Original Article

Postoperative early ultrasensitive prostate-specific antigen identifies patients at risk for biochemical recurrence in margin positive prostate cancers: a single-center study

Koji Hatano, Takuya Okusa, Yu Ishizuya, Yasutomo Nakai, Masashi Nakayama, Ken-ichi Kakimoto, and Kazuo Nishimura*

Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

*For reprints and all correspondence: Kazuo Nishimura, Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan. E-mail: nisimura-ka2@mc.pref.osaka.jp

Received 15 June 2016; Accepted 30 September 2016

Abstract

Objective: To identify predictors for biochemical recurrence among patients with positive surgical margins (RM1) after radical prostatectomy and to examine the effect of ultrasensitive prostate-specific antigen measured early after prostatectomy on biochemical recurrence.

Methods: We identified 705 patients with prostate cancer who were treated with radical prostatectomy without preoperative hormonal therapy at our institution between 2000 and 2014. The patients with RM1 who had a postoperative prostate-specific antigen <0.2 ng/ml without lymph node metastasis were evaluated for biochemical recurrence–free survival. Survival rates were calculated using the Kaplan–Meier method. The Cox regression model was used for multivariate analysis. The prediction of biochemical recurrence was assessed using area under the curve of the receiver operating characteristic.

Results: Among the 705 patients, 190 (27%) had RM1. Biochemical recurrence was evaluated in 164 patients, excluding 26 patients who underwent adjuvant therapy with or without lymph node metastasis. With a median follow-up of 55 months, the biochemical recurrence–free survival rate of the entire RM1 cohort was 78% at 2 years and 64% at 4 years. The multivariate analysis revealed that postoperative early ultrasensitive prostate-specific antigen >0.02 ng/ml was the significant risk factor for biochemical recurrence (hazard ratio 13.10). Meanwhile, the patients with postoperative early ultrasensitive prostate-specific antigen <0.01 ng/ml had a significantly lower risk for biochemical recurrence (hazard ratio 0.12). Area under the curve for the postoperative early ultrasensitive prostate-specific antigen value to predict biochemical recurrence was 0.789.

Conclusions: The ultrasensitive prostate-specific antigen value measured early after prostatectomy was the potent predictor of biochemical recurrence among the patients with RM1.

Key words: biochemical recurrence, positive surgical margin, prostatectomy, prostate cancer, prostate-specific antigen

Introduction

Radical prostatectomy is one of the major treatments for localized prostate cancer. The aim of radical prostatectomy is to improve oncological outcome without harming quality of life aspects such as urinary and erectile functions. Occasionally, however, some peripheral tumor foci are not recognized by surgeons. As a result, a positive surgical margin (RM1) is reported to occur at a rate of 6.5–38% after radical prostatectomy (1,2). Although the clinical effect
of RM1 on cancer prognosis still remains unclear (2), a number of studies have demonstrated that RM1 increases the risk of biochemical recurrence (BCR) after radical prostatectomy (3–9). Thus, patients with RM1 are candidates for immediate adjuvant radiation therapy (RT) to decrease BCR and provide a survival benefit compared with that of patients undergoing observation (10–12). However, several reports indicated that BCR did not occur in over half of the patients, even in the presence of RM1, over 5-year follow-up (4,7,8). This raises an issue for the treatment of patients with RM1 in which a number of patients are overtreated by immediate adjuvant RT. Thus, the predictors for BCR among the patients with RM1 may help to solve this issue by identifying the patients with potential localized failure.

Among predictors of BCR, postoperative ultrasensitive prostate-specific antigen (uPSA) assay is one of the potential candidates. Conventional PSA assays have been applied to detect BCR, in which the detection threshold of 0.2 ng/ml was considered adequate to detect BCR (13). The uPSA was established to detect PSA with a lower limit of detection <0.1 ng/ml (14). Although the clinical usefulness of the uPSA after radical prostatectomy is still unclear, uPSA may have the potential to sensitively predict BCR with a lead time advantage over that of the conventional relapse definition (15). We previously reported that postoperative nadir value of uPSA was a predictor of BCR among the patients with adverse pathological features (16). Recently, several reports focused on a postoperative ‘early’ uPSA value to predict BCR. Inoue et al. reported that the uPSA value measured 3 months after prostatectomy predicted BCR among patients with localized prostate cancer (17). Recent reports also supported the use of postoperative early uPSA value to identify patients who require salvage therapy among those with adverse pathological features (15,18). The postoperative early uPSA may be useful to detect patients who require salvage therapy allowing adequate time for planning eventual therapy without waiting for the ‘nadir’ PSA value.

