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Article

Pre-Treatment Hemoglobin Concentration and Absolute Monocyte Count as Independent Prognostic Factors for Survival in Localized or Locally Advanced Prostate Cancer Patients undergoing Radiotherapy

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Abstract: The prognostic value of inflammatory indices such as absolute monocyte count (AMC) has been a subject of interest in recent prostate cancer (PCa) literature, while hemoglobin concentration (HGB) has been recognized as a survival factor in castration-resistant metastatic prostate cancer, but its value remains unclear in localized disease. The aim of this study was to test the prognostic value of these two simple and inexpensive biomarkers for survival based on a cohort of 1016 patients treated with primary radiotherapy and androgen deprivation therapy for localized or locally advanced intermediate- or high-risk PCa. Complete survival data was available for all cases based on the National Cancer Registry with a median observation time of 120 months (IQR 80.9-144.7). Missing blood test data were supplemented using the Nearest Neighbor Imputation, and the Cox proportional hazards regression model was used for analysis. The median age was 68.8 years (IQR 63.3-73.5). The five-year overall survival was 82.8%, and 508 patients were alive at the time of analysis. The median time between blood tests and the first day of radiotherapy was 6 days (IQR 0-19). HGB ($p = 0.009$) and AMC ($p = 0.003$) were independent prognostic factors for survival, along with age, ISUP Grade Group, clinical T stage and maximum PSA concentration. The study demonstrated that HGB and AMC can be useful biomarkers for overall survival in patients treated with radiotherapy for localized intermediate- or high-risk PCa.

Keywords: hemoglobin; monocytes; overall survival; prostate cancer; radiotherapy

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1. Introduction

There is a range of therapeutic options available for the treatment of localized prostate cancer (PCa). However, it has been shown that it is unlikely for patients to have survival benefit from upfront interventional treatment for localized prostate cancer within 10 years from the diagnosis [1], and in general, asymptomatic patients with life expectancy below five years are discouraged from seeking interventional treatment methods [2]. Therefore, an adequate estimation of a patients' expected survival such as based on WHO's Life Tables [3], or The Memorial Sloan Kettering Male Life Expectancy Tool [4] is crucial for individualized patient-tailored approach in choosing appropriate treatment strategy. The Charlson Comorbidity Index or its 'Prostate Cancer Specific' modification are the most widely used tool for stratifying mortality risk in PCa patients [5–7]. In situations where expected survival is unclear, other prognostic factors are highly demanded.

Hemoglobin concentration (HGB) is a routinely measured blood parameter, and its prognostic value is well recognized across various malignancies [8,9]. Prognostic value of HGB in metastatic prostate cancer has been also documented [10–12]. However, few studies so far evaluated the ability of HGB to predict outcome in localized PCa [13,14]. Considering its value in predicting both disease-specific mortality [10], and all-cause mortality [15,16], HGB promises to be a valuable tool for predicting PCa patients' survival.

Tumor-associated macrophages (TAM) are differentiated circulating monocytes in the tumor site, which have been reported to promote tumor genesis and progression [17]. TAM, which correlates with absolute monocyte count (AMC) [16], has proven to be a prognostic factor for overall survival in PCa patients [15]. Therefore, routinely measured AMC may prove to be a useful prognostic factor for survival in PCa patients, as suggested by recent publications [18,19].

This study aimed to analyze the value of HGB and AMC as independent prognostic factors for overall survival (OS) and freedom from distant metastases (FFDM) in patients treated with radiotherapy for localized and locally advanced intermediate- or high-risk PCa.

2. Materials and Methods

2.1. Patients

From February 2003 to November 2014, 1200 consecutive patients had undergone radical radiotherapy at single tertiary center for histologically proven localized or locally advanced (T_{1c}-T_4, N_0/N_1, M_0) intermediate- or high-risk prostate cancer. A total of 184 cases were excluded due to the lack of pre-irradiation blood tests (n = 183) or a co-existing leukemia (n = 1), and 1016 patients were included in the final analysis. Tumor staging was assessed retrospectively according to the 2017 The Union for International Cancer Control's 8th edition classification [20], based on the available results of digital rectal examination, transrectal ultrasonography, bone scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis and abdomen, chest radiography and in some cases 18F-fluorocholine-PET, later superseded by PET-PSMA. All tumors were confirmed histopathologically based on material obtained from a fine-needle biopsy or from a transurethral resection of the prostate. International Society of Urological Pathology (ISUP) Gleason Grading Group [21] was assessed retrospectively, based on the available Gleason Score data. Blood parameters were collected from tests performed no later than two days after the start of external beam radiotherapy (EBRT) or first fraction of brachytherapy boost (BT-boost), whichever occurred earlier. This retrospective study

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was approved by bioethics committee of Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland (approval no. KB/430-82/21).

