

## Executive Summary

### Outcome Research for androgen deprivation therapy and prostatectomy in prostate cancer

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## □ Background

Prostate cancer is the most common cancer in man in the West, and it has the third highest cancer-related mortality. According to the Korean National Cancer Information Center, as of 2014, prostate cancer shows the fifth-highest incidence rate in Korean men, and the incidence rate has consistently increased after 2000.

As the average life expectancy of Koreans increases, the diagnosis and prevalence of prostate cancer are increasing in men, and the incidence rate of prostate cancer is increasing in people aged 70 years or older. The survival rate of prostate cancer was improved to 93.3% in 2014 compared to

55.9% in 1993, and the trend for the cost of prostate cancer treatment is continuously increasing.

It is necessary to generate baseline data and evidence that can be used in clinical practice through comparison of short and long term effects between surgical therapy and hormone therapy in patients with prostate cancer. The purpose of this study is to establish a clinical evidence based on the results of clinical outcome analysis between two treatments as the clinical evidence for elderly patients with prostate cancer is insufficient.

### Objective

This study is aimed to produce clinical evidence to support decision-making in national health care policy and clinical treatment by analyzing the current status of medical use in patients with prostate cancer, and long and short term clinical outcomes for surgical therapy and hormone therapy.

### Methods

We reviewed the guidelines for the treatment of Korean and overseas patients with prostate cancer and summarized the existing literature on the outcome analysis between surgical therapy and hormone therapy. We referred to them to develop a protocol and various parameters for the clinical outcome analysis of domestic patients with prostate cancer.

To analyze the current status of medical use of domestic prostate cancer, the database specific to national health insurance in 2002-2014 was used (NHIS-2016-1-046), and the behavior of patient using medical service due to prostate cancer (C61) were investigated according to year based on the details of health insurance claims.

The current status of medical use in surgical therapy and hormone therapy from 2003 to 2014 was examined. The demographic characteristics of each patient, the amount of each treatment, and the long- and short-term

treatment patterns of each treatment were investigated.

The clinical outcomes(death, cancer-specific death, cardiovascular events, etc.) by primary treatment of prostate cancer were analyzed by using the linked data of the Korea Central Cancer Registry, National Health Insurance Service, and the cause of death data from Statistics Korea. New users were selected by operational definition, and additional treatments and the risk for death were estimated according to the treatment method of prostate cancer. A retrospective patient cohort was also established by investigating medical records after examining the possibility of collecting clinical variables and outcome variables from seven medical institutions.

Data were stratified into the stage of cancer, localized and regional, based on a subject age of 75 years, and propensity score matching was conducted based on the general clinical features of patients. The primary outcome, mortality rate, was calculated using the Kaplan-Meier survival analysis and the Cox proportional hazards model. Moreover, official medical expenses were analyzed through the payment record (reimbursement, non-reimbursement, optional care) from the cohort study.

This study has been approved by the IRB of the National Evidence-Based Healthcare Collaborating Agency (NECA IRB 16-008) and has obtained prior approval from the IRBs of seven hospitals to investigate the medical records and official medical expenses of patients with prostate cancer.

## □ Results

In case of the number of new prostate cancer medical users by medical security type, there was no difference by year and the number of patients is increasing every year. The number of NHI employee subscribers was 5,598 (68.0%), NHI regional subscribers was 2,298 (28.11%), and NHI beneficiaries was 291 (3.6%) in 2013. The first visit type was claimed through an outpatient visit by 70% or more, and claims of 87% or more were made in general hospitals among healthcare providers. In terms of the stage of cancer, the number of patients with 'Localized' group increased

from 46% in 2005 to 58% in 2013, and number of patients with 'Regional' group increased from 17% in 2005 to 26% in 2013. The number of patients with unknown stage of cancer was decreasing. Patients that the Charlson's Comorbidity Index is 1 point at the time of the first diagnosis had the most proportion at 26.78%, and the proportion of 4 points or more tended to increase annually for 11 years from 2003 to 2013.

