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Lactate Dehydrogenase Is a Serum Prognostic Factor in Clinically Regional Lymph Node-positive Prostate Cancer

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Abstract. *Background/Aim: Currently, there is no established prognostic serum parameter except PSA in clinically regional lymph node-positive prostate cancer. The aim of this study was to identify serum prognostic factors in clinically regional lymph node-positive prostate cancer. Patients and Methods: Patients diagnosed with regional lymph node-positive prostate cancer between 2008 and 2017 were included. The prognostic value of serum parameters for progression-free survival (PFS) and overall survival (OS) was investigated. Results: Univariate and multivariate analyses showed a statistically significant increased hazard risk for PFS and OS for men with lactate dehydrogenase (LDH) ≥230 IU/l at diagnosis. PFS at 5 years for patients with high and low LDH levels were 69.9% (95% CI=56.8-79.8%) and 18.9% (95% CI=1.23-53.2%), respectively (p=0.003). OS at 5 years for low and high LDH levels were 89.2% (95% CI=78.6-94.7%) and 46.3 (95% CI=11.2-76.2%), respectively (p=0.006). Conclusion: This study shows that LDH is an independent predictor of PFS and OS in patients with regional lymph node metastatic prostate cancer.*

Clinically regional lymph node-positive (cN1) nonmetastatic prostate cancer is found in about 1.3-15% of new diagnoses (1). The optimal management for cN1 patients remains unclear. Recently, a systematic review that included five retrospective studies suggested survival benefits in both overall survival (OS) and progression-free survival (PFS), when combining local radiotherapy with androgen deprivation therapy (ADT) (2). Moreover, the control arm of the randomized trial STAMPEDE reported improved overall survival in cN1 prostate cancer patients treated for two years with abiraterone plus prednisolone combined with external beam radiation therapy (3). Similarly, even though no randomized controlled trials have yet examined the value of adding local radiotherapy to ADT in cN1 disease, European guidelines, NCCN guidelines and most experts recommend external beam radiation therapy of the primary tumor plus 2 or 3 years neoadjuvant/concurrent/adjuvant ADT (4-6).

Clinically regional node-positive prostate cancer is a heterogeneous disease, ranging from completely local to occult distant metastatic disease. Our previous study suggested that patients with at least 2 criteria among ≥75% biopsy positive core rate, Gleason score ≥9, and ≥2 positive lymph nodes, may be suitable candidates for local radiotherapy (7). Several serum markers such as lactate dehydrogenase (LDH), testosterone level, platelet to lymphocyte ratio, neutrophil to lymphocyte ratio and lymphocyte to monocyte ratio have been reported to be prognostic in prostate cancer (8-10). However, the usefulness of serum markers in the prognosis of cN1 prostate cancer has not been evaluated. Thus, we aimed to determine the prognostic value of serum markers in cN1 disease.

Patients and Methods

Patients. Between 2008 and 2017, we enrolled newly diagnosed patients with cN1 prostate cancer at Kyushu University Hospital and Harasanshin Hospital (Fukuoka, Japan) (7). All patients were histopathologically diagnosed with adenocarcinoma of the prostate. We excluded patients with metastatic disease, history of previous treatment for prostate cancer, and those who did not undergo computed tomography and bone scan. Before progression to castration-resistant prostate cancer, no case received chemotherapy. This study was approved by each institutional review board of Kyushu University Hospital and Harasanshin Hospital.

Analysis of survival. The patients' background information and survival data were retrospectively obtained from medical records. Performance status was assessed by the Eastern Cooperative Oncology Group criteria.

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Key Words: Lactate dehydrogenase, androgen-deprivation therapy, lymph node-positive prostate cancer, prognostic factor, radiotherapy.

