GISTs' Classifications in Predicting Aggressive Behavior: A Single Institution Experience

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A B S T R A C T

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. When making treatment plan it is very important to make proper tumor aggressiveness estimation. Traditionally, the best prognostic factors are tumor size and number of mitoses. The aim of this study was to define which GIST classification (Amin's or Newman's classification or Fletcher's Consensus Criteria) is the most significant determining prognosis and has the strongest impact on survival. This study included 63 GIST patients whose tumor specimens were evaluated by standard histopathological methods and classified based on histological assessment of malignant behavior to the three different systems. Comparison of those classification systems was done and none of them was proven to be statistically significantly better in predicting overall survival and probability of lethal outcome. We conclude that all three classifications are comparable in prediction of malignant behavior. The worst prognostic factor is existence of metastases at the time of disease diagnosis.

***Key words**: GIST, classification system, prognosis, metastase, overall survival*

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. They can evolve in any part of gastrointestinal system, especially in the stomach and small intestine, but can also originate in the mesentery and omentum. They are very rare (0.1–1% of all malignant gastrointestinal system tumors)[1–7].

The most critical development which distinguished GISTs as a unique clinical entity was the discovery of c-Kit proto-oncogene mutations[8]. More than 90% of malignant GISTs have aberrant signal transmission mediated by KIT[9,10].

Immunohystochemical characteristics of GISTs are the following: almost all are KIT (CD 117) positive, 60–70% are CD 34 positive, 30–40% are SMA positive, they are very rarely desmin positive and 5% are S-100 positive[10–12].

GISTs usually develop in patients older than 50 years[13]. The average age is between 55 and 65 years. Some clinical studies have shown that these tumors occur more often in men, while other studies have shown similar distribution between men and women[14–28].

When decision about GIST treatment is made, assessment of it's biological behavior has to be included. Experientially, the best prognostic factors are tumor size and the number of mitoses. Although, there are some tumors which are big in size and have benign course and also some very small tumors which are extremely aggressive and have markedly malignant course. Tumor size by itself is not indisputable prognostic factor, but in combination with other prognostic factors it's meaning becomes important[7].

Over many years, there were discussions and analyses what are criteria for distinction of benign and malignant

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GISTs or at least for detection of lesions which are more likely to metastasize[29–34]. It is still unresolved which are the breaking points suggesting malignant behavior. Factors like mucous invasion, tumor necrosis and high cellularity were shown to be statistically significant but were not reproducible and were not useful in individual cases.

Almost every GIST which causes clinical symptoms or signs requiring therapy has potentially malignant behavior.

The most common place of relapse is abdominal cavity or appearance of hepatic metastases what then implies poor prognosis.

Amin wanted to divide GISTs considering their biological behavior into three categories according to the histology: 1) Benign – less than 5 mitoses / 50 HPF (High Power Field), tumor size less than 5 cm; 2) Borderline – less than 5 mitoses / 50 HPF, tumor size more than 5 cm; 3) Malignant – more than 5 mitoses / 50 HPF, any tumor size.

According to histological criteria Newman and associates had similar attempt of GISTs graduation: 1) Benign – 0–2 mitoses per 30 HPF / spindle-cell type without atypia or 0 mitoses per 30 HPF / spindle-cell type; 2) Borderline – 2–3 mitoses per 30 HPF / spindle-cell type, mild polymorphism and hyperchromasia or 3–4 mitoses per 30 HPF / spindle-cell type without atypia or 1 mitose per 30 HPF / epitheloid type lesion; 3) Malignant – more than 5 mitoses per 30 HPF / spindle-cell type without atypia or more than 3 mitoses per 30 HPF / spindle-cell type, polymorphism and hyperchromasia or more than 2 mitoses per 30 HPF / epitheloid type lesion.

Furthermore, most of the researchers assume it better to categorize lesions according to aggressive behavior risk – a task that is currently still hard to do correctly. The group of authors had idea to develop a scheme based on risk assessment[35]. For the specific case of GIST, risk of aggressive behavior is estimated as either very low, low, intermediate or high. Hopefully, only small proportion of cases (less than 10%) will take an unexpected clinical course, although none of the lesions can be proclaimed benign.

