Original Article

Current Urology

OPEN

Can serum tumor marker densities according to tumor volume and testicle size be used to predict progression in patients with testicular cancer?

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Abstract

Background: The objective of this study is to determine the role of tumor marker density (TMD) values such as alpha-fetoprotein tumor volume ratio (ATVR), beta-human chorionic gonadotropin tumor volume ratio (βTVR), alpha-fetoprotein testicle size ratio (ATSR), beta-human chorionic gonadotropin testicle size ratio (βTSR), lactate dehydrogenase tumor volume ratio (LTVR), and lactate dehydrogenase testicle size ratio (LTSR) in the determination of progression-free survival (PFS) in patients with testicular cancer.

Materials and methods: A retrospective study was conducted of 95 patients followed-up in our clinic with a diagnosis of testicular cancer between January 2015 and August 2022. Patients were grouped according to clinical stage, as either early stage (n = 50) or advanced stage (n = 45). Clinical and pathological data and TMD values for all patients were recorded.

Results: The median age of patients was 35 years (21–63 years). All TMDs except LTVR in advanced stage patients were found to be significantly higher than those of early stage patients ($p < 0.05$). Median ATVR (2.58 vs. 0.0), ATSR (0.63 vs. 0.03), βTVR (0.9 vs. 0.009), and βTSR (0.18 vs. 0.007) of the nonseminoma patients were found to be significantly higher than those of the seminoma patients, respectively ($p < 0.001$). Progression-free survival (months) was decreased in seminoma patients with high values of βTVR (11.3 ± 1.9 vs. 35.2 ± 0.7), βTSR (16.2 ± 3.4 vs. 35.2 ± 0.75), LTVR (17.7 ± 3.4 vs. 35.2 ± 0.7), and LTSR (21.5 ± 3.13 vs. 35.09 ± 0.8) ($p < 0.001$). Decreased PFS (months) was associated with higher values of ATVR (5.37 ± 0.7 vs. 35.05 ± 0.93), βTVR (7.4 ± 1.5 vs. 34.6 ± 1.3), ATSR (5.37 ± 0.75 vs. 35.05 ± 0.9), βTSR (7 ± 1.5 vs. 34.6 ± 1.3), and LTSR (7.9 ± 1.2 vs. 34.3 ± 1.5) in nonseminoma patients ($p < 0.001$). Based on multivariate analysis, βTVR-LTVR and ATVR-ATSR were determined to be independent risk factors for reduced PFS in seminoma and nonseminoma patients, respectively ($p < 0.05$).

Conclusions: The results of this study suggest that the calculation of TMDs could be a promising and simple method for prediction of PFS among testicular cancer patients.

Keywords: Testicular cancer; Progression; Tumor marker density; Prognostic factors

1. Introduction

Approximately 52,000 men are diagnosed with testicular cancer annually worldwide, more often in the first 4 decades of life.[1] In most cases, the diagnosis is made at an early stage, and together with high treatment response rates, a 5-year survival rate of up to 96% according to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification risk-prognostic groups means that testicular cancer is known as a male urogenital system tumor with a good prognosis.[2] However, because the incidence of testicular cancer is as low as 1% of all adult neoplasms, and among testicular cancer patients, there are heterogeneous groups in which several tumor types are found together at the time of diagnosis, it is important to identify prognostic diagnostic tools and adapt them for clinical practice.[3,4]

Although there is no clearly defined limit for small testicular masses, which have a high probability of being benign, an increase in tumor size is associated with a higher risk of metastatic relapse in patients with Stage I seminoma, and the risk of intratubular germ cell neoplasia may increase in testes below normal volume.[5–7] To identify testicular cancer patients at risk of metastasis according to the IGCCCG risk-prognostic groups, levels of serum tumor markers such as alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH) can be examined.

However, as serum tumor markers are not very specific to testicular cancer, the search is ongoing for better prognostic markers and risk factors.[8,9] The relative effects on prognosis of various clinical and pathological characteristics have been examined in several cancer types.[10,11] To the best of our knowledge, there is no study in published literature that has evaluated the correlation between prognosis and serum tumor marker levels according to tumor volume and testicle size in testicular cancer patients.

The aim of this study was to evaluate the relationship of tumor marker density (TMD) values with prognosis in patients diagnosed with testicular cancer.

2. Materials and methods

Approval for the study was granted by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research

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Current Urology, (2024) 18, 3, 218–224

Received December 9, 2022; Accepted March 21, 2023.

http://dx.doi.org/10.1097/CU9.0000000000000212

Hospital (Decision no: 2022-08/2003). All study procedures were performed in compliance with the Helsinki Declaration. All study participants provided informed consent.

2.1. Patient selection

A retrospective examination was made of patients followed-up in the urology clinic with a diagnosis of testicular cancer between January 2015 and August 2022. Patients were excluded from the study if they did not attend follow-up appointments, had incomplete or unavailable data, or if had a history of cancer or any musculoskeletal, hematologic, or liver disease. A total of 95 patients met the criteria and were enrolled in the study.