The number of patients receiving hormonal therapy as a first treatment among new prostate cancer medical users was decreasing from 813 patients (60.4%) in 2003 to 2,841 patients (41.3%) in 2013. However, there was a continuous increasing trend in surgical therapy (including robot surgery) from 23.7% (319 patients) in 2003 to 48.5% (3,336 patients) in 2013. The mean age of patients receiving surgical therapy as a first treatment was 65.6 years old, and the mean age of patients receiving hormonal therapy was 72.3 years old, showing that it was higher than that of patients receiving surgical therapy. And the proportion of patients treated with hormone as a first treatment in prostate medical users aged 75-79 was increasing annually from 20.8% in 2003 to 27.3% in 2013, and patients aged 80 or more tended to increase also.

By using the linked data, the propensity score matching was performed in 4,538 prostate cancer patients who newly diagnosed from 2007 to 2009. As a result, 1,912 patients were matched and the mean age was 62.9 years old. 5-year survival rate in surgical therapy group was 90% and in hormonal therapy group was 74%. In addition, as a result of estimating the overall death risk ratio by applying the Cox proportional hazard model, the overall death risk of hormonal therapy group was 3.39 times (HR=3.39, 95% CI 2.58-4.44) higher compared to that of surgical therapy group, and the death risk tended to be high in patients with aged 75 or more, 'Regional' in terms of the stage of cancer, diabetes, osteoporosis and dementia. As a result of comparing the 5-year survival rate by summary stage in the group aged 75 or more, the survival rate of surgical therapy group in 'Localized' was 79% and that of hormonal therapy group was 72%. The survival rate of surgical

therapy group in 'Regional' was 84% and that of hormonal therapy group was 55%. Also, as a result of estimating the death risk ratio between hormonal therapy group and surgical therapy group by applying the Cox proportional hazard model, in case of 'Localized' in summary stage, the death risk ratio of hormonal therapy group was 1.8 times higher than that of surgical therapy group (HR=1.81, 95% CI 1.01-3.25), and, in case of 'Regional', the death risk ratio of hormonal therapy group was significantly 6.34 times higher than that of surgical therapy group (HR=6.34, 95% CI 1.36-29.59)

Compared to surgical therapy group, the cumulative incidence risk ratio of cardiovascular disease was 1.62 times (HR=1.62, 95% CI 1.40-1.86;  $p < 0.001$ ) higher, and, in case of hormonal therapy group aged 75 or more that summary stage is 'Localized', the cumulative incidence risk was 1.78 times (HR=1.78, 95% CI 1.19-2.66) higher. In comparison with surgical therapy group, the cumulative incidence risk ratio of osteoporosis was 1.64 (HR=1.64, 95% CI 1.36-1.96), that of dementia was 1.33 (HR=1.33, 95% CI 1.03-1.72), and that of additional therapy was 3.26 (HR=3.26, 95% CI 2.69-3.95) in hormonal therapy group.

As a result of analyzing retrospective patient cohort, 5-year survival rate after the first treatment of surgical therapy group was about 87% and that of hormonal therapy group was 63%, indicating that a significant difference was found ( $p < 0.0001$ ). Even in considering only 'localized and regional' stage of prostate cancer, similar survival rate was observed. As a result of the risk rate for overall death, in case of the subgroup limiting the stage of prostate cancer to 'localized and regional', the death risk ratio of hormonal therapy group was 2.89 times higher than that of surgical therapy group ( $p < 0.0001$ ). Concerning the Gleason score as other factors affecting overall death in prostate cancer patients, the death risk ratio of the case that the Gleason score is 8 points or more was 2.7 times ( $p = 0.0002$ , including all stages), 2.4 times ( $p = 0.0026$ , 'localized and regional' stage) higher compared to that of the case that it is 6 points or less. Furthermore, in patients with prostate

cancer, obstructive coronary artery disease, chronic renal disease, chronic hepatic disease and other cancers, etc. was shown as risk factors significant for death.

