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Prognostic value of uterine leiomyosarcoma's histological grade: Clinico-pathological analysis of 22 cases with literature review

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ABSTRACT

The clinical data concerning prognostic value of the grade of uterine leiomyosarcomas (UL) are rare and controversial. To extend data in this direction, we analyzed archival recordings of 22 patients, admitted to the clinic in 2012-2020, and diagnosed as UL. Histological samples of malignant tissue were analyzed by two independent morphologists to determine the histological type and grade of tumor. Immunohistochemical investigation (Desmin, SMA) was used for further analysis of tumor pathogenesis. Descriptive methods as well as Spearman Rank Order Correlations and Cox's F-Test were used for data statistical analysis. The study revealed that in metastatic and recurred cancer tissues have the same grade as in primary tumor, meanwhile low grade UL do not turn into high grade forms. The grade of tumor do not correlate to the age of patients and size of tumor. Therefore, these parameters do not serve as an independent prognostic marker. SMA and desmin intensity were found to be stable UL. Both markers may serve for immunohistochemical characteristic of UL pathogenesis. In sum, according to the obtained data, the grade of tumor is suggested as an independent prognostic factor for the treatment of UL, while the age of patient and cancer size are suggested insignificant in this respect.

Key words: Uterine leiomyosarcoma; metastasis, prognostic value, histological grade;

INTRODUCTION

Leiomyosarcomas (LMSM) is extremely rare tumor with high mortality rate. The incidence of tumor accounts only 1 % among uterine tumors (1). Commonly, LMSM occurs in premenopausal and menopausal patients, although rare cases of LMSM have been reported inpatients as young as 17 years of age (2). In most cases, anasymptomatic course of the disease is observed (3), which makes it difficult to detect the disease at an early stage, and it has negative effects on the outcome of the disease. LMSM Surgical intervention, in particular hysterectomy, is a classical treatment for LMSM (4), although in part of clinical cases, vaginal, abdominal, and endoscopic methods are also used, while the effectiveness of adjuvant radiotherapy and chemotherapy is still debatable (5, 6). LMSM is characterized by a high potential for hematogenous metastasis, and, accordingly, the tumor is highly aggressive. The tumor often metastasizes to the lungs, relatively less often to the liver, bones, and other organs. In the initial stages, the risk of recurrence is about 71% in the period from 8 to 16 months after surgery. To select the optimal postoperative treatment strategy, immunohistochemical assessment of sex hormone receptors expression degree(7, 8) and ki67, p63, p16, and bCL2 in tumor tissue is used (9), although the question of the relevance of this approach remains open.

The mitotic index is considered to be a significant prognostic factor in the treatment of LMSM. However, Beside the proliferative marker, patients' age, tumor size (10) and the histological subtype of LMSM are also considered important prognostic factors (11). For example, myxoid leiomyosarcoma is characterized by a late recurrence with the development of metastases 10 years after surgery, and epithelioid forms of LMSM are distinguished by the frequency of local recurrences 5 or even 10 years after surgery (12).However, other authors have shown that myxoid LMSM does not differ from other forms in terms of the risk of recurrence and metastasis and the risk is mainly related to the degree of tumor grade (13). To date, little is known about the prognostic factors of uterine sarcomas. The accumulation of data about this issue is hampered by the rare occurrence of LMSM, consequently, the small number of patients under the supervision of clinicians (14).Uterine sarcoma belongs to a group of heterogeneous tumors and the small number of patients in each of these groups complicates the generalization of treatment standards. The absence of screeningtests and, also, hematogenous spread of metastases, determinesthe aggressiveness of the tumor, and the identification of prognostic factors for the course of the disease are of particular importance for determining treatment strategies for LMSM.

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Existing evidence is inconsistent. For a long time, the histological subtype, spread of the tumor (TNM tumor) and also the age of the patients has been recognized as a relevant prognostic factor. However, at present, several questions arise regarding the relevance of these factors. For example, it has been shown that poorly differentiated forms of the tumor (G3) are associated with a worse prognosis in patients older than 60 years (15), and compared with the degree of tumor differentiation, the patient's age is a more reliable prognostic factor. The relevance of which increases if the degree of differentiation of tumor coincides with a high mitotic index (16), while other authors completely deny the prognostic value of the tumor grade for assessing the course of the disease and patient survival (17).