2.2. Data collection

A record was made for each patient, including their age, smoking status, comorbidities, Charlson Comorbidity Index score, tumor side, preoperative serum tumor marker levels of AFP (ng/mL), βHCG (mIU/mL), LDH (U/L), presence or absence of microlithiasis on ultrasound, progression status, follow-up period (months), further treatments received, and pathological data such as testicle size (mL), tumor volume (mL), tumor type, lymphovascular invasion, and embryonal carcinoma rates.

All the patients underwent thoracoabdominal computed tomography (CT) for staging purposes before follow-up. The TNM 2016 classification was used to evaluate tumor stage, and patients were grouped according to the staging system recommended by the Union for International Cancer Control group. Stage 1 patients were designated as early stage (n = 50), and patients at stages 1S, 2, and 3 were designated as advanced stage (n = 45). During follow-up after curative treatment, any new development of metastasis and lymph node involvement or enlargement of existing lesions was regarded as disease progression.

The ratios of AFP tumor volume ratio (ATVR = AFP/tumor volume), βHCG tumor volume ratio (βTVR = βHCG/ tumor volume), LDH tumor volume ratio (LTVR = LDH/tumor volume), AFP testicle size ratio (ATSR = AFP/testicle size), βHCG testicle size ratio (βTSR = βHCG/testicle size), and LDH testicle size ratio (LTSR = LDH/testicle size) were calculated and recorded. Tumor volume (mL) and testicle size (mL) were calculated using the formula "width (mm) × length (mm) × height (mm) × 0.71" according to the values measured on pathology specimens.[12]

2.3. Treatment and follow-up protocol

For early stage testicular cancer patients, the treatment plan was made according to the presence of risk factors. When tumor size was >4 cm and there was rete testis invasion in seminoma patients, and in the case of lymphovascular invasion in nonseminoma patients, single-cycle BEP (Bleomycin, Etoposide and Cisplatin) chemotherapy was planned. In the absence of these risk factors, patients were followed-up with active surveillance. If chemotherapy was contra-indicated and/or the patient did not accept other treatment options, retroperitoneal lymph node dissection was performed in early stage nonseminoma patients.

For the follow-up of the early stage seminoma patients, tumor markers were examined twice a year for the first 3 years, then once a year up to the fifth year, and abdominopelvic CT was performed twice in the first 2 years, then once in the third and fifth years. In nonseminoma early stage patients, tumor markers were examined 4 times in the first 2 years, then twice a year up to the fifth year. Chest X-ray and abdominopelvic CT were performed twice in the first year and then once a year up to the fifth year. For advanced stage patients, 3 or 4 cycles of BEP chemotherapy were administered according to IGCCCG.

For stage 2a to 2b seminoma patients who did not accept chemotherapy, 30-Gy radiotherapy was applied to the para-aortic and ipsilateral iliac area as an alternative treatment regimen. If markers were negative in the sixth week of follow-up after completion of chemotherapy, and if a residual mass was determined on the axial axis of the longest diameter on abdominal CT within 3 cm for seminoma patients and within 1 cm for nonseminoma patients, then retroperitoneal lymph node dissection was performed. For these advanced stage patients, tumor markers were examined 4 times a year in the first 2 years, then twice a year up to the fifth year, and thoracoabdominopelvic CT was performed once a year in the first 5 years.[13]

2.4. Statistical analysis

Data obtained in the study were analyzed statistically using SPSS version 22.0 software (SPSS, Chicago, IL). Results were reported as median (range) values. Conformity of the data to normal distribution was assessed using the Shapiro-Wilk test. In the comparisons of independent paired groups, the Mann-Whitney U test was used when parametric test assumptions were not met. The chi-square test was used to determine the difference between categorical variables. Receiver operator characteristic curve analysis was applied to determine the highest sensitivity and specificity of cut-off values. To determine the association of groups with survival, we applied Kaplan–Meier analysis. The independent effect of variables on progression, recurrence, and overall status was determined using uni-multivariate Cox regression analysis. A p value of <0.05 was accepted as statistically significant.

3. Results

The demographic and clinicopathological characteristics of the patients are shown in Table 1. The median age of the patients was 35 years (21–63 years). No statistically significant difference was observed in respect to age or smoking status between the early and advanced stage groups (p = 0.66 and p = 0.96, respectively). Median Charlson Comorbidity Index score was determined to be higher in the advanced stage group than in the early stage group (p < 0.001). The follow-up period was a median of 16 months (2–36 months), with no significant difference found between the groups (p = 0.54). Disease progression was observed in 18.9% of all patients, and 83.3% of those found to have progression were in the advanced stage patient group (p = 0.001) (Table 1).

