Efficacy of Androgen Deprivation Therapy for Localized Prostate Cancer: Analysis of pT0 Evaluated by Radical Prostatectomy Specimen

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Abstract. Aim: In order to investigate which types of localized prostate cancer can be treated most effectively by androgen deprivation therapy (ADT), cases of no residual cancer in radical prostatectomy specimens (pT0) after neoadjuvant ADT were analyzed. Patients and Methods: Patients with localized prostate cancer who underwent radical prostatectomy after neoadjuvant ADT were investigated retrospectively. Results: Thirty-two patients (24.2%) were diagnosed with pT0 disease by pathological evaluation. The positive-core proportion of prostate biopsy was lower, the duration of neoadjuvant ADT was longer, and prostate-specific antigen (PSA) nadir before radical prostatectomy was lower in pT0 cases compared to non-pT0 cases, and these differences were statistically significant. The percentage of pT0 cases with PSA nadir <0.2 ng/ml and <0.008 ng/ml before radical prostatectomy were 29.2% (21 out of 72 cases) and 83.3% (5 out of 6 cases), respectively. The positive-core proportion of prostate biopsy and PSA nadir before radical prostatectomy had a significant impact on pT0 status after neoadjuvant ADT. Conclusion: ADT for localized prostate cancer is thought to be highly effective in cases with low cancer volume. ADT is effective in cases of localized prostate cancer with PSA below the levels of detection by supersensitive PSA assay, and such cases show no cancer recurrence. Treatment options in such cases include intermittent or discontinuation of ADT. Androgen deprivation therapy (ADT) for localized prostate cancer is not necessarily recommended in many clinical guidelines, but is actually widely adopted for elderly patients or patients with complications who are not suitable for radical treatment, such as surgery or radiation (1, 2). ADT tends to be applied for localized prostate cancer even in Western countries, and a trial of a risk scoring system to predict the efficacy of ADT, called the Japan Cancer of the Prostate Risk Assessment (J-CAPRA), was performed by the Japan Study Group of Prostate Cancer (J-Cap) and Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) (3). Long-term continuous ADT is associated with adverse events, such as osteoporosis and cardiovascular events. Intermittent ADT has been used to avoid adverse events induced by continuous ADT and with the expectation of extending the effective period. Intermittent ADT is superior with regard to the quality of life in the off-period, and shows comparable effects to continuous ADT with regard to outcome, such as biochemical failure, progression-free survival, and overall survival (4). Localized prostate cancer with long-term ADT treatment without becoming castration-resistant has been reported clinically (5, 6). However, there is no consensus regarding adaptation of intermittent ADT or cessation after long-term ADT for localized prostate cancer.

We sometimes experience radical prostatectomy cases with neoadjuvant ADT in which no cancer is detected in the resected specimen (pT0). These are regarded as cases in which ADT was the most effective. In the present study, we retrospectively analyzed radical prostatectomy cases treated with neoadjuvant ADT, and examined the predictors of efficacy of ADT in cases of localized prostate cancer cases.

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Key Words: Prostate cancer, androgen deprivation therapy, radical prostatectomy, prostate-specific antigen.
Patients and Methods

This study was conducted using the databases of Kanazawa University Hospital, Kaga Municipal Hospital, and Kanazawa Medical Center with the approval of the Institutional Review Boards of all three hospitals. We retrospectively examined 132 cases of localized prostate cancer treated with radical prostatectomy after at least three months of neoadjuvant ADT between April 2000 and March 2012. Serum prostate-specific antigen (PSA) level was assessed by the supersensitive assay (Beckman Coulter, Brea, CA, USA) after April 2005. Clinical staging was determined by digital rectal examination, transrectal ultrasound, computed tomography, magnetic resonance imaging, and bone scan. The risk categories before neoadjuvant ADT were classified according to D’Amico et al. (7). Prostatic systematic needle biopsy was performed under transrectal monitoring by ultrasound, and the number of needle biopsy cores for each case ranged from 6 to 15. The positive rate of biopsy cores was determined as the proportion of biopsy cores including prostate cancer to the total number of biopsy cores. Combined androgen blockade (CAB) as neoadjuvant ADT was performed until radical prostatectomy by anti-androgen (100 mg/day of chlormadinone acetate, 375 mg/day of flutamide, or 80 mg/day of bicalutamide) and luteinizing hormone-releasing hormone (LHRH) agonist (leuprorelin acetate 3.75 mg/month or goserelin acetate 3.6 mg/month).

PSA nadir, defined as the lowest level of PSA between the time of initiation of neoadjuvant ADT and radical prostatectomy, was divided into three categories, PSA < 0.008 ng/mL, 0.008 ≤ PSA < 0.2 ng/mL, and PSA ≥ 0.2 ng/mL. Cases in which preoperative serum PSA was not measured within one month of the operation were excluded from the evaluation of PSA nadir. The limit of quantification of the supersensitive PSA assay was 0.008 ng/mL; the limit of quantification of PSA before 2005 was 0.2 ng/mL prior to the introduction of supersensitive PSA assay.

