retrospectively. The median follow-up period was 10.4 years. Nineteen (2.9%) patients were diagnosed with prostate cancer, of whom one patient died of the disease. Androgen-deprivation therapy (ADT) was selected for primary prostate cancer treatment in 17 (89.5%) of these 19 patients. Of six prostate cancer patients who underwent primary ADT (PADT) and died of other causes, three died of infectious disease, each one died of cardiovascular disease, liver cancer, and chronic renal failure. No significant difference was observed in regard to overall survival between the prostate cancer patients with PADT and non-prostate cancer patients. Prognosis of hemodialysis patients who were diagnosed with prostate cancer during yearly PSA screening examination and mainly treated with ADT was favorable without increasing cardiovascular events. This result indicates that PSA screening may be useful for detection and management of prostate cancer even in hemodialysis patients. J. Med. Invest. 68 : 42-47, February, 2021

Keywords : hemodialysis, prostate cancer, PSA

INTRODUCTION

Prostate cancer is one of the most common diseases among men in developed countries (1, 2), with the incidence in Japan showing a recently marked increase (3). As the prevalence of prostate cancer in end-stage renal disease (ESRD) patients has been reported to be equal or higher as compared with normal healthy individuals (4-6), it is speculated that there should be a significant number of male hemodialysis patients of middle age or older with prostate cancer. However, initial detection of prostate cancer based on lower urinary tract symptoms is difficult in hemodialysis patients because anuria is observed in the majority of them. Moreover, bone pain caused by metastatic disease in hemodialysis patients with advanced prostate cancer may be confused with symptoms of dialysis amyloidosis, or mineral and bone disorders related to chronic kidney disease.

On the other hand, routine cancer screening, including prostate cancer, is not recommended for dialysis patients, except transplant candidates, because of their limited life expectancies (7, 8), which was a topic recently highlighted by the American Society of Nephrology as one of their five Choosing Wisely recommendations (9). However, given the heterogeneity of the dialysis population, caution should be used in applying population-based mortality data to decision making, thus an individualized approach to cancer screening is considered to be warranted (10). Actually, a considerable number of hemodialysis patients are routinely screened for cancer (11).

Prostate-specific antigen (PSA) testing is known to be

effective for detection of asymptomatic prostate cancer (12). As for hemodialysis patients, PSA screening may be especially useful because of their characteristics, as described above, and the non-invasiveness of the testing. Therefore, we have been screening male hemodialysis patients aged 55 years and older for prostate cancer using yearly PSA testing since January 2004. The outcomes of hemodialysis patients with prostate cancer detected by PSA screening are scarcely reported. Here, we investigated the long-term outcomes of those patients.

PATIENTS AND METHODS

In male hemodialysis patients aged 55 years or older, the PSA level measurement performed for the first time during a consultation at Kawashima Hospital Group, Tokushima, Japan, in the period from January 1, 2004 to December 31, 2012 was defined as the first PSA level measurement. We then retrospectively investigated 646 hemodialysis patients who could be followed after the first PSA level measurement until December 31, 2017 in regard to clinical data, including primary cause of renal insufficiency, time after hemodialysis introduction, PSA level, diagnosis, treatment of prostate cancer, and outcome. Patients who had been diagnosed with prostate cancer before the first PSA level measurement were excluded. Yearly prostate cancer screening by PSA testing was scheduled for all patients who underwent the first PSA level measurement. For those with a PSA level of 4.0 ng/mL or higher, the indication for a prostate biopsy was individually considered by evaluating age, comorbidities, and general status with weighing benefits and harms of a biopsy and subsequent treatment in relation to the patient's values and preferences. Those whose PSA level was 4.0 ng/mL or higher and who did not undergo a prostate biopsy were followed by PSA testing every 3-6 months. If their PSA levels continued to rise, the necessity for intervention was evaluated repeatedly based on

the estimation of malignant potential including PSA doubling time assessment with an individualized approach as described above. In principle, prostate cancer diagnosis was made based on histological findings. However, when a patient who was considered to be affected with prostate cancer which would threaten his life desired the treatment of the disease without a prostate biopsy, prostate cancer diagnosis was made based on clinical findings of positive digital rectal examination and continuous increase of PSA level. As a result, prostate cancer was diagnosed by histological findings in 13 patients and clinical findings in six patients.