Seminoma-type tumor was observed in 47 (49.5%) patients and nonseminoma-type tumor in 48 (50.5%). Nonseminoma-type tumor represented 60.4% of the advanced stage group, which was statistically significantly greater than in the early stage group (p = 0.01). No significant difference was found between the groups with respect to median testicle size (p = 0.73). Median tumor volume was observed to be greater in the advanced stage group than in the early stage group (p = 0.04). Lymphovascular invasion was seen in 37.9% of all patients and in 63.9% of the advanced stage group (p = 0.01). The rate of embryonal carcinoma was significantly higher in the advanced stage group (p = 0.01). Among early stage patients, 75.9% were taken into active surveillance, and the rate of further treatments administered was greater in the advanced stage group (p = 0.001). The median values of ATVR, βTVR, ATSR, βTSR, and LTSR were determined to be significantly higher in the advanced stage patient group than in the early stage group (p = 0.03, p < 0.001, p = 0.004, p < 0.001, and p = 0.008, respectively) (Table 1). In the subgroup analysis of the TMDs based on histological type, the median ATVR, ATSR, βTVR, and βTSR ratios were determined to be higher in the nonseminoma group than in the seminoma group (p < 0.001) (Table 2).

Table 1

Comparison of the clinical and pathology data according to tumor stage.

Variable	All patients (n = 95)	Early stage (n = 50)	Advanced stage (n = 45)	*p*
Age, yr*	35 (21–63)	35 (21–63)	36 (24–61)	0.66†
Smoking, n (%)				
Yes	61 (64.2)	32 (52.5)	29 (47.5)	0.96‡
No	34 (35.8)	18 (52.9)	16 (47.1)	
Comorbidity, n (%)				
None	79 (84.1)	42 (53.2)	37 (46.8)	0.15‡
HTN	7 (7.3)	2 (28.6)	5 (71.4)	
CAD	4 (4.2)	4 (100)	0 (0)	
DM	5 (5.2)	2 (40)	3 (60)	
CCI*	4 (2–8)	2 (2–4)	6 (6–8)	**<0.001†**
AFP, ng/mL*	3.2 (0.7–2864)	2.7 (0.7–366.7)	10.4 (0.7–2864)	**0.007†**
hCG, mIU/mL*	1 (0.03–5906.4)	0.1 (0.03–338.2)	8.9 (0.03–5906.4)	**<0.001†**
LDH, U/L*	236.7 (0–3883)	200.3 (0–638)	339.6 (0–3883)	**<0.001†**
Side, n (%)				
Left	48 (50.5)	26 (54.2)	22 (45.8)	0.76‡
Right	47 (49.5)	24 (51.1)	23 (48.9)	
Tumor volume, mL*	41.3 (1.2–110)	29.2 (1.2–104.5)	42.6 (1.3–110)	**0.04†**
Testicle size, mL*	65 (2.65–200)	65 (2.65–200)	65 (26.3–142.8)	0.73†
ATVR*	0.33 (0.01–31.9)	0.14 (0.01–10.8)	0.71 (0.01–31.9)	**0.03†**
βTVR*	0.05 (0–108.2)	0.02 (0–5.43)	1.39 (0–108.2)	**<0.001†**
ATSR*	0.06 (0.01–31.3)	0.04 (0.01–3.75)	0.17 (0.01–31.3)	**0.004†**
βTSR*	0.02 (0–51.3)	0.003 (0–4.68)	0.21 (0–51.3)	**<0.001†**
LTVR*	6.09 (0–942.4)	4.58 (0–398.4)	9.2 (0–942.4)	0.27†
LTSR*	3.42 (0–195.4)	3.27 (0–195.4)	4.91 (0–147.3)	**0.008†**
Microlithiasis, n (%)				
Yes	18 (18.9)	6 (33.3)	12 (66.6)	0.61‡
No	77 (81.05)	44 (57.1)	33 (42.8)	
Type, n (%)				
Seminoma	47 (49.5)	31 (66)	16 (34)	**0.01‡**
Nonseminoma	48 (50.5)	19 (39.6)	29 (60.4)	
Rete invasion, n (%)				
Yes	28 (29.5)	10 (35.7)	18 (64.3)	**0.03‡**
No	67 (70.5)	40 (59.7)	27 (40.3)	
LVI, n (%)				
Yes	36 (37.9)	13 (36.1)	23 (63.9)	**0.01‡**
No	59 (62.1)	37 (62.7)	22 (37.3)	
ECR*	0 (0–100)	0 (0–100)	2 (0–100)	**0.01†**
Progression, n (%)				
Yes	18 (18.9)	3 (16.7)	15 (83.3)	**0.001‡**
No	77 (81.1)	47 (61)	30 (39)	
Disease status, n (%)				
Alive	92 (96.8)	49 (53.3)	43 (46.7)	0.6
Dead	3 (3.2)	1 (33.3)	2 (66.7)	
Follow-up, mo*	16 (2–36)	15.5 (2–36)	16 (2–36)	0.54†
Adjuvant treatment, n (%)				
Active surveillance	29 (30.5)	22 (75.9)	7 (24.1)	**0.001‡**
Chemotherapy	58 (61.05)	27 (46.5)	31 (53.4)	
Radiotherapy	3 (3.1)	0 (0)	3 (100)	
RPLND	5 (5.2)	1 (20)	4 (80)	

Significant values are shown in bold ($p < 0.05$).