Group of authors, have collected their experiences and opinions and have defined aggressive behavior risk of GISTs as follows: 1) Very low risk: – size* less than 2 cm, number of mitoses** less than 5 mitoses per 50 HPF; 2) Low risk: – size* 2–5 cm, number of mitoses** more than 5 mitoses per 50 HPF; 3) Intermediate risk: – size* less than 5 cm, number of mitoses** 6–10 mitoses per 50 HPF or size* 5–10 cm, number of mitoses** less than 5 mitoses per 50 HPF; 4) High risk: – size* more than 5 cm, number of mitoses** more than 5 mitoses per 50 HPF or size* more than 10 cm, any number of mitoses** or any size, number of mitoses** more than 10 mitoses per 50 HPF

These criteria are called NIH (National Institute of Health) Consensus Criteria.

Patients with metastatic GISTs are candidates for imatinib mesylate (tyrosine kinase receptor inhibitor) therapy from which clinical results are very good and encouraging. Imatinib mesylate is also part of adjuvant therapy in patients with resected high or intermediate risk GISTs and can be part of therapy prior to surgery in patients with unresectable disease[36–43].

Aim

The aim of this study was to define which criteria are of prognostic importance and applicable in clinical praxis.

Amin's and Newman's classification and NIH Consensus Criteria are compared in order to define which of them is prognostically most significant and which one has the strongest impact on survival. This comparison, based on obtained results, could suggest which classification is the most useful one in the routine clinical praxis.

The hypothesis was that NIH Consensus Criteria described by Fletcher and associates were the most useful for determining GIST prognosis as they are the most frequently used and described in the literature. The aim of the study was also to clearly show how existence of metastases at the time of diagnosis affects overall survival.

Patients, Material and Methods

Here presented study included 63 GIST patients diagnosed and surgically treated at University Hospital for Tumors in Zagreb, Croatia, from 01.01.1995 until 31.12. 2012. Available data on patients, their tumors and applied therapies were collected together with their survival length.

Distribution of the patients according to the gender, age, tumor size and number of mitoses was analyzed. Patients were also distributed according to the tumor location within gastrointestinal system and tumor cells morphology defined as spindle-cell type, epitheloid type or mixed lesion type. An overview of immunohistochemical profile of the evaluated GISTs was done.

Tumor specimens were retrospectively analyzed after clinical diagnosis was established and surgery was performed. Histopathological analysis and immunohistochemical diagnosis of GISTs were established.

The tumor specimens, obtained by surgery, were prepared for histopathological analysis by standard routine method consisting of fixation in 10% buffered formalin. Afterwards, tumor tissue was embedded in the paraffin blocks, sectioned at 3 to 5 microns and stained by hema-

* size presents only one dimension of tumor, the biggest diameter can depend on pre- and postfixation, although in small bowel lesions aggressive behavior risk threshold is 1 to 2 cm smaller than in the lesions situated on other localization

** number of mitoses is subjective category based on different identification of mitoses, size of all examined high power fields can be different

toxylin and eosion. The stained tumors sections were than examined by light microscope.

For immunohistochemical analysis eight additional sections were done. Immunohistochemical method using PAP complex (peroxidase-antiperoxidase complex) and ABC (avidin-biotin complex) / HRP (horse-radish peroxidase) DAKO NoK0355 was applied. PAP complex consists of antigen, peroxidase and peroxidase antibody. The standard procedure for immunohistochemical staining was used. In all tumor specimens expression of the CD 117, CD 34, vimentin, SMA, S-100, MAGE A1, MAGE A3/4 and NY ESO 1 was evaluated.

In order to determine biological behavior of the tumors, they can be classified according to the criteria of Amin and associates[44] and Newman and associates[45] as malignant, borderline or benign. Taking into account the fact that small tumor lesions (even smaller than 2 cm in diameter) and lesions with minimal number of mitoses can also metastasize, most of the authors consider that it is better to divide GISTs in groups according to risk of aggressive behavior. According to the National Institute of Health Consensus Criteria, GISTs should be divided into four groups: very low risk, low risk, intermediate risk, and very high risk of aggressive behavior[7].

Based on routine classical histopathological examination, morphology of the tumor cells was examined. The tumors were divided into three groups depending on cell features. They were characterized as spindle-cell lesions, epitheloid or mixed lesions (this is part of Newman classification).