Statistical Analysis

Data are presented as median and interquartile range. For continuous variables, intergroup differences were analyzed using a Kruskal-Wallis test or a Mann Whitney U test adequately. For categorical variables, intergroup differences were analyzed using a Fisher's exact test. Survival curves were generated using the Kaplan-Meier method and compared using a log-rank test. Overall survival was defined as the time from the first PSA level measurement to death from any cause or until the end of the study period. The statistical software package SPSS version 23 was used for analysis. A *P*-value of < 0.05 was considered to indicate significance.

RESULTS

The median follow-up period for all enrolled patients was 10.4 years (interquartile range : 13.3-7.8 years). At the time of the study end (December 31, 2017), 265 patients were alive and 381 died (Fig. 1). Of 19 patients diagnosed with prostate cancer, 12 survived and three died of infectious disease, each one died of prostate cancer, liver cancer, chronic renal failure,

and cardiovascular disease. For patients with prostate cancer, the median follow-up period after cancer diagnosis was 7.8 years (9.1-3.6 years).

Details of the patient who died of prostate cancer are presented as follows. Hemodialysis was initiated at the age of 83 because of chronic renal insufficiency, which cause was unknown. The first PSA level measurement performed at the age of 84, and the level was 0.96 ng/ml. His PSA level elevated to 37.25 ng/ml at the age of 89 without symptoms to indicate prostate cancer. As the patient desired the treatment of prostate cancer at this time without a prostate biopsy because of comorbidities, androgen-deprivation therapy (ADT) was started as his primary treatment for prostate cancer based on a clinical diagnosis. However, primary ADT (PADT) was ineffective from the early stage, and bone metastasis developed and rapidly progressed. The patient died 4 months after the diagnosis.

Among the primary causes for ESRD in the present cohort, diabetic nephropathy (DN) was the most common in 279 (43.2%) patients, followed by chronic glomerulonephritis (CGN) in 203 (31.4%) and hypertensive nephrosclerosis (HTN) in 47 (7.3%) (Table 1). The distribution of the primary causes of ESRD was not significantly different between patients with or without prostate cancer. Furthermore, no significant differences were observed regarding age at initiation of hemodialysis, age at the first PSA measurement, nor follow-up period between patients with and without prostate cancer, though a significant difference was seen for the first PSA level (Table 1). During the study period, PSA level was elevated to 4.0 ng/mL or greater in 139 patients. Of those, 14 (10.1%) patients underwent a prostate biopsy and 13 (9.4%) were diagnosed with prostate cancer based on histological results, while six (4.3%) were diagnosed based on clinical findings of positive digital rectal examination and continuous increase of PSA level without a prostate biopsy. All of six patients diagnosed clinically underwent PADT.
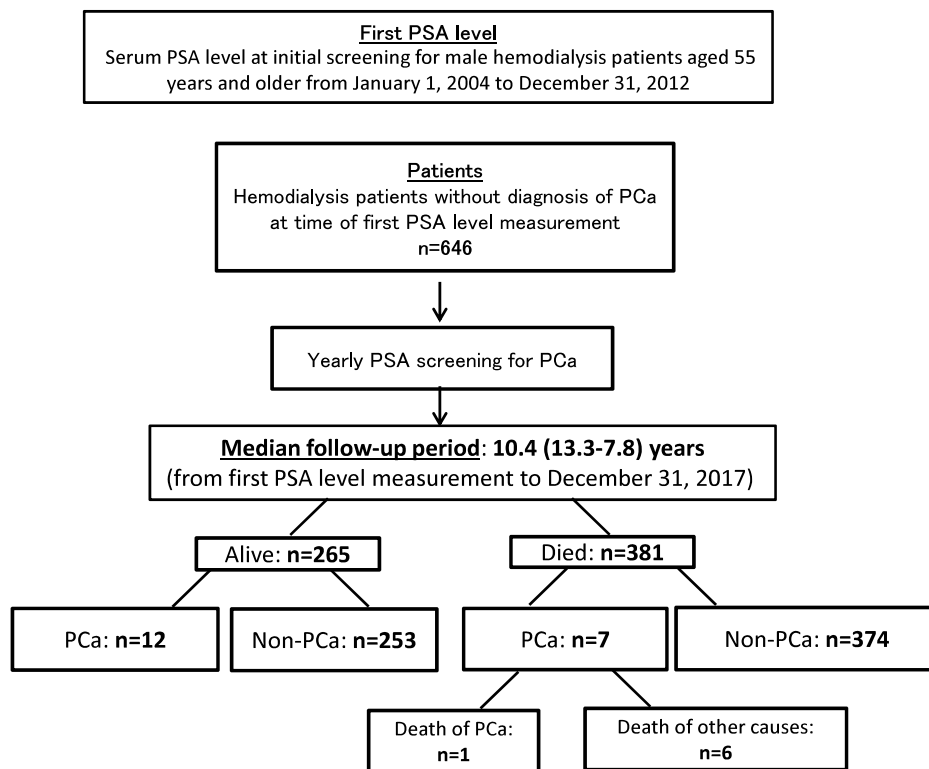

