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Low pre–operative levels of serum albumin predict lymph node metastases and ultimately correlate with a biochemical recurrence of prostate cancer in radical prostatectomy patients

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Introduction. To date, only few studies focusing on the issue of host general and immune activity have been performed in localized prostate cancer (PCa). The aim of this study was to elucidate potent non tumor–related biomarkers that express aggressiveness of PCa treated by radical prostatectomy (RP).
Materials and methods. Data from 179 patients who underwent RP were analyzed. The correlations between various kinds of non tumor–related factors in addition to tumor–related factors and biochemical recurrence (BCR) were analyzed. The correlations between pre–, intra– and post–operative factors were also analyzed.
Results. Thirty–two cases (17.9%) had a BCR. The factors found to be significantly predictive of BCR using a Cox–proportional hazard model were the pre–operative serum prostate specific antigen (PSA) level and the existence of pathological lymph node metastasis (LNM). A low pre–operative serum albumin level (<4.0 g/dl) was significantly correlated with BCR univariately. Logistic regression analysis revealed that a low pre–operative serum albumin level, an American Society of Anesthesiologists (ASA) score above class 2, and a Gleason score above 8 in the biopsy specimens were significantly predictive of pathological LNM.
Conclusions. Tumor–related characteristics are more important for predicting BCR. However, our results suggest that low pre–operative serum albumin level may indicate extensive disease of clinically localized PCa and may ultimately be correlated with BCR. Although multiple reasons may account for the significance of the serum albumin level, it is noteworthy that delayed diagnostic and therapeutic procedures in comorbid patients with low serum albumin levels may lead to PCa progression.

INTRODUCTION

Biochemical recurrence (BCR) in prostate cancer (PCa) has a unique definition in the field of solid malignancies. This definition has been achieved because of the discoveries related to the ultra–specific tumor marker, prostate–specific antigen (PSA). The BCR–free rate is often considered to be the primary endpoint for the oncological outcomes of a radical prostatectomy (RP); this endpoint is based on the low incidence of PCa–related mortality and long post–BCR survival that have been reported in studies of PCa progression after various types of treatment modalities after BCR [1, 2, 3]. Since the era of PSA, the analysis of factors influencing BCR after RP has been a major area for clinical research in

the PCa field. To date, seminal vesicle involvement, lymph node metastasis (LNM), and extra–capsular extension of cancer are well–established predictors of BCR, all of which are obtained by detailed investigations of pathological findings in surgical specimens [4, 5]. Moreover, many physicians can estimate the BCR–free rate in a patient who underwent RP using various established nomograms. Kattan's post–operative nomogram is one of the best predictive tools of BCR, which uses the pre–operative serum PSA levels in addition to the pathological findings in post–surgical specimens [6]. Although detailed investigations of the tumor–related factors that influence BCR have been performed, the utility of other non–tumor–related factors, such as the general characteristics of the patients and the host immune activity, are unknown.

Cancer progression is determined by a balance between cancer cell proliferation and cancer cell death induced by the host immune reaction, which is thought to be complexly related to peripheral blood examination results and the general characteristics of the patients. Tumor progression due to the deficiency of host's immune activity and general characteristics should not be ignored, even though the patients with localized PCa treated by RP are relatively older (approximately of 60 to 75 years of age). Patients in this age range often have other complicating medical problems and diseases. To comprehensively characterize the various factors that influence BCR, we investigated the correlation of BCR with both tumor–related factors and the general and immune characteristics of patients who underwent RP, as obtained from demographic information and peripheral blood examinations. In addition, the correlations between pre– and intra–operative factors and post–operative pathological factors were also analyzed.

MATERIALS AND METHODS

Patients

Between 2002 and 2011, 242 patients with localized PCa underwent RP at our institution or one of our affiliated hospitals. Sixty–three patients received endocrine therapy before surgery. These patients were excluded from the study because of the difficulties in interpreting the pathological findings of radical prostatectomy specimens that were subjected to androgen deprivation. Therefore, 179 patients were eligible for the study. The tumor–related patients' characteristics are summarized according to the International Union against Cancer standards (sixth

