LACTATE DEHYDROGENASE IS A PROGNOSTIC INDICATOR FOR PROSTATE CANCER PATIENTS WITH BONE METASTASIS

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We analyzed clinical data to identify prognostic indicators in prostate cancer patients with bone metastasis. The subjects were 60 patients with bone metastasis out of 165 patients diagnosed with prostate cancer at our clinic over 6 years from January 1998 to December 2003. The age at the initial diagnosis was 61 to 91 (mean : 73.7 ± 7.5) years old. The following items were considered to be possible prognostic indicators : T (type) classification, N (node) classification, Gleason score, prostate specific antigen (PSA) value before therapy, disease grade, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum calcium (Ca), hemoglobin (Hgb), and platelet count (Plt). The 5-year overall survival rate was 45.7% in the 60 patients. Univariate analysis showed statistically significant differences in N (1), Gleason score 7＋8/Gleason score 9＋10, and LDH level (p＝0.0053, 0.0261, and 0.0049, respectively). Multivariate Cox proportional hazard analysis of these three items showed a statistically significant difference in LDH level and Gleason score 9＋10 (p＝0.0167 and 0.0371). LDH was suggested to be an excellent prognostic indicator, because of its objectivity and convenience of measurement, in prostate cancer patients with bone metastasis.

(Hinyokika Kiyo **53** : 287–292, 2007)

Key words : Prostate cancer, Bone metastasis, Lactate dehydrogenase, Clinical study, Prognostic indicator

INTRODUCTION

Since prostate cancer does not show significant symptoms in the early stages, patients who have not received prior prostate specific antigen (PSA) screening present with bone pain and neurological symptoms with metastatic lesions in bone at the time of initial diagnosis[1)]. Most prostate cancers are male hormone-dependent, and patients with metastasis are mostly treated with endocrine therapy, since complete recovery cannot be expected. However, the majority of patients develop resistance to endocrine therapy. An effective therapeutic protocol has not been established for prostate cancers after developing endocrine therapy resistance. Currently, the characteristics of patients who become resistant to endocrine therapy, resulting in a poor outcome, are not known.

In the present study, we examined a variety of clinical data as possible prognostic indicators in prostate cancer patients with bone metastasis.

SUBJECTS AND METHODS

The subjects were 60 patients diagnosed with bone metastasis by X-ray and bone scintigraphy out of 165 prostate cancer patients who were treated at our clinic over 6 years from January 1998 to December 2003.

All patients were treated with endocrine therapy. Treatment consisted of leuteinizing hormone-releasing hormone (LH-RH) agonist plus anti-androgen drug in 56 patients, prostatectomy plus anti-androgen drug in 3 patients, and LH-RH agonist only in 1 patient. PSA was confirmed to be below 4.0 ng/ml after the start of therapy in all patients. There was no case in which chemotherapy with anti-cancer drugs was given after recurrence. The date of final examination was December 31, 2004.

The age at the initial diagnosis was 61 to 91 years, with a mean age of 73.7±7.5 years. At the time of final examination, the outcome was survival in 31 patients, death from prostate cancer in 27 patients, death from other causes in no patient, and drop-out in 2 patients. Table 1 shows the patients' background.

The observation period was 4 to 72 months (mean : 36 months). PSA was measured using a Tandem-R Assay Kit (Hybritech Co.). The starting day of observation (day 0) was the day when the stage of cancer was ascertained. Recurrence, regarded as a biological failure of PSA, was diagnosed when an increase of PSA was found in three consecutive measurements, and the recurrence date was defined as the day when the increase of PSA was found for the first time. Histopathological heteromorphy was assessed by the Gleason score[2)]. Clinical stage was determined according to the International Union Against Cancer (UICC) classifi-

Table 1. Patient characteristics

Patient	60
Age (yr.)	61–91
Average age	73.4±7.4
Median age	72
Serum PSA (ng/ml)	34.0–10,060.0
Average PSA	1,033±1,874.7
Median PSA	360.0
Gleason score	
7	9
8	19
9	29
10	3
EOD grade	
1	17
2	34
3	3
4	6
T stage	
T1	3
T2	19
T3	10
T4	27
Tx	1
N stage	
N0	22
N1	37
Nx	1

cation[3]. The extent of bone metastasis was evaluated by bone scintigraphy and classified into four grades (I to IV) according to the extent of disease (EOD) as reported by Soloway, et al.[4].

