Primary Hormonal Treatment in Localized and Locally Advanced Prostate Cancer: Effectiveness and Survival Predictive Factors

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ABSTRACT

Aim: to evaluate the effectiveness of primary hormonal treatment on localized and locally advanced prostate cancer, including the analysis on the survival predictive factors. Methods: patients with localized (T1, T2N0M0) and locally advanced (T3, T4N0M0) prostate cancer who had received primary hormonal treatment between January 1995 and December 2009 were evaluated retrospectively based on their specific medical records at Department of Urology in Cipto Mangunkusumo Hospital (RSCM) and Dharmais Cancer Hospital (RSKD). Results: about 79 (29.9%) of 264 patients with localized and advanced local prostate cancer received primary hormonal treatment. In the localized prostate cancer group, mean survival was 58.3 months (range: 1.87-170.78) and 5-year survival was 77.3%; while in locally advanced prostate cancer patients, mean survival was 40.87 months (range 7.29-115.29) and 5-year survival was only 22.7%. Hemoglobin level was a significant clinical parameter of survival predictive factors for both localized and locally advanced prostate cancer groups. The lower the hemoglobin level, the survival will be shorter. Conclusion: there were no significant differences between mean survival and 5-year survival rate, between localized and locally advanced prostate cancer patients who had received primary hormonal treatment. Hemoglobin level is survival predictive factors for localized and locally advanced prostate cancer patients.

Key words: survival, LHRH agonist, orchidectomy, androgen deprivation.
INTRODUCTION

Hormonal treatment in prostate cancer has been developed since Huggins and Hodges\(^1\) reported that castration and estrogen treatment are effective in advanced prostate cancer. Although radical prostatectomy is still the gold standard treatment for localized prostate cancer and certain cases of locally advanced prostate cancer\(^2,3\), the primary hormonal treatment may be considered as an alternative option for patients who are not suitable for radical prostatectomy due to their unfavorable general condition for surgical treatment.\(^3\)

Recently, primary hormonal treatment in localized and locally advanced prostate cancer has been more common.\(^4,5\) Moreover, it has been more frequently used after the Early Prostate Cancer Program has provided evidence that antiandrogen treatment is effective for localized and locally advanced prostate cancer.\(^6,7\) Five and 10-year follow up by Akaza et al, in Japan show that primary hormonal treatment may slow down the progression of localized and locally advanced prostate cancer.\(^3,4\)

The present study was aimed to evaluate the effectiveness of primary hormonal treatment on localized and locally advanced prostate cancer, including the analysis on the survival predictive factors. We expect that the study may become the first referral study exploring the effectiveness of primary hormonal treatment on localized and locally advanced prostate cancer.

METHODS

Patients with localized (T1, T2) and locally advanced (T3, T4) prostate cancer who had primary hormonal treatment (LHRH agonist [Leuprolide or Goserelin], either as continuous or intermittent androgen deprivation and orchidectomy), between January 1995 and December 2009, were studied retrospectively based on specific medical records at Department of Urology in Cipto Mangunkusumo Hospital (RSCM) and Dharmais Cancer Hospital (RSKD). Patients were being followed up until December 2010, both through direct visit and contact by phone. Patients who had been followed up over 12 months were included in the analysis. Data on age, Prostate Specific Antigen (PSA), tumor grade and stage, hemoglobin level (Hb), serum ureum and creatinine level, and the presence/absence of retention were analyzed as survival predictive factors. Tumor grade was determined based on WHO classification; while tumor staging was established according to American Joint Committee on Cancer (AJCC) recommendation.\(^9\)

Statistical analysis was performed using Mann-Whitney test for mean survival rate of both localized and locally advanced prostate cancer group; while 5-year survival rate among both groups was analyzed using Chi-square test and \(p < 0.05\) was considered as statistically significant. Survival rate was analyzed using Kaplan-Meier curve; while survival predictive factors were determined by using multivariate Cox regression model.

RESULTS

Between January 1995 and December 2009, there were 789 patients with prostate cancer in both hospitals; among them, 264 patients had localized and locally advanced prostate cancer. About 79 patients, i.e. 51 patients with localized prostate cancer and 28 patients with locally advanced prostate cancer had received primary hormonal treatment. The mean age of the patients with localized and locally advanced prostate cancer were 74 years (median: 74 years) and 68.07 years (median: 67 years), respectively.

During follow up until December 2010, 18 patients died in each group of both localized and locally advanced prostate cancer. The mean survival rate of the dead patients was 48.73 months in localized prostate cancer group and 42.56 months in locally advanced prostate cancer. Mean survival rate in localized prostate cancer group was 58.3 months (range: 1.87–170.78 months); while the mean survival rate in locally advanced prostate cancer group was 40.87 months (range: 7.29-115.29 months). Although there was different survival rate among both groups, yet statistically the difference was not significant. \(p=0.124\).