Table 1. *Demographic and non-tumor-related patients' characteristics*

Characteristics	Values or number of cases
Total number of cases	179
Mean age at surgery (years), range	66.2, 48–81
Pre-operative mean BMI (kg/m2) (SD)	23.4 (3.7)
Pre-operative mean serum albumin (g/dl)	4.3 (0.3)
ASA risk classification system at surgery	
Class 1 / Class 2	107 (59.8%) / 66 (36.9%)
/ Class 3	/ 6 (3.3%)
Surgery type	
Open / Minimum incision endoscopic	129 (72.1%) / 26 (14.5%)
/ Robot-assisted	/ 24 (13.4%)
Blood loss at surgery (ml)	
<1000 / 1000–2000	115 (64.2%) / 49 (27.4%)
/ >3000	/ 15 (8.4%)

BMI – body mass index; SD – standard deviation; ASA – American Society of Anesthesiologists

edition). The demographic and non–tumor–related patients' characteristics are summarized in Table 1. The surgery types were as follows: open radical prostatectomy in 129 patients, minimum incision endoscopic radical prostatectomy in 26 patients, and robot–assisted radical prostatectomy in 24 patients (Table 1).

Data collection

The demographic and clinical non–tumor–related factors analyzed were age, body mass index (BMI), surgery type, amount of blood loss at surgery, complicating diseases, and pre–operative serum albumin level, which is thought to be related to immune activity. Complicating diseases were categorized using the American Society of Anesthesiologists (ASA) risk classification system. The tumor–related factors analyzed were pre–operative serum PSA level, clinical stage, and the tumor pathological findings in biopsy and surgical specimens. All factors were also categorized as pre–, intra–, and post–operative factors. The pre–operative non–tumor–related factors were age, BMI, complicating diseases assessed by the ASA score, and serum albumin level, all of which were collected at a pre–operative visit by the anesthesiologists. The pre–operative tumor–related factors were serum PSA level, clinical stage, and pathological findings of biopsy specimens. Intra– and post–operative factors were surgery type, the amount of blood loss at surgery, and pathological findings of the surgical specimens.

PSA monitoring

PSA monitoring was performed in all patients until their death or last follow–up visit. Initial PSA monitoring was conducted by at the discretion of the attending physician; however, the follow–up PSA monitoring policy was set by consensus of the out–patients clinic physicians. Namely, PSA monitoring was to be performed every three months for two years after surgery and every six months thereafter for at least five years after surgery. None of the patients were lost to follow–up for unexpected reasons. BCR was defined as when the serum PSA level exceeded 0.2 ng/ml or when a radical prostatectomy was carried out and the PSA did not decrease below 0.2 ng/ml after surgery.

Statistical analysis

The BCR–free rate was determined by the Kaplan–Meier method, and comparisons of the rate among groups were analyzed by the log–rank test. Univariate and multivariate analyses of the significance of the demographic and clinico–pathological param-
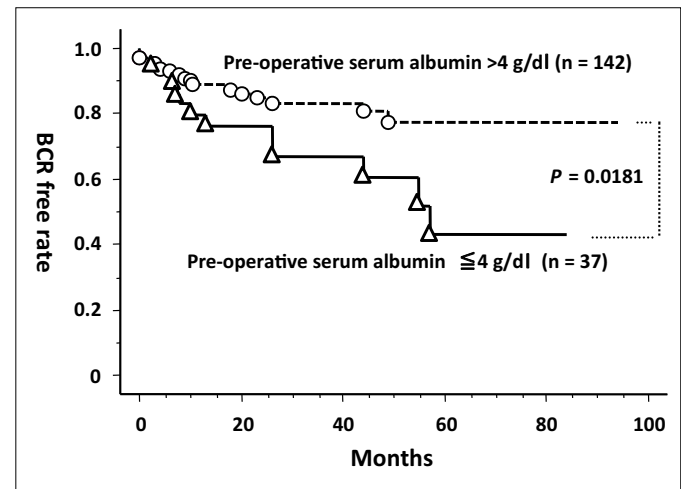

Figure 1. *Comparison of the biochemical recurrence (BCR)–free rate between two groups according to their pre–operative serum albumin levels.*

eters associated with BCR were assessed by a Cox proportional hazards regression model. Variables in univariate analysis with $P <0.05$ were included in the multivariate analysis. The associations between

Table 2. *Univariate and multivariate analyses of parameters predicting BCR in all cases (n = 179)*

