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Influence of Nonregional Lymph Node Metastasis as a Prognostic Factor in Metastatic Prostate Cancer Patients

Seok Cho, Sung Gu Kang, Bum Sik Tae, Jun Cheon

Department of Urology, Korea University Anam Hospital, Seoul, Korea

Purpose: In advanced prostate cancer, malignant cells generally tend to spread into the bone, and metastasis into nonregional lymph nodes (NRLNs) at the time of initial diagnosis is relatively rare. We investigated the prognostic significance of NRLN metastasis in patients receiving hormonal therapy and chemotherapy.

Materials and Methods: From February 2005 to August 2011, we identified 105 patients who had metastatic prostate cancer. First, we assessed the prognostic effect of NRLN metastasis on the prostate-specific antigen response through logistic regression and the progression-free time to castration-resistant prostate cancer (CRPC) by using the Cox proportional hazard regression model. Second, we investigated the prognostic influence of NRLN metastasis on the chemotherapy response through logistic regression and on cancer-specific survival of CRPC patients receiving chemotherapy by using Cox proportional analysis.

Results: Of these 105 patients, 12 patients (11.4%) had only NRLN metastases without bone metastases. Progression-free time to CRPC was significantly less in patients with NRLN metastases by Cox proportional hazard regression multivariate analysis (p=0.020). However, NRLN metastasis was not an independent factor for predicting the response to chemotherapy in CRPC patients, and NRLN metastasis did not reduce cancer-specific survival in the multivariate analysis.

Conclusions: Twelve (11.4%) of 105 patients with NRLN metastases had lymph node metastases without bone metastases. In addition, NRLN metastasis was a significant prognostic factor for predicting reduced progression-free time to CRPC. Thus, although we speculate that prostate cancer with NRLN metastasis exhibits unique tumor biology, additional molecular and genetic studies are needed.

Key Words: *Lymphatic metastasis; Prognosis; Prostatic neoplasm*

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Corresponding Author:
Jun Cheon
Department of Urology, Korea University Anam Hospital, 73 Inchon-ro, Seongbuk-gu, Seoul 136-705, Korea
TEL: +82-2-920-5367
FAX: +82-2-928-7864
E-mail: jcheon@korea.ac.kr

INTRODUCTION

Prostate cancer is the most commonly diagnosed nonskin malignancy in men and is the second leading cause of cancer-related death in the United States [1]. The incidence of prostate cancer is also rapidly increasing in Korea [2]. In the United States, approximately 90% of patients with prostate cancer are diagnosed with early-stage disease, whereas 4% present with metastatic disease. Although early-stage prostate cancer is typically cured with radical surgery, managing prostate cancer in patients with distant metastasis is challenging, and the prognosis is poor, with an average survival of 24 to 48 months [3,4].

Previous reports have shown that localized prostate cancer has a heterogeneous natural history, moving from indolent to aggressive tumor [5,6]. However, prostate cancer with metastasis at the time of initial diagnosis is relatively rare, and few reports have described the biology or natural history of metastatic prostate cancer. In advanced prostate cancer, malignant cells tend to spread into bone and lymph nodes [7]. Regional lymph node metastasis is common in prostate cancer; however, metastasis into nonregional

lymph nodes (NRLNs) at the time of initial diagnosis is relatively rare [8].

To our knowledge, few reports have evaluated the prognostic effect of NRLN metastasis. In 1998, Furuya et al. [9] examined the clinical course of patients with NRLN metastasis. In their study, patients with NRLN metastasis had a better prognosis than did those with bone metastasis owing to a good response to endocrine therapy or an ability to maintain response to hormones. However, the study included only 17 patients and the authors did not perform multivariate analysis. In addition, they did not evaluate the prognostic effect of NRLN metastasis in patients with castration-resistant prostate cancer (CRPC) who were receiving chemotherapy. In the present study, therefore, we performed a multivariate analysis to evaluate the prognostic significance of NRLN metastasis in 30 metastatic patients receiving hormonal therapy and in patients receiving chemotherapy after progression to CRPC.

MATERIALS AND METHODS

1. Definition

Among 1,296 patients diagnosed with prostate cancer at the Korea University Hospital from February 2005 to August 2011, we identified 105 patients with metastatic prostate cancer.

Patient age, initial and follow-up prostate-specific antigen (PSA) level, baseline hemoglobin level, alkaline phosphatase (ALP) level, biopsy Gleason score [10], metastasis site (lymph node or bone), and disease progression were evaluated in every patient. PSA was measured every 3 months during hormone therapy in every patient. Radiographic evaluation included abdominopelvic computed tomography (CT) and radionuclide bone scans, which were performed every 6 months and when clinically indicated.

