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Analysis of reliability of different risk classifications for assessment of relapses of gastrointestinal stromal tumors (GIST) — the impact of primary tumor genotyping

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ABSTRACT

Background. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Radical surgery is the primary treatment for GIST. Unfortunately, 40–50% of patients relapse, mainly due to hepatic and peritoneal metastases. Currently, the treatment of choice for locally advanced, inoperable or metastatic GIST is the use of tyrosine kinase inhibitors, including imatinib. GISTs are a group of tumors with various morphological, pathological and molecular features as well as different clinical courses, therefore their biological course is difficult to determine. Nevertheless, we currently have 5 classifications that assess the risk of relapse after surgery. The aim of this study was to analyze prognostic factors with regard to the risk of recurrence and overall survival, and to compare the clinical reliability of the recurrence risk classifications developed so far with an attempt to present a new classification including the genotype of primary GIST.

Patients and methods. The material consisted of a group of 697 patients with primary GIST treated with the intention to cure, collected prospectively as part of the GIST clinical registry, Department of Melanoma and Soft Tissue and Bone Sarcomas, Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw. All patients were classified based on 5 existing recurrence risk classifications. Univariate and multivariate analysis were performed for disease-free survival (DFS) and overall survival (OS). The relationships of the following factors with DFS and OS were assessed: sex, age, primary tumor mutational status, primary tumor location, primary tumor size, number of mitoses/50 HPF, surgical margins and the presence of tumor rupture. The next analysis concerned the comparison of the accuracy of existing recurrence risk classifications. The analysis was performed using ROC curves and a new classification model was proposed including mutation analysis as well as factors such as gender and age for selected existing recurrence risk assessment models.

Results. Univariate and multivariate analyses showed statistical significance of variables such as male sex ($P = 0.02$), mitotic index 5–10/50 HPF and > 10/50 HPF ($P < 0.001$), primary tumor size 5–10 cm and > 10 cm ($P < 0.001$), primary tumor location outside of the stomach ($P < 0.001$), R1 surgery ($P < 0.001$), tumor rupture ($P < 0.001$), and the presence of mutations in the *KIT* gene exon 11 including deletion 557–558 and the *KIT* gene exon 9 ($P = 0.009$) as negative prognostic factors affecting disease recurrence. Five-year disease-free survival rate was 57.3%. Median DFS was 76 months. Negative prognostic factors for OS are: age < 40 ($P = 0.045$), mitotic index 5–10/50 and > 10/50 HPF ($P < 0.001$), primary tumor size 5–10 cm and > 10 cm ($P < 0.001$), R1 surgery and tumor rupture ($P < 0.001$). All existing recurrence risk classifications showed prognostic value for assessing differences in DFS and OS, no significant differences were found between individual recurrence risk classifications. In addition, the reliability of all these classifications was improved by adding gender, age and mutation status. The value added of mutation status for better risk assessment was most significant when used in intermediate risk groups according to different classifications ($P < 0.01$).

Conclusion. All current GIST recurrence risk classifications allow for reliable assessment of recurrence risk. Mutations involving deletions (557–558) in the *KIT* gene exon 11 are most often present in the group at high risk of recurrence. Patients with confirmed mutations in the *PDGFRA* gene exon 18 and wild-type genotype have a favorable prognostic effect. The reliability of existing classifications for assessing the risk of relapse after GIST resection can be improved by adding mutation status, especially in groups at intermediate risk of relapse, which should facilitate therapeutic decisions in the context of adjuvant therapy.

Key words: GIST, risk classification, genotyping

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. These neoplasms most commonly occur in the stomach (40–70%), the small intestine (20–40%) much less frequently in the large intestine (5–15%), and rarely (> 5%) in the esophagus and intraperitoneally [1–3]. The majority of GIST is characterized by the occurrence of a mutation activating the *KIT* protooncogene (about 70–80%), and the *PDGFRA* gene that is the platelet-derived growth factor receptor alpha (approximately 5–15%). The remaining GIST (approximately 15%) is the so-called wild type (WT), in which no mutations are found in the *KIT* or *PDGFRA* genes. A characteristic immunochemical marker for GIST is CD117 and a positive reaction indicating the presence of this antigen occurs in about 95% cases, which is the most important criterium in differential diagnosis [2, 4, 5].

At this moment we do not have reliable and clear data which would answer the question about the frequency of occurrence and incidence for these tumors, but clinically significant cases are calculated at 3–4 per million inhabitants per year [6–11].