Variables		Univariate P Value	Multivariate		
			Coefficient	Hazards Ratio (95% CI)	P value
*Pre-operative serum PSA (ng/ml):					
	<10	Reference		Reference	
	≥10	0.0004	1.381	3.979 (1.873–8.451)	0.0003
*Pre-operative serum albumin (g/dl):					
	>4	Reference		Reference	
	≤4	0.0407	0.495	1.641 (0.707–3.804)	0.2486
*Pathological Gleason Score:	≤7	Reference		Reference	
	≥8	0.0281	-0.187	0.829 (0.291–2.359)	0.7256
*Positive surgical margin:	No	Reference		Reference	
	Yes	0.0252	0.479	1.615 (0.65–4.015)	0.3023
*Extra-capsular extension:	No	Reference		Reference	
	Yes	0.0015	0.679	2.008 (0.862–4.68)	0.1062
*Seminal vesicle involvement:	No	Reference		Reference	
	Yes	0.0302	-1.035	0.355 (0.076–1.649)	0.1863
*Peri-neural invasion:	No	Reference		Reference	
	Yes	0.0198	-0.077	4.786 (1.37–16.72)	0.8618
*Lympho-vascular invasion:	No	Reference		Reference	
	Yes	0.006	0.518	1.679 (0.705–3.997)	0.2416
*Lymph node metastasis:	No	Reference		Reference	
	Yes	<0.0001	1.566	4.786 (1.37–16.72)	0.0141

BMI, body mass index; SD, standard deviation; ASA, American Society of Anesthesiologists

pre– and intra–operative factors and post–operative factors were analyzed using a logistic regression model. *P* values <0.05 were considered to be statistically significant.

RESULTS

Tumor–related patients' characteristics

The mean (SD) pre–operative PSA was 8.3 (5.3) ng/ml. The number of cases with a Gleason score of 2–6 / 7 / 8–10 in biopsy and surgical specimens was 96 (53.6%) / 52 (29.1%) / 31 (17.3%) and 85 (47.5%) / 62 (34.6%) / 32 (17.9%), respectively. The number of cases with pathological T2a / T2b / T2c / T3a / T3b were 43 (24.0%) / 2 (1.1%) / 78 (43.6%) / 47 (26.3%) / 9 (5.0%), respectively. A positive surgical margin and LNM were detected in 42 (23.5%) and 9 (5.0%) cases, respectively.

The analyses of tumor–related factors influencing BCR

The mean follow–up duration was 25.2 months (maximum 94). Thirty–two cases (17.9%) exhibited BCR, and the 5–year BCR–free rate for all patients was 67.1 %. High pre–operative serum PSA levels (>10 ng/ml), high Gleason scores (≥ 8) in surgical specimen, positive surgical margin, extra–capsular extension, seminal vesicle involvement, peri–neural invasion, lympho–vascular invasion, and LNM were associated with BCR univariately (Table 2). In the multivariate analysis, high pre–operative PSA levels (>10 ng/mL), and LNM were significant predictors of BCR (Table 2).

The analyses of non–tumor–related factors influencing BCR

When the cutoff value for pre–operative serum albumin was defined as 4 g/dl, the BCR–free rate in the low–level group was significantly worse than that in high–level group (Figure 1). Univariate analysis by Cox proportional hazards regression model also demonstrated the significance of low–level of serum albumin associated with BCR (Table 2). None of the other non–tumor–related factors significantly influenced BCR.

The analyses of potent pre– and intra–operative factors predictive of post–operative factors

For each post–operative factor, the associations with all pre– and intra–operative factors were analyzed using a logistic regression model. In case of

Table 3. *The analysis of potent pre- and intra-operative factors predictive of LNM*

Pre-operative variables	Odds ratio (95% CI)	P value
*Age	1.016 (0.874–1.182)	0.8346
*BMI	0.849 (0.637–1.132)	0.2656
*PSA	1.013 (0.851–1.204)	0.8875
*ASA risk classification		
(class 2, 3 vs. 1)	11.311 (1.067–119.910)	0.0440
*Serum albumin		
(≤4 vs. >4 g/dl)	12.295 (1.633–92.545)	0.0148
*Biopsy Gleason Score		
(7 vs. ≤6)	1.977 (0.083–47.378)	0.6740
(≥8 vs. ≤6)	48.585 (3.070–768.999)	0.0058
*Clinical T stage		
(cT1, 2ab vs. cT2c, 3)	0.628 (0.069–5.684)	0.6791
*Blood loss at surgery	1.001 (0.999–1.002)	0.4466

