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Does Determining Tumor Markers from the Testicular Vein Enable Better Diagnosis and Prognosis?

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Keywords
Tumor marker · Testicular vein · Testicular cancer

Abstract
Introduction: β-HCG has been the only tumor marker evaluated in testicular vein (VT) blood until now. ***Objective:*** To evaluate the correlation between the tumor markers β-HCG, AFP, PLAP, and LDH from the VT and peripheral blood as well as their significance in predicting tumor recurrence and tumor stage. ***Methods:*** Patients with testicular cancer undergoing orchiectomy were studied retrospectively over a period of 20 years. Tumor stage, tumor histology, time to tumor recurrence, and tumor markers from VT and peripheral blood were analyzed. Minimal follow-up was 2 years. Statistical analysis was performed by means of Cox- and logistic regression models and Spearman rank correlation coefficients. ***Results:*** A total of 172 patients with an average follow-up of 9.9 years were investigated. The overall recurrence rate was 18% (seminoma patients 20.8%, nonseminoma patients 14.5%). Marker values measured from VT blood were higher than in peripheral blood and correlated strongly with the peripherally measured values. AFP obtained from peripheral blood was the only tumor marker allowing a statement on the recurrence probability. Tumor markers from VT blood showed no correlation with tumor stage. ***Discussion/Conclusion:*** Tumor markers from VT blood are significantly higher than in peripheral blood. Tumor markers obtained from VT blood do not provide clinical advantage in terms of assessing tumor stage and recurrence probability.

Introduction

Tumor markers obtained from peripheral blood in patients diagnosed with testicular cancer can only be interpreted in conjunction with other diagnostic tools, such as sonography or computed tomography. They are helpful in the evaluation of tumor progression and recurrence [1]. The low sensitivity of tumor markers in peripheral blood led to the question of whether a sample of these markers obtained from the testicular vein (VT) might differ from the peripheral serum values. The assumption was that even tumors with normal marker levels in peripheral blood might produce larger amounts of these enzymes, which become diluted in the circulatory system.

In a first study by Light and Tyrrell [2], a significant difference of β-HCG values in peripheral and VT blood was found. A total of 3 studies from Mumperow et al. [3], Zenico et al. [4], and again by Mumperow and Hartmann [5] confirmed this finding. A study by Hartmann et al. [6]

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Table 1. Testicular tumor markers from peripheral blood and VT

Variable	Value	Q1–Q3
AFP VT, *n* = 57, 75.0%		
Nonseminoma	37.70 μg/L	6.35–447.65 μg/L
AFP peripheral blood, *n* = 67, 88.2%		
Nonseminoma	34.70 μg/L	5.70–309.50 μg/L
Beta-HCG VT, *n* = 148, 86.0%		
Seminoma, *n* = 65, 85.5%	19.10 mU/mL	5.80–90.00 mU/mL
Nonseminoma, *n* = 83, 86.5%	43.70 mU/mL	6.85–490.50 mU/mL
Beta-HCG peripheral blood, *n* = 154, 91.9%		
Seminoma, *n* = 84, 87.5%	1.00 mU/mL	1.00–5.00 mU/mL
Nonseminoma, *n* = 70, 89.5%	7.80 mU/mL	0.55–70.50 mU/mL
LDH VT, *n* = 90, 52.3%		
Seminoma, *n* = 52, 54.2%	564.50 U/L	294.75–988.50 U/L
Nonseminoma, *n* = 38, 50%	550.00 U/L	310.50–810.00 U/L
LDH peripheral blood, *n* = 158, 91.9%		
Seminoma, *n* = 88, 91.7%	197.00 U/L	158.25–281.00 U/L
Nonseminoma, *n* = 70, 92.1%	184.50 U/L	151.00–261.00 U/L
PLAP VT, *n* = 37, 74.0%		
Seminoma	1,000.00 μU/mL	510.00–1,883.00 μU/mL
PLAP peripheral blood, *n* = 43, 86.0%		
Seminoma	125.00 μU/mL	30.00–490.00 μU/mL

VT, testicular vein.

stated that β-HCG measured from VT does not provide any further clinical information in addition to peripherally measured values.

Hence, β-HCG has been the only marker evaluated in VT blood until now. Other tumor markers routinely utilized in the evaluation of testicular cancer (AFP, LDH, and PLAP) have not been investigated in the VT so far.

