

# Contribution of Serum Biomarkers to Prognostic Assessment in Patients With Oligometastatic Prostate Cancer

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**Abstract.** *Background/Aim:* The aim of this study was to analyze the prognostic impact of biomarkers, such as serum lactate dehydrogenase (LDH), in patients with oligometastatic castration-resistant prostate cancer, arbitrarily defined as a maximum of five metastatic lesions. *Patients and Methods:* This was a retrospective single-institution analysis. Overall 34 patients were included, all of whom received first-line docetaxel without ablative local treatment. *Results:* Twelve patients (35%) had elevated LDH ( $\geq 255$  U/l). Their median survival was significantly shorter than that of patients with normal LDH. Due to an interaction with other biomarkers, multivariate Cox regression analysis was performed. The latter showed that serum hemoglobin was the only significant predictor of survival. *Conclusion:* Correct diagnosis of oligometastatic disease is not trivial, because all radiological modalities are limited by certain thresholds for detection of small metastases. Serum biomarkers may reflect the total burden of malignant disease. However, this relatively small study did not clearly demonstrate that elevation of LDH may be useful for clinical decision-making, e.g. in terms of adding local treatment for all sites of metastatic spread.

Increasing attention has recently been paid to patients with oligometastatic disease, *i.e.* a state between curable locoregional disease and incurable dissemination throughout large parts of the body (1-4). If only few distant metastases are present, ablative local treatment or resection of all these lesions might result in longer survival than historically

observed (5-7). However, not all patients become long-term survivors, a finding that emphasizes the challenges associated with detecting true oligometastatic disease. If additional micrometastases go undetected, rapid disease progression might be encountered. It would, therefore, be prudent to include staging examinations that are not limited by the detection thresholds of radiological methods (8-10). For example, the number of circulating tumor cells, cell-free DNA or other emerging biomarkers may aid in the detection of true and pseudo-oligometastatic disease (11, 12). Given that many patients, especially in low- and middle-income countries, lack access to advanced imaging and biomarker evaluations, widely available and inexpensive biomarkers may also contribute to improved prognostic assessment and decision-making. Therefore, we studied the prognostic impact of serum lactate dehydrogenase (LDH), prostate-specific antigen (PSA), alkaline phosphatase (ALP) and hemoglobin in patients with oligometastatic castration-resistant prostate cancer (MCRPC) who received first-line chemotherapy with docetaxel. We hypothesized that such biomarkers might reflect the overall disease burden in patients presumed to harbor oligometastases. If true, patients with elevated serum biomarkers due to otherwise undetectable additional metastases are expected to have poorer survival and may be spared the burden of aggressive local treatment.

## Patients and Methods

*Patients and treatment.* A retrospective study of all patients with MCRPC and a maximum of five distant metastases treated with first-line docetaxel at our hospital was performed. An existing database was used to identify eligible patients (13). These patients had not received docetaxel for hormone-sensitive metastatic disease earlier. Further treatment was individualized and consisted of additional lines of systemic therapy (Ra-223, enzalutamide, abiraterone acetate, cabazitaxel) or best supportive care. Systemic treatment was usually prescribed as judged appropriate by the patients' clinical oncologists and was tailored to performance status (typically 0-1), organ function and comorbidity. The patients

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*Key Words:* Palliative chemotherapy, docetaxel, prostate cancer, oligometastases, prognostic factors, biomarkers, lactate dehydrogenase.

Table I. Patient characteristics.

Baseline parameter	Value
Bone metastases only, n (%)	16 (47)
Lymph node metastases only, n (%)	9 (26)
Visceral metastases only, n (%)	2 (6)
Bone and lymph node metastases, n (%)	7 (21)
Median serum PSA (range), µg/l	93 (6-1487)
Median serum ALP (range), U/l	123 (47-916)
Median serum LDH (range), U/l	211 (146-675)
Median hemoglobin (range), g/dl	13.6 (9.6-16.0)

ALP: Alkaline phosphatase; LDH: lactate dehydrogenase; PSA: prostate-specific antigen.

were treated between January 01, 2007 and December 31, 2017. Staging consisted of computed tomography and bone isotope scan. Biomarkers were assessed at the start of chemotherapy or within the preceding week (the normal value was defined as <255 U/l for LDH, <105 U/l for ALP, and 13.4-17.0 g/dl for hemoglobin).