$R2 = 0.47$

LNM – lymph node metastasis; PSA – prostate specific antigen; BMI – body mass index; ASA – American Society of Anesthesiologists

a low R–squared value, the data were not used because they did not fit the logistic regression model. Only LNM was predictive of the pre– and intra–operative factors. Namely, a high ASA score (class 2 or 3 *vs*. 1), low pre–operative serum albumin levels (≤ 4 *vs*. >4 g/dl), and high Gleason scores (≥ 8 *vs*. ≤ 6) in the biopsy specimens were the significantly predictive for LNM (Table 3). In this analysis, the intra–operative factor of surgery type was excluded because there was no case that showed LNM in minimum incision endoscopic radical prostatectomy and robot–assisted radical prostatectomy. In the sub–group analysis of the characteristics of patients with a high ASA score (class 2 and 3), there was a significantly positive correlation of high ASA score with low serum albumin levels and high serum pre–operative PSA levels. Namely, 23 out of 72 patients with ASA class 2 and 3 (31.9%) had low pre–operative serum albumin levels (≤ 4 g/dl), whereas 19 out of 107 patients of ASA class 1 (17.8%) had low pre–operative serum albumin levels ($P = 0.0293$). The mean (SD) serum pre–operative PSA level in ASA class 2 and 3 patients was 10.3 (4.2), whereas it was 7.1 (5.9) ng/ml in ASA class 1 patients ($P = 0.0022$).

DISCUSSION

Early PCa detection efforts have been substantially improved with the introduction of PSA. Patients'

characteristics treated by RP have shifted toward earlier stages and more localized disease. Additionally, the retropubic RP has been substantially refined in the past two decades, transforming it into a highly reliable, oncological safe, and anatomically accurate procedure [7, 8, 9]. Such trends and progress in RP provide patients with localized PCa notably high probabilities of a cancer–free survival. Moreover, the progress of other therapeutic modalities, such as radiation, endocrine therapy and chemotherapy, also provide patients after BCR a long survival time. Therefore, the oncological focus of surgeons is characterizing the factors that influence BCR. A recent review article [10] on predicting for survival and BCR in a large number of patients treated with RP demonstrated that the post–operative outcome could be predicted by PSA and some pathological factors, such as T stage, Gleason score, and positive surgical margin [11, 12, 13]. In addition, extra–capsular extension, seminal vesicle involvement, and LNM were demonstrated as significant predictors for BCR [12, 13]. We have demonstrated the significance of the following predictors for BCR: 1) high pre–operative serum PSA levels (>10 ng/ml), high Gleason scores (≥8) in surgical specimens, positive surgical margin, extra–capsular extension, seminal vesicle involvement, peri–neural invasion, lympho–vascular invasion, and LNM in the univariate analysis and 2) high pre–operative PSA levels (>10 ng/mL) and LNM in the multivariate analysis. These results are generally in accord with the previous reports mentioned above. The strong impact of LNM on BCR, which is defined as the systemic expansion of PCa in our study, is in accord with previous studies that have demonstrated the order of prognostic impact to be LNM > seminal vesicle involvement > extra–capsular extension [4, 5].

To our knowledge, this is the first report demonstrating the significance of serum albumin level as a potential predictor for BCR. Albumin is frequently part of a standard preoperative evaluation and has also been shown important in predicting survival in various types of cancers, including urological malignancies, such as bladder carcinoma [14], renal cell carcinoma [15], and hormone refractory PCa [16]. Most studies cited that poor nutritional status of the host was reflected by low levels of serum albumin and consequently led to short survival. Other than nutritional status, inflammatory mediators, which are produced by tumor progression and host immune reaction to malignancies, lower serum albumin levels in patients with malignancies. First, inflammatory mediators increase the transcapillary escape rate of albumin such that albumin is lost into tissue spaces [17]. Second, inflammatory mediators, such as IL–6, TNF, and acute phase reactants, lead to decreased production of albumin [18]. Hypoalbuminemia is a poor prognostic indicator because it reflects malnutrition and existence of inflammation in the host, both of which are correlated with advanced stages of cancer.