The basic method of treating GIST is radical resection based on removing the tumor within the borders of healthy tissues. Radical surgery allows for 5-year survivals without relapse in 35–65% patients [12–16]. Unfortunately, in 40–50% patients after potentially therapeutic resection a relapse occurs, mainly in the form of metastases to the liver and peritoneum [5, 17].

Because of relapses in such a large group of patients and the therapeutic success of the low molecular weight tyrosine kinase inhibitor (IKT) imatinib monosulphate in the therapy of locally non-resectable and/or metastatic GIST [18–23], adjuvant therapy with imatinib was introduced to clinical practice in order to reduce disease recurrence/improve patient cures [19, 24–28]. These analyses also indicated that the effect of adjuvant treatment is associated with the tumor genotype and the effectiveness of longer adjuvant treatment with imatinib was most clearly seen in the group of GIST patients with deletion or insertion/deletion in exon 11 of *KIT*. Of course, it remains to be discussed whether imatinib should be used in GIST patients with an intermediate recurrence risk and also which of the existing recurrence risk classifications should be used, as well as whether adjuvant therapy should be used for GIST with genotypes with low susceptibility to imatinib [26–28].

GIST is a group of tumors with diverse morphological and pathological characteristics and varied clinical course [2]. Their biological course is difficult to define and as is known from analyses conducted so far it depends on several basic criteria: the size and localization of the primary tumor and the mitotic index [29]. A consensus elaborated by the NIH (National Institutes of Health) in the United States in 2001, presented for the first time a practical scheme for evaluating the risk of a clinical course taking into consideration the size of the primary tumor and the mitotic index of GIST (Table 1) [13, 30].

The next classification evaluating recurrence risk and the tightly associated prognosis for the patients is the classification based on the location of the primary tumor proposed by Miettinen and Lasota from AFIP (Armed Forces Institute of Pathology). They proved by analyzing about 1600 GIST cases that large (> 10 cm) neoplasms in the stomach with a low mitotic index have only a 12% recurrence risk whereas for GIST located in the small intestine for similar parameters the recurrence risk increases to > 50% [31, 32].

A successive additional negative prognostic factor of GIST recurrence risk after resection is perforation of the primary tumor (regardless of whether it is spontaneous or a result of surgery). This idea became the basis for the next classification proposed by Joensuu who modified the NIH classification including the neoplasm location (stomach *vs*. other) and tumor perforation as a prognostic factor independent of size and mitotic index. Patients with tumor perforation have a high recurrence risk due to the possibility of formation of intraperitoneal implantation during perforation [33].

One of the last classifications proposed by AJCC (American Joint Committee on Cancer) based to a large extent on the classification of Miettinen and Lasota was presented in January 2010 and the current TNM system

Table 1. Factors taken into consideration in the classification of recurrence risk plus a model with added mutation evaluation

Characteristic	National Institutes of Health (NIH)	Miettinen and Lasota (AFIP-NCCN)	NIH according to Joensuu	TNM (according to AJCC 2010 and 2017)	Nomogram according to Gold	Model with mutation evaluated in this work
Tumor size	X	X	X	X	X	X
Mitotic number	X	X	X	X	X	X
Tumor location		X	X	X	X	X
Tumor rupture			X			X
Presence of metastases characteristics N and M				X		
Probable progression — ree survival 2 and 5 years in %					X	
Addition of mutation						X

was created especially for GIST. This classification divides the localization of the primary tumor into those derived from the stomach and others [34, 35].

A nomogram presented at the end of 2009 by Gold et al. is the next classification evaluating recurrence risk taking into consideration the mitotic index, the size of the primary tumor and localization. On the basis of the number of points it evaluates and expresses in percent the probable survival time (2 and 5 years) without GIST recurrence. The nomogram is suggested to better evaluate the recurrence risk in comparison with the NIH classification and is similar to the classification proposed by AFIP Mettienen and Lasota and as the earlier systems can be used to qualify patients and to make decision on adjuvant treatment [36]. However, it does not take possible tumor perforation into consideration and takes tumor size as a continuous variable.

