ORIGINAL ARTICLE

CONTENTS

State of extracellular matrix in testicular embryonal carcinoma

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ABSTRACT

Aim: To study peculiarities of the state of extracellular matrix in testicular embryonal carcinoma.

Materials and Methods: Samples of testicular embryonal carcinoma tissue were collected from 3 groups of patients (group «1» – stages $T_1N_0S_{0-2}$, group «2» – $T_2N_{1-3}S_{0-2}$, group «3» – $T_{2-3}N_{0-3}S_{0-2}$ with distant metastases) to assess the state of its extracellular matrix investigating MMP-1, MMP-3 and MMP-9 expression.

Results: The levels of MMP-1, MMP-3 and MMP-9 expression were statistically significantly higher in patients with tumorous vascular/lymphatic invasion, metastases in regional lymph nodes, distant metastases and invasion into the spermatic cord (except of lightness of MMP-3 expression) in comparison with patients without these characteristics.

Conclusions: MMP-1, MMP-3 and MMP-9 are involved in carcinogenesis already at the early stages of embryonal carcinoma and at the transition to late stages there is an increase of their synthesis, what proves their significant role in the destruction of extracellular matrix, invasion and metastatic process. Studied MMPs can be regarded as a prognostic factors of the embryonal carcinoma course as well as a potentially important therapeutic targets.

KEY WORDS: testicular germ cell tumors, embryonal carcinoma, matrix metalloproteinases, extracellular matrix.

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INTRODUCTION

More than 90% of all testicular neoplasias are testicular germ cell tumors (TGCT). The incidence of these tumors showed a progressive increase during the 20th century [1]. At the same time there are mathematical models which predict that incidence of TGCTs in European countries will continue to grow over the period of 2010-2035. The predicted increase in the number of patients by 2035 will be greatest in Eastern Europe, where cancer survival estimates are currently among the lowest [2]. For example, according to the National Cancer Institute of Ukraine, the malignant testicular tumors' ratio in males, at the age of 18 to 29, makes 16.4 % and ranks first [3]. And even though these tumors are rare neoplasms, they affect mainly young men (at the age of 15 to 44) [4], what makes this problem of great medical and social significance.

Embryonal carcinoma (EC) of the testis is the second most frequent TGCT after seminoma. And despite the fact that only 4-16% of cases are represented by "pure" forms of EC, this tumor is the most frequent predominant component of mixed TGCT (82.5% of cases) [5-7].

Important task of modern oncomorphology is not only the correct diagnostics of tumor, but also the assessment of its possible prognosis. Currently, various molecular biological characteristics of tumors are being actively studied, but use of only one biological marker cannot provide risk assessment of further progression and relapse of the tumor. Therefore, the choice of adequate panel of immunohistochemical (IHC) markers is a relevant task. It is known that matrix metalloproteinases (MMPs) are overexpressed in many malignancies, and tumor characteristics such as low differentiation, high invasiveness and metastatic activity correlate with increased expression levels of many MMPs [8-11]. At the same time, scholarly literature lacks the information concerning significances of MMP-1, MMP-3 and MMP-9 in progression of TGCT.

AIM

To study peculiarities of the state of extracellular matrix (ECM) in testicular EC depending on degree of tumor progression.

MATERIALS AND METHODS

The study was performed on the material of 34 observations of testicular EC (including 22 cases when EC was a component of mixed TGCT), as well as medical case histories of the patients of Communal non-commercial enterprise of the Kharkiv Regional Council "Regional Medical Clinical Center of Urology and Nephrology named after V.I. Shapoval".

All the observations of EC were distributed in accordance with pTNM classification of WHO [1], what is highly important, as the precise diagnosis and staging, which is made in compliance with the advanced science, are fundamental [12].

Thus, guided by the pTNM classification, the following groups were formed according to the degree of tumor progression: 1) Group «1» (n=13): tumor limited to testis and epididymis, without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis; no regional and distant lymph node metastases; serum tumor markers had different levels. Tumors of this group corresponded to the stages $T_1N_0S_{0-2}$; 2) Group «2» (n=12): tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis; presence of metastases in regional lymph nodes but absence of distant metastases; serum tumor markers had different levels. Tumors of this group corresponded to the stages $T_2N_{1-3}S_{0-2}$; 3) Group «3» (n=9): patients of this group had distant metastases; regional lymph node metastases could be absent; serum tumor markers had different levels. Tumors of this group corresponded to the stages $T_{2-3}N_{0-3}S_{0-2}$.