Material and Methods

This study was carried out retrospectively (City of Vienna's Ethics Committee EK No. 18-119-VK/14.06.2018) with patients who underwent orchiectomy due to a testicular tumor at the urological department of the Rudolfstiftung Hospital in Vienna, from January 1990 to May 2010. Exclusion criteria were patients in whom no germ cell tumor was found, patients with an extragonadal tumor and patients with an observation period of <2 years.

The following basic characteristics and demographic factors were utilized for this study: patient's age at orchiectomy, histology of the testicular tumor, tumor stage, follow-up period, time until tumor recurrence, smoking behavior, and tumor markers (AFP, β-HCG, PLAP, and LDH) from VT and peripheral blood (e.g., a cubital vein).

The primary questions of the study were:

a. Is there a correlation between VT tumor markers and time until tumor recurrence?
b. Is there a correlation between peripheral tumor markers and time until tumor recurrence?

Secondary questions were

a. Is there a correlation between tumor markers from VT and peripheral blood?
b. Is there a correlation between VT tumor markers and tumor stage?

Data were evaluated utilizing IBM® SPSS® Statistics Version 23. Tumor markers from peripheral and VT blood were evaluated using Cox- and logistic regression models with regard to their prediction for stage and recurrence probability. The differences between tumor markers obtained from peripheral blood and VT blood were evaluated by Spearman rank correlation coefficients.

Results

Data from 172 (96 seminoma and 76 nonseminoma) patients were analyzed and evaluated. Median age was 35.7 years for seminoma patients and 30 years for nonseminoma patients. Median follow-up period was 7.9 years for seminoma patients and 9 years for nonseminoma patients.

At the time of their first tumor staging, 81.4% of patients were classified as stage I (48.3% seminoma, 33.1% nonseminoma), 16.3% as stage II (7.6% seminoma, 8.7% nonseminoma), and 2.3% (0% seminoma, 2.3% nonseminoma) as stage III. Testicular tumor markers from pe-

Table 2. Correlation between VT, tumor markers, and tumor recurrence

	Hazard ratio	95% CI	*p* value
Seminoma			
β-HCG VT	0.963	0.781–1.188	0.725
β-HCG peripheral blood	0.976	0.834–1.142	0.761
LDH VT	1.023	0.945–1.108	0.547
LDH peripheral blood	0.894	0.698–1.144	0.372
PLAP VT	1.004	0.967–1.042	0.833
PLAP peripheral blood	1.033	0.927–1.152	0.556
Nonseminoma			
AFP VT	1.018	0.991–1.046	0.192
AFP peripheral blood	1.081	1.021–1.144	0.008
β-HCG VT	1.008	0.996–1.021	0.191
β-HCG peripheral blood	1.112	0.995–1.242	0.061
LDH VT	1.061	0.969–1.160	0.200
LDH peripheral blood	0.904	0.587–1.392	0.647

VT, testicular vein.

Table 3. Correlation between tumor markers from VT and peripheral blood

	Rank correlation coefficient	*p* value
Seminoma		
β-HCG VT/peripheral	0.650	<0.001
LDH VT/peripheral	0.642	<0.001
PLAP VT/peripheral	0.704	<0.001
Nonseminoma		
AFP VT/peripheral	0.810	<0.001
β-HCG VT/peripheral	0.820	<0.001
LDH VT/peripheral	0.488	<0.01

VT, testicular vein.

Table 4. Correlation between VT, tumor markers, and tumor stage

	Odds ratio	95% CI	*p* value
Seminoma			
Beta-HCG VT	0.994	0.952–1.037	0.778
LDH VT	1.093	0.984–1.214	0.099
PLAP VT	1.040	0.990–1.094	0.120
Nonseminoma			
AFP VT	1.008	0.973–1.044	0.672
Beta-HCG VT	0.993	0.968–1.019	0.592
LDH VT	0.948	0.784–1.147	0.584

VT, testicular vein.

ripheral blood and VT are shown in Table 1. Median time until tumor recurrence was 2.7 years for a total of 20.8% of seminoma patients and 1.1 years for 14.5% of nonseminoma patients.

Primary questions:

a. Is there a correlation between VT tumor markers and time until tumor recurrence?

No, there is no correlation between the VT tumor markers and time until tumor recurrence, no marker showed a significant correlation (Table 2).

b. Is there a correlation between peripheral tumor markers and time until tumor recurrence?

Yes, there is a significant correlation between AFP found in peripheral blood and tumor recurrence in nonseminoma patients (Table 2).

Secondary questions:

a. Is there a correlation between tumor markers from VT and peripheral blood?