Molecular analysis of GIST detected the presence of two mutually exclusive mutations in the *KIT* and *PDGFRA* genes. These mutations cause excessive expression and activation of the *KIT* and *PDGFRA* protooncogenes. GIST mutations are commonly observed in the *KIT* gene (80–90%) and most of them occur in exon 11 and less frequently in exon 9 and sporadically in exons 13 and 17. A mutation in the *PDGFRA* gene is less common and is found in about 5 to 10% GIST and most often is in exon 18 and less frequently exon 12. In about 10–15% GIST no mutations in these two genes are observed, they are WT (wild type) [37–40]. Analyses performed so far indicate that the presence of mutations in the *KIT* or *PDGFRA* genes is important for predicting responses to imatinib treatment, moreover the data show that a significant role is also played by a mutation in a defined exon. Patients with mutations in exon 11 of *KIT* respond better to imatinib treatment while patients with mutations in exon 9 are more often resistant to therapy with this drug. The results of analyses confirm the idea of using a dose of 800 mg/day in patients with mutations in exon 9 of *KIT* [41–43].

It seems that determining the type of mutation may also be of prognostic significance in primary GIST, though at present we do not have data which would allow unequivocal confirmation of this idea. Difficulties in showing such relations are due to GIST pathogenesis as *KIT* mutations are a very early stage in the formation of these neoplasms and cannot be an independent factor determining an aggressive course of GIST. Several investigations have confirmed the association between some *KIT* mutations and a more aggressive course. However other analyses confirmed that these mutations also occur in very small GIST with a clinically benign course [44–46]. The results of analyses performed so far suggest further investigations are required in order to evaluate the prognostic significance of *KIT* mutations in larger patient groups [47]. There are also suggestions that the *PDGFRA* mutation in the primary tumor occurs almost exclusively in GIST originating in the stomach and is characterized by a more indolent course of the disease [48].

The most important problem after treatment of primary GIST is to determine significant and independent prognostic factors. This statement is important as at present we know about at least several clinical and/or molecular parameters which can affect the prognosis and treatment of GIST patients.

We currently have 5 systems of evaluating the recurrence risk for GIST after resection (Table 1), none of the proposed systems encompasses the mutation status as one of the factors which could affect recurrence risk. An attempt to include the mutation status was made during

the creation of the TNM AJCC system, but it was finally not included because of the small amount of data [34].

Determining which of the present systems which are used for evaluating risk on the basis of prognostic factors is the best for foreseeing recurrence risk so that it can be used in clinical practice and whether and if so what would be the significance of including the status of the mutation in primary GIST is the subject of this paper (Table 1).

Material and methods

The analysis was performed for a group of 697 patients with primary GIST treated with the intention to cure (R0/R1 resection), collected prospectively in the Department of Melanoma and Soft Tissue and Bone Sarcomas, Maria Skłodowska-Curie National Research Institute of Oncology from 2001. The analyzed group consisted of 375 (53.8%) women and 322 (46.2%) men, treated by radical resection in the years 2001–2011. Data about the patients and their treatment were obtained on the basis of the analysis of the patients' medical records and data concerning their survival from the National Neoplasm Registry. The analyzed group encompassed only patients after surgical resection of primary GIST without metastases at the moment of diagnosis and with a confirmed histopathological analysis. All patients in the analyzed group underwent radical (macroscopically) resection and did not receive adjuvant treatment. After resection of the primary GIST the patients were subjected to careful medical observation during which a physical examination and computer tomography of the abdominal cavity and pelvis were performed according to recommendations for GIST patients with a high and intermediate recurrence risk, every 3–4 months for the first 2 years after resection of the primary GIST, and subsequently every 6 months until 5 years after the original resection and after 5 years once a year in the case of resection of a GIST with a low degree of aggressiveness [48]. In 291 cases mutations in *KIT* and *PDGRFA* genes were analyzed. The material for molecular analysis was taken from paraffin blocks and/or freshly frozen tumor tissue. Molecular analysis was performed for exons 9, 11, 13, 14 and 17 of the *KIT* gene and exons 12 and 18 of the *PDGFRA* gene.

All patients were classified based on 5 existing recurrence risk classifications. Detailed clinical, pathological and molecular data are presented in Table 2.

Statistical analysis

The analyzed patients were observed from 2001 (date associated with the creation of the Clinical GIST Registry) until August 2013. The final date of the surgery of the patients included in the analysis was December 2010. The frequency of recurrence was evaluated on the basis of computer tomography during the period of observation. Disease-free survival (DFS) was calculated from the date of GIST resection to the date of local recurrence, date of distant metastases or date of the last observation. Overall survival (OS) was calculated from the resection to the date of the last observation or the date of death.

