Bio-Clinical Parameters with a Predictive Role in Advanced Prostate Cancer

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Abstract

Background: Advanced forms of prostate cancer include a heterogeneous group of patients with an uneven prognosis. The lack of consensus on a precise definition of this group of patients prevents clinical decision-making and adequate patient counseling.

Methods: In this retrospective study, we investigated a series of preoperative bio-clinical parameters (age, patient comorbidities, tumor clinical stage, serum PSA, preoperative Gleason score, the neutrophil / lymphocyte ratio value and hormonal profile of patients), in relation to some postoperative parameters (histopathological type of tumor, tumor pathological stage, postoperative Gleason score, extra-prostatic extension, positive margins, seminal vesicle invasion, perineural invasion, positive lymphadenopathy), in a group of 96 patients with radical prostatectomy (RP) between 2016 and 2020, for a better understanding of the behavior of the disease and adequate counseling of patients proposed for RP.

Results: Of all the clinical and biological parameters analyzed, only the clinical T stage $\geq$ cT3a was statistically associated with an unfavorable pathological prognosis ($p = 0.03$). In the multivariate logistic regression model, the presence of a clinical tumor stage at clinical examination $\geq$ cT3a was associated with a 4.73-fold increase in the risk of unfavorable pathological prognosis. Moreover, the presence of a clinical T stage $\geq$ cT3a identifies with a sensitivity of 68.74% and a specificity of 65.71% patients with an unfavorable pathological prognosis. At the same time, the neutrophil / lymphocyte ratio (NLR) value was statistically significantly correlated only with the presence of secondary lymph node determinations ($p = 0.006$), and the serum level of dehydroepiandrosterone was statistically significantly correlated with the presence of extra-prostatic extension ($p = 0.05$).

Conclusions: The results obtained can have a significant impact in improving the knowledge of the pathogenesis of advanced forms of prostate cancer and in making clinical decisions, with immediate positive clinical effect (survival, quality of life) and socio-economic.

Introduction

Despite advances in modern medicine, prostate cancer (PCa) remains a major public health problem affecting the male population, with a growing prevalence. It ranks first in incidence and ranks 2nd in terms of cancer mortality in men (1). According to Globocan Romania, in 2020, PCa represents 14.9% of new cases of cancer in men. Prostate cancer is difficult to treat due to molecular, cellular and clinical heterogeneity (2). Currently, there are not enough means to be able to characterize the aggressive behavior of PCa and there is no unanimously accepted consensus on precise diagnostic methods or optimal therapeutic management for these patients. The factors that determine the risk of developing PCa are not well known, although age and genetic factors have a significant impact on the risk and progression of the clinical disease. Current prognostic factors for newly diagnosed patients with PCa used in current clinical practice are serum levels of preoperative PSA, histological grade Gleason, and / or clinical stage of the tumor assessed by a digital rectal examination (DRE) (3). In addition, several biomarkers have been extensively studied and could be used to identify patients with aggressive disease. The neutrophil / lymphocyte ratio (NLR) is a systemic inflammatory marker, which has been shown to be associated with a poor prognosis in several types of neoplasms, with implications for carcinogenesis and metastasis (4). It has been observed that an inflammatory environment is an essential component of all types of neoplasms, regardless of whether their occurrence is determined by the presence of chronic inflammation or not (5). Moreover, the inflammatory mechanisms in cancer are complex, as the presence of a neoplasm also causes an inflammatory response of the

host, which leads to the development of a pro-neoplastic environment. Therefore, the inflammatory tumor environment contains innate cells, such as macrophages, neutrophils and mast cells, but also adaptive immune cells (T and B lymphocytes). Depending on the intercellular communication through cytokines and the expression of different immune mediators, the balance between the inflammatory environments that allows tumor growth is maintained, respectively the one that fights against it. In advanced tumors, the balance tends much towards pro-tumor inflammation, responsible for angiogenesis, invasion and metastasis. The importance of inflammatory markers has also been confirmed in PCa. Regarding castration-resistant prostate cancer (CPRC), under treatment with enzalutamide, Conteduca et al. observed that patients with NLR over 3 before the start of treatment had a 4.2-month lower progression-free survival than patients with NLR below 3 (6). Overall, the overall survival of NLR patients over 3 was significantly reduced in compared with those with NLR below 3 (10.4 months vs 16.9 months, $p < 0.0001$). Therefore, not only the increased value of pre-treatment NLR, but also its persistence during therapy has prognostic value for patients with castration-resistant PCa. Despite advances in surgical technique or patient selection, up to 40% of patients diagnosed with PCa progress to biochemical relapse, often rapid post-surgical and a subsequent unfavorable prognosis marked by metastatic progression and even death by PCa. Thus, a personalized diagnostic and treatment approach for these patients will have a positive impact on mortality and morbidity caused by this disease.