*Median (range).

†Mann-Whitney *U* test.

‡Chi-square test.

AFP = alpha-fetoprotein; ATSR = AFP testicle size ratio; ATVR = AFP tumor volume ratio; βTSR = βHCG testicle size ratio; βTVR = βHCG tumor volume ratio; CAD = coronary artery disease; CCI = Charlson Comorbidity Index; DM = diabetes mellitus; ECR = embryonal carcinoma rates; hCG = human chorionic gonadotropin; HTN = hypertension; LDH = lactate dehydrogenase; LTSR = LDH testicle size ratio; LTVR = LDH tumor volume ratio; LVI = lymphovascular invasion; RPLND = retroperitoneal lymph node dissection.

Based on receiver operator characteristic curve analysis according to TMD values in the nonseminoma group, the optimal cut-off points for risk of disease progression for ATVR, ATSR, βTVR, βTSR, and LTSR were determined to be 13.5 (area under the curve [AUC], 0.91; $p < 0.001$), 5.4 (AUC, 0.99; $p < 0.001$), 7.5 (AUC, 0.91; $p < 0.001$), 7.52 (AUC, 0.98; $p < 0.001$), and 5.93 (AUC, 0.93; $p < 0.001$), respectively. In the seminoma group, the optimal cut-off points for risk of disease progression for βTVR, βTSR, LTVR, and LTSR were determined to be 0.4 (AUC, 0.97; $p < 0.001$), 0.05 (AUC, 0.94; $p < 0.001$), 15.8 (AUC, 0.91; $p < 0.001$), and 4.32 (AUC, 0.87; $p < 0.001$), respectively (Table 3).

Table 2

Subgroup analysis of tumor marker densities based on histological type.

Variable	Seminoma patients (n = 47)	Nonseminoma patients (n = 48)	p
ATVR	0.06 (0.01–2.72)	2.58 (0.06–31.9)	**<0.001**
ATSR	0.03 (0.01–0.6)	0.63 (0.02–31.3)	**<0.001**
βTVR	0.009 (0–4.38)	0.9 (0–108.2)	**<0.001**
βTSR	0.007 (0–0.58)	0.18 (0–51.3)	**<0.001**
LTVR	5.25 (0–942.4)	11.6 (0–112.3)	0.13
LTSR	3.16 (0–195.4)	3.52 (0–15.51)	0.23

Values were presented as median (range).
Mann-Whitney *U* test was used for comparison of the groups.
Significant values are shown in bold ($p < 0.05$).
AFP = alpha-fetoprotein; ATSR = AFP testicle size ratio; ATVR = AFP tumor volume ratio; βTSR = βHCG testicle size ratio; βTVR = βHCG tumor volume ratio; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; LTSR = LDH testicle size ratio; LTVR = LDH tumor volume ratio.

A statistically significant shorter progression time was identified in the nonseminoma group patients with higher ATSR, ATVR, βTVR, βTSR, and LTSR values ($p < 0.001$). A shorter duration of progression-free survival (PFS) was associated with higher values of βTVR, βTSR, LTVR, and LTSR in the seminoma group ($p < 0.001$) (Figs. 1 and 2).

Based on univariate Cox regression analysis, T stage (hazard ratio [HR], 12.49; $p = 0.002$), βTSR (HR, 31.5; $p = 0.001$), βTVR (HR, 48.53; $p < 0.001$), LTSR (HR, 16.13; $p = 0.009$), and LTVR (HR, 26.54; $p = 0.002$) were each determined to be significant risk factors for reduced PFS in the seminoma group. In the nonseminoma group, T stage (HR, 13.16; $p < 0.001$), ATSR (HR, 40.91; $p < 0.001$), ATVR (HR, 3.6; $p = 0.007$), βTVR (HR, 27.98; $p = 0.002$), βTSR (HR, 30.84; $p = 0.001$), and LTSR (HR, 17.97; $p = 0.007$) were each determined to be significant risk factors for reduced PFS (Table 4).

According to multivariate analysis of PFS, when T stage was evaluated in separate models together with βTVR and βTSR and with LTSR and LTVR, it was determined that βTVR (HR, 15.37; $p = 0.04$) and LTVR (HR, 10.74; $p = 0.04$) were significant risk factors for the seminoma group. In the nonseminoma group, when T stage was evaluated in separate models together with ATSR and ATVR and with βTVR, βTSR, and LTSR, it was determined that ATSR (HR, 33.52; $p = 0.005$) and ATVR (HR, 2.04; $p = 0.01$) were significant risk factors for reduced PFS (Table 5).