2.2. Follow-up

The clinical follow-up was collected retrospectively, based on patient's medical records for FFDM, and Polish National Cancer Registry data for OS. The follow-up duration was calculated from the first day of radiotherapy. Follow-up visits were scheduled every 3 months in the first 1-2 years, every 6 months until 5 years after treatment and annually thereafter. In case of rising PSA level and reasonable presumption of distant metastases medical imaging was performed including methods like bone scintigraphy, 18F-fluorocholine- or PSMA-PET, MRI, and CT-scan.

2.3. Statistical analysis

The primary endpoint was OS. Secondary endpoint was FFDM. Both endpoints were calculated from the first day of radiotherapy, to the day of death or last known time point when patient was alive for OS, and occurrence of distant metastases or last follow-up visit for FFDM. Nearest Neighbor Imputation was used to impute missing laboratory test values with K = 3 and based on the values of available parameters. Summary of all parameters before and after imputation are presented in Supplementary table 1. Continuous variables were described using medians with interquartile ranges (IQR) due to the non-normality of distribution verified with Shapiro-Wilk test. Differences between groups were assessed using Mann-Whitney U test or Kruskal-Wallis test, depending on the number of groups, and associations between continuous variables were tested using Spearman rank correlation test. Cox Proportional Hazards models were used for survival analysis and hazard ratios (HR) with 95% confidence intervals (95% CI) were reported. Laboratory parameters were selected for inclusion in multivariate analysis based on significance in univariate analysis, co-linearity and known prognostic value for prostate cancer. Akaike Information Criterion (AIC) was used to evaluate the models. P values lower than 0.05 were considered statistically significant and all tests were two-sided. All calculations were performed using Statistica 13.3 software by StatSoft (TIBCO Software, Palo Alto, CA, USA).

3. Results

3.1. Treatment and patient outcomes

The patients were treated with EBRT, or EBRT combined with high-dose-rate BT-boost in 192 (18.9%) cases. There were 14 patients with metastasis in single regional lymph node (N_1) which has been given a boost with irradiation. Pelvic lymph node irradiation was performed in 76% (n = 772) patients, up to a total dose of 44-50 Gy in 2 Gy fraction doses. Detailed data on irradiation doses are described in Supplementary table 2. Majority of patients (n = 953) received neoadjuvant ADT (Neo-ADT), mostly based on gonadotropin-releasing hormone agonist (GnRH) combined with nonsteroidal anti-androgen drug (NSAA) (85%, n = 810). GnRH agonist was used as monotherapy in 116 cases (12.2%), and NSAA in 31 patients (3.3%). Median duration of Neo-ADT was 4.6 months (IQR 3.2-7), and median total duration of ADT was 28.6 months (IQR 14.9-41.9). Median time from the blood tests to the first day of EBRT or BT-boost was 6 days (IQR 0-19). Detailed patient and treatment characteristics are described in Table 1.

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Table 1. Baseline patient characteristics.