Univariate analysis was performed overall survival and for disease-free survival using Kaplan-Meier and the log-rank test (univariate analyses). Survival of the patients was expressed in the form of probability of death during 5 years from the operation (with a 95% confidence interval) and graphically on figures showing survival curves. In order to identify independent variables affecting the patients' survival a multivariate Cox model was used. Significant variables were selected by a progressive stepwise approach. The results are presented as a hazard ratio (HR) with a 95% confidence interval. In the next step of the analysis using methods of logistic regression, a model was constructed in which probability of disease-free survival and overall survival was estimated for 1 and 5 years. We checked whether taking the mutation code into consideration significantly improved the predictive abilities of the model. To models selected *a priori* variables signifying the mutation code were added and then ROC curves were constructed and then ROC curves constructed on the basis of values calculated from the models were compared. The same method was used to compare different classifications.

The calculations were performed using the software package R 3.0.1 (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/), the survival package (Therneau T (2013). _A Package for Survival Analysis in S_. R package version 2.37-4, URL: http://CRAN.R-project.org/package=survival) and pROC (Xavier Robin, Natacha Turck, Alexandre Hainard, Natalia Tiberti, Frédérique Lisacek, Jean-Charles Sanchez and Markus Müller (2011). pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics, 12, p. 77. DOI: 10.1186/1471-2105-12-77 URL: http://www.biomedcentral.com/1471-2105/12/77/).

Results

Univariate analysis

Progression-free survival

The basic evaluated parameter was disease-free survival (DFS). During the observations, 265 (38.3%) recurrences were observed. Median disease-free survival

Table 2. Characteristics of the analyzed patients

Characteristic		Number (%)
Sex	Women	375 (53.8%)
	Men	322 (46.2%)
Age at diagnosis (years)	< 40	62 (8.9%)
	41–65	422 (60.6%)
	> 65	213 (30.5%)
Localization	Stomach	373 (53.5%)
	Duodenum	36 (5.2%)
	Small intestine	237 (34.0%)
	Large intestine/rectum	25 (3.6%)
	Other	26 (3.7%)
Size of primary tumor [cm]	< 5	266 (39.1%)
	> 5–10	254 (37.4%)
	> 10	160 (23.5%)
	No data	17 (2.4%)
Number of mitoses in 50 visual fields at large magnification	≤ 5	401 (63%)
	> 5–10	98 (15.4%)
	> 10	138 (21.7%)
	No data	60 (8.6%)
Surgical margins	R0	554 (80.4%)
	R1	135 (19.5%)
	No data	8 (1.1%)
Tumor rupture	No	596 (92.5%)
	Yes	48 (7.5%)
	No data	53 (7.6%)
Mutation analysis	*KIT* 11 deletion 557–558	65 (22.3%)
	KIT 11 point mutation or insertion	63 (21.6%)
	KIT 11 other deletions	45 (15.5%)
	KIT 9	23 (7.9%)
	PDGFRA 18 D842V	25 (8.6%)
	Other *PDGFRA* mutations	21 (7.2%)
	Other *KIT* mutations	11 (3.8%)
	Wild type (WT) — no *KIT* or *PDGFRA* mutations	38 (13.1%)
	No data	406 (58.2%)
Recurrence risk according to NIH (National Institutes of Health Classification)	Very low	32 (4.9%)
	Low	171 (26.1%)
	Intermediate	150 (22.9%)
	High	303 (46.1%)
	No data	41 (5.9%)

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Table 2 cont. Characteristics of the analyzed patients

Characteristic		Number (%)
Recurrence risk according to Joensuu	Very low	49 (7.4%)
	Low	162 (24.4%)
	Intermediate	98 (14.8%)
	High	355 (53.5%)
	No data	33 (4.7%)
Recurrence risk according to Miettinen and Lasota (AFIP-NCCN)	Very low	153 (23.9%)
	Low	135 (21.1%)
	Intermediate	105 (16.4%)
	High	246 (38.5%)
	No data	58 (8.3%)
Recurrence risk according to AJCC	Tumor stage I	281 (40.3%)
	Tumor stage II	115 (16.5%)
	Tumor stage IIIA	79 (11.3%)
	Tumor stage IIIB	160 (23.0%)
	No data	62 (8.9%)
Recurrence risk within 2 years according to Gold's nomogram	[1,25)	148 (21.2%)
	[26,50)	56 (8.0%)
	[51,75)	72 (10.3%)
	[76,98]	324 (46.5%)
	No data	97 (13.9%)
Recurrence risk within 5 years according to Gold's nomogram	[1,8)	160 (23.0%)
	[9,68)	149 (21.4%)
	[69,91)	179 (25.7%)
	[92,96]	112 (16.1%)
	No data	97 (13.9%)