4. Discussion

To the best of our knowledge, this is the first study in the published literature to have examined the relationship between TMDs and disease progression in testicular cancer. The TMDs were evaluated not only in relation to tumor volume but also with respect to ratios according to testicular size. The results of this study showed that, with the exception of LTVR, TMD values were higher in advanced stage patients, and these values could have a significant association with shortened PFS according to different histological subtypes. In addition, the effect of the density values was examined together with other risk factors such as tumor stage, lymphovascular invasion, and rete invasion, and in the submodels developed, βTVR-LTVR and ATVR-ATSR values were each found to be risk factors for reduced PFS in seminoma and nonseminoma patients.

Alpha-fetoprotein is synthesized from fetal yolk sac cells and βHCG from trophoblasts. Although LDH is a type of isoenzyme, it shows an increase associated with tumor size and spread throughout the body. Tumor markers such as AFP, βHCG, and LDH, which are examined in the blood of testicular cancer patients, are recommended by the IGCCCG in the evaluation of prognosis in addition to treatment planning, especially for advanced stage patients.[14] However, in previous studies, abnormal marker levels could only be determined in 60% of germ cell testis tumors, elevated LDH was seen in 60% to 80% of advanced stage patients, and the βHCG level may be increased in only 30% of seminoma patients.[14,15] Moreover, these markers are not specific to testis tumors, and it is known that they can increase in association with benign conditions such as hereditary and metabolic diseases.[16] Therefore, there is a need to find new prognostic tools to enhance the reliability of currently available markers, especially given the high cost and special equipment required for new markers under development for testicular cancer patients, creating significant obstacles to their widespread use.[9]

Tumor size is another morphological characteristic used in the evaluation of prognosis in testicular cancer patients. It is thought that increasing tumor size represents both a greater tumor burden and the presence of a more aggressive tumor.[17] A systematic review showed that, especially in early stage seminoma patients, recurrence-free survival fell from 95.5% to 73% in patients with tumor size >4 cm compared with patients with smaller tumors.[6] However, previous studies have focused more on seminoma patients, and the effect on prognosis of an increase in tumor size in nonseminoma patients, and indirectly, the effect of increasing tumor volume on changes in marker density, has not been investigated.

Consistent with the literature, tumor volume was determined to be high in advanced stage patients in the current study. When nonseminoma patients were compared with seminoma patients, except for density values related to LDH, the other TMDs were seen to be high in nonseminoma patients. Moreover, when the effects on PFS were evaluated, AFP marker density values for

Table 3

Receiver operator characteristics curve analysis of tumor marker densities for prediction of disease progression.

	Seminoma patients (n = 47)					Nonseminoma patients (n = 48)				
Variable	Cut-off point	AUC (95% CI)	Sensitivity	Specificity	p	Cut-off point	AUC (95% CI)	Sensitivity	Specificity	p
ATVR	-	-	-	-	-	13.5	0.91 (0.820–1.000)	0.89	0.95	**<0.001**
ATSR	-	-	-	-	-	5.4	0.99 (0.979–1.000)	0.88	0.94	**<0.001**
βTVR	0.4	0.97 (0.939–1.000)	0.88	0.97	**<0.001**	7.5	0.91 (0.828–0.995)	0.89	0.87	**<0.001**
βTSR	0.05	0.94 (0.883–1.000)	0.88	0.94	**<0.001**	7.52	0.98 (0.947–1.000)	0.88	0.94	**<0.001**
LTVR	15.8	0.91 (0.818–1.000)	0.88	0.89	**<0.001**	-	0.48	-	-	0.9
LTSR	4.32	0.87 (0.752–0.990)	0.88	0.79	**<0.001**	5.93	0.93 (0.860–1.000)	0.89	0.87	**<0.001**

Significant values are shown in bold ($p < 0.05$).
AFP = alpha-fetoprotein; ATSR = AFP testicle size ratio; ATVR = AFP tumor volume ratio; AUC = area under the receiver operator characteristics curve; βTSR = βHCG testicle size ratio; βTVR = βHCG tumor volume ratio; CI = confidence interval; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; LTSR = LDH testicle size ratio; LTVR = LDH tumor volume ratio.