The site of lymph node metastasis in each patient was classified by the tumor-node-metastasis classification of malignant tumors, III edition 1978, by Harmer [11], as follows: regional lymph nodes included internal iliac lymph nodes, external iliac lymph nodes, common iliac lymph nodes, and obturator lymph nodes; NRLNs included any other lymph nodes apart from those classified as regional lymph nodes.

The extent of disease (EOD) grade of the bone metastases in each patient was classified by the method described by Soloway et al. [12], as follows: EOD 1, less than 6 bone metastases, each of which is less than 50% of the size of a vertebral body (1 lesion that is around the size of a vertebral body would be counted as 2 lesions); EOD 2, between 6 and 20 bone metastases, with consideration of the size of lesions as described above; EOD 3, greater than 20 bone metastases, but less than a "super scan"; and EOD 4, a "super scan" or its equivalent, i.e., greater than 75% of the ribs, vertebrae, and pelvic bones contain lesions.

PSA response was defined as the criteria used for determining response on the basis of the guidelines of the PSA working group [13]. A PSA decline of $\geq 50\%$, confirmed by a second value obtained at least 4 weeks after the first measurement, was considered to be a complete remission (CR). Additionally, partial remission (PR) was defined as a PSA decrease that did not satisfy the PSA response criteria. Progression was defined as an increase of PSA. Baseline PSA was defined as the PSA value obtained within the 2-week period before starting the study medication. Hormonal response was defined as either CR or PR.

Biochemical recurrence after hormone therapy was defined as 3 consecutive serum PSA concentration measurements >0.2 ng/ml, and clinical progression was defined as local recurrence or distant metastasis on imaging study. CRPC was defined as progression of an osseous lesion or 3 consecutive rises in PSA, occurring 1 week apart under hormonal therapy, despite a testosterone level <0.5 ng/ml and after exclusion of antiandrogen syndrome.

Chemotherapy response was also defined by the criteria used for determining response that were based on the guidelines of the PSA working group [13]. A PSA decline of $\geq 50\%$, confirmed by a second value obtained at least 4 weeks after the first measurement, was considered to be CR. Additionally, PR was defined as a PSA decrease that did not satisfy the PSA response criteria. Progression was defined as an increase of PSA. Chemotherapy-baseline PSA was defined as the PSA value obtained within the 2-week period before starting each medication. In a measurable lesion, chemotherapy response was evaluated by radiologic findings by using the response evaluation criteria in solid tumors criteria [14]. A complete response was defined as disappearance of the metastasis lesion. A partial response classification required a $\geq 30\%$ decrease, and progression of disease required a $\geq 20\%$ increase in the sum of the largest diameters of the metastasis lesions. In bone metastasis patients, the defined response categories are not applicable, but the appearance of one or more new lesions or unequivocal progression of existing bone metastasis lesions was defined as progression. Chemotherapy response was defined as either CR or PR.

There were four types of chemotherapy medications. Among 57 patients who underwent chemotherapy, 43 patients underwent docetaxel treatment, 3 patients received etoposide, 8 patients received mitoxan, and 3 patients received estra.

2. Study design

This study consisted of 2 steps, divided according to the time of progression to CRPC. In the first step, we assessed the prognostic effect of NRLN metastasis on both the PSA response through logistic regression and the progression-free time to CRPC by using the Cox proportional hazard regression model in 105 metastatic prostate cancer patients [15]. In the second step, we investigated the prognostic influence of NRLN metastasis on the response to chemotherapy and on the cancer-specific survival of 57 CRPC patients receiving chemotherapy. In addition, other prognostic factors were investigated in both steps of the