Parameter	Study group N = 1016
Age (median) [years]	68.8 (IQR 63.2-73.5)
ZUBROD	
0	79.3%
1	20.5%
2	0.2%
NCCN Risk Group	
Favorable intermediate	6.3%
Unfavorable intermediate	23.9%
High	45.7%
Very high	24.1%
ISUP Grade Group	
1	38.8%
2	29.5%
3	12.5%
4	8.9%
5	8.2%
Missing data	2.2%
Clinical T stage	
T1c	35.8%
T2a	11.7%
T2b	18.7%
T2c	17.2%
T3a	9.8%
T3b	5.5%
T4	1.2%
Pre-radiation PSA (median) [ng/mL]	0.6 (IQR 0.11-3.42)
PSA density (median) [ng/mL^2]	0.64 (IQR 0.33-1.14)
mPSA (median) [ng/mL]	24.39 (IQR 13.28-41.99)
mPSA	
< 10 ng/mL	16%
≥ 10 ng/mL, < 20 ng/mL	21.7%
≥ 20 ng/mL	61.1%
Missing data	1.2%
TURP	5.8%
Neo-ADT	93.8%
Duration of Neo-ADT (median) [months]	4.6 (IQR 3.2-7)
Adjuvant ADT	86.8%
Total duration of ADT (median) [months]	28.6 (IQR 14.9-41.9)
Radiation modality	
EBRT	81.1%
EBRT + single BT-boost	12.3%
EBRT + double BT-boost	6.6%
Lymph node irradiation	76%
NLR (median)	1.92 (IQR 1.42-2.62)
PLR (median)	114.8 (IQR 90.1-145)
LMR (median)	3.32 (IQR 2.57-4.28)
WBC (median) [10^3/μL]	6.43 (IQR 5.3-7.7)
LYMPH (median) [10^3/μL]	1.86 IQR 1.5-2.35)
NEUT (median) [10^3/μL]	3.61 (IQR 2.87-4.56)

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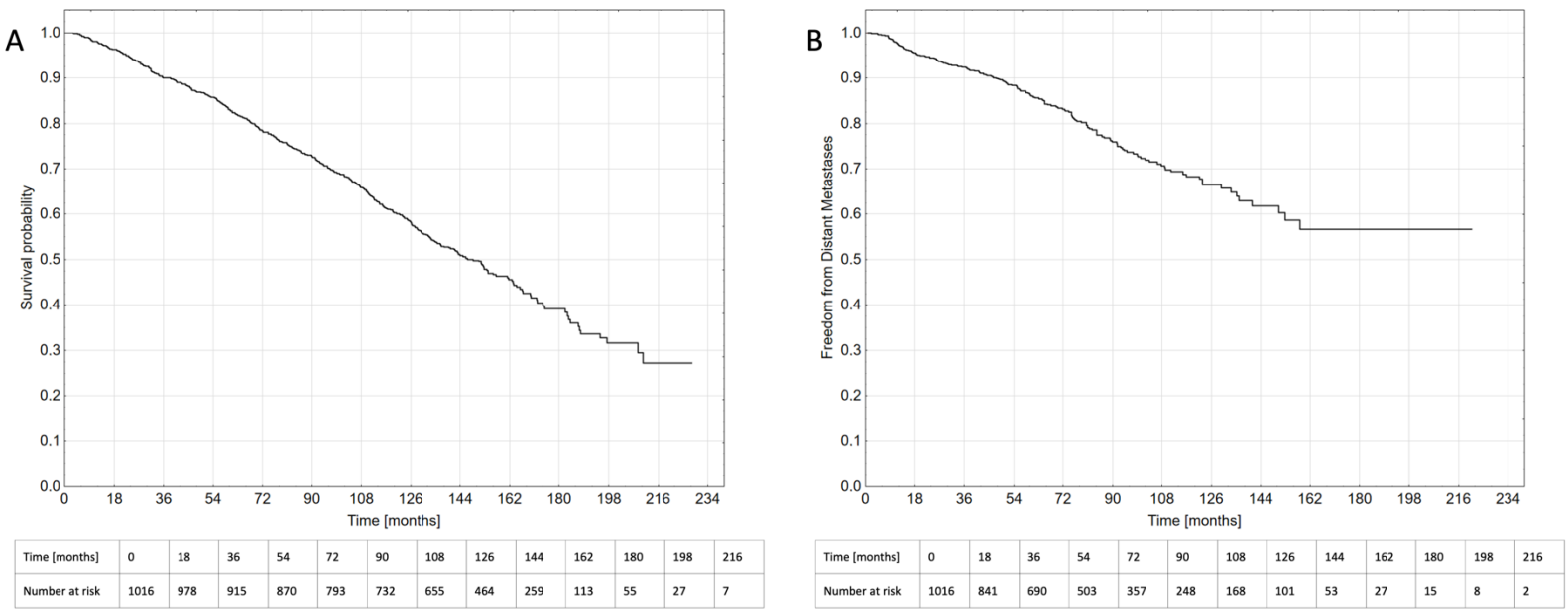
AMC (median) [10^3/μL]	0.56 IQR 0.45-0.71)
EO (median) [10^3/μL]	0.15 (IQR 0.09-0.22)
BASO (median) [10^3/μL]	0.03 (IQR 0.02-0.04)
RBC (median) [10^6/μL]	4.48 (IQR 4.2-4.77)
HGB (median) [g/dL]	13.8 (IQR 13-14.6)
HCT (median)	40.6% (IQR 38.7-42.9)
RDW (median)	13.4% (IQR 12.8-14)
PLT (median) [10^3/μL]	211 (IQR 179-249.5)
PDW (median) [fL]	12.3 (IQR 11.2-13.6)