The material for IHC investigation was fixed in 10% neutral buffered formalin for 24 hours and embedded in paraffin. From the prepared blocks serial sections thick $4\text{-}5\times10^{-6}$ m were made, then plotted on high-adhesive slides «SUPER FROST PLUS» («DAKO», Denmark) and dried at temperature 37°C for 18 hours. Disclosure was performed by boiling of sections in citrate buffer (pH 6,0). For visualization the Ultra Vision Quanto Detection Systems HRP Polymer (Thermo Fisher Scientific Inc., USA) was used. DAB (diaminobenzidine) was used as a chromogen. Slides were stained with Mayer's hematoxylin and enclosed in Canadian balsam. For each marker in order to exclude false-positive or erroneous results control researches were performed.

To assess the state of ECM in EC, the expression of following IHC markers was studied: MMP-1 (Rb a-Hu MMP1 Polyclonal Antibody, "Thermo Fisher Scientific Inc.", USA), MMP-3 (Rb a-Hu MMP3 Polyclonal Antibody, "Thermo Fisher Scientific Inc., USA) and MMP-9 (Rb a-Hu MMP9 (92kDa Collagenase IV) Polyclonal Antibody, Thermo Fisher Scientific Inc., USA).

Stained histological sections of tumor tissue were registered using microscope «Olympus BX-41TF» and digital camera «Olympus C3040-ADU». The obtained photos were processed in the Matlab software package using standard digital image processing tools. For the morphometric evaluation of the relative area (S) occupied by immunopositive structures, the correlation between number of immunopositive pixels in the digital image and total number of pixels in this image (determined in percentage) was automatically calculated in the selected area. Using the brightness values of the RGB color channels in each pixel of immunopositive structures in the original image the auxiliary color coordinates of the CIE XYZ and then the color coordinates of the CIE Lab were calculated. Thus, the original digital image corresponded to a three-dimensional array of CIE Lab color coordinates. One of these coordinates is lightness (L), the value of which ranged from 0 to 100. L=0-40 corresponds to the strong, L=40-50 to moderate, and L=50-100 to weak level of the intensity of marker expression [13]. S and L of markers expression were studied in 30 randomly selected fields of vision of the microscope «Olympus BX-41TF» (Japan) at magnification ×200 ($31{,}2\times10^{-6}$ m^2) in each observation.

Statistical processing of the obtained data was performed using the statistical analysis package STATISTICA 13.3 EN. The indicators were compared using the non-parametric Mann-Whitney U test. The results in groups were presented in the form of median (Me) and interquartile ranges (IQR). Spearman's rank correlation coefficient (r) was counted for measure of the strength of relationship between paired data. The accepted level of significance was at $p<0.05$ [14].

RESULTS

Quantitative data of the MMP-1, MMP-3 and MMP-9 expression is presented in Table 1. Thus, study of MMP-1 in EC of group «1» revealed weak L and low S of its expression with non-uniform distribution of immunopositive cells. In EC of group «2» a significant increase of the S of MMP-1 expression was noted, while L of immunostaining of this marker remained weak (Fig. 1, A), but was slightly higher than in the previous group. As for the group «3», the S of MMP-1 expression was close in value with that of group «2» and was also greater than in group «1». The L level of MMP-1 expression in group «3» corresponded to the moderate level and was the highest among the studied groups. In addition, increase of MMP-1 expression in the zones of vascular and lymphatic invasion was defined (Fig. 1, B).

Table 1. Levels of MMP-1, MMP-3 and MMP-9 expression in testicular EC (Me (IQR))