All the collected GISTs were also examined immunohistochemically. Results of immunohistochemical staining were shown with semiquantitative method as follows:

- negative reaction (–) : there is no tumor cell staining
- weekly positive reaction (+): less than 10% of tumor cells are stained positively
- moderately positive reaction (++): 11–50% of tumor cells are stained positively
- extremely positive reaction (+++): more than 50% of tumor cells are stained positively.

As positive expression were considered moderately positive, extremely positive and weekly positive reaction whereas negative expression was considered negative reaction.

Statistics

The obtained data were statistically analyzed by interrogating differences and correlations using SSPS 17 (IBM, Somers, New York) and MedCalc Software 12.2.1 (Mariakerke, Belgium). Normal distribution of continuous variable was considered reduced and rounded distribution less than 1. Regularity of distribution was checked by Smirnov-Kolmogorov test. Nominal indicators were shown by prevalence distribution considering groups and participation. In order to establish differences between two independent samples, student T test was employed. Mann-Whitney test was used for determining differences between two independent samples which show irregular distribution. For defining differences between proportions of two independent samples χ^2-test was used and for defining differences between proportions of more than two independent samples Pearson χ^2-test was used. Kendall tau b test was employed for determining correlation between samples for nonparametric analysis. Influence of covariance group on overall survival was investigated by Cox regression analysis and influence of individual variable on overall survival was investigated by Kaplan-Meier model. Statistical relevance was accepted for $p<0.05$.

Results

The overall number of 63 patients with clinically and pathologically diagnosed GISTs since 01.01.1995 until 31.12.2011 at the University Hospital for Tumors, Zagreb, Croatia was included in this study.

Of all patients, 31 (49.2%) were men and 32 (50.8%) were women. The average age of all patients was 58,7 years (median 62, min 16, max 80), the average age of all male patients was 59.4 years (median 61, min 18, max 79) and the average age of all female patients was 57.9 years (median 63, min 16, max 80), without statistically significant difference between genders ($p=0.700$).

The average overall survival for all patients was 74.5 months (median 71, min 1, max 176), the average overall survival for female patients was 70.01±53.46 months (median 87 months) and for male patients was 78.25± 47.44 months (median 61 months), but without statistically significant difference between genders ($p=0.551$).

TABLE 1
DISTRIBUTION OF THE GISTS BASED ON PRIMARY TUMOR LOCALIZATION IN THE GASTROINTESTINAL SYSTEM AND IMMUNOHISTOCHEMICAL EXPRESSION OF THE CD 117, CD 34, VIMENTIN, SMA, S100, MAGE A1, MAGE A/4, NY ESO

Tumor localization	Number of cases	
Oesophagus	1 (1.6%)	
Stomach	39 (61.9%)	
Small intestine	13 (20.6%)	
Large intestine	7 (11.1%)	
Omentum	3 (4.8%)	
Immunohisto-chemistry	Positive expression	Negative expression
CD 117	63 (100%)	0 (0%)
CD 34	50 (79.4%)	13 (20.6%)
Vimentin	63 (100%)	0 (0%)
SMA	39 (61.9%)	24 (38.1%)
S-100	24 (37.1%)	39 (61.9%)
MAGE A1	22 (34.9%)	41 (65.1%)
MAGE A3/4	4 (6.3%)	59 (93.7%)
NY ESO– 1	7 (11.1%)	56 (88.9%)

TABLE 2
AMIN'S CLASSIFICATION OF THE GISTS, OVERVIEW OF PATIENTS' WHO DIED AND OVERALL SURVIVAL MEDIAN EXPRESSED IN MONTHS

Amin's classification

Type	Number of cases	Lethal outcome		Overall survival median in months
		Yes	No	
Benign	24 (38.1%)	3 (4.8%)	21 (33.3%)	87
Borderline	18 (28.6%)	2 (3.2%)	16 (25.4%)	120
Malignant	21 (33.3%)	9 (14.3%)	12 (19.0%)	29

TABLE 3
NEWMAN'S CLASSIFICATION OF THE GISTS, OVERVIEW OF PATIENTS WHO DIED AND OVERALL SURVIVAL MEDIAN EXPRESSED IN MONTHS

Newman's classification

Type	Number of cases	Lethal outcome		Overall survival median in months
		Yes	No	
Benign	25 (39.7%)	2 (3.2%)	23 (36.5%)	97
Borderline	17 (27.0%)	4 (6.3%)	13 (20.6%)	68
Malignant	21 (33.3%)	8 (12.7%)	13 (20.6%)	29