Gleason score and clinical TNM stage were determined according to the 2005 International Society of Urological Pathology (ISUP) Consensus and the UICC 7th edition (11, 12). A lymph node ≥10 mm by computed tomography or magnetic resonance imaging was considered positive. The regional lymph nodes included the external iliac, obturator and internal iliac regions. Androgen-deprivation therapy was performed by surgical, castration monotherapy, or combined androgen blockade with a first-generation nonsteroidal anti-androgen (bicalutamide and flutamide). The decision of radiotherapy was made according to the decision between the physician and patient. Radiotherapy was performed by external radiation to the whole pelvis (range=41.4-50.0 Gy) followed by a boost to the prostate (range=22.0-30.0 Gy) as described previously (7). We considered a value higher than normal level as a cut-off point or an LDH level of 230 IU/L or higher. Disease progression was assessed by biochemical and/or radiologic progression. Biochemical progression was defined as a prostate-specific antigen (PSA) increase in >2 ng/mL and a 25% increase over the nadir, and radiologic progression was defined as the appearance of 2 new lesions or the progression of 1 or more known lesions classified according to the Response Evaluation Criteria in Solid Tumors (13).

Statistical analysis. Baseline values were expressed as the median and interquartile range (IQR), and the baseline was defined as the date of initial hormone therapy. PFS was defined as the time during which there was no recurrence. OS was defined as the time from initial hormone therapy to death or last contact with the patient. Survival rates were estimated using the Kaplan–Meier method with the Rothman 95% confidence interval (CI) and compared between groups using the log-rank test method. Associations between patient death and clinicopathological characteristics were evaluated using the Cox proportional risk model. All statistical analyses were performed with Stata v14 (College Station, TX, USA) (14, 15). Differences in the prognostic impact of subgroups were investigated through interaction tests. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

This study included 93 Japanese cases with cN1 prostate cancer; the patients' characteristics are shown in Table I. The median number of metastatic lymph nodes was 1 (IQR=1-2). Forty-eight patients (51.6%) were treated with radiotherapy. During a median follow-up of 54 months (IQR=36-83 months), 36 patients (38.7%) experienced progression to castration-resistant prostate cancer, and 16 patients (17.2%) died, of whom 12 (12.9%) were by disease. The median PFS and OS were 99 months (95% CI=69-110 months) and 130 months (95% CI=100 months–not reached), respectively.

Univariate Cox-model analysis showed a statistically significant increased hazard risk for PFS and OS for men with LDH ≥230 IU/l at diagnosis (Table II). On the other hand, other serum parameters including hemoglobin, white blood cell count, platelet count, C-reactive protein, creatinine, neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio did not show statistical association with PFS or OS (Table II). The multivariable analyses showed that LDH and Gleason Score >8 were significantly associated with PFS and OS, whereas radiation therapy and higher PSA levels were only associated with OS (Table III). PFS at 5 years for patients with LDH lower and higher than 230 IU/L were 69.9% (95% CI=56.8-79.8%) and 18.9% (95% CI=1.23-53.2%), respectively (Figure 1A, $p=0.003$). OS at 5 years was 89.2% (95% CI=78.6-94.7%) and 46.3% (95% CI=11.2-76.2%), for patients with LDH lower and higher than 230 IU/l, respectively (Figure 1B, $p=0.006$).

Table I. *Patients' background at diagnosis.*

Variables	All (n=93)
Median age at diagnosis, years (IQR)	69 (65-76)
Performance status, n (%)	
0	79 (84.9%)
1	14 (15.1%)
Gleason score, n (%)	
≤8	42 (45.2%)
>8	51 (54.8%)
Clinical T-stage, n (%)	
T1-2	29 (31.3%)
T3-4	64 (69.7%)
Median number of lymph node metastasis	1 (1-2)
Median PSA, ng/ml (IQR)	47.1 (23.6-97.1)
Median hemoglobin, g/dl (IQR)	14.5 (13.4-15.1)
Median white blood cell count, /ml (IQR)	5830 (4,860-6,810)
Median platelet count, 10,000/ml (IQR)	19 (16.4-23.3)
Median C-reactive protein, mg/dl (IQR)	0.1 (0.0-0.2)
Median LDH, IU/l (IQR)	186 (165-214)
Median creatinine, mg/dl (IQR)	0.82 (0.75-0.94)
Median neutrophil to lymphocyte ratio, (IQR)	2.00 (1.53-2.87)
Median platelet to lymphocyte ratio, (IQR)	113 (95-153)
Median lymphocyte to monocyte ratio, (IQR)	4.53 (3.66-5.88)

IQR, Interquartile range; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.