The following items were analyzed : T classification, N classification, Gleason score, PSA value before therapy (normal value : >4.0 ng/ml), EOD, alkaline phosphatase (ALP) (normal value : 100–358 U/l), lactate dehydrogenase (LDH) (normal value : 104–224 U/l), serum calcium (Ca) (normal value : 8.7–10.9 mg/dl), hemoglobin (Hgb) (normal value : 13.9–16.0 g/dl), and platelet count (Plt) (normal value : 180–350×103/μl).

The overall survival rate was estimated using the Kaplan-Meier method, and the significance of differences was analyzed by log-rank-test. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 10.0 for Windows.

RESULTS

The average observation period was 3 years, and the 3-year overall survival rate was 59.2% (95% confidence interval : 45.9–74.3%). The 5-year overall survival rate was 45.7 (95% confidence interval : 30.5–60.9%) in the 60 patients (Fig. 1). There was no statistically significant difference in survival according to T classification ($p=0.8728$) (Fig. 2). The outcome was the poorest in N (1) ($p=0.0053$) (Fig. 3) in the N classification.

The outcome tended to be poor in EOD III+IV when EOD I+II (51 patients) and EOD III+IV (9 patients) were compared, although there was no statistically significant difference ($p=0.2985$).

For Gleason score, statistical analysis could not be performed because there was no patient of death in Gleason score 7 during the observation period. When Gleason score 7+8 and 9+10 were analyzed separately, there was a statistically significant difference in the survival rate between Gleason score 7+8 and Gleason score 9+10 ($p=0.0261$) (Fig. 4).

The PSA value before therapy was examined separately in two groups in which the median value was higher (31 patients) and lower (29 patients) than 360 ng/ml. There was no statistically significant difference in the outcome between the two groups ($p=0.1342$) (Fig. 5). No statistically significant difference was found even when examined in groups separated at median values of 500 and 1,000 ng/ml ($p=0.2202$ or $p=0.8169$).

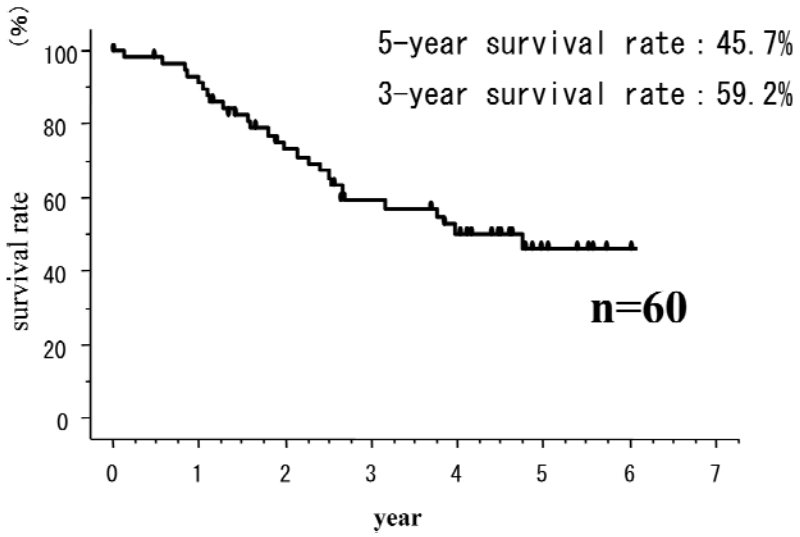

Fig. 1. Overall survival rates in 60 patients.

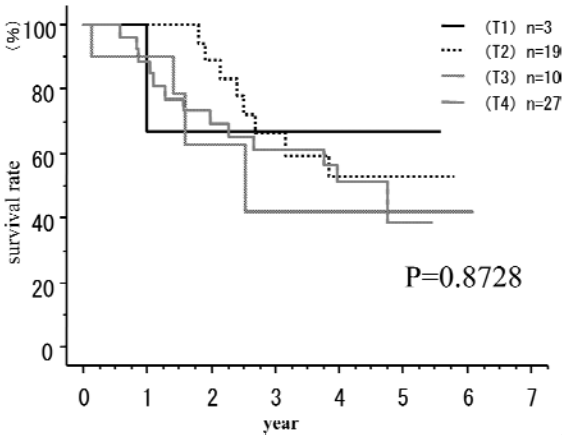

Fig. 2. Overall survival rates by T classification.