Because of effective screening with PSA, PCa is detected at an earlier stage, and the deleterious effects of the disease are not as frequent in PCa as in other cancers with less effective screening methods, and metastases and resulting cachexia observed in these primary cancers may alter albumin levels. Moreover, candidates selected for RP as their treatment modality are generally healthy and without significant co–morbid diseases because other therapeutic modalities, such as radiation and endocrine therapies, preclude patients with extensive PCa, serious morbidities and short life expectancies. Therefore, the potential of serum albumin as a prognostic biomarker has not been identified in localized PCa treated by RP. The only report describing the value of the serum albumin level as a biomarker of PCa progression treated by RP demonstrated that it had no value as a predictive indicator for BCR [19]. This study compared BCR–free rates between two groups (≥3.8 *vs.* ≤3.7 g/dl). The mean value of serum albumin level was 4.3 g/dl in our study, and only ten patients (5.6%) had their serum albumin levels below 3.7 g/dl. Relatively low cut–off values in their study should be changed for the purpose of investigating if the pre–operative serum albumin level has the potential to be a predictive indicator for BCR.

PCa is known to be hormonally sensitive to testosterone. Bioactive testosterone is thought to be albumin–binding testosterone and free testosterone in circulating plasma. Free testosterone is thought to have an impact on hormonally sensitive PCa because of its active effect on the synthesis of dihydrotestosterone in prostate tissue. In normal human males, 57%, 40%, and less than 1% of testosterone in the plasma is bound to testosterone–binding globulin (TeBG), serum albumin, and corticosteroid–binding globulin, respectively, and only 2% of total testosterone is free [20]. The difference of testosterone–binding protein characteristics between TeBG and albumin is that the former is high–affinity and low capacity, whereas the latter is low–affinity and high capacity. Because a large percent of TeBG is saturated, low levels of serum albumin may decrease the level of albumin–binding testosterone and ultimately increase the level of free testosterone. Our results of pre–operative low serum albumin levels as a predictor for BCR and LNM may be related to increased free testosterone contributions. Richter et al. also demonstrated pre–operative low serum albumin levels to be

a predictor for non–organ confined disease assessed by RP specimens and hypothesized the role of free testosterone [19]. The associations between pre–operative sex hormones, including testosterone and sex hormone–binding globulin, with BCR were recently demonstrated in a prospective patient cohort treated with RP [21]. The authors concluded that increased sex hormone–binding globulin was an independent predictor for BCR, whereas neither total nor free testosterone was associated with BCR. There are two conflicting reports in patient cohorts treated with therapies other than RP: one study demonstrated the positive association between high levels serum testosterone and worsening PCa disease [22, 23, 24], and the other study demonstrated the inverse association [25, 26, 27]. However, no studies have demonstrated the specific association between serum free testosterone in combination with albumin and PCa progression. It is suggested that multiple factors, including hormonal, nutrition, inflammatory, and immune–reactive aspects triggered by low levels of serum albumin, were reflected in our results.

Along with low levels of serum albumin, high Gleason scores in biopsy specimens and co–morbid diseases expressed by the ASA score were also significantly correlated with LNM. The Gleason score is known to be a predictive factor for extensive disease as assessed by pathological findings in surgical specimens; however, no previous report has demonstrated the significance of the ASA score as a predictor for the PCa disease burden. There were a significantly high percentage of patients with pre–operative low levels of serum albumin in ASA class 2 and 3 as compared with the levels in class 1, which may reflect the significance of our results. It is also suggested that significantly higher pre–operative serum PSA levels in ASA class 2 and 3 patients compared with those in class 1 patients had effects on the positive correlation between the high ASA score and LNM. The reason for higher pre–operative serum PSA levels in ASA class 2 and 3 patients was the hesitation by physicians to conduct the invasive diagnostic and therapeutic procedure of PCa; this led to an increased delay between the first detection of abnormal serum PSA levels and the initiation of therapy in these patients. However, the influence of co–morbid diseases on PCa progression remains unknown. Detailed studies focused on co–morbid diseases in a large number of patients with localized PCa are needed to discover new non–tumor–related potent biomarkers.

CONCLUSIONS

Tumor–related characteristics are more important than other factors for predicting BCR. However, our results suggest that a low pre–operative serum albumin level may indicate extensive disease of clinically localized PCa and may ultimately be correlated with BCR. Although multiple reasons, including general patient characteristics, suppressed immune activity and changes in the serum free testosterone level caused by hypoalbuminemia, may be responsible for the progression of PCa, it is noteworthy that delayed diagnostic and therapeutic procedures in comorbid patients with low serum albumin levels may lead to PCa progression. Additional investigations based on large numbers of patients are needed to fully understand the potent non–tumor–related biomarkers of clinically localized PCa.

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