Prostate Cancer

Preoperative Serum Testosterone Level as an Independent Predictor of Treatment Failure following Radical Prostatectomy

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Abstract

Objectives: Preoperative low serum testosterone (TS) level has been reported to be associated with adverse pathologic results in patients with clinically localized prostate cancer (pCA) treated with radical prostatectomy (RP). However, prior studies failed to show prognostic impact of preoperative low TS in these patients. The aim of this study was to investigate the relationship between preoperative TS and prostate-specific antigen (PSA) failure in these patients.

Methods: Of 304 patients diagnosed with clinically localized pCA who had been treated with RP alone, 272 patients whose preoperative TS level had been measured were eligible for this analysis. Postoperative TS levels were also available in 222 of the 272 patients. Cox proportional hazard model was used to elucidate factors predictive for PSA failure.

Results: Of the 272 patients 49 had low (<300 ng/dl) and 223 had normal preoperative TS level. In a stepwise multivariate analysis, preoperative TS (p = 0.021) was an independent and significant predictor of PSA failure along with RP Gleason score (p = 0.006), surgical margin status (p = 0.0001), and PSA (p = 0.0001). Five-year PSA failure–free survival rate of the patients with preoperative low TS (67.8%) was significantly worse than that with normal TS (84.9%) (p = 0.035). Serum TS levels increased significantly after RP (p < 0.0001). The increment of TS level in preoperative low TS group was significantly greater than that in preoperative normal TS group (p = 0.0003).

Conclusions: The current results demonstrated that preoperative TS level is an independent and significant predictor of PSA failure after RP in patients with clinically localized pCA.

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1. Introduction

Low serum testosterone (TS) level has been reported to be associated with poorer outcome in metastatic prostate cancer (pCA) [1–3]. In a recent clinically localized pCA series treated with radical prostatectomy (RP), preoperative low TS level was associated with high pathologic stage [4–6]. However, whether preoperative low TS predicts poor prognosis in clinically localized pCA series treated with RP remains to be elucidated. Therefore, we retrospectively tested whether preoperative low TS is associated with the treatment outcome in patients with clinically localized pCA treated with RP alone.

The overall or cause-specific survival rates in patients with clinically localized pCA treated with RP remains usually very high during 10–15 yr of follow-up periods; therefore, we used prostate-specific antigen (PSA) failure as a surrogate end point for assessment of prognosis in these patients as suggested previously [7,8].

2. Methods

2.1. Patient population

We retrospectively reviewed the clinical records of 304 Japanese patients diagnosed with clinically localized pCA treated with RP without neoadjuvant therapy between January 1998 and December 2005 at Cancer Institute Hospital, Tokyo, Japan. Of the 304 patients, a total of 272 patients for whom preoperative TS levels were available were eligible for this analysis. There was no statistical difference in perioperative clinicopathologic variables (eg, age, PSA, pathologic stage) between the 272 patients with preoperative TS level available and the 32 patients with preoperative TS level unavailable. Postoperative serum TS level was also available in 222 of the 272 patients. There was no statistical difference in perioperative clinicopathologic variables (eg, age, PSA, pathologic stage) between the 222 patients with postoperative TS level available and the 50 patients with postoperative TS level unavailable. After the surgery, no one received any adjuvant therapy before PSA failure was confirmed. The median (quartile range) value of age, total PSA, and follow-up period were 67 yr (range: 51–80), 8.1 ng/mL (range: 0.5–80.0), and 32.2 mo (range: 3.3–97.2), respectively.

2.2. TS measurement

Blood samples for TS measurement were obtained in the morning when TS concentration is relatively stable at their high concentration level. TS level was measured by radioimmunoassay with the use of the DPC total testosterone kit (Nippon DPC Corp, Tokyo, Japan). Because a TS level of less than 300 ng/dl is defined as partial androgen deficiency [9,10], a level of 300 ng/dl was chosen as the cut-off value of TS.

2.3. Staging and follow-up

The 1997 TNM classification was used to define clinical stage [11]. To measure serum PSA level, Tandem-R Test (Beckman Coulter, San Diego, CA, USA) was used until July 2003, and AxSYM (Abbott Laboratories, Japan) kit was used thereafter.

After the RP, serum PSA measurement was performed every 3 mo during year 2, every 6 mo during years 3–5, and yearly thereafter. Various radiographic examinations were performed when PSA failure was confirmed. PSA failure was defined as a PSA level greater than 0.2 ng/ml on two consecutive measurements.

2.4. Pathology

Histopathologic grading of the needle biopsy and the RP specimens was performed according to the Gleason score (GS) system by a single pathologist (Y. I.), and GS was stratified into two groups, namely GS 4–6 (Gleason pattern 4 or 5 is absent) and GS 7–10 (Gleason pattern 4 or 5 is present). RP specimens were fixed intact in 20% neural buffered formalin and sectioned transversely at 5-mm intervals. All specimens were whole mounted. The presence of extracapsular extension, seminal involvement, pelvic lymph node metastasis, surgical margin status, and GS were recorded.