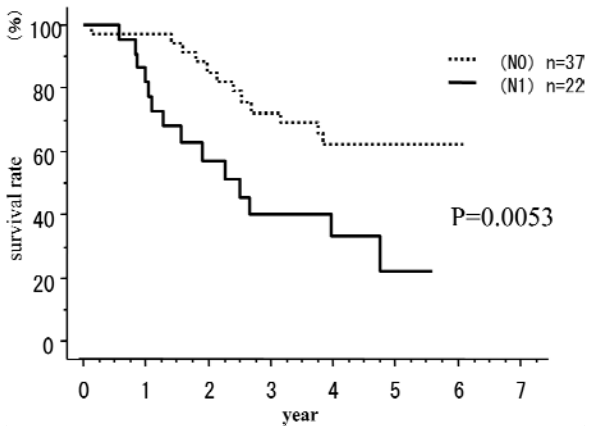

Fig. 3. Overall survival rates by N classification.

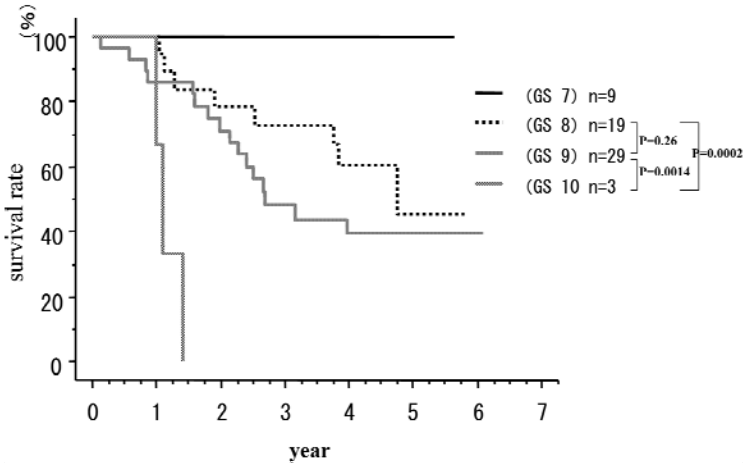

Fig. 4. Overall survival rates by Gleason grading system.

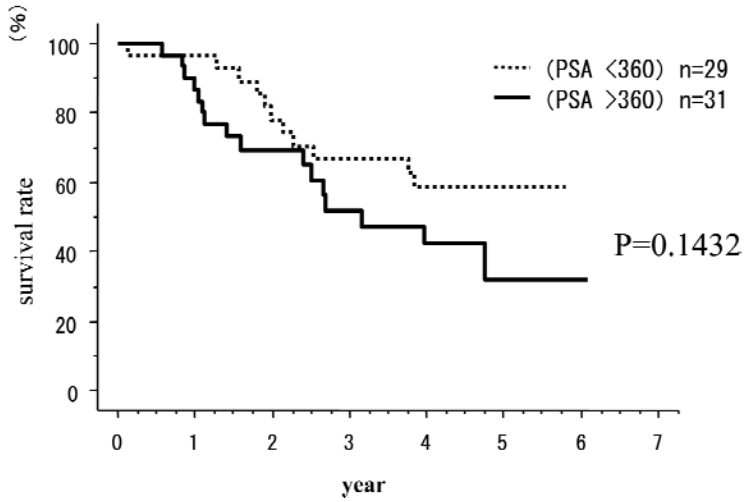

Fig. 5. Overall survival rates in patients with pre-therapy PSA below or above 360 ng/ml.

No significant difference in survival was observed between the groups with normal and abnormal values of ALP, serum Ca, Hgb, and Plt ($p = 0.1896$, 0.5373, 0.0919, and 0.3528, respectively). On the other hand, there was a statistically significant difference between the groups with normal (range: 104–224 U/l) (38 patients) and abnormal (range: 231 – 1,115 U/l) (22 patients) values of LDH ($p=0.0049$) (Fig. 6).