	Group «1» (n=13)	Group «2» (n=12)	Group «3» (n=9)	p value
S of MMP-1, %	3.65 (3.38;3.96)	8.08 (7.41;8.69)	9.00 (7.60;9.34)	p_{1-2}<0.001 p_{1-3}<0.001 p_{2-3}=0.189
L of MMP-1, units	58.05 (55.57;58.44)	55.30 (55.12;55.63)	49.70 (49.05;49.96)	p_{1-2}=0.024 p_{1-3}<0.001 p_{2-3}<0.001
S of MMP-3, %	10.02 (9.27;11.18)	14.40 (13.40;15.08)	15.42 (14.84;16.27)	p_{1-2}<0.001 p_{1-3}<0.001 p_{2-3}=0.030
L of MMP-3, units	49.56 (48.92;50.34)	48.80 (48.15;49.20)	48.44 (48.26;49.45)	p_{1-2}=0.019 p_{1-3}=0.011 p_{2-3}=0.915
S of MMP-9, %	24.56 (23.47;25.78)	28.20 (27.26;28.69)	33.00 (31.95;33.23)	p_{1-2}<0.001 p_{1-3}<0.001 p_{2-3}<0.001
L of MMP-9, units	39.07 (38.63;39.34)	38.57 (38.36;39.07)	38.11 (37.83;38.49)	p_{1-2}=0.092 p_{1-3}=0.005 p_{2-3}=0.088

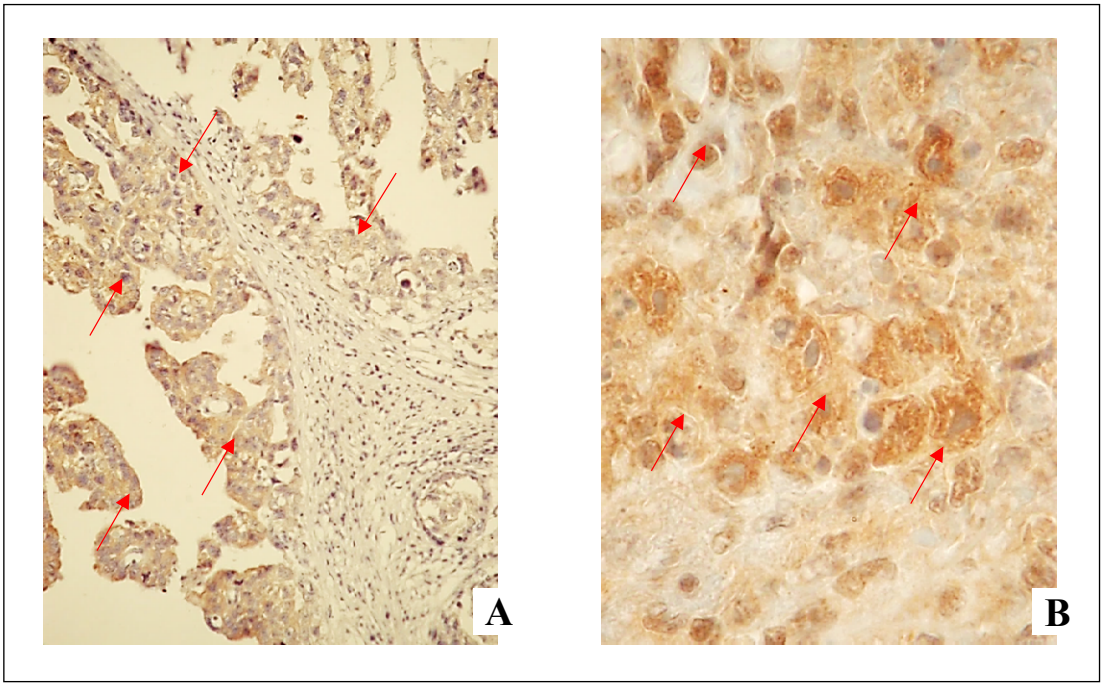

Fig. 1. A) Group «2». Weak and non-uniform reaction with MMP-1 in tumor cells of EC (marked with red arrows). Immunohistochemical reaction with antibodies to MMP-1. ×200. B) Group «3». Moderate reaction with MMP-1 in tumor cells of EC in the zone of angioinvasion (marked with red arrows). Immunohistochemical reaction with antibodies to MMP-1. ×1000

At studying of MMP-3 expression in the observations of EC of group «1» it was revealed that its expression was characterized by a uniform distribution. At the same time, the average S of MMP-3 expression was quite significant, and L though it was moderate on average was approaching a weak level. In ECs of group «2», MMP-3-immunopositive cells or their groups were also evenly distributed both in the central and peripheral areas of the tumor tissue (Fig. 2, A). The average S and L of MMP-3 expression in ECs of group «2» were statistically significantly higher than the corresponding indices of the previous group. In ECs of group «3» the average S of MMP-3 expression was significantly higher than that in groups «2» and «1». As for the L of MMP-3 expression in ECs of group «3», it was moderate and did not differ from this figure in group "2", but it was higher than in group «1». In the zones of angioinvasion (both in the vascular walls and perivascular spaces) as well as in the foci of expressed dissociation of tumor cells increased expression of MMP-3 was revealed (Fig. 2, B).