TABLE 4
NIH CONSENSUS CRITERIA CLASSIFICATION OF THE GISTS, OVERVIEW OF PATIENTS WHO DIED AND OVERALL SURVIVAL MEDIAN EXPRESSED IN MONTHS

NIH Consensus Criteria classification

Type	Number of cases	Lethal outcome		Overall survival median in months
		Yes	No	
Very low risk	3 (4.8%)	0 (0%)	3 (4.8%)	36
Low risk	22 (34.9%)	3 (4.8%)	19 (30.2%)	95
Intermediate risk	17 (27.0%)	2 (3.2%)	15 (23.8%)	94
High risk	21 (33.3%)	9 (14.3%)	12 (19.0%)	29

TABLE 5
PROBABILITY OF LETHAL OUTCOME

			Lethal outcome
Kendall tau b test	Amin's classification	r	0.281
		P	0.019
		N	63
	Newman's classification	r	0.291
		P	0.015
		N	63
	NIH Consensus Criteria Classification	r	0.290
		P	0.014
		N	63

The average tumor size of all collected cases was 6.0 cm (median 5.0, min 0.9, max 25).

Detailed description of the tumors was given considering different tumors' characteristics (Table 1). According to the localization of the primary GISTs, patient were distributed into five groups. All the tumor specimens were immunohistochemically assessed and the expression of the CD 117, CD 34, vimentin, SMA, S-100, MAGE A1, MAGE A3/4 and NY ESO was determined. The results of the immunohistochemical staining was determined by usage of semiquatitative method.

In all GIST cases, histopathological examination defined number of mitoses, tumor size and morphology of the tumor cells. Considering two parameters (tumors size and number of mitoses) patients were first classified into three groups according to Amin's classification (Table 2).

Afterwards, all those GISTs were divided into three groups according to Newman's classification considering number of mitoses and tumor cell morphology (Table 3).

All the tumor cases were also classified considering number of mitoses and tumor size into four groups according to National Institute of Health Consensus Criteria (Table 4).

There was statistically significant positive correlation between grades of Amin's, Newman's and Fletcher's NIH classification and probability of patients' death. In other words, the higher group tumor belonged to (malignant tumors in Amin's and Newman's classification and intermediate and high risk tumors in Fletcher's classification) the probability of death as outcome was more likely (Table 5).

There was statistically significant positive correlation between classification groups within Amin's, Newman's and NIH Consensus Criteria classifications and overall survival. In other words, patients with benign or low risk tumors had statistically significantly longer overall survival then those with more aggressive forms of tumors (see Table 6).

Distribution of the GIST patients considering extension of disease and overall survival expressed in months was also shown (Table 7).

According to Kaplan-Meier analysis of survival, patients having metastases at the time of diagnosis lived statistically significantly shorter ($p<0.001$) (Figure 1)

There was statistically significant correlation between existence of metastases at the time of diagnosis and probability of lethal outcome ($r=0.541$; $p<0.001$).

Logistic binary regression considering influence of existence of metastases at the time of disease diagnosis on possibility of patients' death was done. The patient who had metastatic disease at the time of diagnosis had 16 times more chances to die then the patients who had no metastases at the time of disease diagnosis ($p<0.001$).

TABLE 6
OVERALL SURVIVAL OF THE PATIENTS CATEGORIZED ACCORDING TO THE THREE CLASSIFICATION SYSTEMS

		Overall survival (months)			Statistics	
		Median	25. P.	75. P.	Z	p (post hoc)
Amin's classification	Benign (A)	87	38	101	11,360	0.003
	Borderline (B)	120	68	140		A:B p=0.058
	Malignant (C)	29	15	68		A:C p=0.046
						B:C p=0.001
Newman's classification	Benign (A)	97	61	128	7,532	0.023
	Borderline (B)	68	30	93		A:B p=0.098
	Malignant (C)	29	18	100		A:C p=0.010
						B:C p=0.256
NIH risk	Very low (A)	36	12	91	9,275	0.026
	Low (B)	95	56	115		A:B p=0.112
	Intermediate (C)	94	39	135		A:C p=0.168
	High (D)	29	18	75		A:D p=0.965
						B:C p=0.681
						B:D p=0.013
						C:D p=0.019