Methodology

The current prognostic factors used in clinical practice are insufficient to characterize the aggressive behavior of PCa. Thus, our study aimed to identify predictive factors that improve the diagnosis of prostate cancer and adapt the therapeutic attitude according to the prognosis of each patient. The secondary outcome was to evaluate the predictive role of NLR in terms of oncological outcomes in the group of patients with localized and locally-advanced prostate cancer in whom radical prostatectomy (RP) was performed.

The study included 96 patients diagnosed with localized and locally advanced PCa and who were hospitalized for radical prostatectomy with pelvic lymphadenectomy at the Constanța County Emergency Clinical Hospital from January 2016 until December 2020.

The major criterion for inclusion in the study group was the histopathological diagnosis of prostate adenocarcinoma, and the exclusion criteria from the study were the administration of neo-adjuvant hormone therapy and the presence of urinary tract infection at the time of intervention. Histopathological examination of prostatectomy pieces included the following parameters: histological type, Gleason score, pathological stage of the disease, the presence of the intraductal component, lympho-vascular invasion, respectively perineural infiltration, resection margin status and excised lymph node status. Patients were evaluated according to the Charlson Comorbidity Index (CCI) (7). Based on the distribution of the CCI score in our cohort, patients were classified into two categories of CCI score: ≤ 3 or > 4 . Reporting histological grading was done according to ISUP 2014 and the guide for reporting pathological elements with prognostic value according to Association guidelines European Institute of Urology in force (3). All cases were recorded in a database that included a preoperative clinical parameter (age, patient comorbidities, tumor clinical stage, serum PSA, preoperative Gleason score), but also some postoperative parameters (histopathological type of tumor, tumor pathological stage, postoperative Gleason score, extra-prostatic extension, positive margins, seminal vesicle invasion, perineural invasion, positive lymphadenopathy). In addition, the neutrophil / lymphocyte ratio value and hormonal profile of patients was analyzed by serum determination of free testosterone, DHT, DHEA, DHEAS, androstenedione. Data obtained were

analyzed and graphs were constructed using SPSS version 20.0 software (SPSS, Chicago, IL) and MedCalc version 19.0.3 software (MedCalc, Ostend, Belgium). The effectiveness of selected bio-clinically parameters to function as prognostic biomarkers were evaluated by using Receiver operating characteristics (ROC). Sensitivity and specificity were then defined by the optimal cut-off point, which refers to the maximized value of the area under the ROC (Youden index). The univariate prognostic analysis revealed the parameters which affected the prognosis of PCa patients, as hormones expression levels and clinicopathological characteristics. The multivariate logistic regression model was used to identify the clinical and biological parameters associated with an unfavorable pathological prognosis.

Results

The clinical and biological preoperative characteristics of the patients included in the study are presented in Table 1. The mean age of the patients included in the study was 63 years (± 5.2 years). The median pre-treatment PSA values were 18 ng / ml (95% CI: 9–28 ng / ml), and the median number of positive biopsies was 5 (95% CI: 4–6). The preoperative Gleason score had a mean value of 7.6 ± 0.8 , and 46 cases (47.9%) had a score value of ≥ 8 . The extra-prostatic tumor extent assessed by DRE (clinical tumor stage $\geq$ cT3a) was reported in more than half of cases (56.3%; 54 patients). In our group, 15 patients (15.6%) were > 60 years old, the preoperative PSA value ≥ 20 and the preoperative Gleason score ≥ 8 .

Table 1
Clinico-biological preoperative characteristics of the patients included in the study.

Variables	Total cases (N = 96)
Age (average; years)	63 ± 5.2
Age > 60 years (%)	71 (73.9%)
Charlson comorbidity index (CCI) (%)	
≤ 3	69 (71.8%)
> 4	27 (28.2%)
Preoperative PSA value (median; ng / ml)	18 (9–26)
Preoperative PSA value ≥ 20 (%)	43 (44.8%)
Preoperative Gleason score (average)	7.6 ± 0.8
Preoperative Gleason score (%)	
≤ 6	4 (4.2%)
7 (3 + 4)	18 (18.7%)
7 (4 + 3)	28 (29.2%)
8	37 (38.5%)
9–10	9 (9.4%)
Preoperative Gleason score ≥ 8 (%)	25 (52.1%)
Age > 60 years + Preoperative PSA ≥ 20 + Preoperative Gleason score ≥ 8 (%)	15 (15.6%)
Clinical T stage (cT)	
≤ cT2c	42 (43.7%)
≥ cT3a	54 (56.3%)
<i>PSA - prostate specific antigen; CCI - Charlson comorbidity index;</i>	