Here, we retrospectively evaluated the patients with RM1 after radical prostatectomy. The goal of this study was to identify predictors for BCR among patients with RM1 after radical prostatectomy. We examined the effect of uPSA measurement early after prostatectomy on BCR as well as the traditional predictors for BCR.

Patients and methods
Patient selection
We retrospectively reviewed our clinicopathological database of patients with prostate cancer who were treated with radical prostatectomy at the Osaka Medical Center for Cancer and Cardiovascular Diseases between January 2000 and December 2014. We identified 1023 patients, including 856 cases of open surgery and 167 cases of robotic surgery. The exclusion criteria of this study were patients with preoperative hormonal therapy or insufficient clinicopathological data. Among the 1023 patients, 705 were eligible for this study. RM1 was defined if cancer cells were in touch with the ink on the surface of the radical prostatectomy specimen. The patients with RM1 who had a postoperative PSA <0.2 ng/ml were further evaluated for BCR-free survival. The patients with RM1 who received adjuvant RT and/or adjuvant hormonal therapy as well as those with lymph node metastasis were excluded from the analysis.

PSA follow-up
For PSA follow-up, uPSA was used after radical prostatectomy. The cut-off value of uPSA was 0.02 ng/ml from 2000 to 2003 and 0.003 ng/ml from 2004 to 2015. The uPSA kit had been changed from Elecsys (Roche, Basel, Switzerland) to Architect (Abbott, Chicago, Illinois) where the compatibility between the two kits was confirmed in our institution. uPSA values were measured at least every 3 months until 2 years after surgery, every 6 months until 5 years and annually thereafter. The postoperative early uPSA value was defined as the uPSA value measured 3 months after prostatectomy.

Evaluation
The primary endpoint of this study was BCR, which was defined as a PSA value ≥0.2 ng/ml. Disease progression was defined as BCR, objective progression evaluated in a radiographic study or the start of salvage therapy due to the serial increase of PSA. Progression-free survival (PFS) was measured from the date of surgery to the date of the progression or the last follow-up. Survival rates were calculated using the Kaplan–Meier method, and the univariate comparisons were made using the log rank test. The Cox regression model was used for the multivariate analysis. The prediction of BCR was assessed using area under the curve of the receiver operating characteristic. JMP software was used for the statistical analysis. P < 0.05 was considered statistically significant.

Results
Among the 705 patients, 190 (27%) showed RM1. Among the 190 patients with RM1, pelvic lymphadenectomy was performed in 189 patients excluding 1 patient with National Comprehensive Cancer Network (NCCN) low-risk group. Disease progression was evaluated in 164 patients, excluding 23 patients who underwent immediate adjuvant radiation or hormonal therapy. Five patients who had lymph node metastasis were also excluded from the analysis. The clinicopathological data of the 164 patients are shown in Table 1. Based on the preoperative PSA value, Gleason score at biopsy and clinical stage, patients were stratified according to the NCCN risk groups (19). The pathological features of the patients such as pathological stage and Gleason score at surgery are also shown in Table 1. Further evaluation of the postoperative early uPSA value showed that although most of the cases had a postoperative early uPSA value <0.02 ng/ml, 23 cases (14%) had a postoperative early uPSA value >0.02 ng/ml.