Expression of MMP-9 in the observations of ECs of group «1» was generally uniform. The average S of immunopositive areas was significant, while the L of MMP-9 expression was strong. In group «2» distribution of the MMP-9 in the tumor was also uniform and the average S of its expression was significantly higher than in ECs of group «1». The L of MMP-9 expression in ECs of this group was also strong and

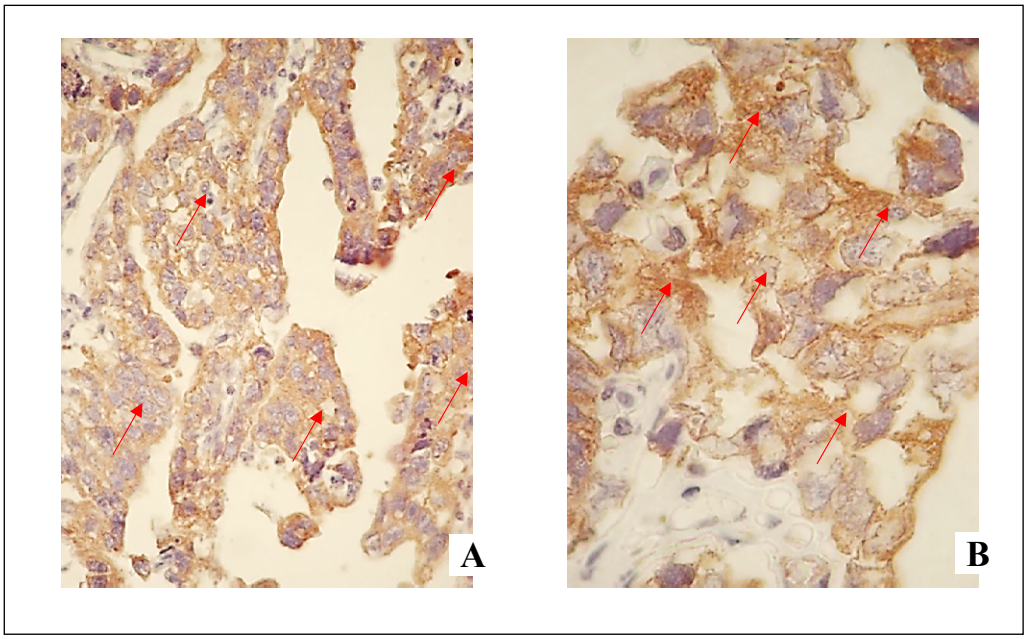

Fig. 2. A) Group «2». Moderate uniform expression of MMP-3 in tumor cells of EC (marked with red arrows). Immunohistochemical reaction with antibodies to MMP-3. ×400. B) Group «2». A moderate expression of MMP-3 in the focus of expressed dissociation of tumor cells of EC (marked with red arrows). Immunohistochemical reaction with antibodies to MMP-3. ×1000