was 76 months. In Table 3 univariate analysis for particular variables which could affect disease recurrence is presented. The variables for which statistical significance was demonstrated were: male sex ($P = 0.02$), mitotic index 5–10/50 HPF and > 10/50 HPF ($P < 0.001$), size 5–10 cm and > 10 cm ($P < 0.001$), localization outside the stomach ($P < 0.001$), extent of surgery R1 ($P < 0.001$), tumor rupture $P < 0.001$), and presence of a mutation in the *KIT* gene in exon 11 encompassing the 557–558 deletion an in the *KIT* gene in exon 9 ($P = 0.009$).

Overall survival

The next parameter evaluated during the analysis was overall survival (OS) estimated by the Kaplan-Meier method. 118 (17.2%) of the patients died and the OS median was not attained.

Based on univariate analysis, the following factors were found to have a negative effect on OS: the number of mitoses > 10/HPF ($P < 0.001$), size of the primary tumor > 10 cm ($P < 0.001$), surgical margins R1 ($P = 0.004$), tumor rupture ($P < 0.001$) and age < 40 ($P = 0.045$). Detailed results for individual variables are presented in Table 4.

Multivariate analyses

In order to identify independent variables affecting progression-free survival and overall survival of the patients, Cox's multiparameter model was used. Significant variables were selected by the progressive stepwise approach. 2 models were constructed: the first one for variables without adding the mutations and the second

Table 3. Results of univariate analysis for disease-free survival (DFS)

Characteristic		Number of cases	5 year survival	95% confidence interval	p
Sex	Women	372	59.7	(53.7–66.5)	0.024
	Men	320	54.2	(48.1–61.1)	
Age (years)	< 40	61	56.6	(44.0–72.8)	0.389
	41–65	421	55.9	(50.4–62.0)	
	> 65	210	60.3	(52.4–69.5)	
Localization	Stomach	370	74.5	(69.3 - 80.2)	< 0.001
	Duodenum	36	48.5	(31.8–73.9)	
	Small intestine	236	41.7	(35.0–49.6)	
	Large intestine/rectum	24	45.8	(28.1–74.7)	
	Other	26	17.4	(5.5–55.0)	
Size of primary tumor [cm]	< 5	263	86.2	(79.8–93.1)	< 0.001
	> 5–10	253	55.2	(48.5–62.7)	
	> 10	169	27.8	(21.1–36.5)	
	No data	17	41.8	(22.8–76.6)	
Number of mitoses in 50 visual fields (mitotic index, MI)	≤ 5	398	80.2	(75.3–85.4)	< 0.001
	> 5–10	98	44.5	(33.8–58.5)	
	> 10	138	16.8	(10.8–26.0)	
	No data	58	46.4	(33.8–63.8)	
Surgical margins (R0, R1)	R0	551	63.2	(58.4–68.4)	< 0.001
	R1	133	34.7	(26.3–45.7)	
	No data	8	55.6	(23.1–100.0)	
Tumor rupture	No	592	60.9	(56.3–65.9)	< 0.001
	Yes	48	24.3	(13.8–43.0)	
	No data	52	45.3	(26.4–78.0)	
Mutation evaluation	*KIT* 11 deletion 557–558	65	35.1	(23.8–51.8)	0.009
	KIT 11 PM/INS	63	59.2	(46.5–75.4)	
	KIT 11 other deletions	45	50.4	(35.5–71.6)	
	KIT 9	23	38.5	(21.2–69.9)	
	PDGFRA 18 D842V	25	83.6	(68.2–100.0)	
	Other mutations of the *PDGFRA* gene	21	87.8	(73.4–100.0)	
	Other mutations of the *KIT* gene	10	50.6	(24.6–100.0)	
	Wild type (WT)	38	44.3	(29.5–66.6)	
	No data	402	61.2	(55.4–67.6)	
Recurrence risk evaluation according to NIH (National Institutes of Health Classification)	High	302	30.8	(25.5–37.2)	< 0.001
	Intermediate	150	79.3	(71.5–88.0)	
	Low	169	94.7	(88.9–100.0)	
	Very low	31	100	(100.0–100.)	
	No data	40	55.7	(40.0–77.5)	