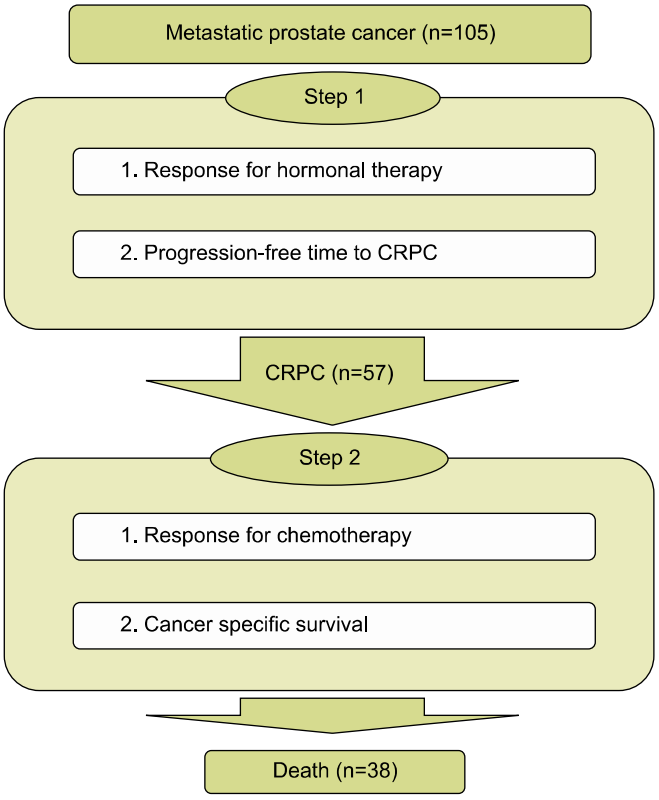

FIG. 1. Experimental design flow chart. CRPC, castration-resistant prostate cancer.

TABLE 1. Patient characteristics (n=105)

Characteristic	Value
Age (yr)	73.24±7.46
Prostate volume (ml)	51.33±20.56
Initial PSA (ng/ml)	294.18±165.11
Baseline hemoglobin (g/dl)	13.31±1.74
LDH (IU/l)	115.29±142.64
ALP (IU/l)	115.29±84.09
Mean follow-up period (mo)	46.30±33.15
Gleason score	
6	14 (13.3)
7	15 (14.3)
8	30 (28.6)
9	24 (22.9)
10	22 (21.0)
Lymph node metastasis	
None	38 (36.2)
Regional	37 (35.2)
Nonregional	30 (28.6)
Bone metastasis	
None	34 (32.4)
EOD 1	39 (37.1)
EOD 2	20 (19.1)
EOD 3	7 (6.6)
EOD 4	5 (4.8)
Sold organ metastasis	6

Values are presented as mean±SD or number (%).
PSA, prostate-specific antigen; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; EOD, extent of disease.

present study. Our study design is described in Fig. 1.

3. Statistical analysis

Statistical analysis was performed by using SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered statistically significant. PSA response to hormonal therapy and response to chemotherapy were evaluated by using multivariate logistic regression analysis with the backward stepwise method. Progression-free time to CRPC and cancer-specific survival of CRPC patients were evaluated by using Cox proportional hazard regression with the backward stepwise method.

RESULTS

Patient and disease characteristics are summarized in Table 1. A total of 105 patients were included in this study; the patients' mean age was 73.24 years, and their mean initial PSA level was 294.18 ng/ml. The mean prostate volume was 51.33 ml, and the mean baseline hemoglobin was 13.31 g/dl. The mean level of lactate dehydrogenase (LDH) was 115.29 IU/l, and the mean ALP level was 115.29 IU/l.

Gleason scores were 6 in 14 patients (13.3%), 7 in 15 patients (14.3%), 8 in 30 patients (28.6%), 9 in 24 patients (22.9%), and 10 in 22 patients (21.0%). Of 105 patients, 67 patients had lymph node metastases, 71 patients had bone metastases, and 33 patients had metastases of both organs. Among 67 patients with lymph node-metastatic prostate cancer, 37 patients (35.2%) had only regional lymph node metastases at the time of diagnosis, whereas 30 patients (28.6%) had NRLN metastases [11]. Diagnosis of NRLN metastases was made by CT imaging studies. Among 71 patients with bone metastases, bone scans and EOD grading revealed that 39 patients were EOD grade 1, 20 were EOD grade 2, 7 were EOD grade 3, and 5 patients were EOD grade 4. Six patients had another solid organ metastasis. At study closure, 61 patients were alive, 38 patients had died of prostate cancer, 2 patients had died of other causes, and 4 patients were lost to follow-up. The median observation period for the surviving patients was 46.3 months (standard deviation, 33.15).