In Table 2, we present the relationship between the preoperative clinical-biological parameters. In the study group, the age of the patients correlated poorly with the preoperative Gleason score ($r = 0.429$, $p = 0.002$) and with the Charlson comorbidity index ($r = 0.349$, $p = 0.010$), and the preoperative PSA value showed a statistically significant correlation but inversely proportional to the pre-operator Gleason score ($r = -0.363$, $p = 0.014$).

Table 2
The relationship between preoperative clinico-biological parameters.

	Age		Preoperative PSA value		Preoperative Gleason score		cT		CCI	
	r	p	r	p	r	p	r	p	r	p
Age	1	-	-0.220	0.151	0.429*	0.002*	-0.096	0.517	0.349*	0.010*
Preoperative PSA value	-0.220	0.151	1	-	-0.363*	0.014*	-0.026	0.507	-0.062	0.677
Preoperative Gleason score	0.429*	0.002*	-0.363*	0.014*	1	-	-0.056	0.704	0.148	0.314
cT	-0.096	0.517	-0.026	0.507	-0.056	0.704	1	-	0.028	0.851
CCI	0.349*	0.010*	-0.062	0.677	0.148	0.314	0.028	0.851	1	-
<i>PSA - prostate specific antigen; CCI - Charlson comorbidity index; cT- clinical tumor stage; r - correlation coefficient; p - statistical significance; * - statistically significant.</i>										

The postoperative clinical and biological characteristics of the patients are presented in Table 3. The postoperative Gleason Score had an average value of 7.6 ± 0.8 , and 37.5% had a pathological Gleason Score higher than 8. At the same time, 63 patients (65.6%) had concordance between pre- and postoperative Gleason score; 15 patients (15.6%) had a higher postoperative Gleason score compared to the preoperative Gleason score (upgrading), and 19 patients (19.8%) had a lower postoperative Gleason score than the reported preoperative (downstaging). In the studied group, the most common histological type encountered was acinar adenocarcinoma (88.5%), followed by mixed form (9.4%) and only 2.1% had the ductal type at the pathological examination. Of these, 89 patients (92.7%) had extra-prostatic tumor extension at the pathological examination, of which the majority, 62 of patients (64.6%), had bilateral tumor extension.

Table 3
Postoperative clinico-biological characteristics of patients
included in the study and treated with radical prostatectomy

Variables	Total cases (N = 96)
Pathological Gleason score (average)	7.5 ± 0.8
Pathological Gleason score (%)	
≤ 6	1 (1.1%)
7 (3 + 4)	16 (16.6%)
7 (4 + 3)	43 (44.8%)
8	24 (25%)
9–10	12 (12.5%)
Histopathological type of tumor (%)	
Ductal	
Acinar	2 (2.1%)
Mixt	85 (88.5%)
	9 (9.4%)
Lymphadenopathy (%)	37 (38.5%)
≤ 2 ganglions	24 (25%)
> 3 ganglions	13 (13.5%)
Seminal vesicles invasion (%)	54 (56.3%)
Unilaterally	13 (13.6%)
Bilateral	41 (42.7%)
Extraprostatic extension (%)	89 (92.7%)
Unilaterally	27 (28.1%)
Bilateral	62 (64.6%)
Positive resection margins (%)	11 (11.4%)
Perineural invasion (%)	68 (70.8%)
Pathological staging (%)	
pT2a	8.1%
pT2b	4.9%
pT2c	37.4%
pT3a	35.5%
pT3b	14.2%

Variables	Total cases (N = 96)
Grup de risc D'Amico (%)	
Low risk	17.2%
Intermediate risk	32.3%
High risk	50.4%

Tumor invasion of the seminal vesicles was highlighted in 54 patients (56.3%), of which 13 patients (13.6%) had unilateral invasion and 41 patients (42.7%) had bilateral extension. 71.8% of patients were diagnosed postoperatively with a more advanced stage of the disease than that reported for DRE (upstaging). Also, 37 patients (38.5%) had invasion in the removed ganglions, of which 24 patients (25%) in less than 2 ganglions, and 13 patients (13.5%) had at least 3 invaded ganglions. Resection margins were positive only in 11 cases (11.4%). Postoperative perineural invasion was diagnosed in 68 patients (70.8%). The pathological staging showed that the most frequent cases were in the pT2c stages (37.4%), respectively pT3a (35.5%) followed by pT3b stage (14.2%). The clinical and biological data obtained allowed the classification of cases by D'Amico risk groups, so that 32.3% had an intermediate risk and 50.4% were classified as having an increased D'Amico risk.