In addition, we were unable to find in clinical literature data regarding changes tumor grade and disease recurrence. The aim of our study is to fill the gap in knowledge about prognostic value of the LMSC grade, and particulary, to investigate the changes of low grade tumor into high grade tumors.

Material and methods

Primary and progressive cases of LMSM were analyzed. Archival records of 22 cases between 2012-2020 years were used.

Also, corresponding histological slides stored at the Institute of Clinical Oncology were rechecked by two morphologists who independently assessed the histological form and degree of the tumor. The histological form was assessed according to the criteria of the WHO and the degree of microscopic malignancy was determined according to the criteria of the French Federation of Tumor Centers (sarcoma group). Cases were analyzed regarding the age of the patients, TNM and grade, time and site of recurrence (Table2). Morphological investigation was done on H&E stained slides and IHC investigation was done with Desmin (clone DE-R-11) and SMA (clone ASM-1) (Novocastra, Leica,USA) by using Leica Bond Max apparatus. In IHC slides conventionally, weak expression was designated as"+", strong expression – "++", and absence of expression (negative expression) - "-". The data obtained were statistically processed using Spearman Rank Order Correlations and Cox's F-Test, as well as the descriptive statistics method. Core biopsy were done in all metastatic and recurrent patients, respectively the tumor type, grade and IHC analysis were done in biopsy material.

Results and discussion

The results of the study are presented in following tables.

TABLE 1. Distribution of clinical material according to the degree of tumor tissue differentiation

Score	Form of sarcoma
1	The structure of the sarcoma is similar to the mesenchymal tissue of healthy adults.
2	Myxoid sarcoma
3	Sarcoma of unknown type, embryonic undifferentiated sarcoma
	Tumor necrosis
1	Necrosis is not detected
2	≤ 50% necrotic tissue
3	≥50% necrotic tissue
	Mitotic index
1	0-9/10 HPF
2	10-19/10 HPF
3	≥ 20 HPF

The grade of differentiation of the tumor tissue was judged by the sum of points scored on three indicators

Grade 1 (2-3 points); Grade 2 (4-5 points); Grade 3 (6-8 points).

TABLE 2. Distribution of clinical cases by demographic and clinical indicators

Age	tumor localization	pT	Grade of Primery Tumor	Desmin	SMA	Site of MTS	Desmin/SMA expression	Time of recurrence	Grade of MTS
50	intramural	pT1	3	++	++	lung	++/++	17	3
64	intramural	pT2	1	++	++	local recurrence	++/++	24	1
49	submucosal	pT1	2	++	++	lung	++/++	16	2
55	intramural	pT2	3	++	+	lung	++/-	19	3
39	intramural	pT1	1	++	++	local recurrence	++/++	26	1

Age	tumor localization	pT	Grade of Primery Tumor	Desmin	SMA	Site of MTS	Desmin/SMA expression	Time of recurrence	Grade of MTS
54	intramural	pT3	2	++	++	local recurrence	++/++	35	3
55	intramural	pT1	1	++	++	local recurrence	++/+	16	1
61	intramural	pT3	3	++	++	lung	+/-	20	3
53	intramural	pT2	3	++	++	lung	++/++	13	3
59	intramural	pT1	3	++	++	lung	+/ -	11	3
60	intramural	pT1	1	++	++	local recurrence	++/++	41	1
62	intramural	pT3	1	++	++	lung	+/+	13	1
66	intramural	pT3	3	++	+	lung	+/-	7	3
55	intramural	pT3	3	++	+++	lung	+ +/+	16	3
42	intramural	pT3	1	++	++	local recurrence	+ +/+	36	1
51	intramural	pT2	3	++	+	lung	+ +/+	14	3
77	intramural	pT3	2	++	++	local recurrence	+ +/+	41	1
65	intramural	pT2	3	++	++	lung	++/++	16	3
71	intramural	pT3	2	++	++	local recurrence	++/++	14	2
80	intramural	pT3	2	++	+++	lung	++/++	26	2
51	intramural	pT3	3	++	+	lung	++/-	8	2