The 5-year survival rate in localized prostate cancer may reach 77.3%; while in locally
In the present study, there were approximately thirty percent (29.9%) of 264 patients with localized and locally advanced prostate cancer had received primary hormonal treatment. Moreover, the percentage of patients with localized prostate cancer who received primary hormonal treatment was 23.7%. In the United States, an observational study, CaPSURE, showed increased percentage of primary hormonal treatment for localized and locally advanced prostate cancer, from 4.6% into 14.2% for low-risk group; 8.9% into 19.7% for moderate-risk group; and 32.8% into 48.2% for high-risk group.

![Figure 1](image)

**Figure 1.** Survival rate of patients with prostate cancer who had received primary hormonal therapy

### Table 1. Subject characteristics of patients with prostate cancer who received primary hormonal treatment

<table>
<thead>
<tr>
<th></th>
<th>Localized Prostate Cancer (n=51)</th>
<th>Locally Advanced Prostate Cancer (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (range) (years)</td>
<td>Mean (range) (years)</td>
</tr>
<tr>
<td></td>
<td>74.00 (57-84)</td>
<td>68.07 (50-92)</td>
</tr>
<tr>
<td>PSA (ng/mL)a</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>78.35</td>
<td>32.66</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>75.47</td>
</tr>
<tr>
<td>Tumor Gradingb</td>
<td>Grade 1 (%)</td>
<td>Grade 2 (%)</td>
</tr>
<tr>
<td></td>
<td>6 (11.8)</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td></td>
<td>Grade 2 (%)</td>
<td>20 (39.2)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>23 (46.1)</td>
</tr>
<tr>
<td>Tumor Staging (T)</td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td></td>
<td>51 (100)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>0</td>
</tr>
<tr>
<td>Survival (months)c</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>58.30</td>
<td>50.14</td>
</tr>
<tr>
<td></td>
<td>Survival &gt; 5 years (%)</td>
<td>Survival &lt; 5 years (%)</td>
</tr>
<tr>
<td></td>
<td>17 (77.3)</td>
<td>24 (61.5)</td>
</tr>
</tbody>
</table>

**Note:**
- a Four patients with localized prostate cancer and two patients with locally advanced prostate cancer did not have data on PSA.
- b Two patients with localized prostate cancer did not have data on tumor grading.
- c Ten patients with localized prostate cancer and eight patients with locally advanced prostate cancer had been lost for follow up.

Advanced prostate cancer group was only 22.7%. However, statistically, there was insignificant difference between both groups (p=0.209).

The comparison of survival period of time between both groups could be observed in **Figure 1**.

The correlation between parameters including age, PSA, tumor grading, staging, hemoglobin level, serum ureum and creatinine level, as well as the presence of retention on survival could be seen in **Table 2**. After performing multivariate analysis, we found that hemoglobin level was a significant clinical parameter for survival predictive factors, both in localized and locally advanced prostate cancer groups.

### Table 2. Correlation between parameters of age, PSA, tumor grading, tumor staging, Hb level, serum ureum and creatinine level, as well as the presence of retention on survival rate

<table>
<thead>
<tr>
<th></th>
<th>Localized Prostate Cancer (p)</th>
<th>Locally Advanced Prostate Cancer (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.962</td>
<td>0.019</td>
</tr>
<tr>
<td>PSA</td>
<td>0.835</td>
<td>0.393</td>
</tr>
<tr>
<td>Tumor Grading</td>
<td>0.501</td>
<td>0.072</td>
</tr>
<tr>
<td>Tumor Staging</td>
<td>a</td>
<td>0.627</td>
</tr>
<tr>
<td>Hb</td>
<td>0.059</td>
<td>0.001</td>
</tr>
<tr>
<td>Ureum</td>
<td>0.798</td>
<td>0.411</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.80</td>
<td>0.496</td>
</tr>
<tr>
<td>Retention/not</td>
<td>0.261</td>
<td>0.191</td>
</tr>
</tbody>
</table>

**Note:**
a All patients with localized prostate cancer had stage 2 tumor; therefore, we could not analyze the correlation between tumor staging and survival rate

### DISCUSSION

In the present study, there were approximately thirty percent (29.9%) of 264 patients with localized and locally advanced prostate cancer had received primary hormonal treatment. Moreover, the percentage of patients with localized prostate cancer who received primary hormonal treatment was 23.7%. In the United States, an observational study, CaPSURE, showed increased percentage of primary hormonal treatment for localized and locally advanced prostate cancer, from 4.6% into 14.2% for low-risk group; 8.9% into 19.7% for moderate-risk group; and 32.8% into 48.2% for high-risk group. Another study by Nara Uro-oncological Research Group Registration
in Japan found that 38% of 1699 patients with localized prostate cancer and 58% of 604 patients with locally advanced prostate cancer had received primary hormonal treatment.11