Evaluation of hormonal parameters

The serum testosterone level had a median value of 4 [IQR 2.2–5.2] ng/ml, and the mean value was 4.1 ± 2.2 ng/ml. The serum level of dihydrotestosterone had a median value of 592.5 [IQR 325.6-914.2] ng/ml, and the mean value was 649.7 ± 366.9 ng/ml. The serum level of dehydroepiandrosterone sulfate had a median value of 407.5 [IQR 241.2-770.2] µg/ml, and the mean value was 619.1 ± 552.8 µg/ml. The serum level of dehydroepiandrosterone had a median value of 2.6 [IQR 1.1–4.3] ng/ml, and the mean value was 3.1 ± 2.8 ng/ml. The serum level of androstenedione had a median value of 476.1 [IQR 352.7-705.9] ng/ml, and the mean value was 552.2 ± 311.2 ng/ml (Table 4).

Table 4
Hormonal parameters evaluated in the study

Variables	Total cases (N = 96)
Testosterone	
- Median (ng/ml)	4 (2.2–5.2)
- Average (ng/ml)	4.1 ± 2.2
Dihydrotestosterone (DHT)	
- Median (ng/ml)	592.5 (32.6-914.2)
- Average (ng/ml)	649.7 ± 366.9
Dehydroepiandrosterone sulfate (DHEA-S)	
- Median (ng/ml)	407.5 (241.2-770.2)
- Average (ng/ml)	619.1 ± 552.8
Dehydroepiandrosterone (DHEA)	
- Median (ng/ml)	2.6 (1.1–4.3)
- Average (ng/ml)	3.1 ± 2.8
Androstenedione	
- Median (ng/ml)	476.1 (352.7-705.9)
- Average (ng/ml)	552.2 ± 311.2

Prognostic value of neutrophil / lymphocyte ratio in prostate cancer

In the studied group, the median NLR was 1.8, 95% CI: 1.7–1.9. We observed that the NLR value was statistically significantly correlated only with the presence of secondary lymph node determinations ($p = 0.006$). There was no statistically significant correlation between NLR and prostate cancer characteristics (Table 5). We noticed that an NLR value above 1.99 has a moderate predictive value for the presence of positive lymph nodes, with an AUC of 0.75, sensitivity 77.7%, specificity 65.3%, $p = 0.001$ (Fig. 1).

Table 5
Correlation between NLR, clinical features and
histopathological patterns of patients

Variable	NLR
Age	p = 0.75
Preoperative PSA	p = 0.94
Number of positive biopsies	p = 0.06
The clinical stage	p = 0.48
The pathological stage	p = 0.99
Gleason group degree	p = 0.99
Primary Gleason degree	p = 0.78
Histological type	p = 0.21
Intraductal component	p = 0.1
Perineural infiltration	p = 0.11
Lymphovascular invasion	p = 0.54
Positive resection margins	p = 0.46
Presence of lymph node metastases	p = 0.006
<i>PSA - prostate specific antigen; p - statistical significance;</i>	

Relationship between the value of preoperative and histopathological parameters (Table 6)

Table 6
Relationship between the value of preoperative and histopathological parameters

	Age		Pre-operative PSA		Pre-operative Gleason score		cT		CCI	
	r	p	r	p	r	p	r	p	r	p
Pathologic Gleason score	0.06	0.068	-0.10	0.50	0.55	< 0.001	0.15	0.30	-0.02	0.89
Histopathological type	0.27	0.05	0.13	0.38	-0.07	0.62	0.02	0.85	0.11	0.43
Lymphadenopathy (present / absent)	0.10	0.48	0.28	0.04	0.45	0.04	0.16	0.26	0.09	0.53
Adenopathy ≤ 2 ggl > 3 ggl	-0.03	0.80	0.34	0.01	-0.03	0.81	0.16	0.53	0.24	0.23
Extraprostatic extension (present / absent)	0.03	0.80	0.16	0.25	0.01	0.93	0.11	0.40	0.14	0.32
Extraprostatic extension (uni/bilateral)	-0.07	0.63	0.06	0.68	0.04	0.74	0.40	0.02	0.21	0.34
Positive resection margins	0.25	0.08	0.11	0.42	-0.07	0.61	0.03	0.79	0.16	0.25
Perineural invasion	-0.26	0.07	0.11	0.43	-0.05	0.69	0.08	0.57	0.02	0.87
Seminal vesicles invasion (present/absence)	-0.005	0.97	0.25	0.08	0.46	0.03	0.27	0.06	0.05	0.68
Seminal vesicles invasion (uni/bilateral)	0.09	0.76	0.22	0.13	0.40	0.04	0.40	0.02	0.15	0.56
<i>PSA - prostate specific antigen; CCI - Charlson comorbidity index; cT- clinical tumor stage; ggl - ganglions; r - correlation coefficient; p - statistical significance;</i>										