NCCN – National Comprehensive Cancer Network, ISUP – International Society of Urological Pathology, PSA – prostate-specific antigen, mPSA – maximum PSA concentration, TURP – transurethral resection of the prostate, ADT – androgen deprivation therapy, EBRT – external beam radiation therapy, BT-boost – brachytherapy boost, RT – radiotherapy, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, LMR – lymphocyte-to-monocyte ratio, WBC – absolute white blood cell count, LYMPH – absolute lymphocyte count, NEUT – absolute neutrophile count, AMC – absolute monocyte count, EO – absolute eosinophile count, BASO – absolute basophile count, RBC – absolute red blood cell count, HGB – hemoglobin concentration, HCT – hematocrit, RDW – red blood cell distribution width, PLT – absolute platelet count, PDW – platelet distribution width

Median follow-up was 120 months. (IQR 80.9-144.7) for OS and 57.4 months (IQR 30.3-97.4) for FFDM. Five-year overall survival was 82.8%, and 508 (50%) patients were alive at the date of analysis (Figure 1A). Distant metastases occurred in 177 (17.4%) cases (Figure 1B). The main metastatic sites were bones (n = 96) and lymph nodes (n = 40) or both (n = 23). The metastatic spread was diagnosed in majority of cases with bone scintigraphy (n = 58), 18F-fluorocholine-PET (n = 53), CT-scan (n = 33), PSMA-PET (n = 12) or MRI (n = 11). Second malignancy was diagnosed during the follow-up in 81 patients, including 28 cases of colon cancer, 13 cases of lung cancer and nine cases of non-melanoma skin cancer.



Time [months]	0	18	36	54	72	90	108	126	144	162	180	198	216
Number at risk	1016	978	915	870	793	732	655	464	259	113	55	27	7

Time [months]	0	18	36	54	72	90	108	126	144	162	180	198	216
Number at risk	1016	841	690	503	357	248	168	101	53	27	15	8	2

Figure 1. Overall Survival (A) and Freedom from Distant Metastases (B) in patients treated with radiotherapy for localized or locally advanced prostate cancer.

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3.2. Predicting overall survival based on clinical variables and blood parameters

In univariate analysis (UVA) age, ISUP Grade Group, clinical T stage, ZUBROD, RT modality and maximum PSA concentration (mPSA) were significant for OS, along with HGB, NLR, WBC, NEUT, AMC, EO, RBC, HCT and RDW (Table 2). Several moderate to strong correlations were observed between blood parameters (Supplementary table 3), and based on the significance in UVA, known clinical relevance and collinearity with other predictors HGB and AMC were included in multivariate model for survival prediction.

HGB ($p = 0.009$), AMC ($p = 0.003$), age ($p < 0.001$), clinical T stage, ISUP Grade Group and mPSA ($p = 0.021$) remained significant predictors for OS in MVA (Table 2). Adding HGB and AMC to the model reduced the AIC to 6102.68 compared with 6111.54 for a model with clinical prognostic factors alone.

Table 2. Cox Proportional Hazards Regression Analysis for overall survival in patients treated with radiation therapy for localized or locally advanced prostate cancer.

