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Original Article

# Outcomes of patients older than 75 years with non-metastatic prostate cancer



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## KEYWORDS

Prostate cancer;  
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**Abstract** *Objective:* Prostate cancer in elderly patients was formerly treated with androgen deprivation therapy. Since the latter of the 1990s new technologies were introduced into treatments, then strategies have varied. We aimed to observe the outcomes of elderly patients treated during transition period and compare each stage with others.

*Methods:* During 2008 and 2010, 255 patients with prostate cancer older than 75 years were sequentially treated. With exception of patients with bone and/or visceral metastasis, outcomes of 199 patients with localized and locally advanced stages were examined. Complete records were obtained by the end of 2015.

*Results:* In total, 122 (61%), 28 (14%), 37 (19%) and 12 (6%) of patients were in stages T1c-T2a, T2b-c, T3 and T4, respectively. Patients generally presented with abnormal screening or lower urinary tract symptom. Seventy-one percent of patients received androgen deprivation therapy as monotherapy and 22% of the radiation-treated patients added androgen deprivation therapy. Patients in stage T1c-T2a and T2b-c showed a favorable prognosis. Some cancer death appeared in patients with T3 and T4 during observation periods. Twenty-seven percent of patients died from prostate cancer-independent complications: pneumonia, heart disease, and brain vascular disease. Tendency is similar to that of Japanese elderly male population. No remarkable side effects from androgen deprivation therapy were noticed.

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**Conclusion:** Elderly patients with localized prostate cancer showed favorable prognosis by androgen deprivation therapy with/without radiation, thus efficacy of androgen deprivation therapy is suitable to elderly patients with applicable stages. Prognosis of patients with locally advanced stage is serious and remains to be improved.

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## 1. Introduction

Recently the incidence of prostate cancer has increased in Japan, with 98,000 cases and 12,200 deaths in 2015 [1]. This increase in patients is attributed to the prolonged life span, widely distributed screening and the routine assay of total prostate-specific antigen (PSA) for patients with lower urinary tract symptom. Approximately half of all prostate cancer deaths occurred in elderly patients over 70 years of age. Consequently, the management of elderly prostate cancer patients is a newly important issue. Prostate cancer in elderly patients exhibits equal or greater malignant properties than in younger patients [2].

Elderly prostate cancer was formerly treated with androgen deprivation therapy (ADT) as a pivotal standard. Since the latter of the 1990s, remarkable progresses in technology, such as laparoscopic surgery, external beam radiation therapy with increased dosage and hypofractionation, and anticancer drugs, were introduced into managements for elderly patients, and use of ADT was changed. Thereafter, there have been many discussions on the treatment of elderly patients [3–7]. Crucial aspects on management include age, life expectancy, comorbidity and predictive effect of treatment. To evaluate various treatment strategies, the present study was aimed to examine the outcomes of elderly patients variously treated between 2008 and 2010 as a transition period from ADT only to introducing new technology. The outcomes of the respective stages were compared with others.

## 2. Materials and methods

The ethical committee of the Asahi General Hospital approved this research. Between January 2008 and December 2010, 255 cases of prostate cancer who were over 75 years old were sequentially treated at Asahi General Hospital after informed consent was obtained. With the exception of patients with bone and/or visceral metastases, the outcomes of 199 patients with localized and locally advanced stages were followed up. These patients were in good health with a score of 0 or 1 on the Charlson risk index [8] before start of treatment. A complete record of patient outcomes was obtained by the end of 2015. A prostate biopsy was performed with 8–12 cores via the perineal route and histological classification was performed using the Gleason patterns modified in the International Society of Urological Pathology [9]. Staging was classified by National Comprehensive Cancer Network Guidelines 2014 [10]. PSA was assayed with an Architect PSA kit (Abbot, Chiba, Japan). PSA was determined every 3

months, and then every 6 months after treatment. Pre-treatment assessment was performed with an echogram and whole body scan, and if necessary, magnetic resonance imaging and computed tomography of pelvic and abdominal areas.

Radical retropubic prostatectomy was performed with a regional lymphadenectomy. External beam radiation therapy was performed with 2 Gy/day to the prostate gland for a total of 66 Gy. Before radiation therapy 3 months of ADT were prescribed, and after radiation therapy ADT was continued for 2–3 years. Brachytherapy with iodine seeds was administered with 145 Gy of a prescription dose as a monotherapy according to the manual.