The age of the patients included in the study correlated poorly with the histopathological type of the tumor ($r = 0.27$, $p = 0.05$), and did not correlate with the pathological Gleason score, the presence of lymphadenopathy, seminal vesicle invasion, perineural invasion, extra-prostatic extension and margins positive resection on histopathological examination.

The Charlson comorbidity index (CCI) was not statistically significantly correlated with histopathological type of tumor, pathological Gleason score, and presence of lymphadenopathy, seminal vesicle invasion, perineural invasion, extra-prostatic extension and positive resection margins on histopathological examination.

The value of preoperative serum PSA was positively correlated with the presence of positive lymphadenopathy ($r = 0.28$, $p = 0.04$) and with the presence of lymph node invasion in more than 2 lymph nodes on anatomopathological examination ($r = 0.34$, $p = 0.01$), but did not correlate statistically significant with the histopathological type of tumor, pathological Gleason score, seminal vesicle invasion, perineural invasion, extra-prostatic extension and the presence of positive resection margins on histopathological examination.

The value of the preoperative Gleason score correlated positively with the pathological Gleason score ($r = 0.55$, $p < 0.001$), moderately positive with the presence of ganglion invasion ($r = 0.45$, $p = 0.004$), moderately positively with the presence of seminal vesicle invasion ($r = 0.46$, $p = 0.03$) and with the presence of bilateral invasion of seminal vesicles ($r = 0.40$, $p = 0.04$), but did not correlate statistically significantly with the histopathological type of tumor, the presence of perineural invasion, extra-prostatic extension and positive resection margins at histopathological examination.

Clinical T stage (cT) was positively correlated with the presence of extra-prostatic extension ($r = 0.40$, $p = 0.02$) and with the presence of a bilateral invasion of seminal vesicles ($r = 0.40$, $p = 0.02$), but did not correlate statistically significantly with the pathological Gleason score, histopathological type of tumor, the presence of perineural invasion, extra-prostatic extension and positive resection margins at histopathological examination.

The relationship between the value of the hormonal and the histopathological parameters

Serum levels of testosterone, dihydrotestosterone, dehydroepiandrosterone-sulfate and androstenedione were not statistically significantly correlated with the pathological Gleason score, with the histopathological type of tumor, with the presence of lymph node invasion, seminal vesicle invasion, of extra-prostatic extension and positive resection margins on histopathological examination.

The serum level of dehydroepiandrosterone was statistically significantly correlated with the presence of extra-prostatic extension ($r = 0.29$, $p = 0.05$), but did not correlate with the pathological Gleason score, with the histopathological type of tumor, with the presence of ganglion invasion, vesicle invasion seminal, perineural invasion, and positive resection margins on histopathological examination (Fig. 2).

Evaluation of clinical-biological parameters associated with an unfavorable pathological prognosis

Univariate analysis

Regarding the analysis of clinical-biological parameters associated with an unfavorable pathological prognosis, the data are summarized in Table 7, which includes the main variables analyzed. Of all the clinical and biological parameters analyzed, only the clinical stage $T \geq cT3a$ was statistically associated with an unfavorable pathological prognosis (67.7% vs. 35.3%, $p = 0.03$).

Table 7

Clinico-biological parameters investigated in the groups defined according to the presence of an unfavorable pathological prognosis