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
HGB [g/dL]	0.853 (0.789-0.922)	**<0.001**	0.899 (0.83-0.975)	**0.009**
AMC [10^3/μL]	2.216 (1.497-3.282)	**<0.001**	1.918 (1.243-2.959)	**0.003**
Age [years]	1.067 (1.052-1.082)	**<0.001**	1.065 (1.05-1.081)	**<0.001**
ISUP Grade Group				
2 vs 1	1.296 (1.042-1.611)	**0.019**	1.215 (0.970-1.523)	0.089
3 vs 1	1.287 (0.963-1.72)	0.088	1.140 (0.846-1.538)	0.389
4 vs 1	1.58 (1.156-2.159)	**0.004**	1.235 (0.891-1.713)	0.205
5 vs 1	1.957 (1.438-2.662)	**<0.001**	1.717 (1.234-2.389)	**0.001**
Clinical T stage				
T2a vs T1c	0.886 (0.651-1.204)	0.438	0.922 (0.667-1.273)	0.621
T2b vs T1c	1.049 (0.812-1.353)	0.716	0.991 (0.761-1.291)	0.947
T2c vs T1c	1.527 (1.195-1.953)	**<0.001**	1.361 (1.047-1.769)	**0.022**
T3a vs T1c	1.191 (0.867-1.636)	0.281	1.163 (0.834-1.621)	0.373
T3b vs T1c	1.431 (0.977-2.097)	0.066	1.446 (0.965-2.165)	0.074
T4 vs T1c	2.165 (1.065-4.402)	**0.033**	1.157 (0.532-2.518)	0.712
ZUBROD (1-2)	1.542 (1.257-1.892)	**<0.001**	1.194 (0.961-1.483)	0.091
RT modality (EBRT)	1.701 (1.336-2.164)	**<0.001**	1.212 (0.925-1.589)	0.163
mPSA [ng/mL²]	1.003 (1.001-1.005)	**<0.001**	1.002 (1-1.004)	**0.021**
NLR	1.113 (1.044-1.186)	**0.001**		
PLR	1 (0.998-1.002)	0.819		
LMR	0.952 (0.898-1.01)	0.101		
WBC [10^3/μL]	1.084 (1.037-1.134)	**<0.001**		
LYMPH [10^3/μL]	1.024 (0.916-1.145)	0.680		
NEUT [10^3/μL]	1.121 (1.057-1.189)	**<0.001**		
EO [10^3/μL]	1.842 (1.128-3.006)	**0.014**		
BASO [10^3/μL]	1.166 (0.052-25.997)	0.923		
RBC [10^6/μL]	0.684 (0.552-0.849)	**<0.001**		
HCT	0.957 (0.93-0.984)	**0.002**		
RDW	1.144 (1.054-1.242)	**0.001**		
PLT [10^3/μL]	0.999 (0.997-1.001)	0.323		
PDW [fL]	1.013 (0.965-1.063	0.613		

HGB – hemoglobin concentration, AMC – absolute monocyte count, ISUP – International Society of Urological Pathology, RT – radiotherapy, EBRT – external beam radiotherapy, mPSA – maximum prostate specific antigen concentration, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, LMR – lymphocyte-to-monocyte ratio, WBC – absolute white blood cell count,

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LYMPH – absolute lymphocyte count, NEUT – absolute neutrophile count, EO – absolute eosinophile count, BASO – absolute basophile count, RBC – absolute red blood cell count, HCT – hematocrit, RDW – red blood cell distribution width, PLT – absolute platelet count, PDW – platelet distribution width

3.3. Predicting freedom from distant metastases based on clinical factors and blood parameters

In UVA, ISUP Grade Group, clinical T stage, ZUBROD, RT modality, mPSA HGB and AMC were significant prognostic factors for FFDM (Table 3). Despite lack of significance in UVA, age was included for the MVA based on known prognostic value. In MVA, only ISUP grade group, clinical T stage and RT modality remained significant (Table 3).

Table 3. Cox Proportional Hazards Regression Analysis for freedom from distant metastases in patients treated with radiation therapy for localized or locally advanced prostate cancer.