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Table 3 cont. Results of univariate analysis for disease-free survival (DFS)

Characteristic		Number of cases	5 year survival	95% confidence interval	p
Recurrence risk evaluation according to Joensuu	High	354	34.2	(29.1–40.3)	< 0.001
	Intermediate	98	90.2	(83.9–96.9)	
	Low	207	94.1	(88.9–99.7)	
	No data	33	68.2	(52.7–88.3)	
Recurrence risk evaluation according to Miettinen and Lasota (AFIP-NCCN)	High	254	25.6	(20.1 – 32.6)	< 0.001
	Intermediate	105	66.9	(57.0–78.5)	
	Low	133	89.7	(83.0–96.8)	
	Very low	151	95.4	(91.0–99.9)	
	No data	58	48.4	(35.3–66.5)	
Recurrence risk evaluation according to AJCC	Tumor stage I	277	93.8	(89.8–97.9)	< 0.001
	Tumor stage II	115	68.7	(59.2–79.7)	
	Tumor stage IIIA	79	34.4	(24.2–48.9)	
	Tumor stage IIIB	160	20.4	(14.5–28.8)	
	No data	61	45.4	(33.1–62.3)	
Recurrence risk evaluation within 2 years according to Gold's nomogram	(1,28)	155	22.7	(16.5–31.3)	< 0.001
	(28,83)	154	58.1	(49.4–69.4)	
	(83,96)	169	85.5	(78.8–92.8)	
	(96,98)	119	96.9	(92.7–100.0)	
	No data	95	39.4	(29.4–52.9)	
Recurrence risk evaluation within 5 years according to Gold's nomogram	(1,8)	155	22.7	(16.5–31.3)	< 0.001
	(8,68)	153	58	(49.2–68.2)	
	(68,91)	147	83.3	(75.7–91.7)	
	(91,96)	142	97.4	(93.9–100.0)	
	No data	95	39.4	(29.4–52.9)	

one with the mutations added. Risk classification was not taken into consideration in multivariate analyses as they link individually analyzed parameters.

The factors with a negative effect on the probability of disease recurrence in the Cox regression analysis were: the mitotic index > 5/50 HPF, localization of the primary tumor outside the stomach, the size of the primary tumor > 5 cm and the male sex (Table 5).

In the model taking the GIST genotype into consideration the negative factors were the presence of a mutation other than in *PDGFRA*, the mitotic index > 5/50 HPF, male sex and the size of the primary tumor > 5 cm (Table 6). Similar results were obtained for the evaluation of factors affecting OS (Table 7).

Comparison of the accuracy of classification of GIST recurrence risk

The comparison of the existing recurrence risk classifications was performed using ROC curves. They were compared in the context of 5-year DFS and also 5-year OS. None of the statistically significant differences were found between individual classifications both for 5-year DFS and for 5-year OS.

The comparison of the prognostic value of recurrence risk for 5-year DFS is presented in Figures 1–3.

All analyses indicate a lack of statistically significant differences between individual risk classifications, the graphs are nearly identical. This is due to the fact that

Table 4. Results of univariate analysis for overall survival (OS)

Characteristic		Number of cases	5 year survival	95% confidence interval	p
Sex	Women	369	87.3	(83.0–91.8)	0.141
	Men	318	83.7	(78.8–88.9)	
Age	< 40	61	88.3	(79.9–97.6)	0.045
	41–65	417	86.8	(82.9–91.0)	
	> 65	209	81.5	(74.5–89.0)	
Localization	Stomach	367	89.1	(84.9–93.4)	0.06
	Duodenum	36	81.2	(67.2–98.2)	
	Small intestine	234	84.1	(78.7–89.9)	
	Large intestine/rectum	24	79.9	(64.0–99.7)	
	Other	26	74.3	(56.8–97.0)	
Size of primary tumor	< 5	261	99.5	(98.5–100.0)	< 0.001
	> 5–10	252	82.9	(77.4–88.7)	
	> 10	157	75.6	(68.5–83.5)	
	No data	17	84.6	(67.1–100.0)	
Number of mitoses in 50 visual fields (mitotic index MI/HPF)	≤ 5	395	92.8	(83.3–96.4)	< 0.001
	> 5–10	98	87.2	(79.5–95.7)	
	> 10	136	68.8	(60.5–78.3)	
	No data	58	85.1	(75.5–96.0)	
Surgical margins (R0, R1)	R0	545	89.3	(86.0–92.7)	0.004
	R1	134	72.1	(63.6–81.8)	
	No data	8	100	(100.0–100.0)	
Tumor rupture	No	588	86.6	(83.2–90.2)	0.005
	Yes	48	81.4	(69.6–95.2)	
	No data	51	76.9	(62.1–95.2)	
Mutation evaluation	*KIT* 11 deletion 557–558	65	81.8	(70.0–94.3)	0.75
	KIT 11 PM/INS	62	87	(77.7–97.5)	
	KIT 11 other deletions	45	86.6	(75.1–99.9)	
	KIT 9	23	87.7	(73.0–100.0)	
	PDGFRA 18 D842V	25	82	(65.1–100.0)	
	Other mutations of the *PDGFRA* gene	21	87.4	(72.4–100.0)	
	Other mutations of the *KIT* gene	10	87.5	(67.3–100.0)	
	Wild type (WT)	37	66.4	(51.3–86.0)	
	No data	399	88.5	(84.5–92.6)	