Variables	Unfavorable pathological prognosis	Favorable pathological prognosis	p
Age (average, years)	65.1 ± 5.7	65.8 ± 4.4	0.69
Age > 60 years (%)	42 (77.4%)	29 (82.4%)	0.68
Charlson comorbidity index > 3 (%)	17 (22.6%)	10 (23.5%)	0.94
Preoperative PSA (median, ng / ml)	18 (9–28)	12 (7.5–22,.)	0.16
PSA ≥ 20 ng/ml (%)	15 (48.4%)	6 (35.3%)	0.38
Preoperative Gleason score ≥ 8 (%)	32 (51.6%)	14 (52.9%)	0.93
Clinical T stage ≥ cT3a (%)	45 (67.7%)	9 (35.3%)	0.03
Age > 60 years + preoperative PSA ≥ 20 + preoperative Gleason score ≥ 8 (%)	13 (19.4 %)	2 (5.9%)	0.17
Testosterone (median, ng / ml)	3.7 (1.9–5.3)	4.5 (2.9–5.5)	0.18
Dihydrotestosterone (DHT) (median, ng / ml)	649 (335–960)	475 (283.2-727.5)	0.33
Dehydroepiandrosteronesulfate (DHEA-S) (median, µg / ml)	398.9 (235.9-886.8)	460.3 (305.1-742.2)	0.67
Dehydroepiandrosteronedione (DHEA) (median, ng / ml)	3 (1-4.9)	2 (1.3–3.3)	0.43
Androstenedione (median, pg / ml)	471.9 (349.7-741.1)	480.3 (349.7-741.1)	0.99
<i>PSA - prostate specific antigen; cT- clinical tumor stage; p - statistical significance;</i>			

Multivariate analysis (logistic regression)

The multivariate logistic regression model included the following parameters: preoperative PSA value, clinical stage T ≥ cT3a, the association between age > 60 years + preoperative PSA ≥ 20 ng / ml + preoperative Gleason score ≥ 8 and serum testosterone level. The results of this analysis are presented in Table 8. As in the case of the univariate analysis, only the presence of a clinical stage T ≥ cT3a was the parameter retained in the final model being independently associated with an unfavorable histological prognosis. The presence of a clinical stage T ≥ cT3a was associated with a 4.73-fold increase in the risk of an unfavorable pathological prognosis (Table 8).

Table 8

Identification of clinico-biological parameters associated with an unfavorable pathological prognosis (multivariate logistic regression model)

	Univariate logistic regression			Multivariate logistic regression		
	OR	CI 95%	P	OR	CI 95%	P
Pre-operative PSA	1.05	0.98–1.12	0.11	1.06	0.98–1.13	0.07
Clinical T stage $\geq$ cT3a	3.75	1.11–13.40	0.03	4.73	1.23–18	0.02
Age > 60 years + preoperative PSA $\geq$ 20 + preoperative Gleason score $\geq$ 8 (%)	3.74	0.42–34.93	0.23	-	-	-
Testosterone	0.82	0.62–1.08	0.17	-	-	-
<i>PSA - prostate specific antigen; cT- clinical tumor stage; OR – odds ratio, CI – confidence interval; p - statistical significance;</i>						

The prognostic utility for independent determinants of the identified unfavorable pathology

To evaluate the prognostic utility of the clinical T stage $\geq$ cT3a for identification patients with an unfavorable pathological prognosis, the analysis of areas under the receiver operator curves (ROC) was used. The presence of a clinical T stage $\geq$ cT3a identifies with a sensitivity of 68.74% and a specificity of 65.71% patients with an unfavorable pathological prognosis (Table 9, Fig. 3).

Table 9

Sensitivity and specificity of clinical T stage $\geq$ cT3a for identification patients with unfavorable pathological prognosis.

	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy
Clinical T stage $\geq$ cT3a	68.74% (49.64% – 83.34%)	65.71% (38.34% – 87.69%)	77.76% (63.75% – 84.32%)	52.36% (36.79% – 84.34%)	67.66% (51.59% – 79.62%)
<i>PPV – positive predictive value; NPV – negative predictive value</i>					

Discussions

Currently, there is an interest in optimizing the management of patients diagnosed with advanced PCa. Although advanced PCa generally has an unfavorable prognosis, under this definition there are also neoplasms that have a favorable prognosis or can even be cured by current treatment strategies, including surgery. Today, researchers are making special efforts to identify patients who will benefit from surgical therapy. Numerous recent studies have analyzed the pathological parameters with unfavorable prognosis present on the radical prostatectomy specimen. Among them, the most important unfavorable prognostic factors are considered the presence of positive resection margins, extra-prostatic extension, seminal vesicles invasion and the presence of positive lymphadenopathy. The