Multivariate Cox proportional hazard analysis was performed for N classification, Gleason score and LDH, in which a significant difference was observed by univariate analysis. The hazard ratio was 2.55, 2.656, and 2.17, respectively, for Gleason score 9 + 10 vs. Gleason score 7 + 8, abnormal LDH value vs. normal

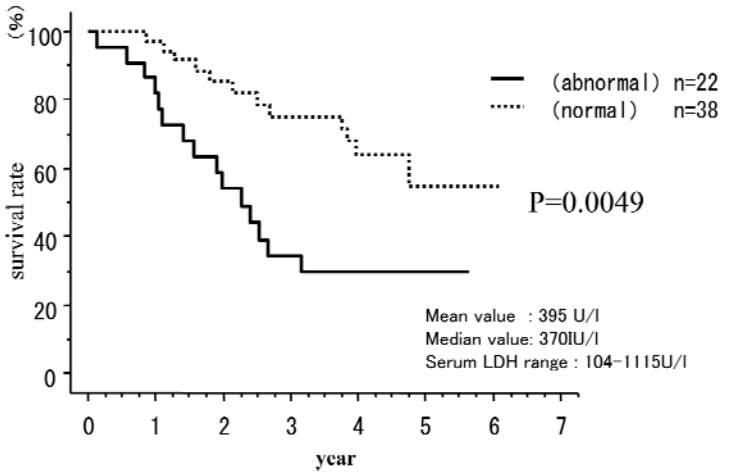

Fig. 6. Overall survival rates in patients with normal and abnormal LDH levels.

Table 2. Multivariate Cox proportional hazard analysis

Prognostic factor	Hazard ratio	95% CI	P-value
Lynph node meta			
N0	1.00		
N1	2.170	0.977–4.830	0.0572
Gleason Score			
7+8	1.00		
9+10	2.551	1.058–6.154	0.0371
LDH			
Normal	1.00		
Abnormal	2.656	1.194–5.908	0.0167

value, and N (1) vs. N (0). There were statistically significant differences in LDH and Gleason score ($p = 0.0167$ and 0.0371) (Table 2).

DISCUSSION

About 80% of prostate cancer patients with bone metastasis initially show a favorable response to endocrine therapy. However, more than half of the patients develop resistance to endocrine therapy within several months to several years, resulting in a five-year survival rate of about 30% for patients with bone metastasis[5].

One of the mechanisms of the development of endocrine therapy resistance is considered to be abnormality of the androgen receptor, and the other mechanism is independent of the androgen receptor. The former could involve (1) amplification of the androgen receptor (with responses to lower levels of androgen), (2) mutations in the androgen receptor gene (which cause the androgen receptor to bind and respond to anti-androgen drugs other than androgen, estrogen and steroids), (3) abnormalities in co-activators which activate the transcription activity of the androgen receptor, and (4) activation of the androgen receptor due to abnormal production of growth hormones or cytokines. On the other hand, possible mechanisms not involving the androgen receptor include (1) avoidance of apoptosis due to abnormalities in apoptosis-related genes, and (2) appearance and growth of neuroendocrine cells. The mechanism remains unclear, although it has been suggested that instead of any one abnormality, several factors could be involved in combination during the process[6].

In the present study, the overall five-year survival rate was 45.7%. Unfortunately, this result may have been due to the short observation period of 36 months. The period until PSA failure occurred was not studied for the same reason. Performance status, Gleason score, extent of bone metastasis, and responsiveness to endocrine therapy have been suggested to be prognostic indicators for prostate cancer in some reports, but no conclusive viewpoint has been reached. Ernst, et al. reported a correlation of the extent of lesions on bone scintigraphy to the survival rate[7]. Soloway, et al. showed the importance of EOD grade as a prognostic indicator[4]. In the present results, outcome appeared to be poorer in EOD III + IV, although this was not statistically significant, suggesting the possibility of obtaining statistically significant values by increasing the number of cases in the future. It is widely known that the presence or absence of metastasis to lymph nodes and Gleason score are clinically important indicators, being reported to be associated with the prognosis of prostate cancer[8,9]. The outcome was poor in our patients with lymphatic metastasis and higher Gleason score.