Until now, no study has been conducted randomly comparing the effectiveness of three modalities of treatment for localized prostate cancer, i.e. radical prostatectomy, radiotherapy and hormonal treatment. Data from the Agency for Healthcare Research and Quality, Department of Health of the United States, based on the results of systematic review on 18 Randomized Controlled Trials (RCT) and 473 observational studies revealed that there is no evidence concluding that one is better than the other modalities of treatment. Therefore, patient's preference and clinical consideration on patients’ age and predictive/biological characteristics of prostate cancer is very important to determine the treatment of choice in patients with localized prostate cancer.3,5,10-12

In addition to the patient’s preference, Cooperberg et al found that the rationale of clinicians in selecting primary hormonal treatment for localized prostate cancer was based on patient’s consideration, including low-risk group of patients with prostate cancer, short life expectancy rate, and radical treatment, which is assumed to bring little clinical improvement for the patients.13,14 Schymura et al added that aging, normal results of digital rectal examination, PSA >20 ng/mL, low Gleason Score and other comorbidities are the rationales in selecting primary hormonal treatment over radical treatment for patients with localized prostate cancer.15

The overall 5-year survival rate in the present study was 77.3%; while Akaza et al. in Japan found similar results, i.e. 72%. However, on the 10-year follow up by Akaza et al. they found that the overall survival rate was only 41% with specific survival rate of 78%.4 A study in our institution in 2010 reported 5-year survival rate of the patients with prostate cancer who had received radical treatment, prostatectomy or radiotherapy was 68.4% and 69.2%, respectively.16

Nevertheless, Lu-Yao et al. found different results revealing that primary hormonal treatment was not associated with survival rate in patients with localized prostate cancer and elder age compared to patients who had undergone radical prostatectomy or radiotherapy.17 Another study by Wong et al demonstrated that primary hormonal treatment did not improve the survival rate in patients with localized prostate cancer and even provide worse outcome compared to patients with localized prostate cancer who had only been treated with observation.18

Although primary hormonal treatment has become an alternative for localized and locally advanced prostate cancer, its effectiveness is still controversial. Moreover, the side effect of hormonal treatment, including hypogonadism should be considered. Hypogonadism may cause loss of libido, metabolic syndrome including increased serum lipoprotein level, reduced insulin sensitivity and obesity; and all of them may increase the risk of cardiovascular disease.19-22 Reduced bone mass up to the resulting fracture,19,21,22 and the development of psychocognitive impairment, which are known as Androgen Deprivation Syndrome,23,24 are also the effect of hypogonadism due to hormonal treatment. Testosterone replacement therapy, which is usually used for hypogonadism due to aging factor, is contraindicated in patients with localized prostate cancer who have not or did not received radical treatment as well as for patients with advanced prostate cancer who still show responses with hormonal treatment.25

Among all of the side effects, we should consider that in such treatment, besides it may reduce survival rate, it may also reduce the patient’s quality of life; therefore, appropriate thought which is consistent with indication and the characteristic of prostate cancer for each patients should be considered before suggesting primary hormonal treatment as an alternative treatment option for patients with localized and locally advanced prostate cancer.

In the present study, hemoglobin levels were a significant clinical parameter as survival predictive factors, both in localized and locally advanced prostate cancer group who had received primary hormonal treatment; while PSA, tumor grading and staging did not show any significance. It explains that the survival rate of patients with prostate cancer is possibly determined not only by PSA, tumor grading or staging, but also by other comorbidities. Such results are consistent with the results in the study by Schymura et al reporting that comorbidities do have effect on 5-year survival rate.15

Irregular medical visits by patients with prostate cancer has caused a number of patients
to be lost to follow up; therefore, we could not have any data about the confirmed cause of death. Thus, the survival rate found in our study is overall survival rate instead of specific survival rate for prostate cancer. Both issues are the limitations of our study. However, to our knowledge, the present study is the first study in Indonesia reporting on the role of primary hormonal treatment in localized and locally advanced prostate cancer.

CONCLUSION

There were 29.9% patients with localized and locally advanced prostate cancer who had received primary hormonal treatment between January 1995 and December 2009. There are no significant statistic differences regarding mean survival rate and 5-year survival rate between the localized and locally advanced prostate cancer group.

Hemoglobin level is a significant clinical parameter of survival predictive factors, both in localized and locally advanced prostate cancer group, i.e. the lower the hemoglobin level, the lower the survival rate.

Considering a significant number of side effects of hormonal treatment that may reduce the patient’s quality of life, hormonal therapy as primary treatment in patients with localized and locally advanced prostate cancer should be applied according to the indications.

REFERENCES

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