1. Step 1

As outlined in the experimental flow chart (Fig. 1), the first evaluation of step 1, "response to hormonal therapy," is shown in Table 2. In this step, the factors that potentially affected the response to hormonal therapy were evaluated. The response to hormonal therapy was not significantly different among clinicopathologic parameters such as patient age, initial serum PSA level, baseline hemoglobin level, EOD with bone metastasis, and site of lymph node metastasis by use of multiple logistic regression with the backward stepwise method. Whereas the response to hormonal therapy was significantly different according to Gleason score (Gleason score 9: odds ratio [OR], 33.789; 95% con-

TABLE 2. Effects of multiple variables on the response to hormonal therapy and the response to chemotherapy

Characteristic	Response to hormonal therapy		Response to chemotherapy	
	OR (95% CI)	p-value[a]	OR (95% CI)	p-value[b]
Event	40		13	
Age	-	0.695	-	0.159
Initial PSA	-	0.200	-	0.849
Baseline hemoglobin	-	0.751	-	0.665
Gleason score				
6		0.013		0.620
7	2.161 (0.355–13.154)	0.403	-	0.204
8	3.724 (0.752–18.438)	0.107	-	0.977
9	33.789 (4.356–262.129)	0.001	-	0.626
10	5.642 (0.942–33.795)	0.058	-	0.270
Bone metastasis (EOD)				
0		0.321		0.470
1	-	0.207	-	0.723
2	-	0.139	-	0.314
3	-	0.999	-	0.329
4	-	0.342	-	0.507
No LN metastasis		0.243		0.550
Regional LN metastasis	-	0.879	-	0.666
Non regional LN metastasis	-	0.221	-	0.276

OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; EOD, extent of disease; LN, lymph node.
[a,b]:Effects of variables were examined by analysis of variance (multivariate logistic regression with the backward stepwise method).

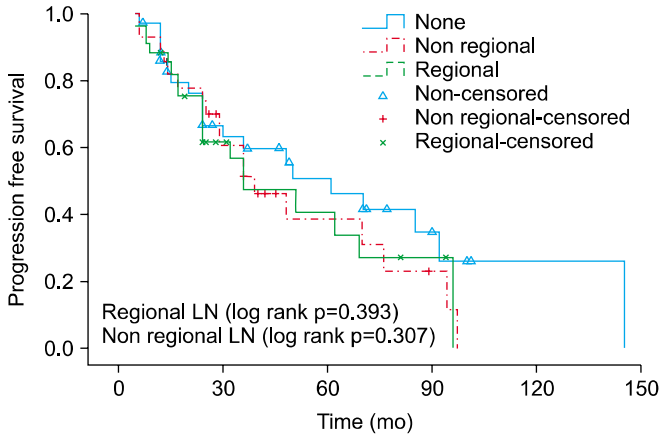

FIG. 2. Differences in progression-free time to castration-resistant prostate cancer between lymph node metastasis groups (Kaplan-Meier method, p=0.393, 0.307, respectively). LN, lymph node.

fidence interval [CI], 4.356 to 262.129; p=0.001, Gleason score 10: OR, 5.642; 95% CI, 0.942 to 33.795; p=0.058) (Table 2), there was no statistical difference between hormonal therapy response and the site of lymph node metastasis (p=0.879 and 0.221, respectively; Table 2).

The second evaluation performed in step 1 was "progression-free interval to CRPC." The progression-free time to CRPC was not significantly reduced with lymph node metastasis burden by Kaplan-Meier analysis (p=0.393 and 0.307, respectively) (Fig. 2). Patient age, Gleason score, initial PSA level, and baseline hemoglobin level were not significant predictors of progression-free time to CRPC. However, regional lymph node metastasis and NRLN metastasis were significant predictive factors for progression-free time to CRPC (regional lymph node metastasis: hazard ratio [HR], 2.519; 95% CI, 1.082 to 5.863; p=0.032, NRLN metastasis: HR, 2.529; 95% CI, 1.160 to 5.512; p=0.020) (Table 3). Additionally, patients with EOD grade 2 and EOD grade 3 had an increased risk of a shortened castration-resistant-free interval relative to those with EOD grade 0 (EOD 2: HR, 4.429; 95% CI, 1.636 to 11.995; p=0.003, EOD 3: HR, 8.451; 95% CI, 2.644 to 27.012; $p \leq 0.001$).

2. Step 2

The first evaluation conducted in step 2, the "response to chemotherapy," is shown in Table 2; the factors that potentially affected the response to chemotherapy were analyzed. The response to chemotherapy was not significantly different among clinicopathologic parameters that we evaluated, such as patient age, initial serum PSA level, baseline hemoglobin level, Gleason score, EOD with bone metastasis, and lymph node metastasis site by use of multiple logistic regression with the backward stepwise method. There was no statistical difference between the response to chemotherapy and any parameter that we evaluated, including the site of lymph node metastasis (p=0.666 and 0.276, respectively).