Figure 1.   Flow chart of study and patient outcomes.
Abbreviations : PCa, prostate cancer, PSA, prostate-specific antigen.

Analysis of hemodialysis patients with prostate cancer according to primary causes showed that CGN group had significantly better outcome than other groups, whereas significant differences were not observed for age at time of diagnosis of prostate cancer, the first PSA level, diagnostic method, or treatment (Table 2). A comparison of overall survival between patients with and without prostate cancer found no significant difference (Fig. 2a). Finally, overall survival was not significantly different between prostate cancer patients with PADT and non-prostate cancer patients (Fig. 2b).

DISCUSSION

Recent trends show a continuous decrease in the prostate cancer mortality rates in developed countries (2). Although it remains controversial whether PSA-based population screening contributes to decrease the rate of mortality related to prostate cancer (13-16), a growing percentage of PSA testing among middle-aged males along with progress in treatment modalities have most likely contributed to this (17, 18). It has also been reported that the incidence of metastatic disease is likely to increase if the opportunity for PSA screening is reduced (19).

Table 1. Characteristics of PCa and non-PCa groups

		PCa (n = 19)	Non-PCa (n = 627)	P value	Total (n = 646)
Primary kidney disease (n)	DN	6	273		279
	CGN	6	197		203
	HTN	1	46		47
	PKD	1	14		15
	Gout kidney	0	7		7
	Chronic pyelonephritis	0	2	0.259	2
	Urinary tract obstruction	0	1		1
	Myeloma	0	1		1
	Urinary tract tuberculosis	0	1		1
	Urinary tract tumor	0	1		1
	Unknown	5	84		89
Median age at initiation of hemodialysis (interquartile range)		67 (72-60)	62 (71-54)	0.18*	62.5 (71-54)
Median age at first PSA level measurement (interquartile range)		68 (74.5-61)	66 (74-58)	0.319*	66 (74-58)
Median first PSA level (ng/ml) (interquartile range)		4.60 (12.1-2.2)	1.0 (1.8-0.6)	<0.001*	1.0 (1.9-0.6)
Median follow-up period (years) (interquartile range)		9.5 (12.4-8.8)	10.4 (13.3-7.8)	0.931*	10.4 (13.3-7.8)

Abbreviations : CGN, chronic glomerulonephritis ; DN, diabetic nephropathy ; HTN, hypertensive nephrosclerosis ; PCa, prostate cancer ; PKD : polycystic kidney disease ; PSA, prostate-specific antigen.
*Mann Whitney U test

Table 2. Characteristics and outcomes of PCa-patients based on primary kidney disease

		DN (n = 6)	CGN (n = 6)	Other causes* (n = 7)	P value	Total (n = 19)
Median age at diagnosis of PCa (interquartile range)		74 (76.3-72.5)	67.5 (70.8-64.3)	69 (77.5-64)	0.293**	71 (75.5-66)
Median first PSA level (ng/ml) (interquartile range)		6.4 (10.5-4.1)	2.48 (3.2-1.4)	12.7 (32.1-4.3)	0.21**	4.6 (12.1-2.2)
Median PSA level at diagnosis of PCa (ng/ml) (interquartile range)		23.6 (119.3-14.6)	12.1 (16.4-6.8)	37.3 (57.9-17.8)	0.148**	17.8 (45.8-12.9)
Outcome	Alive	2	6	4		12
	Death from PCa	0	0	1	0.034	1
	Death from other causes	4	0	2		6
Diagnosis method	Biopsy	4	5	4	0.413	13
	Clinically	2	1	3		6
Treatment	Radical prostatectomy	0	1	0		1
	PADT	6	4	7	0.088	17
	Watchful waiting	0	1	89		1