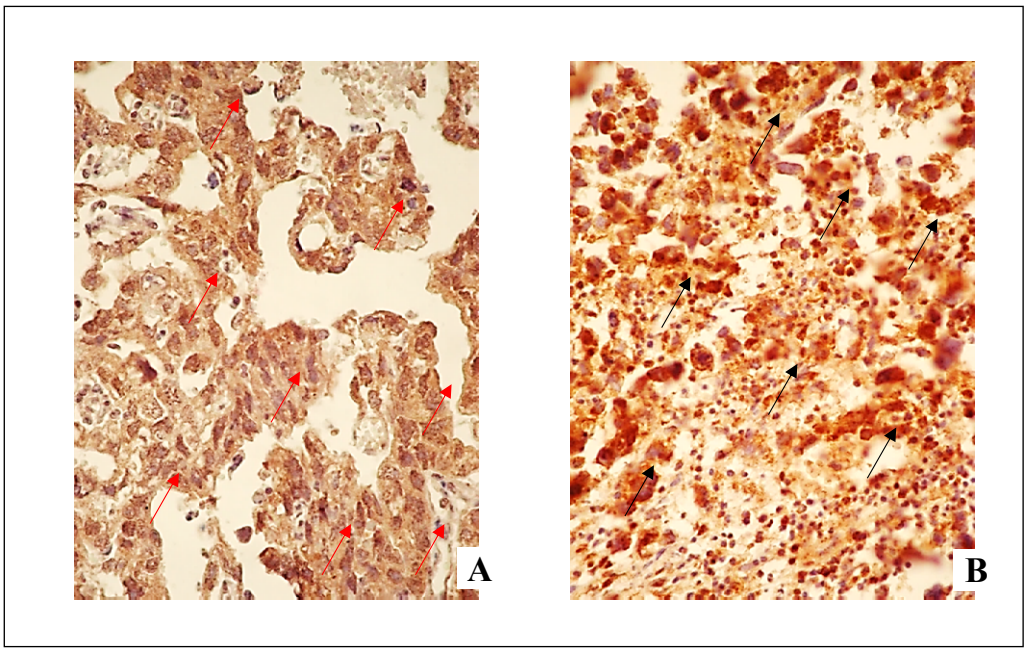

Fig. 3. A) Group «2». Strong uniform MMP-9 immunostaining in tumor cells of EC (marked with red arrows). Immunohistochemical reaction with antibodies to MMP-9. ×400. B). Group «3». Strong MMP-9 immunostaining in the zone of angioinvasion and dissociation of tumor cells of EC (marked with black arrows). Immunohistochemical reaction with antibodies to MMP-9. ×400

did not differ from the corresponding index of the previous group (Fig. 3, A). In group «3» the average S of MMP-9-immunopositive staining was the highest among studied groups, and L of its expression was strong and did not differ from that in group «2», but was higher than in group «1». The level of MMP-9 expression in the zones of angioinvasion and dissociation of tumor cells was slightly increased (Fig. 3, B). It also comes under notice that in all the studied groups S of MMP-9 expression was higher than S of MMP-3 which in its turn was higher than S of MMP-1 ($p<0.001$).

When assessing the indices of studied biomarkers expression using Spearman's rank correlation coefficient, it was found that at transition from the initial to late stages of tumor progression, significant moderate, strong and very strong positive strength of relationship was observed between S and L of MMP-1, MMP-3 and MMP-9 expression (with the exception between L of MMP-1 and MMP-9 expression and L of MMP-3 and MMP-9 expression (Table 2).

It was also established that levels of S and L of MMP-1, MMP-3 and MMP-9 expression were significantly higher in patients with tumorous vascular/lymphatic invasion and metastases in regional lymph nodes in comparison with patients without these characteristics. A similar picture was observed in the comparison of patients with distant metastases and invasion into the spermatic cord (except of L of MMP-3 expression). As regards the tumor invasion into the tunica albuginea and tunica vaginalis, the differences in values of the studied markers concerned only the expression of MMP-9, which was significantly higher in these patients (Table 3).

Table 2. Correlations of IHC markers expression in patients with testicular EC (r)

	S of MMP-1	L of MMP-1	S of MMP-3	L of MMP-3	S of MMP-9	L of MMP-9
S of MMP-1, %	1.00	0.66[1 **]	0.86[1 *]	0.63[1 **]	0.78[1 **]	0.50[1 ***]
L of MMP-1, units	0.66[1 **]	1.00	0.64[1 **]	0.43[1 ***]	0.63[1 **]	0.27[2]
S of MMP-3, %	0.86[1 *]	0.64[1 **]	1.00	0.65[1 **]	0.89[1 *]	0.49[1 ***]
L of MMP-3, units	0.63[1 **]	0.43[1 ***]	0.65[1 **]	1.00	0.49[1 ***]	0.18[2]
S of MMP-9, %	0.78[1 **]	0.63[1 **]	0.89[1 *]	0.49[1 ***]	1.00	0.60[1 **]
L of MMP-9, units	0.50[1 ***]	0.27[2]	0.49[1 ***]	0.18[2]	0.60[1 **]	1.00

Notes: [1] $p<0,05$; [2] $p>0,05$
* - very strong strength
** - strong strength
*** - moderate strength

Table 3. Correlations of values of IHC markers expression with aggressiveness of EC