The second evaluation conducted in step 2 was "cancer-specific survival." The cancer-specific survival was not significantly reduced according to the site of lymph node metastasis by Kaplan-Meier analysis (p=0.111 and 0.105,

TABLE 3. Effects of multiple variables on the progression-free time to castration-resistant prostate cancer (CRPC) and cause-specific survival

Characteristic	Progression-free time to CRPC		Cause-specific survival	
	HR (95% CI)	p-value[a]	HR (95% CI)	p-value[b]
Event	57		38	
Age	-	0.100	-	0.753
Initial PSA	-	0.837	-	0.687
Baseline hemoglobin	-	0.931	-	0.770
Gleason score				
6		0.090		0.641
7	0.703 (0.160-3.090)	0.641	-	0.460
8	2.277 (0.637-8.143)	0.206	-	0.178
9	1.675 (0.451-6.227)	0.441	-	0.327
10	2.966 (0.791-11.116)	0.107	-	0.904
EOD				
0		0.001		0.219
1	1.257 (0.572-2.761)	0.570	-	0.072
2	4.429 (1.636-11.995)	0.003	-	0.026
3	8.451 (2.644-27.012)	<0.001	-	0.786
4	4.375 (0.790-24.244)	0.091	-	0.638
No LN metastasis		0.046		0.135
Regional LN metastasis	2.519 (1.082-5.863)	0.032	-	0.222
Non-regional LN metastasis	2.529 (1.160-5.512)	0.020	-	0.285

HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; EOD, extent of disease; LN, lymph node.
[a,b]:Effects of variables were examined by analysis of variance (Cox proportional hazard regression model with the backward stepwise method).

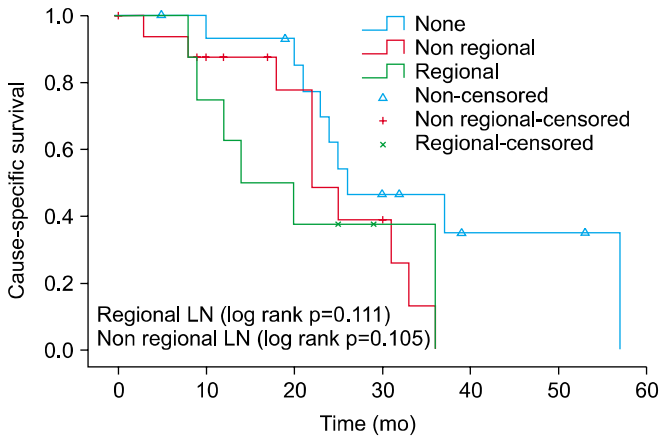

FIG. 3. Differences in cancer-specific survival rates between lymph node metastasis groups (Kaplan-Meier method, p=0.111, 0.105, respectively). LN, lymph node.

respectively) (Fig. 3). Patient age, initial PSA level, baseline hemoglobin level, Gleason score, EOD grade, and the site of lymph node metastasis were not significant predictors of cancer-specific survival (p=0.753, 0.687, 0.770, 0.641, 0.219, and 0.135, respectively) (Table 3).

DISCUSSION

Localized prostate cancer follows a heterogeneous natural course from indolent to aggressive tumor, and various studies are ongoing to determine the biological differences between these types of tumors [5,6]. However, there are few reports demonstrating differences in the nature of specific tumors or prognosis in metastatic prostate cancer. Prostate cancer exploits various routes of metastasis, and understanding the distribution patterns of distant metastasis from primary prostate cancer has been both a therapeutic challenge and an important issue [16]. One preferred metastatic site of prostate cancer is bone; the second preferred site of prostate cancer metastasis is the regional lymph nodes, whereas metastasis into the NRLNs at the time of initial diagnosis is relatively rare [8]. A previous study showed that 17 (8.3%) of 205 metastatic prostatic cancer patients had only NRLN metastasis without bone metastasis [9]. In our study, 12 (11.4%) patients had only NRLN metastasis without bone metastasis. However, there are few relevant reports regarding the proportion of NRLN metastasis and its prognostic influence. As shown in our study, approximately 10% of patients with metastatic prostate cancer may have NRLN metastasis without bone metastasis. Thus, we speculated that patients with NRLN metastasis might have a different tumor biology and prognosis.