ADT was performed as a monotherapy with an luteinizing hormone-releasing hormone (LHRH) analog and concomitant use of 80 mg of bicalutamide daily until PSA relapse. In some cases, surgical castration was used instead of LHRH. Relapse was judged by a linear increase of PSA, and when relapse occurred, other hormone therapy and/or chemotherapy were performed.

Statistical analysis was performed with the SPSS statistical software (ver 22, IBM-SPSS Inc, Tokyo, Japan). Follow-up time was measured from the date of treatment initiation. Survival was measured using the Kaplan–Meier method. A  $p$  value  $<0.05$  was considered statistically significant.

## 3. Results

ADT was well tolerated in elderly patients who were accepted during the treatment periods. Hot flashes were controlled temporarily with the prescription of a weak progestational agent. To prevent the loss of bone mineral density, supplementation with calcium and vitamin D was advised. Caution was paid for patients to heart disease, hypertension and diabetes. During ADT treatment, there were no serious adverse effects. The patients were satisfied with the adequate treatment of their prostate cancer.

One hundred and seven patients with T1c-T2a and all the patients with T2b-c received ADT and their outcomes were favorable. Fifteen patients with T1c-T2a were initially treated without ADT: active surveillance, operation and brachytherapy. Some experienced PSA relapse but they received ADT as delayed ADT, and thereafter revealed favorable outcome (Table 1). Their outcomes were included in the respective stage.

Prognosis was calculated on base in the respective stages. The overall survival rates were 77%, 76%, 52% and 35% in stages T1c-T2a, T2b-c, T3 and T4 at 5 years,

**Table 1** Patient characteristics.

	T1c-T2a	T2b-c	T3	T4	Total
No. of patients	122	28	37	12	199
Age (year) <sup>a</sup>	79 (75–88)	80 (75–85)	80 (75–90)	80 (75–84)	79 (75–90)
Complain ( <i>n</i> )					
Screening	56	10	11	1	78
LUTS	47	13	21	10	91
Other urinary symptom	19	5	5	1	30
PSA (ng/mL) <sup>a</sup>	9.2 (1–20)	13.8 (3–44)	30.9 (5–186)	153.9 (112–1630)	
Gleason score ( <i>n</i> )					
≤6	30	4	—	—	34
3 + 4	32	4	—	—	36
4 + 3	15	3	5	1	24
≥8	45	17	32	11	105
Treatment ( <i>n</i> )					
Active surveillance	6	—	—	—	6
Operation	4	—	—	—	4
Brachytherapy	5	—	—	—	5
External beam radiation	33	4	4	2	43
ADT	74	24	33	10	141
Death					
Cancer-specific ( <i>n</i> )	1	1	4	4	10
Duration (month) <sup>a,b</sup>	54	61	19 (12–22)	39 (17–66)	35 (12–61)
Others ( <i>n</i> )	32	10	10	2	54
Duration (month) <sup>a,b</sup>	39 (6–82)	52 (24–74)	38 (10–74)	6 (5–7)	40 (5–82)

PSA, prostate specific antigen; ADT, androgen deprivation therapy; LUTS, lower urinary tract symptoms.

<sup>a</sup> Mean (range).

<sup>b</sup> Duration between treatment initiation and death.

respectively (Fig. 1A). The overall survival rates in advanced stage patients were worse primarily because of the occurrence of cancer-specific death. The cause-specific survival rates were 100%, 94%, 89% and 48% in stages T1c-T2a, T2b-c, T3 and T4 at 5 years, respectively (Fig. 1B). The effect of ADT was therefore limited to the localized stage, and death from prostate cancer in localized stage was rare.

We found that 27% of patients died from causes other than prostate cancer: 26%, 36%, 27% and 17% in stages T1c-T2a, T2b-c, T3 and T4, respectively. The causes of death were as follows: 14 (26%) from other malignancies, 16 (29%) from pneumonia, 7 (13%) from heart disease, 7 (13%) from brain vascular disease and 10 (19%) from others. With the exception of patients in stage T4, the periods between diagnosis and death were rather long time with healthy life styles.