In the present study, there was a statistically significant difference in abnormal values of LDH in patients with a poor outcome. In addition, the hazard ratio was 2.656 by multivariate Cox proportional hazard analysis, showing the highest value for LDH. These results show the usefulness of LDH as a prognostic indicator.

LDH is an intracellular enzyme that is present in every tissue within the living body. Serum LDH level increases from leakage into the blood following injury to any tissue. It is used for initial diagnosis in general

screening. Isozyme fractionation is useful for identifying the injured tissue. Abnormally high levels are known to occur in acute myocardial infarction, acute hepatitis, leukemia, malignant lymphoma, and other conditions. In the urological field, an abnormally high level is known to occur in testicular tumors and it is used as an index of therapeutic response. However, since a limited number of malignant tumors show an elevated level in the early stages, LDH level is generally used for assessment of prognosis, therapeutic efficacy, and worsening of symptoms. In prostate cancers as well, an increase in LDH is rarely seen in the early stages. In the present study, prostate cancer patients with bone metastasis with abnormally high LDH levels showed a poor outcome. Since a high LDH level indicates tissue disorder due to metastasis, this result suggests that a high LDH level could be an index of tissue disorder in advanced cancers. Whether the prognosis worsens with an increase of LDH is an interesting point; however, it was not studied in this research. The prognosis has been reported to be poor in patients with lymphatic metastasis or high Gleason score[8,9]. However, metastasis to lymph nodes is diagnosed by diagnostic imaging technology in many patients. On the other hand, in terms of pathological diagnosis, the complete consensus rate for Gleason score was 50%, and even agreement within ±1 was 85% by Gleason himself[1]. Furthermore, in one report[10] the consistency rate of the Gleason grade between individual observers was 31 to 49%. Therefore, the pathological diagnosis is also associated with problems of reproducibility. The present study showed that LDH could be an excellent prognostic indicator from the viewpoint of objectivity and convenience, as it can be measured as part of routine blood biochemical tests.

Although no statistically significant values of EOD score or ALP were found our results suggested that they could be obtained by increasing the number of cases. The period until PSA failure occurred was not studied in our research because of the short observation period. Further analysis of each parameter, with an increased number of cases and extended observation period, is needed.

CONCLUSIONS

LDH is an excellent prognostic indicator because of its objectivity and convenience of measurement for prostate cancer patients with bone metastasis.

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(Received on August 31, 2006
Accepted on December 11, 2006)

和文抄録

Lactate dehydrogenase（LDH）は前立腺癌骨転移症例の予後予測因子である

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目的：どのような前立腺癌骨転移症例が内分泌療法抵抗性へと移行し，予後不良な転帰をたどるのであるか，詳細は明らかにされていない．今回，われわれは前立腺癌骨転移症例に対し，各種臨床データにおける予後予測因子としての可能性を検討した．

対象と方法：1998年1月から2003年12月までの6年間に当院において前立腺癌と診断された165例中，骨転移を有する60例を対象とした．初診時年齢は61～91歳（平均73.7±7.5歳）であった．検討項目としては，T classification，N classification，Gleason score（GS），治療前 prostate specific antigen（PSA）値，extent of disease grade，alkaline phosphatase（ALP），lactate dehydrogenase（LDH），血清 calcium（Ca），hemoglobin（Hgb），platelet（Plt）とした．

結果：60例の 5-year overall survival rate は45.7％であった．単変量解析にて統計学的に有意差が認められた項目は，N（1），GS 7＋8 と GS 9＋10，LDH 異常値であった（p＝0.0053，p＝0.0261，p＝0.0049）．これら3群の multivariate Cox proportional hazard analysis では LDH 異常値と GS 9＋10 で統計学的有意差が認められた（p＝0.0167，p＝0.0371）．

結論：LDH は，その客観性および簡便性から，前立腺癌骨転移症例に対し有力な予後予測因子であると考えられた．

（泌尿紀要 **53**：287-292，2007）