data from the literature, regarding prognostic significance of the clinical and biological parameters analyzed in our cohort of patients, are contradictory. Thus, while some authors have demonstrated the association of serum PSA level with tumor volume, pathological stage and tumor extension, other authors have not shown significant correlations (8, 9). Moreover, the PSA level was inversely correlated with the Gleason score. And in another study, the serum level of preoperative PSA > 20 ng/ml was statistically significantly correlated with lymph node invasion and vesicle invasion (10). Due to recent studies, radical prostatectomy for patients with preoperative PSA greater than 20 ng/ml is considered a viable option, demonstrating encouraging results in this group of patients. In our cohort of PCa patients, 44.8% of patients had preoperative PSA levels > 20 ng/ml. Pre-operative PSA values correlated positively with the presence of positive lymphadenopathy ($r = 0.28$, $p = 0.04$) and the presence of lymph node invasion in more than 2 lymph nodes observed at the anatomopathological examination ($r = 0.34$, $p = 0.01$), but it was not statistically significantly correlated with the other elements of unfavorable pathology. Also, the Gleason score compared to prostate biopsy is considered a significant predictor of pathological outcomes after radical prostatectomy, and in addition, may predict unfavorable postoperative evolution. In our study, 37.5% of patients had a preoperative Gleason score higher than 8. The preoperative Gleason score correlated positively with the pathological Gleason score ($r = 0.55$, $p < 0.001$) and moderately positively with the presence of lymph node invasion ($r = 0.45$, $p = 0.04$) and with the presence of seminal vesicle invasion ($r = 0.46$, $p = 0.03$) or with the presence of bilateral invasion at the level of seminal vesicles ($r = 0.40$, $p = 0.04$). The results of our study are consistent with other clinical studies on the importance of the Gleason score in predicting seminal vesicle invasion (10) or the presence of positive lymphadenopathy (11, 12).

Digital rectal examination (DRE) is used in the clinical examination of patients to determine the local tumor stage and is associated with the local extension of the disease (clinical T stage). DRE has also been associated with an increased risk of detecting forms of PCa with a Gleason score above 8 (13). Currently, DRE is used in combination with other parameters to improve the predictive power of tumor extension. In our study, the clinical T stage was positively correlated with the presence of extra-prostatic extension ($r = 0.40$, $p = 0.02$) and with the presence of a bilateral seminal vesicle invasion ($r = 0.40$, $p = 0.02$). Of all the clinical and biological parameters analyzed, only the clinical T stage $\geq$ cT3a was statistically associated with an unfavorable pathological prognosis (67.7% vs. 35.3%, $p = 0.03$). Moreover, in the multivariate analysis the presence of a clinical T stage $\geq$ cT3a was associated with a 4.73-fold increase in the risk of unfavorable pathological prognosis. The sensitivity and specificity of this parameter in our study was 68.74% and 65.71%, respectively. These data are consistent with the studies of Cooperberg MR et al. (2005) which included this parameter in their model of assessing the risk of recurrence of localized disease (14). Numerous clinical studies have analyzed the impact of age on the course of patients with PCa and have concluded that age is a significant predictor of biochemical relapse, tumor progression and specific mortality after RP (14 15). Some authors have shown that old age is significantly associated with the risk of biochemical relapse, tumor progression or distant metastases (15). In our group of patients, the mean age of patients was 65.1 years, and it correlated poorly with the preoperative Gleason score ($r = 0.429$, $p = 0.002$), the histopathological type of the tumor ($r = 0.27$, $p = 0.05$) and did not have statistical significance for the unfavorable pathological prognosis.

The Charlson Comorbidity Assessment Index (CCI) is the most commonly used oncology index and an important predictor of specific PCa mortality or mortality from other causes after RP. Albertsen et al. (2005) studied the probability of survival of 767 patients diagnosed with localized PCa and treated conservatively (observation or therapy of immediate or delayed androgenic deprivation). They found that for a Charlson score between 0 and 1, the overall survival rates at 15, 20, and 25 years were 26%, 15%, and 8%, respectively; at a Charlson score of > 1,

overall survival rates at 15, 20, and 25 years were 11%, 6%, and 3%, respectively (16). Obviously, in this study, a higher Charlson score was correlated with a more unfavorable result (16). Although the Charlson score is probably the most commonly used comorbidity assessment index in the context of RP, in our study, CCI was not associated with unfavorable pathological aspects for patients with advanced PCa. However, we consider that this parameter, alone or in combination with the other parameters, will be useful in assessing the specific survival for the patients in our study.