**Statistical methods.** Overall survival (time to death) from the first day of chemotherapy was calculated employing the Kaplan–Meier method, and different groups were compared using the log-rank test (SPSS 25; IBM Corp., Armonk, NY, USA). Only four patients were censored after a median follow-up of 48 months. Date of death was known for all other patients. A Cox forward conditional regression model was employed for multivariate analysis. Statistical significance was defined as  $p < 0.05$  throughout this study.

## Results

**Patient characteristics.** A total of 34 patients were identified from the database. Their median age was 69 (range=56-78) years. Six patients (18%) already had distant metastases when diagnosed with prostate cancer, the others developed metachronous metastases. Nine patients (26%) had pelvic lymph node metastases (N+ disease) at first diagnosis. Thirteen patients (38%) were initially treated with curative radiotherapy or radical prostatectomy. Two patients (6%) received palliative radiotherapy to the prostate before chemotherapy. Further patient characteristics are shown in Table I.

**Treatment for MCRPC.** Twenty patients (59%) received docetaxel every 3 weeks (75 mg/m<sup>2</sup>) and the remainder every 2 weeks or every week at lower doses. Oligometastases were not treated with local measures such as surgery or ablative radiotherapy. Bisphosphonates were given to 11 patients (32%) concomitant to chemotherapy. Except for nine patients (26%), further systemic treatment with approved agents (Ra-223, enzalutamide, abiraterone acetate, cabazitaxel) was given after disease progression on docetaxel (14).

**Survival.** The median overall survival of the whole patient cohort was 27.7 months. As shown in Figure 1, LDH was significantly associated with survival. Survival beyond 5 years was observed in patients with normal LDH only. Survival was not significantly associated with previous treatment of the primary tumor (surgery or curative radiotherapy vs. none), bisphosphonate use, patterns of metastasis (bone only, lymph nodes only etc.), age, ALP and PSA. However, patients with a normal hemoglobin level survived significantly longer than their counterparts with abnormally low values. In the Cox regression model, hemoglobin retained statistical significance ( $p=0.008$ ), whereas LDH did not ( $p=0.21$ ).

## Discussion

We performed a retrospective study on patients with a limited number of distant metastases (maximum five in total) and evaluated biomarkers which previously have been studied in different other settings (15, 16). We found that elevated LDH and reduced hemoglobin were associated with significantly shorter survival, however in multivariate analysis, hemoglobin outperformed LDH.

Limitations of the present study include the limited number of patients, statistical power of subgroup analyses, and retrospective design. The presence of oligometastatic disease was not confirmed by positron-emission tomography (PET) staging. However, PET staging is also associated with false-negative and otherwise inaccurate findings (7). Moreover, the availability of PET is limited or, in some low- and middle-income countries, even non-existent. Under these circumstances, readily available biomarkers might complement computed tomographic- and isotope scan-based staging, with the ultimate goal of avoiding overtreatment in patients with pseudo-oligometastatic disease. Emerging biomarkers such as those based on circulating tumor cells are not widely available yet (17), in contrast to hemoglobin, LDH or ALP measurement.

We limited this analysis to patients treated with first-line docetaxel rather than a variety of different approved options in order to eliminate bias arising from differences in first-line systemic treatment. As recently discussed by different groups, aggressive local treatment of oligometastatic cancer is expected to improve survival (2-4, 18). Even in the absence of metastasis-directed local treatment, we found long-term survivors in the group with normal hemoglobin (and also LDH). Our results suggest that readily available blood tests may add value when designing further clinical trials and in resource-limited settings.