Discussion

LDH is an enzyme that is found in most organs in the human body and is elevated in numerous clinical conditions including cancer (16-19). LDH is a well-known tumor marker which is useful for risk stratification and monitoring in various cancers (16, 17).

We have previously reported that LDH was a robust prognostic serum marker in men with de novo metastatic prostate cancer treated with androgen-deprivation therapy, and men with castration-resistant prostate cancer treated with cabazitaxel (20, 21). Consistently, a systematic review and meta-analysis including 59 articles showed that higher LDH levels presented worse PFS and OS in metastatic prostate cancer (22). Moreover, several studies showed that LDH was independently associated with OS in both patients with metastatic prostate cancer at hormone-sensitive and castration-resistant status (22-26). However, to our knowledge, no previous studies have investigated the prognostic value of

Table II. *Association between serum markers at diagnosis and prognosis.*

		PFS			OS		
Variable	n	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
PSA							
<50 ng/ml	49	Ref	-	-	Ref	-	-
≥50 ng/ml	44	0.74	0.38-1.44	0.39	0.27	0.08-0.87	**0.028**
Hemoglobin							
<12 g/dl	5	Ref	-	-	Ref	-	-
≥12 g/dl	86	0.41	0.09-1.75	0.23	0.28	0.03-2.22	0.23
White blood cell count							
<4,000/ml	9	Ref	-	-	Ref	-	-
≥4,000/ml	82	0.84	0.32-2.18	0.73	0.75	0.20-2.77	0.66
Platelet count							
<150,000/ml	11	Ref	-	-	Ref	-	-
≥150,000/ml	80	0.62	0.27-1.42	0.26	0.59	0.16-2.14	0.42
Neutrophil to lymphocyte ratio							
<2	44	Ref	-	-	Ref	-	-
≥2	46	1.59	0.80-3.16	0.17	2.68	0.86-8.35	0.088
Lymphocyte to monocyte ratio							
<3	18	Ref	-	-	Ref	-	-
≥3	73	0.58	0.26-1.26	0.16	0.76	0.21-2.74	0.68
Platelet to lymphocyte ratio							
<150	67	Ref	-	-	Ref	-	-
≥150	24	0.86	0.40-1.83	0.70	1.34	0.48-3.71	0.57
LDH							
<230 IU/l	79	Ref	-	-	Ref	-	-
≥230 IU/l	12	3.24	1.38-7.50	**0.007**	4.57	1.36-15.3	**0.014**
Creatinine							
<1 mg/dl	79	Ref	-	-	Ref	-	-
≥1 mg/dl	11	0.47	0.11-1.99	0.31	1.22	0.27-5.56	0.79
C-reactive protein							
<0.1 mg/dl	39	Ref	-	-	Ref	-	-
≥0.1 mg/dl	45	0.78	0.39-1.54	0.48	1.16	0.43-3.12	0.76

Statistically significant *p*-values are shown in bold. LDH, Lactate dehydrogenase; IU, International Unit; HR, hazard ratio; CI, confidence interval.

LDH in cN1 prostate cancer. Consistently with the prognostic value in metastatic prostate cancer, patients with higher LDH levels had a worse prognosis even in cN1 prostate cancer, suggesting that the LDH value is useful to predict prognosis in men with cN1 prostate cancer.

There are several limitations in this study. Firstly, the study design was retrospective, and the sample size was small, which may lead to insufficient statistical power. The protocol for radiotherapy and the follow-up schedule were not protocoled. In addition, the enrollment period included the era before novel agents, including enzalutamide, abiraterone acetate, radium-233, and cabazitaxel for castration-resistant prostate cancer became available, although docetaxel was available for all patients.