		Mann-Whitney U test					
		S of MMP-1, %	**L of MMP-1, units**	**S of MMP-3, %**	**L of MMP-3, units**	**S of MMP-9, %**	**L of MMP-9, units**
Distant metastasis	«+»	n=9	n=9	n=9	n=9	n=9	n=9
	«–»	n=25	n=25	n=25	n=25	n=25	n=25
	p	0.003	<0.001	0.001	0.118	<0.001	0.009
Regional lymph node metastasis	«+»	n=21	n=21	n=21	n=21	n=21	n=21
	«–»	n=13	n=13	n=13	n=13	n=13	n=13
	p	<0.001	0.001	<0.001	0.004	<0.001	0.009
Vascular/lymphatic invasion	«+»	n=22	n=22	n=22	n=22	n=22	n=22
	«–»	n=12	n=12	n=12	n=12	n=12	n=12
	p	<0.001	<0.001	<0.001	0.003	<0.001	0.012
Invasion into Epididymis	«+»	n=6	n=6	n=6	n=6	n=6	n=6
	«–»	n=28	n=28	n=28	n=28	n=28	n=28
	p	0.378	0.874	0.403	0.331	0.074	0.067
Tumor extending through tunica albuginea and tunica vaginalis	«+»	n=2	n=2	n=2	n=2	n=2	n=2
	«–»	n=32	n=32	n=32	n=32	n=32	n=32
	p	0.200	0.176	0.200	0.200	0.037	0.134
Tumor invades spermatic cord	«+»	n=5	n=5	n=5	n=5	n=5	n=5
	«–»	n=29	n=29	n=29	n=29	n=29	n=29
	p	0.001	0.002	0.001	0.046	0.001	0.003

DISCUSSION

Thus, in our research when studying MMP-1, MMP-3 and MMP-9 in all groups the same type of changes were revealed. Namely, as the stage of tumor progression increases, the synthesis of these biomarkers increases as well. This fact allows us to admit a significant role of studied MMPs in the destruction of ECM, invasion and metastasing [15-17].

From the conducted research it also became evident that MMP-1, MMP-3 and, especially, MMP-9 take part in carcinogenesis of testicular EC starting from the early stages of tumor progression. Besides, the significant expression of MMPs in testicular EC suggests a tendency to a more aggressive behavior of this tumor, because it is known that mentioned biomarkers are involved in a wide spectrum of roles, which can promote proliferation, migration, selection of apoptosis-resistant subpopulations of tumor cells as well as angiogenesis, invasion and metastasing [18-22]. And mentioned above facts prove that development of clinical and morphological signs of testicular EC aggressiveness, such as vascular/lymphatic invasion, development and progression of metastatic process are mediated by increase in the expression of markers of the ECM state (MMP-1, MMP-3 and MMP-9).

Taking into consideration the stated above, MMP-1, MMP-3 and MMP-9 can be considered as prognostically significant biomarkers.

In our research, immunohistochemical reaction with antibodies to TIMP-1 was negative in all observations of ECs of all studied groups, which is coincident with data in scholarly literature, which indicate that an increase of MMPs expression is accompanied by a decrease of TIMP-1 expression [23, 24]. At the same time, according to some scientific researches, the lack of TIMP-1 expression implies a favorable prognosis and tumor sensitivity to chemotherapy in certain types of cancer [25]. And vice versa, a number of studies show that overexpression of TIMP-1 is associated with unfavorable prognosis and early relapses for many cancers, including prostate and breast carcinoma [26, 27].

Thus, in our opinion, regardless of whether the level of TIMP-1 expression increases or decreases as the stage of tumor progression increases, this marker is a potentially important therapeutic target and requires further study.

CONCLUSIONS

It was established that reaction with antibodies to TIMP-1 was negative in all observations of ECs of all studied groups, whereas the level of MMP-1, MMP-3 and MMP-9 expression depends on the stage of EC progression. Furthermore, these MMPs are involved in carcinogenesis already at the early stages of EC ($T_1N_0S_{0-2}$) and at the transition to late stages ($T_2N_{1-3}S_{0-2}$ and $T_{2-3}N_{0-3}S_{0-2}$ in the patients who have distant metastases) there is an increase of their synthesis, what proves their significant role in the destruction of ECM, invasion and metastatic process. Thus, MMP-1, MMP-3 and MMP-9 can be regarded as a prognostic factors of the testicular EC course as well as a potentially important therapeutic targets.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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