Previous reports showed that patients with prostate cancer that metastasized into only the lymph nodes (even NRLNs) had a better prognosis than did patients with bone metastasis owing to the good response to endocrine therapy or the ability to maintain response to hormones [9]. The authors concluded that endocrine therapy was effective in

prostate cancer patients with NRLN metastasis; however, the presence of bone metastasis could predict worse prognosis. They explained that metastases and primary tumors have different clonal compositions and that there is a preferential environment for the growth of prostate cancer cells, particularly in the bone rather than soft tissue. In our study, patients with regional lymph node metastases had a 2.574-fold higher HR relative to those without lymph node metastases, and patients with NRLN metastasis had 2.740-fold higher HR with regard to progression-free time to CRPC. Additionally, patients with EOD 1 grade had a 4.263-fold higher HR relative to those without bone metastases, and patients with EOD grade 2 had a 7.668-fold increased HR. These results of our study were similar to the findings to a previous study [9], because NRLN metastasis decreased the progression-free time to CRPC, although EOD grade more strongly influenced the progression-free time to CRPC than did lymph node metastasis burden.

The mechanisms by which prostate cancer metastasizes to bone tissues are not yet fully understood [16], although the "seed and soil" hypothesis and the "homing" mechanism provide some explanation [17,18]. The "seed and soil" hypothesis was the first proposed by Stephen Paget in 1889 and is based on the idea that primary tumors spread into distant metastatic sites as a plant disperses its seeds [19]. The seeds are carried in all directions, but they can only grow in the most suitable soil. However, this hypothesis was challenged by a recent gene expression study [20,21]. Cancer cells may hone in to specific metastatic sites in organs with specific metastatic gene expression signatures; these gene signatures might be superimposed on a poor-prognosis signature in the parent tumor, which might account for the various gene expression patterns observed in certain tumors [21]. Furuya et al. [9] explained their results in terms of the seed and soil hypothesis; however, this homing mechanism could also explain our results in which the EOD grade more strongly influenced the progression-free time to CRPC than did the lymph node metastasis burden.

In the present study, we also evaluated the prognostic effect of NRLN metastasis in patients with CRPC receiving chemotherapy and evaluated other potential prognostic predictors. Berry et al. [22] identified factors that predicted decreased survival in an analysis of 85 patients with metastatic hormone-resistant prostate cancer. They reported that age ($>$65 years), severe bone pain, poor performance status, the presence of soft tissue metastases, anemia, and elevated levels of LDH, acid phosphatase, ALP, and prolactin were poor prognostic factors. Emrich et al. [23] identified in an analysis of 1,020 patients the following factors predictive of survival in order of importance: previous hormone response, anorexia, elevated acid phosphatase, pain, elevated ALP, obstructive symptoms, tumor grade, performance status, anemia, and age at diagnosis. Kantoff et al. [24] identified prognostic factors on the basis of 242 metastatic hormone-resistant prostate cancer patients; the factors they identified included ALP, LDH, baseline PSA, and hemoglobin. In our study, however, we could not identify independent prognostic factors among previously mentioned parameters such as performance status, baseline hemoglobin level, visceral involvement, baseline acid phosphatase, ALP and LDH levels, time from initiation of androgen deprivation to initiation of chemotherapy, response to therapy, decline in post-therapy serum PSA ($\geq$4 weeks), baseline PSA, EOD on bone scan, and continuation of androgen deprivation. In addition, NRLN metastasis and EOD of bone metastasis were not significant independent factors that were predictive of chemotherapy response, progression of disease, or overall survival by multivariate analysis.

As shown in our study, NRLN metastasis is an independent prognostic factor for predicting reduced progression time to CRPC, although the associated relative risk was lower than that of bone metastasis. However, NRLN was not an independent prognostic factor for predicting the chemotherapeutic response or decreased cancer-specific survival. Although the sample size was relatively small, this is the first study that investigated the prognostic significance of NRLN metastasis with regard to both hormonal therapy and chemotherapy response in metastatic prostate cancer. To select the proper treatment strategy in metastatic prostate cancer patients and to determine those with very low survival rates, additional studies aimed at identifying factors to predict poor prognosis are needed.

CONCLUSIONS

Twelve (11.4%) of 105 patients with NRLN metastasis had only lymph node metastases without bone metastases. Therefore, we speculate that prostate cancer with NRLN metastases exhibits a unique tumor biology. In addition, NRLN metastasis was a significant prognostic factor for predicting decreased progression-free time to CRPC. We suggest that large-scale, multicenter studies including metastatic prostate cancer patients and those with lymph node metastasis are required, and studies aimed at delineating the mechanisms underlying the unique tumor biology associated with metastatic prostate cancer are also needed.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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