→

Table 4 cont. Results of univariate analysis for overall survival (OS)

Characteristic		Number of cases	5 year survival	95% confidence interval	p
Recurrence risk evaluation according to NIH (National Institute of Health Classification)	High	299	75.7	(70.4–81.4)	< 0.001
	Intermediate	150	97.5	(94.0–100.0)	
	Low	166	100	(100.0–100.0)	
	Very low	32	100	(100.0–100.0)	
	No data	40	82	(68.6–97.9)	
Recurrence risk evaluation according to Joensuu	High	351	78.4	(73.6–83.5)	< 0.001
	Intermediate	98	98.6	(96.0–100.0)	
	Low	205	99.2	(97.5–100.0)	
	No data	33	84	(70.5–99.9)	
Recurrence risk evaluation according to Miettinen and Lasota (AFIP-NCCN)	High	243	76.5	(70.6–82.9)	< 0.001
	Intermediate	104	89.5	(82.7–96.9)	
	Low	133	98.9	(96.9–100.0)	
	Very low	149	96	(91.4–100.0)	
	No data	58	78.9	(70.5–99.9)	
Recurrence risk evaluation according to AJCC	Tumor stage I	275	98.9	(97.3–100.0)	< 0.001
	Tumor stage II	114	91	(84.7–97.8)	
	Tumor stage IIIA	78	75.9	(65.8–87.6)	
	Tumor stage IIIB	159	73.5	(66.1–81.8)	
	No data	61	83	(72.8–94.6)	
Recurrence risk evaluation within 2 years according to Gold's nomogram	[1,28)	154	75.2	(67.9–83.4)	< 0.001
	[28,83)	153	85.9	(79.5–92.8)	
	[83,96)	167	95	(90.7–99.6)	
	[96,98]	118	100	(100.0–100.0)	
	No data	95	80.4	(71.6–90.3)	
Recurrence risk evaluation within 5 years according to Gold's nomogram	[1,8)	154	75.2	(67.9–83.4)	< 0.001
	[8,68)	152	85.9	(79.4–92.8)	
	[68,91)	145	94.4	(89.4–99.6)	
	[91,96]	141	100	(100.0–100.0)	
	No data	95	80.4	(71.6–90.3)	

all classifications include the most significant prognostic factors.

New classification model including mutation analysis for progression-free survival

In the next step of the analysis using logistic regression, a model was constructed in which probability of survival for 1 and 5 years was calculated. The effect of including the mutation code on the predictive value of the model was tested. Variables marking the mutation code were added to models selected *a priori*, and then ROC curves were prepared on the basis of predicted values calculated from the models. The analysis indicated that adding variables such as sex, age and mutation status to the existing classifications improved their reliability.