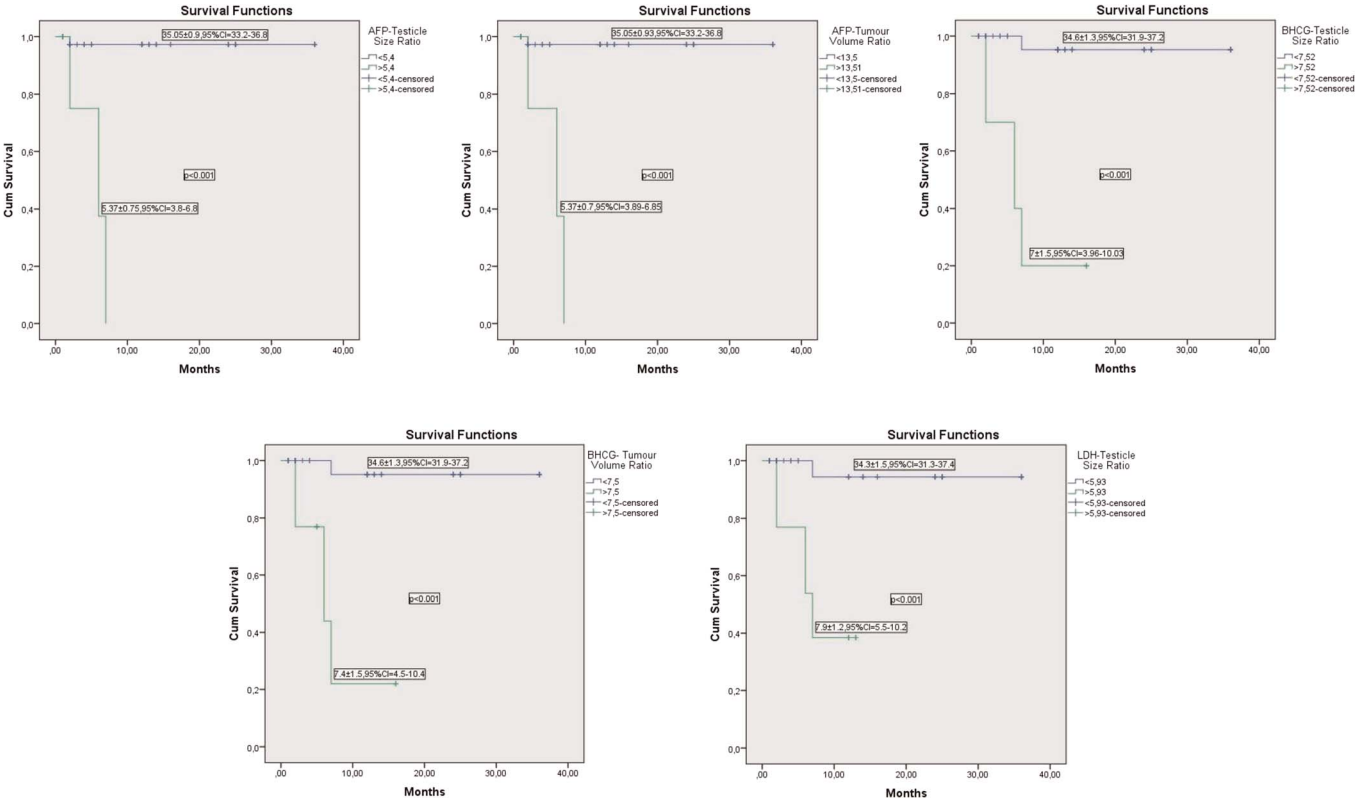

Figure 1. Kaplan–Meier analysis of PFS according to tumor marker densities in nonseminoma patients. AFP = alpha-fetoprotein; CI = confidence interval; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; PFS = progression-free survival.

nonseminoma patients and βHCG and LDH levels for seminoma patients according to tumor volume were each found to be significant risk factors. Based on the density value results obtained, in addition to providing information about how much cancerous tissue is present and the tumor markers produced by that tissue, the effects of these values on prognosis demonstrated in this study can provide a new perspective for the current literature. However, it must be kept in mind that when using these density values, tumor markers may be synthesized from metastatic and nonmetastatic cells, and there is no AFP production in seminoma patients.

The determination of risk groups and treatment planning is performed according to clinical staging recommended by the Union for International Cancer Control group, in which tumor local spread, lymph node involvement, the presence of metastasis, and serum tumor marker levels are evaluated together. The PFS rate is known to fall from 90% to 54% in advanced stage tumors compared with those at an early stage.[18] In addition, the embryonal carcinoma rate and pathological risk factors used in T staging such as rete testis invasion and lymphovascular invasion are used in prognosis evaluation. In a study of 88 patients with a median of 12.1 years of follow-up, rete testis invasion and relapse rates were seen to be significantly increased, but this effect was not found with regard to lymphovascular invasion.[19] In another study of 59 patients with a mean follow-up period of 39.8 months (range, 3–96 months), the reverse was reported, with greater lymphovascular invasion seen in patients with metastasis but no difference with respect to rete testis invasion.[20] In another cohort group with a median of 38 months (range, 6–265 months) of follow-up and a relapse rate of 24%, the embryonal carcinoma rate was seen to be an independent risk factor, whereas in another study, no difference was seen with respect to relapse between patients with >50% embryonal carcinoma and those without.[21,22] Therefore, conflicting results have been reported in the literature with respect to the effects on progression of well-defined risk factors. Moreover, as yet, there is no clear cut-off value for embryonal carcinoma rate as a pathological risk factor for occult metastatic disease in stage I nonseminoma testicular cancer.[23]

In addition to TMDs, evaluations were made in this study of other parameters used routinely in our clinic in decision-making and determination of prognosis for patients with testicular cancer. When patients were classified according to the clinical staging according to marker levels and TNM classification, patients who developed disease progression were at a more advanced stage, consistent with the literature. In addition, the 18.9% progression rate in the current cohort was similar to that reported in other studies.