#### 4. Discussion

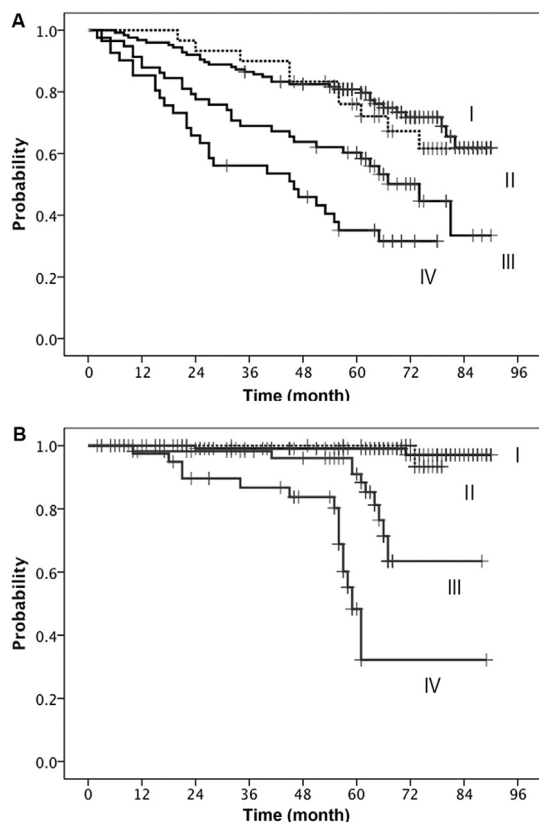
More than half of early stage prostate cancer is indolent cancer, which may not disturb daily life. Moreover, prostate cancer detected at the early stages proceeds slowly. These findings demonstrate that elderly patients who suspect less than 10 years of the remaining life need not treat thereafter. Conversely, life expectancy in patients who are treated in the early stages is predicted to be better compared to men without cancer [11]. Patients older than 80 years still die from prostate cancer [12], thus aggressive treatments are recommended in elderly patients [13–15]. Radical prostatectomy is considered in these patients

[16,17]. Radiation therapy is also recommended [18]. In the present study, the average age of the patients was approximately 79 years. Therefore, they may be candidates for either aggressive or non-aggressive treatments.

According to Japanese Government Lifetable [19], average predictive time of life remaining for men who are 80 years is 8.8 years. The cause of death in elderly men is pneumonia, followed by malignant neoplasm, heart disease and brain vascular disease, and the causes of death in the present patients were the same as those found in the Japanese male population. Patients who died from causes independent of prostate cancer appeared to have the same life span as the general population of elderly men. This indicates that ADT may not cause the serious side effects including cardiovascular system.

During the treatment of prostate cancer patients, complications from other diseases are a serious issue. The estimation for the influence of comorbidities is performed using a Charlson score and its weighted method [20–22]. Patients with comorbidities tend to receive non-aggressive treatment [16,23,24]. Conservative treatment for elderly patients showed favorable results with a Gleason score of 5–7 but patients with a score of 8–10 had a serious prognosis [25]. Localized stage patients with a Charlson score of 0 and most patients with a Gleason score ≤7 had a good outcome. The similar tendency was obtained in the present study.

Although ADT is a milestone therapy for prostate cancer, adverse effects have been observed. Most serious events are cardiovascular disease and metabolic disturbances [26–28]. Care is required to mitigate adverse effect



**Figure 1** Overall survival rates (A) and cause-specific survival rates (B) of elderly patients with prostate cancer. I,II,III and IV as stages in T1c-T2a, T2b-c, T3 and T4, respectively.

[29,30]. Although the reason why Japanese patients with prostate cancer experience slight adverse effects by ADT is not explained, adverse events including cardiovascular disease certainly appear to be less in Japanese patients when compared to foreign reports. Chinese (from Taiwan province) men do not have a risk of coronary heart disease from ADT [31]. Treatment with ADT shows an anticancer effect and less of adverse events, thus it could be beneficial and not harmful [32,33]. To obtain more benefits from therapy, the use of ADT required to reduce more adverse events. In the present study, ADT was performed for a rather long time, but treatment duration may be considered. For this purpose, the treatment schedule will be improved to reduce adverse effects, such as intermittent administration [34].

Psychological deterioration was discussed in European studies [35]. The present patients approved prior to treatment and were satisfied with adequate anticancer treatment without anxiety from progression of disease and adverse effects. Although there did not seem to occur serious psychological trouble in Japan, it requires a psychological care.

Advanced prostate cancer is a fatal disease. Most of these cases progress to castration resistant disease 2–3 years after diagnosis [36]. Chemotherapy and next generation hormonal drugs are being developed, but their efficacy remains to be confirmed for elderly patients.

## 5. Conclusion

Patients with T1c-T2a and T2b-c prostate cancer may proceed to favorable course by treating with ADT as monotherapy or combined with radiotherapy. Although care is necessary, ADT was well tolerated and adverse effect was slight. ADT is one of the selective treatments for elderly localized prostate cancer. However, patients with locally advanced stage prostate cancer showed serious outcomes and management remains to be developed.

## Conflicts of interest

The authors declare no conflict of interest.

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