As a result of estimating prostate cancer specific death and the death risk rate, the 5-year survival rate was 98.1% in surgical therapy group, demonstrating that it survives significantly more than hormonal therapy group of 91.4% ( $p=0.004$ ). In case of considering only localized and regional stage, the survival rate of surgical therapy group was 98.2%, in hormonal therapy group it was 93.8%, and there was no significant difference. In case the death risk specific to prostate cancer within 5 years includes all stages of it, it was shown that the death risk rate of hormonal therapy group is 3.86 times higher ( $p<0.00412$ ), but, in case the death risk was limited to the subgroup of 'localized and regional', a significant difference was not observed.

Patients restored to impotence in surgical therapy group was 796 patients (51%) among 1,561 patients and it took 261 days (median 225 days) until recovered, and, in case of urinary incontinence, the average necessary period was 318 days (median 180 days) until 219 patients (14%) is restored. Also, as a result of verifying the safety of hormonal therapy, it was found that the side effect rate was not great on the whole and the side effect caused most is a urogenital organ disorder (5%), which is followed by hot flush and diaphoresis (3.7%), gynecomastia and mastalgia (3.5%), digestive disorder (2.4%), and musculoskeletal disorder (1.7%).

## □ Conclusions

Hormonal therapy in prostate cancer patients is not established as a primary treatment of localized prostate cancer, but it has been conducted about 80% of patients with low-risk prostate cancer in Japan. And the possibility as a primary treatment in low-risk group of Asian patients with prostate cancer is being referred to the Asia consultative group of the NCCN (National Comprehensive Cancer Network) guideline because the

effect was proved that the cancer-specific survival rate for 8 years reaches about 97.6%. However, our study showed that 5-year survival rate of hormonal therapy group in localized prostate cancer was 74%, and it was lower than that of surgical therapy group (90%). There was a limitation to compare survival rates of prostate cancer patients who received hormonal therapy by country because clinical stage, age, and underlying diseases were different.

Through a prospective study about conducting hormonal treatment as a primary treatment of localized prostate cancer reported that there were no special problems in terms of side effect and compliance. Our result of retrospective cohort study also showed similar results.

Also, in the situation that old-aged patients with prostate cancer is growing because the guarantee expansion for 4 major serious illnesses causing a large amount of medical expenses is enhanced, although the accessibility of hormone treatment can be raised in accordance with the disease status different from clinical stage in old-aged patients with prostate cancer restricted to the existing surgical treatment, basic materials for calculating medical expenses of hormone treatment were insufficient.

Therefore, in this study, clinical outcome analysis for prostate cancer treatment was performed establishing retrospective cohort by connecting with a variety of secondary data resources such as patient enrollment data of 7 multi-centers, materials of the Korea Central Cancer Registry, data specific to the National Health Insurance Service, and materials for cause of death of the Statistics Korea. It is considered that such an essay is strong point of the study. However, there was a limit to verify domestic clinical treatment outcomes due to limitation of clinical variables, insufficient monitoring period, and limitation of oncological result index, etc. by retrospective study design.

To overcome such limits, oncological outcome analysis considering age, summary stage and clinical features, etc. through a prospective long-term monitoring study is required. Moreover, in case of prostate cancer, as its

survival rate is greater compared to that of patients with other cancer, it is crucial to reduce medical expenses by raising quality of life of patients and minimizing side effects caused by cancer reoccurrence and its treatment. Therefore, follow-up studies such as cost-utility analysis considering quality of life and utility values, etc. according to side effect aspects of old-aged patients by each treatment and progress status of cancer, etc. will be consistently required because, even if the clinical outcome indexes are major determinants for clinical doctors in selecting treatments, a difference in the treatment preference can be caused owing to old-aged patients and their family affected by various socio-environmental factors.

As, in this study, the 5-year survival rate for surgical therapy group and hormonal therapy group and the cumulative incidence risk of cardiovascular disease and osteoporosis, etc were verified with retrospective study design, we need to prepare domestic clinical evidences determining the treatment direction of patients with prostate cancer and supporting clinical decision-making by conducting additional studies with improved evidence level on the basis of this results.

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#### **Key words**

Prostate cancer, Prostatectomy, Androgen deprivation therapy, Outcomes Research