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
HGB [g/dL]	0.852 (0.745-0.974)	**0.019**	0.897 (0.78-1.031)	0.125
AMC [10^3/μL]	2.119 (1.073-4.187)	**0.031**	1.409 (0.643-3.091)	0.392
Age [years]	1.017 (0.995-1.04)	0.131	1.015 (0.992-1.039)	0.205
ISUP Grade Group				
2 vs 1	1.590 (1.073-2.355)	**0.021**	1.417 (0.945-2.124)	0.092
3 vs 1	1.746 (1.036-2.942)	**0.036**	1.45 (0.853-2.464)	0.169
4 vs 1	2.426 (1.441-4.084)	**<0.001**	1.81 (1.043-3.139)	**0.035**
5 vs 1	3.648 (2.324-5.726)	**<0.001**	2.643 (1.607-4.346)	**<0.001**
Clinical T stage				
T2a vs T1c	0.577 (0.301-1.106)	0.098	0.523 (0.256-1.072)	0.077
T2b vs T1c	1.252 (0.798-1.962)	0.328	1.02 (0.626-1.659)	0.938
T2c vs T1c	2.112 (1.148-3.145)	**<0.001**	1.651 (1.07-2.549)	**0.024**
T3a vs T1c	1.361 (0.804-2.306)	0.252	1.02 (0.579-1.797)	0.946
T3b vs T1c	1.657 (0.918-2.99)	0.094	1.318 (0.708-2.453)	0.383
T4 vs T1c	2.769 (1.106-6.936)	**0.029**	1.186 (0.432-3.255)	0.741
ZUBROD (1-2)	1.555 (1.084-2.232)	**0.017**	1.138 (0.762-1.701)	0.527
RT modality (EBRT)	2.381 (1.566-3.619)	**<0.001**	1.649 (1.016-2.675)	**0.043**
mPSA [ng/mL^2]	1.006 (1.004-1.008)	**<0.001**	1.003 (1-1.006)	0.055
NLR	1.035 (0.914-1.172)	0.586		
PLR	0.999 (0.995-1.002)	0.387		
LMR	0.923 (0.834-1.021)	0.120		
WBC [10^3/μL]	1.065 (0.984-1.154)	0.121		
LYMPH [10^3/μL]	1.075 (0.886-1.305)	0.463		
NEUT [10^3/μL]	1.091 (0.982-1.212)	0.105		
EO [10^3/μL]	0.413 (0.116-1.475)	0.173		
BASO [10^3/μL]	1.123 (0.005-255.1)	0.967		
RBC [10^6/μL]	0.782 (0.541-1.129)	0.189		
HCT	0.962 (0.917-1.010)	0.116		
RDW	0.988 (0.838-1.164)	0.884		
PLT [10^3/μL]	0.998 (0.995-1.001)	0.230		
PDW [fL]	1.031 (0.954-1.115)	0.437		

HGB – hemoglobin concentration, AMC – absolute monocyte count, ISUP – International Society of Urological Pathology, RT – radiotherapy, EBRT – external beam radiotherapy, mPSA – maximum prostate specific antigen concentration, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, LMR – lymphocyte-to-monocyte ratio, WBC – absolute white blood cell count, LYMPH – absolute lymphocyte count, NEUT – absolute neutrophile count, EO – absolute eosinophile count, BASO – absolute basophile count, RBC – absolute red blood cell count, HCT –

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hematocrit, RDW – red blood cell distribution width, PLT – absolute platelet count, PDW – platelet distribution width

3.4. Hemoglobin and monocytes association with prognostic factors

An exploratory analysis was conducted to investigate association of HGB and AMC with relevant clinical factors. HGB was not associated with ZUBROD score ($p = 0.592$), RT modality ($p = 0.982$), ISUP Grade Group ($p = 0.576$) or clinical T stage ($p = 0.075$), however it was weakly correlated with patient age ($p < 0.001$, $R = -0.164$), duration of Neo-ADT ($p < 0.001$, $R = -0.144$) and mPSA ($p = 0.036$; $R = -0.067$).

AMC was not correlated with patient age ($p = 0.152$, $R = 0.045$), mPSA ($p = 0.135$, $R = 0.047$) or duration of Neo-ADT ($p = 0.952$, $R = 0.002$) and was no associated with clinical T stage ($p = 0.071$). There was a positive association between AMC and BT-boost as RT modality ($p < 0.001$), ZUBROD score of 1 or 2 ($p = 0.035$) and ISUP Grade Group ($p = 0.004$).