Abbreviations : CGN, chronic glomerulonephritis ; DN, diabetic nephropathy ; HTN, hypertensive nephrosclerosis ; PADT, primary androgen-deprivation therapy ; PCa, prostate cancer ; PKD, polycystic kidney disease ; PSA, prostate-specific antigen.
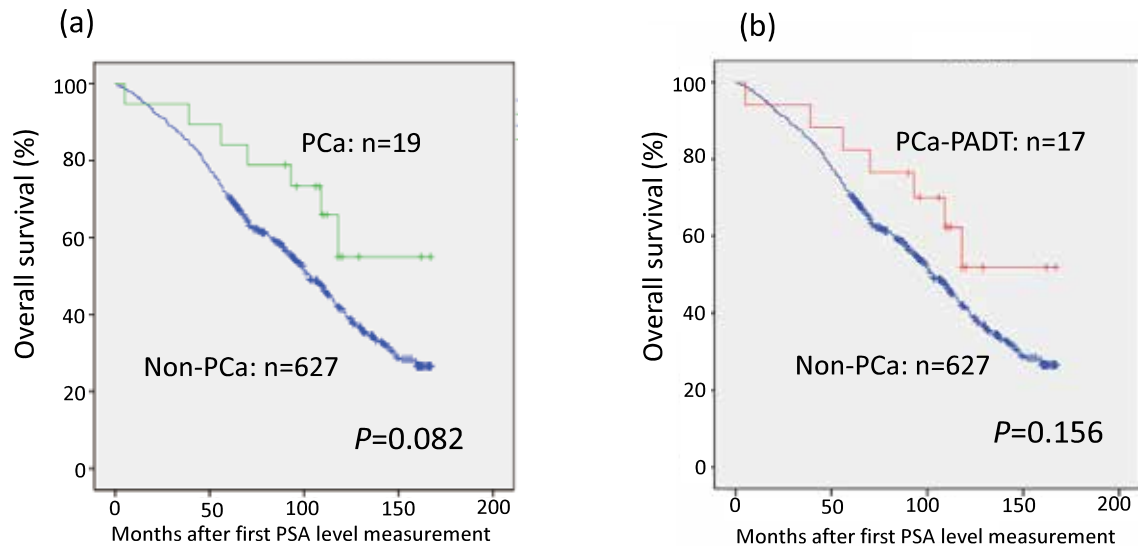*HTN : 1, PKD : 1, unknown : 5
**Kruskal-Wallis test

(a)

(b)

Figure 2.   Overall survival comparisons. (a) PCa and non-PCa groups. (b) PCa with PADT and non-PCa groups.
Abbreviations : PADT, primary androgen-deprivation therapy ; PCa, prostate cancer ; PSA, prostate-specific antigen.

As detection of prostate cancer on the basis of symptoms in hemodialysis patients is difficult because of their pathological state, PSA screening is considered to be useful to avoid missing prostate cancer in male hemodialysis patients who are middle aged or older. Prior reports have noted that prostate cancer in elderly patients is generally highly malignant (20, 21), and the patient who died of prostate cancer in the present study was also diagnosed at the age of 89 years. Accordingly, we consider that an upper age limit for screening should not be set at present. As for the lower age limit for screening, though that was set as 55 years for the present study, we consider that it should be 50 years for community health checkup examinations, even for hemodialysis patients, from the standpoint of administering effective radical treatment for those with a longer prospect of survival.

Although PSA screening is a simple and non-invasive test to perform with only a small amount of blood drawn, it leads to the diagnosis of prostate cancer in some men whose cancer would never have become symptomatic during their lifetime. Treatment of these men results in harms and provides them with no benefit. This is known as over-diagnosis, and follow-up of large randomized trials suggests that 20% to 50% of men diagnosed with prostate cancer through screening may be over-diagnosed (22). Over-diagnosis rates would be expected to be higher in hemodialysis patients because they have high risk of death from competing causes. Therefore, we carefully evaluated the necessity for intervention for the hemodialysis patients who screened positive with a highly individualized approach to avoid over-diagnosis.