Conclusion

This study showed that LDH was an independent predictor of PFS and OS in patients with regional lymph node metastatic prostate cancer. However, this study failed to show the significance of other serum parameters. This may be helpful to predict prognosis and choose an appropriate treatment.

Conflicts of Interest

Masaki Shiota, Akira Yokomizo, and Masatoshi Eto have received honoraria from Janssen Pharma, Astellas Pharma, and Sanofi.

Authors' Contributions

LB designed the study, analysed the data and wrote the draft of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. MS and EM supervised the study.

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Table III. *Multivariate analysis on association between serum markers and prognosis.*

PFS	HR	95% CI	*p*-Value
Age	0.97	0.92-1.02	0.318
Gleason score >8	2.39	1.16-4.91	**0.018**
Clinical T3b/T4	0.94	0.43-2.06	0.886
PSA ≥50 ng/ml	0.63	0.32-1.28	0.205
Radiation therapy	0.66	0.32-1.37	0.258
LDH ≥230 IU/l	3.57	1.32-9.58	**0.012**
OS	**HR**	**95% CI**	***p*-Value**
Age	0.93	0.82-1.02	0.141
Gleason score >8	4.61	1.19-17.8	**0.026**
Clinical T3b/T4	0.67	0.18-2.64	0.576
PSA ≥50 ng/ml	0.16	0.07-0.75	**0.006**
Radiation therapy	0.18	0.07-0.81	**0.007**
LDH ≥230 IU/l	8.53	1.83-39.7	**0.006**

Statistically significant *p*-values are shown in bold. LDH, Lactate dehydrogenase; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

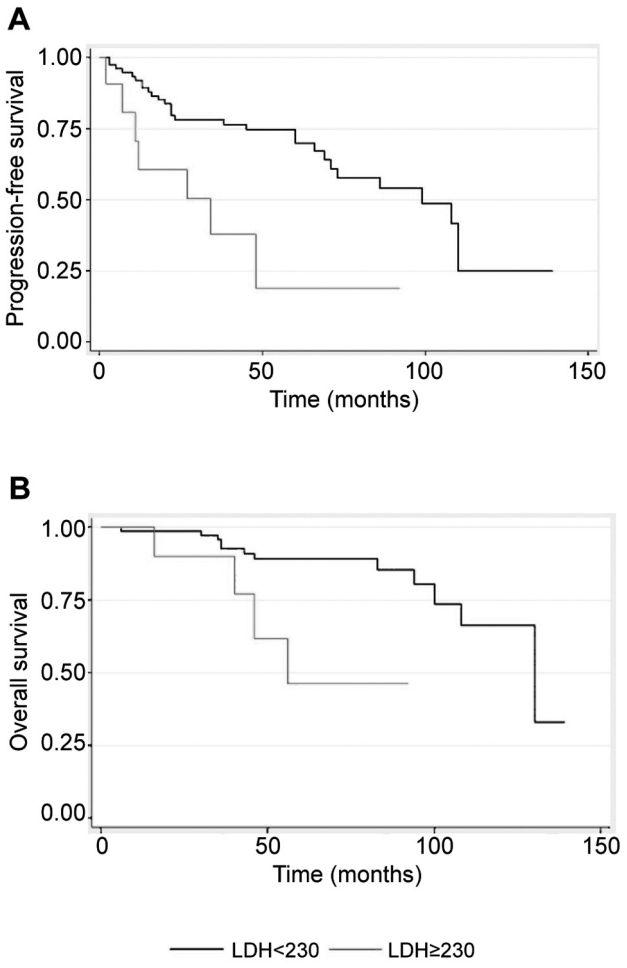

Figure 1. *Prognosis according to serum LDH values among men with clinically regional lymph node metastatic prostate cancer. PFS (A) and OS (B) according to serum LDH value (LDH, <230 IU/L vs. ≥230 IU/l). A, p=0.003; B, p=0.006 (log-rank test).*

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