4. Discussion

Unnecessary treatment in PCa patients whose life expectancy is insufficient for the treatment to have a noticeable impact on their survival can be associated with the risk of side effects and significantly reduce the patient's quality of life [22,23]. Personalized approach towards the treatment of each patient requires to properly estimate the expected survival, especially if aggressive treatment is planned. This publication shows that HGB and AMC may provide additional information about the expected survival of patients with PCa in daily practice. Most importantly, this study showed that HGB and AMC contribute independent prognostic information on OS.

4.1. Hemoglobin concentration

The literature data on HGB prognostic value in localized or locally advanced PCa is very limited with mixed results. D'Amico et al. [24] found that ADT-related decline in pre-treatment HGB resulted in increased risk of biochemical failure, but OS was not assessed as an endpoint. Parker et al. failed to reproduce those results [14]. Pai et al. analyzed the relationship of pre-treatment HGB level with survival in PCa patients undergoing EBRT but were unable to find significant association with OS nor biochemical control [13]. All these studies focused on ADT-induced anemia, which translated into reduced tumor oxygenation, was expected to result in worse local control and increased risk of biochemical failure. However, ADT can lead to the improvement in tumor vascularization, which on the contrary, could improve the oxygenation [25]. In our study 93.8% of patients received Neo-ADT and its duration had weak correlation with HGB ($R = -0.144$), therefore its potential impact on results seems limited.

The phenomenon of pretreatment HGB association with PCa patients' survival could be explained by several different hypotheses, including above-mentioned ADT-induced anemia. It is highly probable that patients' general condition is reflected in part by HGB level as many diseases are known to influence either the total amount of HGB or the ability of molecules to bind oxygen at the same partial pressure of oxygen [26]. Unfortunately, in this study it was impossible to collect reliable data on the general patient condition and comorbidities, which would be sufficient to conclude it in the analysis. It is also possible that HGB, through its association with patients' general condition, or with the primary tumor itself, reflects the body's subclinical ability to eliminate metastatic cells [27]. Since the proportion of patients with known distant metastases in our study population accounted for 26.4% of total deaths, the association of HGB with the occurrence of distant metastases could partially explain its relationship with OS. However, HGB was a significant parameter in UVA for FFDM (HR 0.852; 95% CI 0.745-0.9744; $p = 0.0192$), but it was not significantly associated with FFDM after controlling for clinical variables.

Taking everything into account, the most plausible hypothesis would probably be the product of both HGB association with patients' general condition and PCa severity.

4.2. Absolute monocyte count

Hayashi et al. [18] found that AMC can predict adverse pathological features and risk of postoperative biochemical failure. The authors reported a significant correlation between AMC and TAM in tumor site. AMC has been shown as prognostic factor for both cancer-specific survival and OS in a large retrospective analysis by Wang et al. [19]. In our study, TAM presence in the tumor site has not been analyzed, however, AMC was found to be higher in patients with higher ISUP Grading Group ($p = 0.004$), which was previously reported by Hayashi et al. [28]. Some authors suggest that predictive value of AMC is related to TAM [29,30], which were reported to be associated with progression in various malignancies [17,28]. In this study AMC was associated with FFDM in UVA, but not in the MVA, likely due to the inclusion of ISUP Grade Groups. However, AMC remained an independent prognostic factor for patients' survival. This suggest that AMC association with survival is more complex than just its correlation with tumor pathological adverse features. Further studies are highly warranted.

4.3. Limitations

Main limitations of this study are its retrospective character, missing comorbidity, and smoking data. This study doesn't include low risk patients, for whom survival length estimation during treatment strategy planning could be especially important. The Neo-ADT used in the majority of patients could be a confounding factor in the interpretation of pre-treatment blood tests, and pre-ADT data could prove to be more useful in this scenario. Although all patients had been treated with EBRT, the wide range of RT modalities and fractionation schemes could have influenced the results.

5. Conclusions

Hemoglobin concentration and absolute monocyte count are simple and inexpensive biomarkers associated with survival in patients treated for intermediate or high risk localized or locally advanced prostate cancer and can improve patient-tailored treatment decision making.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1/

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