Although a difference was found in embryonal carcinoma, lymphovascular invasion, and rete testis invasion according to clinical stage, they were not seen to have an effect on disease progression. The fact that these risk factors are dependent on pathologist examination and the fact that lower relapse rates were seen in seminoma patients than those in nonseminoma patients were thought to have an effect on these results.

Prospective evaluation of testicular cancer is difficult, as these are relatively rarely seen tumors. This study was limited by a retrospective, single-center design, low numbers of patients in the groups, and short follow-up time. In addition, overall survival analysis could not be performed because of the small number of deaths (3 of 95 patients) during the study, limiting the generalizability of these study findings. Alpha-fetoprotein levels were not increased in seminoma patients, which had a negative effect on the

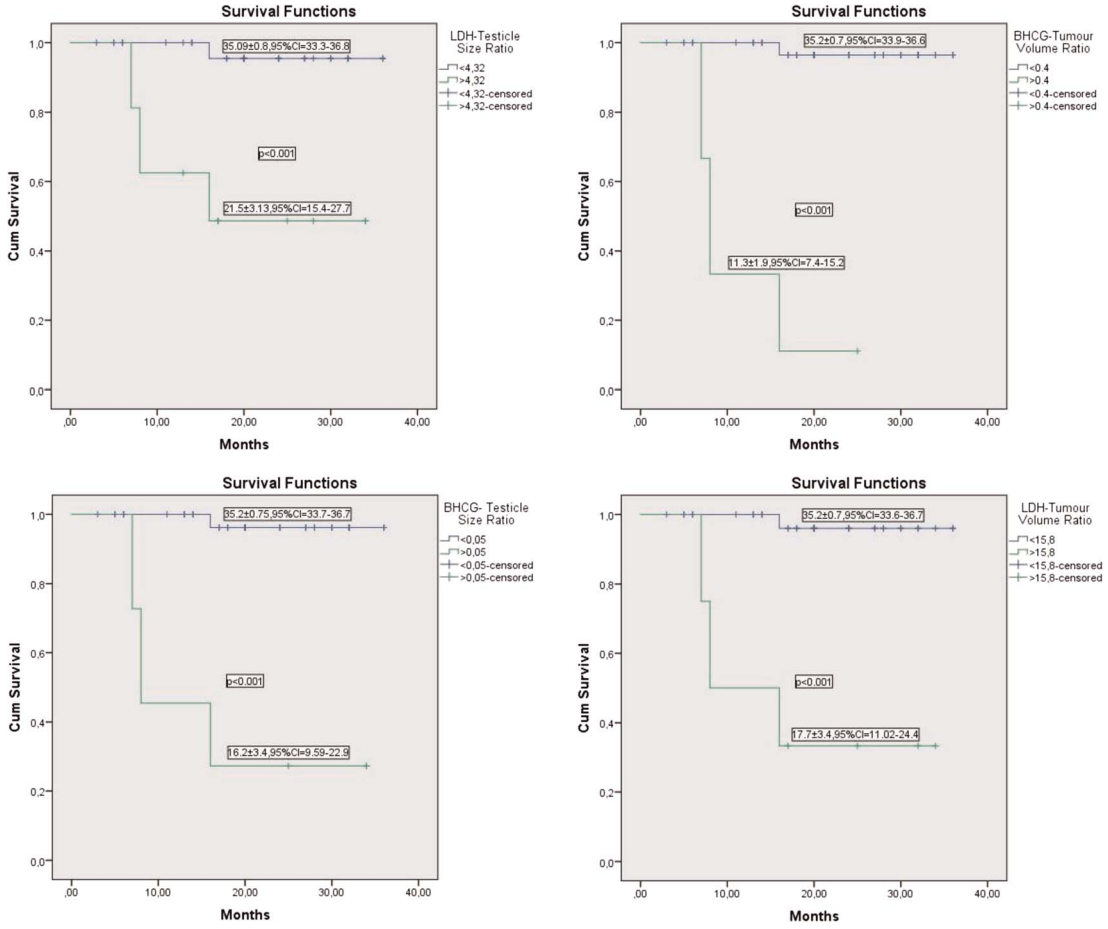

Figure 2. Kaplan–Meier analysis of PFS according to tumor marker densities in seminoma patients. AFP = alpha-fetoprotein; CI = confidence interval; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; PFS = progression-free survival.

Table 4

Univariate Cox regression analysis of variables for prediction of progression-free survival.