TABLE 7
DISTRIBUTION OF THE GIST PATIENTS CONSIDERING EXTENSION OF DISEASE AND OVERALL SURVIVAL EXPRESSED IN MONTHS

Disease extension	Number of cases	Lethal outcome		Overall survival median in months
		Yes	No	
Without metastases	37 (77.08%)	5 (7.9%)	44 (69.8%)	92
Metastatic disease	11 (22.92%)	9 (14.3%)	5 (7.9%)	35

ROC curve showed sensitivity and specificity of test or sensitivity and specificity of metastases existence at the time of diagnosis on probability of lethal outcome (Figure 2).

Sensitivity of metastases existence at the time of diagnosis for predicting patient's death was 64.3% (95% IP 35.1–87.2), whereas specificity was 89.80% (95% IP 77.8–96.6).

When comparing three classifications (Amin's, Newman's and Fletcher's NIH classification system) and their influence on overall patients' survival no statisti-

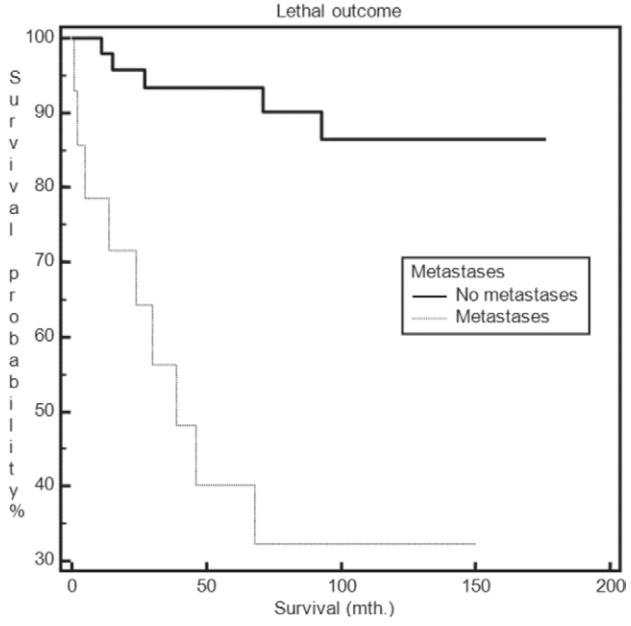

Fig. 1. Overall survival of patients with and without metastases at the time of GIST diagnosis. Kaplan Meier survival analysis.

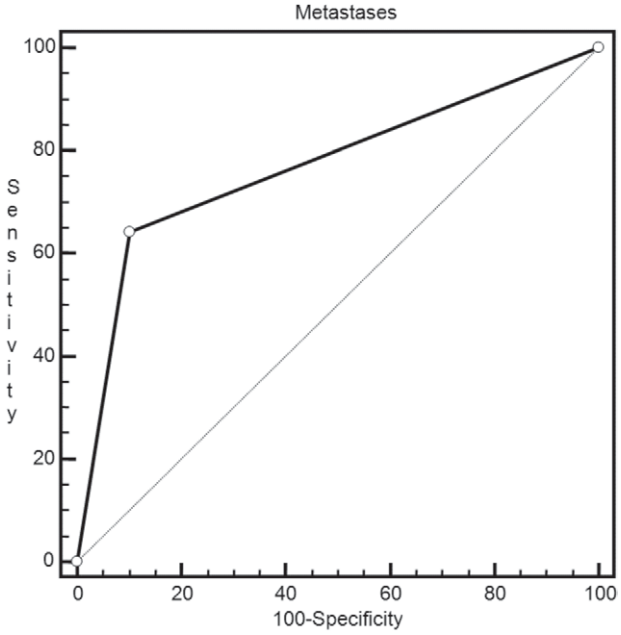

Fig. 2. Sensitivity and specificity of metastases existence at the time of GIST diagnosis in predicting lethal outcome.

cally significant difference between three groups was found (Figure 3, Table 8). So the primary hypothesis which considered Fletcher's NIH classification the most powerful in predicting prognosis of patients with GISTs is not sustainable.