The relationship between preoperative levels of endogenous sex hormones and RP outcomes is controversial in the literature. Some studies have reported a higher incidence of poorly differentiated tumors in patients with PCa and low serum testosterone levels (17). Three other retrospective studies have shown that low total testosterone is associated with unfavorable pathological features in RP specimens, but found no association with biochemical recurrence (18, 19). In addition, a clinical study from 2006, suggested that age-adjusted free testosterone correlates with poorly differentiated prostate tumors (20). Many circulating androgenic compounds, including testosterone, androstenedione (A), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) can be converted to the metabolically active dihydrotestosterone (DHT). DHT, which is the most potent intraprostatic androgen, appears to play a significant role in initiating PCa. The inevitable occurrence of androgen-refractory PCa after hormone treatment suggests that androgens play a rather "permissive" role in tumor progression (20). Morote J et al. (2009), in a study of subjects with nonmetastatic PCa and independent androgens, pointed out that the lower the testosterone levels, the longer period of disease progression (21). In our study, the serum levels of testosterone, dihydrotestosterone, DHEA-S and androstenedione were not statistically significantly correlated with unfavorable prognosis at the histopathological examination of the biopsy specimen. In contrast, the serum level of dehydroepiandrosterone was statistically significantly correlated with the presence of pathological extra-prostatic extension ($r = 0.29$, $p = 0.05$). The researchers tried to improve the characterization of high-risk patients and created different predictive models by combining preoperative variables to predict postoperative outcomes, such as prediction of extracapsular extension, seminal vesicle invasion, lymph node invasion (22). For example, Baccala Jr AA et al. (2010) or Gallina A et al. (2007), combined clinical T stage, serum PSA, biopsy Gleason score with age or percentage of tumor invasion on the biopsy fragment to predict seminal vesicle invasion (23, 24). Regarding the prediction of lymph node invasion, the most used models were established by Cagiannos I et al. (2003) and Briganti A et al (2006) (25, 26). Preoperative serum PSA, clinical T stage, biopsy Gleason score, and the institution where surgery was made, were predictors included in the Cagiannos nomogram (25), while PSA value, clinical T stage, biopsy Gleason score, and number of lymph nodes removed had were used in the Briganti nomogram (83% accuracy) to predict ganglion invasion (26). The combination of age > 60 years + preoperative PSA ≥ 20 ng/ml + preoperative Gleason score ≥ 8 was not statistically significantly associated in our study with unfavorable pathology parameters ($p = 0.17$).

In last years, markers of systemic inflammation and especially the neutrophils / lymphocytes rate have been studied in relation to the occurrence and prognosis of several types of neoplasms. Although the mechanisms of the immune response and its influence on neoplastic development are not fully known at present, many studies confirm a significant link between them (4). In a review published by Tang L. et al. (2016) it was shown that an increased NLR associated an increased risk of recurrence for localized and locally-advanced PCa, respectively a lower survival for patients with locally advanced PCa compared to those who had a low ratio before treatment (27). Moreover, a meta-analysis of 14 studies that included a total of 16,266 patients confirmed the prognostic role of NLR for a shorter survival and a shorter non-recurrence interval even for metastatic CRPC (mCRPC) (28). The results of our study confirm what has been previously published and support the premise that inflammation has a

role in promoting metastasis, but does not influence the intrinsic characteristics of the tumor (Gleason score, tumor stage). NLR has a prognostic value for the presence of secondary lymph node determinations ($p = 0.006$). It is estimated that for these patients, overexpressed lymphadenectomy has the potential to improve oncological results.

Conclusions

Simultaneous analysis of a panel of biomarkers to predict the pathological stage is a strong point of the present study, but nevertheless, when analyzing the research results, we must consider the characteristics of the group, the small number of patients and the possibility of combining preoperative parameters or the inclusion of other risk factors in order to be able to predict with great accuracy the final pathological stage. In order to widely introduce such models into clinical practice, it is necessary to further improve the models currently available and to develop more reliable, flexible, simple and easily accessible tools by incorporating conventional clinicopathological factors as well as molecular biomarkers. We consider that the results obtained can be useful for current clinical practice allowing us to analyze the predictive power of preoperative parameters for the subsequent oncological evolution of patients with advanced PCa treated by RP, including the risk of metastatic progression or death by PCa.

Declarations

Ethics approval and consent to participate

The study was conducted according to good laboratory practice and in accordance with the national and institutional standards and informed consent was obtained from all patients. The study was approved by the Local Ethics Commission for the Approval of Clinical and Research Developmental Studies.

Consent for publication

Authors confirmed that this work can be published. The content of this manuscript is original and it has not yet been accepted or published elsewhere.

Availability of data and material

Research Data are not shared.

Conflicts of interest

There are no conflicts to declare.

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Figures

Figure 1

Predictive value of NLR for the presence of lymph node secondary determinations

Figure 2

Correlation between the presence of extraprostatic extension and the serum level of dehydroepiandrosterone ($r = 0.29$, $p = 0.05$).

Figure 3

Usefulness of clinical T stage in identifying patients with unfavorable pathological prognosis (area under the curve 0.662; 95% CI 0.499 - 0.826).