Variable	HR	95% CI	*p*
Seminoma patients (n = 47)			
T stage	12.49	2.52–61.9	**0.002**
Invasion of rete testis (yes vs. no)	1.23	0.3–4.9	0.77
Adjuvant treatment (yes vs. no)	0.37	0.09–1.51	0.16
βTSR (<0.05 vs. >0.05)	31.5	3.91–253.4	**0.001**
βTVR (<0.4 vs. >0.4)	48.53	5.97–393.95	**<0.001**
LTSR (<4.32 vs. >4.32)	16.13	2.01–129.3	**0.009**
LTVR (<15.8 vs. >15.8)	26.54	3.3–213.1	**0.002**
Nonseminoma patients (n = 48)			
T stage	13.16	3.26–53.19	**<0.001**
LVI (yes vs. no)	1.97	0.47–8.16	0.34
Embryonal carcinoma rate (<50% vs. >50%)	0.03	0–26.18	0.31
Adjuvant treatment (yes vs. no)	40.4	0.12–12981.9	0.2
ATSR (<5.4 vs. >5.4)	40.91	5.07–330.1	**<0.001**
βTSR (<7.52 vs. >7.52)	30.84	3.83–248.2	**0.001**
ATVR (<13.5 vs. >13.5)	3.6	1.4–9.2	**0.007**
βTVR (<7.5 vs. >7.5)	27.98	3.45–226.4	**0.002**
LTSR (<5.93 vs. >5.93)	17.97	2.24–144.02	**0.007**

Significant values are shown in bold ($p < 0.05$).

AFP = alpha-fetoprotein; ATSR = AFP testicle size ratio; ATVR = AFP tumor volume ratio; βTSR = βHCG testicle size ratio; βTVR = βHCG tumor volume ratio; CI = confidence interval; HR = hazard ratio; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; LTSR = LDH testicle size ratio; LTVR = LDH tumor volume ratio; LVI = lymphovascular invasion.

Table 5

Prediction models for progression-free survival.

Variable	HR	95% CI	*p*
Seminoma patients (n = 47)			
Model 1[§]			
T stage	1.33	0.25–7.08	0.73
βTSR (<0.05 vs. >0.05)	5.12	0.97–69.3	0.21
βTVR (<0.4 vs. >0.4)	15.37	1.13–208.01	**0.04**
Model 2[§]			
T stage	2.32	0.44–12.24	0.32
LTSR (<4.32 vs. >4.32)	3.95	0.37–41.37	0.25
LTVR (<15.8 vs. >15.8)	10.74	1.02–112.41	**0.04**
Nonseminoma patients (n = 48)			
Model 1[§]			
T stage	1.3	0.23–7.19	0.75
ATSR (<5.4 vs. >5.4)	33.52	2.9–387.28	**0.005**
ATVR (<13.5 vs. >13.5)	2.04	1.57–2.64	**0.01**
Model 2[§]			
T stage	2.58	0.53–12.5	0.23
βTSR (<7.52 vs. >7.52)	6.65	0–83.7	0.94
βTVR (<7.5 vs. >7.5)	0.02	0–1.46	0.51
LTSR (<5.93 vs. >5.93)	8.3	0.97–71	0.053

[§]Multivariate Cox regression analysis. Significant values are shown in bold ($p < 0.05$).

AFP = alpha-fetoprotein; ATSR = AFP testicle size ratio; ATVR = AFP tumor volume ratio; βTSR = βHCG testicle size ratio; βTVR = βHCG tumor volume ratio; CI = confidence interval; HR = hazard ratio; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; LTSR = LDH testicle size ratio; LTVR = LDH tumor volume ratio.

formation of models showing the effect of AFP density on prognosis. In addition, although the postoperative use of serum tumor marker levels is recommended in the evaluation of prognosis in testicular cancer patients, the methodology of this study required the use of preoperative values, and there should be an awareness that this approach could lead to overdiagnosis. There is a need for further prospective, randomized studies to support these findings.

5. Conclusions

The markers currently used to predict prognosis in testicular cancer patients are insufficiently accurate. Therefore, there is a need to determine new markers. Serum TMD values can be easily calculated at no extra cost and, according to the results of this study, can determine patients at an advanced clinical stage with a highly significant predictive value. In addition to tumor stage, βTVR and LTVR ratios in seminoma patients and ATSR and ATVR ratios in nonseminoma patients could be of benefit in clinical use, as each represent independent risk factors in the prediction of disease progression.

Acknowledgments

None.

Statement of ethics

Approval for the study was granted by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Decision no: 2022-08/2003). All study procedures were performed in compliance with the Helsinki Declaration. All study participants provided informed consent.

Conflict of interest statement

No conflict of interest has been declared by the authors.

Funding source

There was no external funding received in the conduct of this study.

Author contributions

AD: concept, study design, data collection, analysis, writing;
AD, HB: supervision, critical review.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Demirci A, Başar H. Can serum tumor marker densities according to tumor volume and testicle size be used to predict progression in patients with testicular cancer? *Curr Urol* 2024;18(3):218–224. doi: 10.1097/CU9.0000000000000212