This policy led to the results that only 14 (10.1%) of 139 patients who had a PSA level greater than 4 ng/mL during the study period underwent a prostate biopsy and 13 (9.4%) of those were diagnosed with prostate cancer histologically. Prostate cancer diagnosis based on clinical findings of positive digital rectal examination and continuous increase of PSA level was also made carefully for the purpose of the treatment in six (4.3 %) patients. In the result, of 139 patients who screened positive, 137 (98.6 %) were followed up by PSA testing every 3-6 months, and 119 (85.6 %) were not biopsied or clinically diagnosed. The average rate of prostate cancer detection in 1 year was 0.29% in the present study, lower as compared to that obtained in health

checkup screening conducted by local governments performed in 2013 (0.55%) (23), though the prevalence of prostate cancer in ESRD patients has been reported to be equal or higher as compared with normal healthy individuals (4-6). On the other hand, under-diagnosed cases were considered unlikely, as only one patient, for whom PADT was ineffective from the early stage, died of prostate cancer during the study period and none of the prostate cancer patients had metastasis at the time of diagnosis.

For avoiding possible over-diagnosis caused by performance of a prostate biopsy, magnetic resonance imaging (MRI) is considered useful. Recently, PI-RADS version 2, a scoring system that combines imaging findings obtained by T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast enhanced (DCE) MRI, has been widely used for diagnosing clinically significant cancer (24). However, DCE MRI cannot be used for hemodialysis patients, because nephrogenic systemic fibrosis (NSF) is induced by gadolinium contrast media. On the other hand, that report noted that diagnosis with relatively high precision can be obtained by the combination of only T2WI and DWI (24). Although few of hemodialysis patients with prostate cancer in our hospital have been examined using MRI, it should be applied to more hemodialysis patients with abnormal level of PSA hereafter.

Furthermore, for avoiding unnecessary biopsy and treatment procedures for hemodialysis patients with poor general status whose long-term survival cannot be expected, we consider that prediction of PSA level using PSA doubling time after confirming the absence of metastasis and local advance by diagnostic imaging findings can be useful. Another report showed that the risk of cancer metastasis increased when PSA level exceeded 100 ng/ml (25), thus whether predicted PSA level estimated by PSA doubling time assessment increases to greater than 100 ng/ml within the duration of predicted survival may provide important information for determining therapeutic policy.

It is reported that prognosis was more favorable for hemodialysis patients with CGN as the primary cause as compared to those with DN and HTN (26). Our analysis of hemodialysis patients with prostate cancer according to primary causes also showed that CGN group had significantly better outcome than other groups. It indicates that the medical condition accompanied

by primary causes of ESRD has a large impact on life prognosis of hemodialysis patients with prostate cancer. Therefore, treatment strategy for these patients should be made adequately based on their medical condition.

Generally, curative or focal forms of therapy such as radical prostatectomy, external beam radiotherapy, and brachytherapy have been used for patients with localized disease. However, based on data from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a significant proportion of patients received ADT as primary treatment for localized disease (27), although ADT may not be curative and is usually indicated for the treatment of advanced disease. Moreover, CaPSURE data revealed that patients with localized disease who received PADT tended to be older and to have more comorbidities, and such therapy appears to be effective in the majority of patients who receive it, at least up to 5 years (27). In the present study, PADT was selected for 17 (89.5%) of the 19 patients, who were also frequently older and have various other complications, and overall survival was not significantly different between patients with and without prostate cancer. A radical prostatectomy was selected for only one patient with CGN as the primary disease who had a longer predicted survival. Radiation therapy is also an effective treatment method for prostate cancer and is considered to be applicable to hemodialysis patients. Although no patient underwent radiation therapy in the present study, we consider that it should be indicated adequately for the treatment of prostate cancer of hemodialysis patients.

ADT is known to have an association with cardiovascular diseases (28), which is a risk of special concern for hemodialysis patients. Nevertheless, of 6 prostate cancer patients who underwent PADT and died of other causes, only one died of cardiovascular disease. Furthermore, no significant difference in overall survival was observed between prostate cancer patients who underwent PADT and non-prostate cancer patients. In a previous study of non-hemodialysis patients with non-metastatic prostate cancer aged 66 years or older, ADT had no association with death from other causes or cardiovascular disease (29).

In conclusion, PSA screening seems useful even for hemodialysis patients of middle age or older. However, the most important issue is that diagnosis and treatment after positive PSA test should be considered carefully in accordance with the patient conditions.

CONFLICT OF INTEREST

ACKNOWLEDGEMENTS

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