With a median follow-up of 55 months (3–181 months), the PFS of the entire RM1 cohort was 91% at 1 year, 78% at 2 years and 64% at 4 years (Fig. 1). Perioperative factors were evaluated for their relation to PFS (Table 2). Among them, NCCN risk group, Gleason score, seminal vesicle invasion and postoperative early uPSA were the significant risk factors for PFS. The postoperative early uPSA >0.02 ng/ml was the significant risk factor for PFS among different NCCN risk groups (Table 3). No patients with a postoperative early uPSA value >0.02 ng/ml survived without BCR for more than 4 years. There was no significant difference in PFS between the initial PSA level, surgical approach (open vs robotic), RM1 status (single vs multiple) or RM1 location (apical vs non-apical) (Table 2). The multivariate analysis revealed that NCCN high-risk group (hazard ratio [HR] 2.05), Gleason score at surgery and over (HR 2.47) and postoperative early uPSA value >0.02 ng/ml (HR 13.10) were the significant risk factors for PFS (Table 4). Within the follow-up period, 45 (90%) out of 50 patients who developed BCR were treated by salvage RT and/or hormonal therapy. Then, we examined if time to metastatic-free survival was
influenced by the postoperative early uPSA status. The patients with postoperative early uPSA value >0.02 ng/ml had significant worse metastatic-free survival at 4 years compared with those who had postoperative early uPSA <0.02 ng/ml (90% vs 100%, respectively; \( P = 0.0009 \)).
Recently, Toussi et al. (4,7,8) reported that postoperative nadir uPSA value was a predictor of BCR among patients with adverse pathological features such as pathological T3 and/or RM1 (16). The uPSA may be useful to predict early disease recurrence (27) and determine patient follow-up protocol. However, it is still unclear whether earlier detection of BCR translates into prolonged time to metastasis (14). Although the patients with postoperative early uPSA value >0.02 ng/ml had worse metastatic-free survival in this study, the limitations include the relatively small rate of metastatic recurrence and the limited follow-up period.

Patients with RM1 are candidates for both immediate adjuvant RT and salvage RT after BCR (28). Currently, immediate adjuvant RT is applied for the prostate cancer patients with adverse
pathological features such as extracapsular extension, seminal vesicle invasion and/or RM1 (10–12). However, adjuvant RT would not be necessary for all of the patients with RM1 because over half of them did not experience recurrence without any adjuvant treatment. Furthermore, salvage RT is another treatment strategy for the patients with RM1 when they experience BCR. Several studies showed that salvage RT is more effective when initiated at a lower PSA level (29–31). Thus, uPSA may be useful to promote early salvage treatment and minimize overtreatment. Our results suggested that patients with a postoperative early uPSA value $>$0.02 ng/ml may be candidates for early salvage treatment because most of them experienced recurrence within 4 years (Table 2 and Fig. 2). However, most of the patients with a postoperative early uPSA value $<$0.01 ng/ml survived without recurrence (Table 5 and Fig. 2). Although the timing of postoperative uPSA measurement and the cut-off value for uPSA are not yet clearly identified, recent reports support the use of postoperative uPSA measurement to determine patients requiring salvage treatment (15,18).

In conclusion, our study revealed that a postoperative early uPSA value was the most potent predictor of BCR among the patients with RM1. The patients with postoperative early uPSA greater than 0.02 ng/ml may be candidates for salvage therapy. Further studies are needed to determine the threshold and clinical usefulness of the uPSA value after prostatectomy.

Table 6. Multivariate analysis for PFS with uPSA cut-off value 0.01 ng/ml ($n = 149$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN risk group (high vs intermediate/ low)</td>
<td>1.67</td>
<td>0.84–3.20</td>
<td>0.142</td>
</tr>
<tr>
<td>Seminal vesicle invasion (positive vs negative)</td>
<td>2.90</td>
<td>1.04–6.92</td>
<td>0.043</td>
</tr>
<tr>
<td>Gleason score at surgery ($\geq 8$ vs $\leq 7$)</td>
<td>4.45</td>
<td>1.78–10.91</td>
<td>0.002</td>
</tr>
<tr>
<td>Postoperative early uPSA ($&lt;0.01$ vs $\geq 0.01$ ng/ml)</td>
<td>0.12</td>
<td>0.06–0.24</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 3. The receiver operating characteristic curve for postoperative early uPSA to predict BCR. AUC, area under the curve.

Acknowledgements

This work was supported by Osaka foundation for the prevention of cancer and cardiovascular diseases.

Conflicts of interest

None declared.

References

16. Yoshida T, Matsuaki K, Kobayashi Y, et al. Usefulness of postoperative nadir prostate-specific antigen value by ultrasensitive assay as a predictor of prostate-specific antigen relapse for pathological T3 or positive surgical...
margins after radical prostatectomy for prostate cancer. *Int Urol Nephrol* 2012;44:479–85.