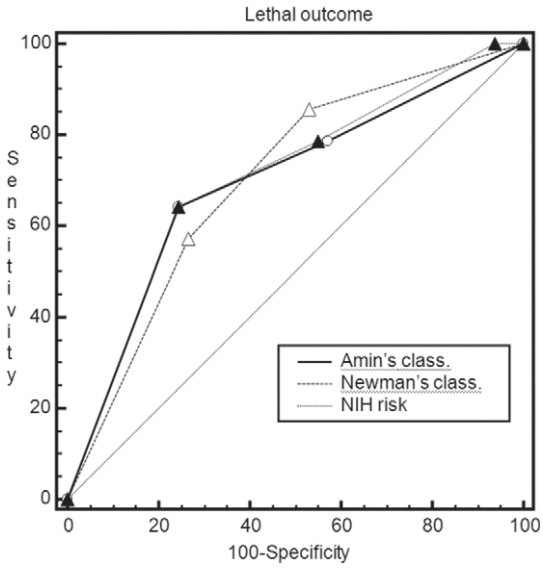

Fig. 3. Sensitivity and specificity of three classifications in predicting lethal outcome.

TABLE 8
COMPARISON BETWEEN AMIN'S CLASSIFICATION, NEWMAN'S CLASSIFICATION AND NIH RISK AUC (AREA UNDER CURVE)

Amin's classification ~ Newman's classification	
Difference between areas	0.007
Standard error	0.040
95% confidence interval	–0.071 do 0.085
z value	0.165
Statistical significance	p=0.869
Amin classification ~ NIH risk	
Difference between areas	0.010
Standard error	0.033
95% confidence interval	–0.054 do 0.074
z value	0.312
Statistical significance	p=0.755
Newman classification ~ NIH risk	
Difference between areas	0.004
Standard error	0.041
95% confidence interval	–0.076 do 0.083
z value	0.090
Statistic significance	p=0.929

Discussion and Conclusions

Considering gender distribution there was no statistically significant difference. Of altogether number of 63 patients, 49.2% (31/63) were men and 50.8% (32/63) were women. When reviewing world literature slightly more males are diagnosed with GISTs than females, although many reviews have reported no sex predilection what corresponds to finding of conducted study[46–49].

GISTs are most commonly diagnosed in the second half of the sixth and the first half of the seventh decades of life (ie, 55–65 y)[47,48]. Rarely GISTs are discovered in younger adults.

The average age of all patients in our study was 58.7 years, the average age of all male patients was 59,4 years and the average age of all female patients was 57.9 years, without statistically significant difference between genders (p=0.700). So our data are completely in concordance with literature findings.

The average overall survival of all patients in our study was 74.5 months, the average overall survival of female patients was 70.01 months and of male patients was 78.25 months. There was no statistically significant difference in overall survival between genders (p=0.551) what is in concordance with some references[48,49]. Literature review shows that in some studies male sex is in positive correlation with statistically significantly worse prognosis[50–54].

According to the literature, GISTs distribution is as follows: the most often they occur in stomach (50–60%), small intestine (20–30%)[30,31], large intestine and rectum (10%), in esophagus they occur rarely in 5% of cases and in 5% they are placed elsewhere in abdominal cavity. Sporadically omentum, mesenterium and retroperitoneum can be revealed as primary site of disease[18–28].

The most common localization of the GIST in our study was stomach (61.9%), followed by small (20.6%) and large intestine (11.1%), what is also observed in some other studies[46,48,49]. In many studies it was observed that non-gastric localization of the primary GISTs has had statistically significant negative influence on survival[48–53].

This study comprised altogether number of 63 GIST cases. When analyzing immunohistochemical characteristics, all of those cases were CD 117 and vimentin positive. SMA was positive in 61.9% (39/63) and negative in 38.1% (24/63), S-100 was positive in 38.1% (24/63) and negative in 61.9% (39/63), further 50/63 (79.4%) cases were CD 34 positive while 13/63 (20.6%) were CD 34 negative. In Cao's Study (2010) positive rate for the KIT protein (CD 117) in immunostaining was 94.5% (171/181), while that for CD34 was 86.2% (156/181). In 2003., Lin in his study found that CD117 was positive in 89% (81/91) tissue samples, there were also 72.8% (59/91) cases positive for CD34, 16% (13/91) positive for SMA and 14.8% (12/91) positive for S100[55]. In Perez's study CD 117 was positive in 71% (25/35), CD 34 in 54% (19/35) and S100 was positive in 37% (13/35)[56]. S100 positivity in Perez's study is comparable to our results.

