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Original article

Evaluation of the platelet-to-lymphocyte ratio as a prognostic indicator in a European cohort of patients with prostate cancer treated with radiotherapy

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Abstract

Objectives: Recent evidence suggests that the presence of a systemic inflammatory response plays an important role in the progression of several solid tumors. The platelet-to-lymphocyte ratio (PLR) has been proposed as an easily assessable marker of systemic inflammation and has been shown to represent a prognostic marker in different cancer entities. To evaluate the prognostic value of the PLR in prostate cancer, we performed the present study.

Methods and materials: Data from 374 consecutive patients with prostate cancer, treated with 3D conformal radiotherapy from 1999 to 2007, were analyzed. Distant metastases–free survival (MFS), cancer-specific survival (CSS), overall survival (OS), biochemical disease–free survival, and time to salvage systemic therapy were assessed using the Kaplan-Meier method. Cox proportional hazards analysis was performed to calculate hazard ratio (HR) and 95% CI. Multivariate Cox regression analysis was performed to adjust for other covariates.

Results: Using receiver operating characteristics analysis, the optimal cutoff level for the PLR was 190. Kaplan-Meier analyses revealed that PLR $\geq$ 190 was a prognostic factor for decreased MFS ($P = 0.004$), CSS ($P = 0.004$), and OS ($P = 0.024$) whereas a significant association of an elevated PLR with biochemical disease–free survival ($P = 0.740$) and time to salvage systemic therapy ($P = 0.063$) was not detected. In multivariate analysis, an increased PLR remained a significant prognostic factor for poor MFS (HR = 2.24, 95% CI: 1.06–4.76, $P = 0.036$), CSS (HR = 3.99, 95% CI: 1.19–13.4, $P = 0.025$), and OS (HR = 1.87, 95% CI: 1.02–3.42, $P = 0.044$).

Conclusions: Our findings indicate that the PLR may predict prognosis in patients with prostate cancer and may contribute to future individual risk assessment in them.

Keywords: Inflammation; Platelet-to-lymphocyte ratio (PLR); Prognosis; Prostate cancer

1. Introduction

Prostate cancer has become the most frequently diagnosed nonskin cancer among men in Western countries and is the third leading cause of cancer-related mortality [1]. Survival in patients with prostate cancer has improved in recent years; however, it is often difficult to discriminate patients who require potentially curative treatment and to identify patients who might benefit from more aggressive treatment approaches.

Considerable efforts have been undertaken to identify novel genetic and immunologic prognostic biomarkers; however, high costs of analyses, time-consuming preparation, and lack of standardization limit their application in routine clinical practice [2–4]. Therefore, in general, current clinical decisions still rely on readily available tumor-related

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factors such as tumor stage, Gleason score (GS), and prostate-specific antigen (PSA) level.

The natural history and progression of prostate cancer is poorly understood; however, some evidence suggests an association between the activation of the systemic inflammatory response and prostate cancer survival [5–7]. Measurable blood parameters that reflect the systemic inflammatory response are elevated levels of C-reactive protein (CRP), hypoalbuminemia, increased levels of some cytokines, and increased levels of leukocytes and their subtypes [5,8–10].

More recently, pretherapeutic indices of systemic inflammation have been suggested to provide prognostic information in various cancer entities. Among these inflammatory parameters, the platelet-to-lymphocyte ratio (PLR) has been proposed as an easily accessible and reliable marker to predict cancer prognosis. Accumulating evidence suggests that a high PLR might represent an independent adverse prognostic factor in ovarian cancer, colorectal cancer, pancreatic cancer, and breast cancer [11–15]. However, data regarding the prognostic significance of the PLR in prostate cancer are sparse. In the Glasgow Inflammation Outcome Study, an increased PLR has been linked with poor prognosis in different types of cancer including prostate cancer [11]. However, for the patients with prostate cancer included in the study cohort, no information on staging, histologic grade, or treatment characteristics was available. It was therefore unclear if the association between an elevated PLR and poor prognosis would remain significant after adjustment for other important measures of prostate cancer prognosis.

The aim of the present study was to validate the prognostic significance of the pretreatment PLR in a large European cohort of patients with nonmetastatic prostate cancer.

2. Material and methods

2.1. Patients

An institutional database of patients with prostate cancer who attended radiation therapy consultation during the years 1999 through 2007 was analyzed.

Eligible for inclusion in the present analysis were male patients with histologically confirmed prostate cancer who had platelet and lymphocyte levels recorded for any reason and underwent radiotherapy at the Department of Therapeutic Radiology and Oncology, Medical University of Graz. Patients were excluded if they had absent demographic information, missing radiation therapy information, or missing information on tumor stage, PSA level, or GS. Applying these criteria, 374 patients were included in the present analysis.

Patients with prostate cancer were stratified into low-, intermediate-, and high-risk groups on the basis of pretreatment PSA level, GS, and tumor stage according to the NCCN guidelines [16].

All patients underwent 3-dimensional conformal radiotherapy for prostate cancer. At the time of the patients' treatment, the total dose administered to the patients was 70 Gy delivered in 2 Gy per fraction (5 times/wk).

Follow-up examinations were performed in regular intervals (3-mo intervals in years 1–3, 6-mo intervals in years 4 and 5, and annually thereafter) and included PSA measurements and digital rectal examinations.

Patients with PSA relapse, defined as an increase by ≥ 2 ng/ml above the nadir PSA level, were regularly checked using a battery of diagnostic tests, comprising isotope bone scan, chest X-ray, abdominal and pelvic computed tomography, and magnetic resonance imaging studies. The study complied with the Declaration of Helsinki and was performed according to the national law. The protocol has been approved by the local Ethical Committee (EK 17-032 ex 14/15).

2.2. Statistical analysis

The primary end point of the study was distant metastases–free survival (MFS) defined as the time from prostate cancer diagnosis to the occurrence of distant metastases. Metastatic involvement of nonregional lymph nodes, bones and other sites counted as metastases for the outcome. Secondary end points included cancer-specific survival (CSS), overall survival (OS), biochemical disease–free survival (BDFS), and time to salvage systemic therapy.

The PLR was calculated as the absolute platelet count measured in G/l divided by the absolute lymphocyte count measured in G/l. First, the PLR was categorized into 3 groups (<150, 150–300, and >300) according to the previously published study by Proctor et al. [11]. In addition, we determined an ideal cutoff value for the continuous PLR by applying receiver operating characteristics analysis testing all possible cutoffs that would discriminate between the patients' MFS and the occurrence of distant metastases in our cohort of patients with prostate cancer. The PLR was correlated with clinicopathologic features by nonparametric tests (Kruskal-Wallis test, Mann-Whitney *U* test, and Spearman correlation). The association of clinicopathologic features and the PLR with the clinical end points was analyzed using Kaplan-Meier curves compared by the log-rank test. Cox proportional hazards analysis was performed to calculate the hazard ratio (HR) and 95% CI to evaluate the association of the PLR with clinical end points. Multivariate Cox regression analysis was performed to adjust for other covariates and included age at diagnosis, tumor stage, PSA level, GS, (neo)adjuvant androgen deprivation therapy (ADT), secondary ADT administered for biochemical relapse, white blood cell and platelet count, and the neutrophil-to-lymphocyte ratio (NLR). The Harrel concordance index (c-index) was used to assess the predictive accuracy of a