2.5. Statistical analysis

For statistical analysis, age, PSA, clinical stage, biopsy GS, pathologic stage, RP GS, and surgical margin status were treated as dichotomous categoric variables: ≤67 yr versus >67 yr, <20 ng/ml versus ≥20 ng/ml, T1c versus T2, GS 4–6 versus GS 7–10, pT2 versus pT3, GS 4–6 versus GS 7–10, and positive versus negative, respectively. The differences in variables between preoperative low TS group (TS <300 ng/dl) and normal TS group (TS ≥300 ng/dl or greater) were analyzed by chi-square test. Actuarial survival rate was calculated by the Kaplan-Meier method. Cox proportional hazard model was used to assess the association of variables with PSA failure–free survival. Preoperative and postoperative TS levels were compared with Wilcoxon test. A p value less than 0.05 was considered statistically significant. Statistical analyses were performed with JMP, version 5.1.1 (SAS Institute Inc, Cary, NC, USA).

3. Results

3.1. Preoperative TS level

Preoperative TS ranged widely from 149 to 943 ng/dl (median: 401 ng/dl). Of the 272 patients, preoperative TS level was less than 200 ng/dl in 6 (2.2%), 200–299 ng/dl in 43 (15.8%), 300–399 ng/dl in 86 (31.6%), 400–499 ng/dl in 76 (27.9%), and equal to or greater than 500 ng/dl in 61 (22.4%). Thus, preoperative low and normal TS groups consisted of 49 (18.0%) and 223 (82.0%) patients, respectively. Table 1 shows the relationship between preoperative TS and clinico-
pathologic features. There was no statistically significant association between perioperative clinicopathologic variables and preoperative TS level.

3.2. Predictors of PSA failure on univariate and multivariate analysis

During the follow-up period (median: 32.2 mo; quartile range: 3.3–97.2), PSA failure was confirmed in 30 of the 272 patients (11.0%). Table 2 shows univariate analysis of selected factors to predict PSA failure–free survival. PSA (p < 0.0001), surgical margin status (p < 0.0001), GS in RP specimen (p = 0.0001), pathologic stage (p = 0.001), and preoperative TS (p = 0.035) were significant predictors of PSA failure.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>Full model</th>
<th>Reduced model</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300</td>
<td>1.00 (ref)</td>
<td>0.023</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>≥300</td>
<td>0.366</td>
<td>0.167–0.862</td>
<td>0.364</td>
</tr>
<tr>
<td>RP Gleason score</td>
<td>7–10</td>
<td>1.00 (ref)</td>
<td>0.006</td>
</tr>
<tr>
<td>≤6</td>
<td>0.438</td>
<td>0.175–0.811</td>
<td>0.438</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>&lt;20</td>
<td>1.00 (ref)</td>
<td>0.0001</td>
</tr>
<tr>
<td>≥20</td>
<td>5.184</td>
<td>2.347–11.16</td>
<td>5.138</td>
</tr>
<tr>
<td>Surgical margin</td>
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<td>1.00 (ref)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td>pT3</td>
<td>1.00 (ref)</td>
<td>0.920</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>0.948</td>
<td>0.338–2.671</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; ref = reference; RP = radical prostatectomy; PSA = prostate-specific antigen.
Stepwise multivariate analysis of predictors of PSA failure according to Cox proportional hazard model is shown in Table 3. Among the five variables evaluated, preoperative TS was a significant and independent predictor of PSA failure ($p = 0.021$) along with GS in RP specimen ($p = 0.006$), PSA ($p = 0.0001$), and surgical margin status ($p = 0.0001$).

3.3. PSA failure–free survival rates according to the preoperative TS level

Of the 272 patients, 2 died but no one died of PCa. Accordingly, 5-yr overall and cause-specific survival rates were 98.4% and 100%, respectively. Fig. 1 shows PSA failure–free survival rates according to preoperative TS level. Five-year PSA failure–free survival rate of preoperative low TS group (67.8%) was significantly lower than that of normal TS group (84.9%) ($p = 0.035$).

3.4. Postoperative TS level

Postoperative TS levels were recorded in 222 of the 272 patients with median and mean values of 480 and 495 ng/dl, respectively. Postoperative TS level was significantly higher than preoperative TS level ($p < 0.0001$). The postoperative median TS level in 38 of 49 patients in preoperative low TS group was 357 ng/dl (quartile range: 186–1430) and 503 ng/dl (quartile range: 136–1090) in 184 of the 223 patients in preoperative normal TS group. The median increments of TS levels were 146 and 104 ng/dl in the low and normal TS groups, respectively. The increment of TS levels in the preoperative low TS group (median: 146 ng/dl) was significantly higher than that in the preoperative normal TS groups (median: 104 ng/dl) ($p = 0.0003$).