The table N2 shows that most often recurrences occur in the lungs (n=15;68.2%), and only in seven cases (31.8%) local relapses were recorded. In the overwhelming majority of cases (n=21, 95.5%) the tumor developed intramurally. SMA expression was the same in all clinical cases (Figure 1). Distribution of patients according to the grade of tumor. X - grade of differentiation in points, Y - number of patients

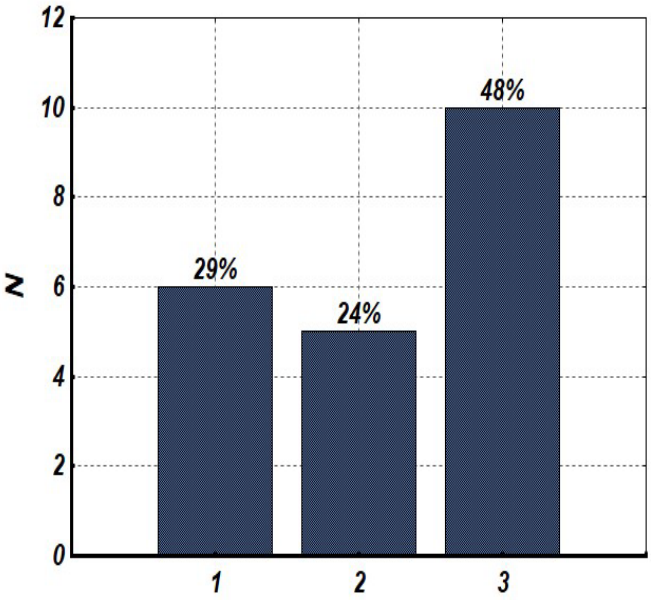

Figure 1: *Distribution of patients according to the grade of tumor. X - grade of differentiation in points, Y - number of patients*

The time of recurrence development was 14 months in patients with G3 (50% of cases), 26 months in patients with G2, and 24 months in patients with g3 (Cox's F-Test, Grade - (1/2) F(10, 12) = 1.04; p = 0.47; Grade - (1/3) F(15, 17) = 2.9; p = 0.016; Grade - (2/3) F(14, 16) = 2.7; p = 0.027).

TABLE 3. Correlation of tumor grades and with number of patients and relapse time

Grade	Median relapse time in months	number of patients
1	25.0 (Mean 26.0; SD +/-10.93)	6
2	26.0 (Mean 26.4; SD +/-11.71)	5
3	15.00 (Mean 14.1; SD +/-4.38)	10

TABLE 4. Statistical significance (p value) of the difference in the time of recurrence development between patients with different tumor histogenesis

GRADE	Cox's F-Test		
	1	2	3
1	*F=1.03; p = 0.47*	*F=2.9; p = 0.016*	
2		F=2.7; p = 0.027	
3			

Statically significant value is defined by p=<0.5

A statistically significant correlation between the quality of tumor histogenesis and the site of recurrence (metastasis)was recorded only between groups of patients 1-3 and 2-3 (Spearman Rank Order Correlations - 0.76, p<0.0013), which indicates an increase in the number of patients with distant metastasis, in parallel to the growth of the quality of tumor histogenesis. Therefore, there is a correlation between the tumor grade and distant metastasis. According to the data obtained, highly differentiated forms are associated mainly with local relapses, and poorly differentiated forms are associated with the formation of distant metastases. The grade of tumor in recurrence and in metastasis do not change. The intensity of SMA expression compared with the expression of Desmin decreased in the metastasized tissue.

This difference in the intensity of expression of SMA and Desmin was not statistically significant, although, in general, it can be assumed that the expression of IHC markers is reduced in some metastatic cells of the tumor tissue. The difference in the clinical course of the disease between grade 2 and grade 3 were not statistically significant. The age of the patients was not a statistically significant parameter for predicting the clinical course of the disease. In contrast to existing literature data, in our study we could not find a correlation between tumor size and metastasis. In general, according to our we suggest that the grades of ULMS do not change in metastasis and in recurrent tumor. Low grade forms do not progress into high grade forms; Tumor size and patients' age are not independent predictors of disease progression;

The intensity of SMA and Desmin expression is a IHC indicator of leiomyoma histogenesis; The grade of tumor is an independent and the most important prognostic marker in the treatment of LMSC.

Conflict of Interest declaration

The authors declare that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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