The prostatectomy specimen was fixed with 10% buffered formalin and cut into sections 3-5 mm thick according to routine procedures and stained with hematoxylin and eosin (H&E). Cases in which histopathological workup failed to detect residual viable cancer were classified as pT0. The PSA level was measured every three months in the first two years after the operation, and then every 4-6 months thereafter. PSA recurrence was defined as two consecutive values of ≥0.2 ng/mL. There were nine cases in which postoperative PSA did not fall to 0.2 ng/mL or below, and the day of operation was defined as PSA recurrence day in these cases.

Comparison of pre-treatment clinical characteristics between pT0 and non-pT0 cases was performed by the Mann–Whitney U-test and chi-squared test. One-way ANOVA was performed for comparisons of three or more groups and Pearson’s correlation coefficient was used to determine the relationships of each factor. PSA progression-free survival following radical prostatectomy was estimated using the Kaplan–Meier method, and the statistical significance of differences between groups was calculated using the log-rank test. Logistic regression analysis was used to determine the significant predictors of pT0. Statistical analyses were performed using SPSS ver.17.0 (SPSS Inc, Chicago, IL, USA) with p<0.05 taken to indicate statistical significance.

Results

A total of 132 cases were analyzed retrospectively. The preoperative clinical characteristics of pT0 and non-pT0 patients included in this study are presented in Table I.

Thirty-two cases were classified as pT0 (24.2%). There were no significant differences in mean age, PSA level at prostate biopsy, Gleason score of prostate biopsy, clinical stage, or D’Amico’s risk classification between pT0 and non-pT0 cases. The positive core proportion of prostate biopsy was significantly lower, the duration of ADT was longer, and PSA nadir before radical prostatectomy was lower in pT0 cases. The positive core proportion of prostate biopsy was <0.2 ng/mL or <0.008 ng/mL were 29.2% (21 out of 72 cases) and 8.5% (6 out of 71 cases), respectively. The percentages of cases with nadir PSA of <0.2 ng/mL and <0.008 ng/mL were 29.2% (21 out of 72 cases) and 83.3% (5 out of 6 cases), respectively.

Table I. Preoperative patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>pT0 (N=32)</th>
<th>non-pT0 (N=100)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>66.3±5.8</td>
<td>67.2±6.7</td>
<td>0.474</td>
</tr>
<tr>
<td>PSA level (ng/mL)</td>
<td>11.0±10.2</td>
<td>18.8±29.3</td>
<td>0.141</td>
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<tr>
<td>Biopsy Gleason score</td>
<td>&lt;7</td>
<td>18</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Positive biopsy core (%)</td>
<td>24.8±19.1</td>
<td>40.9±26.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinical stage (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>19</td>
<td>51</td>
<td>0.538</td>
</tr>
<tr>
<td>T2</td>
<td>12</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>D’Amico Risk group† (n)</td>
<td></td>
<td></td>
<td>0.074</td>
</tr>
<tr>
<td>Low</td>
<td>13</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>11</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Duration of ADT (months)</td>
<td>7.8±5.0</td>
<td>5.9±3.0</td>
<td>0.042</td>
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<td>PSA nadir before RPx (n)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;0.008 ng/mL</td>
<td>5</td>
<td>1</td>
<td></td>
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<tr>
<td>0.008 to &lt;0.2 ng/mL</td>
<td>16</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>&gt;0.2 ng/mL</td>
<td>3</td>
<td>28</td>
<td></td>
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<tr>
<td>Duration of observation (months)</td>
<td>42.0±32.3</td>
<td>42.1±36.5</td>
<td>0.998</td>
</tr>
</tbody>
</table>

Data are presented as number or mean±standard deviation. PSA, Prostate specific antigen; ADT, androgen deprivation therapy; RPx, radical prostatectomy. *Low risk: PSA<10 ng/mL and cT1, cT2a and Gleason score <6; intermediate risk: 10<PSA<20 ng/mL or cT2b or biopsy Gleason score 7; high risk: PSA>20 ng/mL or cT2c, 3 or biopsy Gleason score ≥8.
The cancer-positive core proportion of prostate biopsy, duration of neoadjuvant ADT, and PSA nadir before radical prostatectomy had significant impacts on the pT0 status after neoadjuvant ADT on univariate logistic regression analysis. The cancer-positive core proportion of prostate biopsy and PSA nadir before radical prostatectomy had significant impacts on pT0 status after neoadjuvant ADT on multivariate logistic regression analysis (Table II). PSA progression-free survival was significantly longer in the pT0 group than the non-pT0 group \((p=0.039)\) (Figure 1). No patients showed PSA progression after the operation in the group with PSA nadir <0.008 ng/ml before the operation, and patients in this group tended to escape PSA progression after the operation compared to the groups with PSA nadir <0.2 ng/ml or \(\geq 0.2\) ng/ml, but the differences were not statistically significant (Figure 2). There were no deaths due to prostate cancer or adverse events of the treatment during the observation period in the present study.