The expression of CD 117 is important because targeted therapy such as imatinib mesylate, a KIT tyrosine kinase inhibitor, may play an important role in the treatment of GIST[48].

All three classification systems showed statistically significant positive correlation between grades of Amin's, Newman's and Fletcher's NIH classification and probability of patients' death. In patients whose tumors belonged to more aggressive groups (malignant tumors in Amin's and Newman's classification and intermediate and high risk tumors in Fletcher's classification) lethal outcome was more probable and when overall survival of patients belonging to different groups was compared, statistically significant difference was observed (overall survival of patients belonging to more aggressive groups was shorter).

In our study, we did not found statistically significant difference between three different classification systems (Amin's, Newman's and Fletcher's NIH classification system) in predicting prognosis and overall survival of the patients. None of those systems predicted poor prognosis better than the other.

In 2007 introduction of adjuvant imatinib mesylate in GISTs' therapy raised debate over the accuracy of NIH risk criteria. In univariate analysis, high or intermediate risk group, mitotic index>5/50 HPF, primary tumor size <5 cm, non-gastric primary localization, male sex, R1 resection, tumor rupture and epitheloid cell or mixed cell pathological subtype negatively influenced disease free survival[51]. Many authors found that NIH categorization is simple and effective to evaluate GIST behavior and prognosis[48,49].

Korean author Cho found that GIST classification based on original tumor location, size and mitosis is more efficient than the NIH criteria in predicting patients' survival, but the mechanism still needs to be clarified[52].

Probably some sort of modification of some of these systems could be helpful in predicting prognosis and deciding which tumors should be treated with adjuvant therapy.

Rutkowski and associates studied influence of a new modification of the NIH Consensus Criteria (the Jonescu risk criteria), NCCN-AFIP and several clinical and pathological factors, including tumor rupture on relapse free survival (RFS) in prospectively collected tumor registry series consisting of 640 CD 117 positive GIST cases. In univariate analyses, high Jonescu risk group, tumor mitotic count>5/50HPF, tumor size>5 cm, non-gastric localization, tumor rupture and male were independent poor prognostic factors. Jonescu criteria, which include four prognostic factors (tumor size, site, mitotic count and rupture), were found to be reliable tool for assessing prognosis of operable GISTs. Jonescu criteria can identify particularly well high risk patients who are likely to be proper candidates for adjuvant therapy[52].

In our study, metastases at the time of diagnosis were significantly positively correlated with death as patients' possible outcome. The similar finding had Bertin in 2007 who found that patients with metastases at laparotomy have significantly lower 5-year survival rate[55].

We conclude the following: when comparing three classifications (Amin's, Newman's and NIH) based on histological assessments of malignant behavior of GISTs, neither one classification is better in prediction of overall survival than the other.

We can also conclude that the most negative prognostic factor is the existence of metastases at the time of disease diagnosis.

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KLASIFIKACIJE GIST-OVA U PREDVIĐANJU AGRESIVNOG PONAŠANJA: ISKUSTVO JEDNE USTANOVE

S A Ž E T A K

Gastrointestinalni stromalni tumori (GIST-ovi) su najčešće mezenhimalne neoplazme probavnog sustava. Pri donošenju odluke o planu liječenja vrlo je važno dobro procijeniti agresivnost tumora. Tradicionalno, najbolji prognostički čimbenici su veličina tumora i broj mitoza. Cilj provedenog istraživanja bio je definirati koja klasifikacija GIST-ova (Aminova, Newmanova ili Fletcherova klasifikacija) je najznačajnija u predviđanju prognoze i ima najveći utjecaj na preživljenje. Provedeno istraživanje obuhvatilo je 63 bolesnika s GIST-om čiji su uzorci tumora bili evaluirani standardnim patohistološkim metodama i klasificirani na temelju histološke procjene malignosti u tri različita sustava. Provedena je usporedba spomenutih klasifikacijskih sustava i niti jedan se nije pokazao statistički značajno boljim u predviđanju duljine preživljenja i vjerojatnosti smrtnog ishoda. Zaključno, sve tri klasifikacije podjednako dobro predviđaju maligno ponašanje tumora. Najlošiji prognostički čimbenik je postojanje metastaza u trenutku postavljanja dijagnoze osnovne bolesti.