4. Discussion

We demonstrated for the first time that preoperative TS level lower than 300 ng/dl is a significant and independent predictor of PSA failure in patients with clinically localized prostate cancer treated with RP alone. After adjusting for other prognostic factors, risk of PSA failure increased 2.7-fold for men with preoperative TS level lower than 300 ng/dl compared with those with preoperative TS level equal to or greater than 300 ng/dl. One strength of the current study is that it was a single-institute study in which all surgical procedures were performed in a consistent method.

Several reports have shown the positive relationship between preoperative low TS level and poor pathologic findings in RP series [6–8,12]. Massengill et al [6] retrospectively analyzed 879 patients treated with RP from multiple institutions and showed that patients with non–organ-confined PCa have significantly lower preoperative TS levels than those with organ-confined PCa, and that preoperative TS level is a significant predictor of extraprostatic disease in multivariate analysis. These findings have been confirmed in patients with different ethnic background by two other investigators [7,8]. Recently, although a small study cohort, Teloken et al [12] from Brazil reported preoperative low TS level was associated with positive surgical margin in RP.

A few investigators reported the association between GS and pretreatment TS level in PCa [9,13]. Hoffman et al [9] indicated that lower serum-free testosterone might be a marker for more aggressive disease (any clinical stage with high GS). Schatzl et al also reported statistically significant difference in mean GS between patients with partial androgen deficiency (TS < 300 ng/dl) and those without androgen deficiency (TS ≥ 300 ng/dl) [13], suggesting that PCa with high GS had lower pretreatment TS level [9,13]. Unfortunately, our result cannot be compared with their result directly, because metastatic or locally advanced PCAs were included in their study cohort. Association between pretreatment TS level and GS was not shown in the reports of Massengill [6], Imamoto [7], and Isom-Batz et al [8] in which study populations were limited to patients with clinically localized PCa. In the future,
another larger study will be needed to confirm the relationship.

Although in a recent clinically localized pCA series treated with RP, preoperative low TS level was associated with high pathologic stage [4–6], we found no association between preoperative TS level and pathologic findings in the current cohort. The cause of this discrepancy is unclear. However, in multivariate analysis, preoperative TS level was proved to be a significant and independent predictor of PSA failure.

Although the cause of the positive association between pretreatment low TS level and prognosis of pCA is unclear, Miller et al [14] revealed that TS and gonadotropin levels were significantly increased after RP. According to Lukkarinen et al [15], these endocrine changes were not seen after simple prostatectomy for benign hypertrophy. From these findings, Miller et al [14] have suggested that inhibin-α produced by the pCA cells suppresses hypothalamic pituitary axis, resulting in a lowering of TS level. Significant postoperative rise of TS level, especially in patients with preoperatively low TS level, suggests that pCA cells in these patients might produce some substance that suppress TS level. Also, Risbridger et al [16] evaluated tumor expression of inhibin-α in 174 RP specimens and concluded that elevated expression of inhibin-α is related to higher risk of PSA failure. From these findings, we speculated that, as one of the causes of positive association between pretreatment low TS level and poor prognosis, pCA cells in patients with lower pretreatment TS level might produce inhibin-α, resulting in poorer prognosis. Morgentaler et al [17] recently reported that pCA was present in more than one of seven hypogonadal men with PSA of 4.0 ng/mL or less, and they concluded that lower TS levels were associated with an increased risk of cancer. Although the cause of the positive association between low TS level and pCA risk is unclear, their results might be explained by the suppressive action of the presence of pCA on the low TS level of the patient. In contrast, Freedland et al [18] recently reported that the TS might not reflect intraprostatic androgenicity; accordingly, simply comparing outcomes between men with low and high TS level might not lend insight into the association between low androgenicity and pCA aggressiveness. Also, Marks et al [19] recently reported that, although TS replacement therapy for men with hypogonadism increases serum TS levels to the normal range, TS levels in the prostatic tissue remain unchanged. Accordingly, in the future, measurement of both serum TS and TS in the prostatic tissue might be required to further investigate the association between TS level and prognosis for pCA.

In the current study, there are several limitations, including its retrospective nature, relatively small population size, and short follow-up period. Another large study is needed to confirm the adverse impact of low TS level on prognosis of patients with clinically localized pCA and to basically resolve the mechanism.

5. Conclusions

We showed preoperative TS level could predict risk of PSA failure in patients with clinically localized pCA treated with RP alone. Our findings suggest a possible role for pretreatment TS level as an independent prognostic factor in risk stratification for clinically localized pCA treated surgically. To gain further insight in the association of hormonal status with pCA aggressiveness, a prospective study in a larger cohort is warranted.

Conflicts of interest

Our manuscript is not supported by any commercial relationship, financial grants, or funding.

References