### Discussion

Most studies of neoadjuvant ADT before radical prostatectomy were conducted with a short administration time of approximately three months, and only 5% of cases achieved pT0 (8-10). However, in the present study, pT0 was obtained in 24.2% of all cases using ADT for an average period of 6.3 months. Previous studies also showed higher percentages of pT0 cases associated with longer periods of neoadjuvant ADT, as observed here (11). There have been some reports that a small number of cancer-positive biopsy cores, low Gleason score (≤ 6), low clinical stage, and the duration of neoadjuvant ADT are associated with pT0 (12). In the present study, cancer-positive biopsy cores and PSA nadir before radical prostatectomy were predictors of pT0 on multivariate logistic regression analysis. The duration of ADT was also a significant predictor of pT0 on univariate logistic regression analysis. A statistically significant negative correlation between duration of ADT and PSA nadir was observed using Pearson’s correlation coefficient \((p<0.001)\), and PSA nadir tended to decrease with increasing duration of ADT. We evaluated prostate cancer volume before ADT using the positive-prostate biopsy core proportion as it was reported previously that the number of positive biopsy cores is significantly correlated with cancer volume evaluated in resected specimens obtained by radical prostatectomy (13). Cases of localized prostate cancer with low cancer volume and low PSA nadir before the operation tended to achieve pT0. The number of cases with undetectable PSA nadir before the operation, as measured by supersensitive PSA assay was six (8.5%) in this study; however, the number of cases may increase after longer-term ADT. Five out of these six cases with undetectable PSA level on supersensitive PSA assay achieved pT0. Therefore, cases with PSA level below the limit of detection on supersensitive

![Table II. Multiple logistic regression analysis for pT0 after androgen deprivation therapy (ADT).](image-url)
PSA assay may achieve radical cure of the cancer. Prognostic evaluation of matched-pair analysis on clinical stage and Gleason score between pT0 and non-pT0 cases revealed no statistically significant differences (14).

Cases of prostate cancer with low cancer volume and low Gleason score evaluated by prostate biopsy may tend to become pT0, and once pT0 status has been obtained, these cases are thought to have better PSA progression-free survival rates than non-pT0 cases (11, 15). Although ADT for localized prostate cancer is not necessarily recommended in many guidelines, ADT is selected clinically according to advanced age or co-morbidity (5, 6, 16), while long-term ADT has been suggested to be efficacious (17). However, the risk of adverse events, including osteoporosis and metabolic disorders, increases with the duration of ADT (18-20). To avoid such risks, various schedules of intermittent ADT have been examined and were reported to show anticancer effects comparable to those of continuous ADT with reduced incidence rates of adverse events (4, 21). Fujimoto et al. reported that continuous ADT with CAB for 10 months after PSA reached <0.2 ng/ml, may be sufficient to obtain complete response (11). However, the appropriate period of ADT for localized prostate cancer, the criteria for complete response, and criteria for cessation of ADT after long-term treatment remain unclear. In the present study, 5 out of 6 cases (83.3%) with PSA <0.008 ng/ml by supersensitive assay after ADT were classified as pT0, and such cases of localized prostate cancer with PSA <0.008 ng/ml during ADT may have the possibility of complete response and cessation of the ADT. In addition, none of the six cases with PSA nadir <0.008 ng/ml before the operation showed progression of PSA after the operation, and the patients in the group with PSA nadir <0.008 ng/ml tended to escape PSA progression after surgery in comparison to the groups with PSA nadir <0.2 ng/ml or ≥0.2 ng/ml, but the differences between each group were not statistically significant.

The present study had some limitations. This was a retrospective study, the number of cases included was small, and preoperative PSA measurement was not carried out in all cases and the day of PSA measurement before the operation was not necessarily the same day. In the present study, pT0 was determined by routine pathological diagnosis with H&E staining; however, re-evaluation using thinner sliced pathological samples of the same specimen may reveal very small cancer remnants in these cases (22). In fact, 4 out of 32 (12.5%) pT0 cases had PSA recurrence during the observation period in the present study. Therefore, pT0 by routine pathological diagnosis did not necessarily indicate a complete lack of cancer in the specimen. Further prospective investigations are necessary to clarify our results. However, neoadjuvant ADT before radical prostatectomy for localized prostate cancer was reported to be ineffective (23-25), hence future similar studies using prostatectomy specimens after neoadjuvant ADT may be difficult for ethical reasons.

**Conclusion**

Our results indicate that cessation of ADT may be suitable in patients with localized prostate cancer achieving undetectable PSA levels using the supersensitive assay by ADT, even without radical prostatectomy.

**References**


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