Yes, the present data show significantly higher values of the tumor markers in VT when compared to peripheral blood, with a strong positive correlation for all 4 markers (Table 3).

b. Is there a correlation between VT tumor markers and tumor stage?

No, the data show that tumor marker values from VT have no correlation with tumor stage, neither in seminoma nor in nonseminoma patients (Table 4).

Discussion

In the present study, data from 172 patients undergoing surgery due to testicular cancer at the Rudolfstiftung Hospital were analyzed. The time frame of more than 20 years allowed a comparatively high number of patients to be analyzed. Of these, 31 patients (18.0%) had a tumor recurrence during the observation period. In 14 of them (8.1%), this occurred more than 2 years after surgery. The latest tumor recurrence was diagnosed 15 years after the primary diagnosis. The number of cases with tumor recurrence coincides with the number of cases of similar studies on tumor markers in testicular tumors, such as studies by Neumann et al. [7] and Hoshi et al. [8]. The absolute number of patients with a tumor recurrence in the observation period available for the prognostic analyses is low, therefore, limiting statistical information. Another limiting factor of this study is the retrospective study design. All analyses performed are based on data collected over the course of more than 20 years, and all

data relevant to the analyses have been entered by a number of people into the database, with all the sources of error that result from it.

The strength of this study is the long median observation period, and a comparatively high number of patients analyzed. In addition, an exact statistical evaluation of all tumor markers in VT blood with regard to stage and prognosis was possible.

Up to date, only one study investigating β-HCG in VT blood carried out in 1997 by Hartmann reported no additional diagnostic benefits when compared to peripheral blood [6]. As a result, the same was assumed for all other VT blood markers, although AFP, LDH, and PLAP were not investigated at all.

Regarding our primary questions, only one parameter achieved a *p* value of less than 0.05, namely AFP in peripheral blood with a *p* value of 0.008 and a hazard ratio of 1.08. The peripheral blood β-HCG also reached a low *p* value of 0.061 with a hazard ratio of 1.11. Unfortunately, the confidence interval also included the value 1; therefore, it is impossible to conclude that the result is significant, despite the high *p* values. *p* values obtained from all other markers; in particular, all samples extracted from the VT showed no significant difference. Therefore, tumor markers from VT have no predictive value concerning a possible tumor recurrence. The present data show a strong positive correlation for all 4 markers when comparing the respective values measured from the VT and the peripheral blood. Hartmann reported a correlation for β-HCG in seminoma patients with a correlation coefficient of 0.77 in a study from 1997 [6]. In the present study, the correlation coefficient was slightly lower at 0.65.

Earlier studies drew the conclusion that all tumor markers produced in the testicular tumor are present in peripheral blood in a very diluted form, but that ratios between VT blood and peripheral blood remain stable. A clear difference in HCG values from peripheral blood and blood from the VT was first described by Light and Tyrrell [2]. Mumperow et al. [3] confirmed this finding, in particular, that all seminoma produce HCG, but most of them only to a very small extent. These studies stated that HCG can be detected at an even lower level in peripheral blood [2, 5]. The present study demonstrates that all hormones utilized as tumor markers for testicular cancer are present in the VT blood near the place of their production with correspondingly higher values than in peripheral blood. Concerning the secondary questions, the present study shows no correlation between VT markers and tumor stage.

The data for seminoma patients as well as for nonseminoma patients show odds ratios around 1.00 with confidence intervals that each include the value 1 and have *p* values that indicate no significance of the results. The minimum number of 25 patients per group of the dependent variable could not be achieved in all subgroups, with 13 for seminoma patients and 19 nonseminoma patients with tumor stages 2 or 3.

Conclusion

The present study is the first to show that there is a strong positive correlation between VT and peripheral vein samples in all 4 tumor markers utilized in the evaluation of testicular cancer (AFP, β-HCG, PLAP, and LDH). Tumor markers extracted from the VT do not offer any further diagnostic information when compared to results obtained from peripheral blood.

Statement of Ethics

All subjects have given their written informed consent and City of Vienna's Ethics Committee (EK No. 18-119-VK/14.06.2018) approved the study protocol.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Walter Albrecht and Florian Wimpissinger: conception of the work. Walter Albrecht and Florian Wimpissinger: data acquisition. Thomas Zauner: data analysis. Thomas Zauner and Florian Wimpissinger: interpretation of data. Stefan Heidler and Lukas Lusuardi: drafting and revising the work critically for important intellectual content.

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