## Conclusion

Correct diagnosis of oligometastatic disease is not trivial because all radiological modalities are limited by certain thresholds for the detection of small metastases. Serum

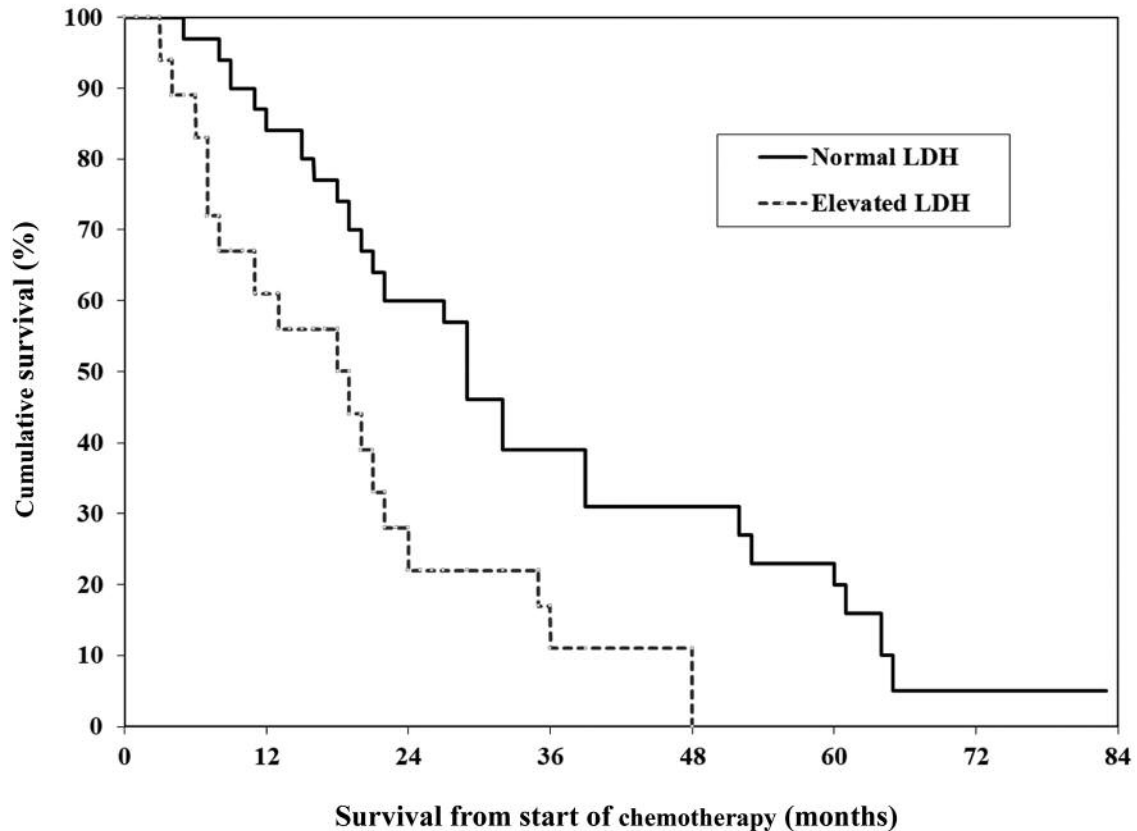


Figure 1. Actuarial overall survival stratified by serum lactate dehydrogenase (LDH). Normal LDH: Median 29.8 months, elevated LDH: median 20.0 months ( $p=0.036$ ).

biomarkers may reflect the total burden of malignant disease. However, this relatively small study did not clearly demonstrate that elevation of LDH may be useful for clinical decision-making, *e.g.* in terms of adding local treatment for all sites of metastatic spread.

### Conflicts of Interest

The Authors declare that they have no competing interests.

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*Received November 2, 2018*

*Revised November 22, 2018*

*Accepted November 28, 2018*