Table 5. Results of multivariate analysis of factors affecting DFS

Characteristic		HR	95% CI	P
Sex	Women	1		
	Men	1.3	(0.99–1.71)	0.6
Age	< 40	1		
	41–65	1.21	(0.76–1.95)	0.42
	> 65	1.13	(0.68–1.88)	0.64
Localization	Duodenum	1		
	Small intestine	0.79	(0.45–1.4)	0.43
	Large intestine/rectum	0.97	(0.42–2.23)	0.94
	Stomach	0.5	(0.28–0.88)	0.02
	Other	1.09	(0.51–2.34)	0.83
Tumor size	< 5	1		
	> 5–10	3.36	(2.09–5.4)	0
	> 10	6.25	(3.84–10.18)	0
Number of mitoses in 50 visual fields (mitotic index MI/HPF)	≤ 5	1		
	> 5–10	2.86	(1.95–4.19)	0
	> 10	5.08	3.67–7.01)	0

Table 6. The results of multiparameter analysis of factors affecting DFS including the type of mutation

Characteristic		HR	95% CI	P
Sex	Women	1		
	Men	1.62	(1.07–2.46)	0.02
Age	< 40	1		
	41–65	1.67	(0.89–3.15)	0.11
	> 65	1.46	(0.71–3.02)	0.31
Localization	Duodenum	1		
	Small intestine	0.98	(0.29–3.34)	0.98
	Large intestine/rectum	1.26	(0.31–5.03)	0.75
	Stomach	0.93	(0.27–3.15)	0.9
	Other	1.24	(0.3–5.13)	0.76
Tumor size	< 5	1		
	> 5–10	2.12	(1.08–4.18)	0.03
	> 10	5.86	(2.84–12.07)	0
Number of mitoses in 50 visual fields (mitotic index MI/HPF)	≤ 5	1		
	> 5–10	3.07	(1.69–5.58)	0
	> 10	4.38	(2.61–7.36)	0
Genotype (mutation evaluation)	*KIT* 11 deletion 557–558	1		
	KIT 11 PM/INS	1.03	(0.58–1.81)	0.92
	KIT 11 other deletions	1.13	(0.63–2.03)	0.69
	KIT 9	1.38	(0.68–2.77)	0.37
	PDGFRA 18 D842V	0.41	(1.14–1.23)	0.05
	Other mutations of the *PDGFRA* gene	0.61	(0.18–2.13)	0.44
	Other mutations of the *KIT* gene	0.76	(0.26–2.25)	0.63
	Wild type (WT)	1.66	(0.86–3.21)	0.13

Table 7. The results of the multiparameter analysis of factors affecting OS including the type of mutation

Characteristic		HR	95% CI	P
Age	< 40	1		
	41–65	2.84	(0.89–9.06)	0.08
	> 65	6.23	(1.83–21.26)	0
Tumor size	< 5	1		
	> 5–10	4.81	(1.1–20.95)	0.04
	> 10	7.31	(1.67–31.97)	0.01
Number of mitoses in 50 visual fields (mitotic index MI/HPF)	≤ 5	1		
	> 5–10	1.91	(0.79–4.62)	0.15
	> 10	3.2	(1.64–6.24)	0
Genotype (mutation evaluation)	*KIT* 11 deletion 557–558	1		
	KIT 11 PM/INS	0.89	(0.37–2.15)	0.79
	KIT 11 Other deletions	0.84	(0.34–2.09)	0.71
	KIT 9	1.12	(0.43–2.92)	0.82
	PDGFRA 18 D842V	2	(0.55–7.34)	0.3
	Other mutations of the *PDGFRA* gene	1.4	(0.3–6.64)	0.67
	Other mutations of the *KIT* gene	0.85	(0.11–6.7)	0.88
	Wild type (WT)	2.59	(1.13–5.96)	0.03

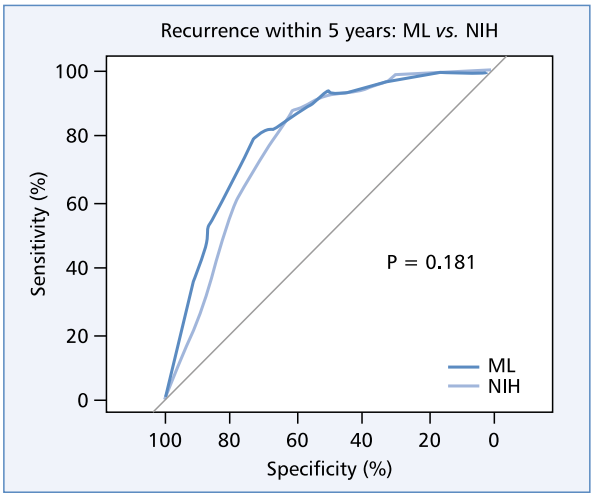

Figure 1. The prognostic value of the Miettinen and Lasota AFIP-NCCN (ML) classification in comparison to National Institutes of Health (NIH) in comparing recurrence risk within 5 years

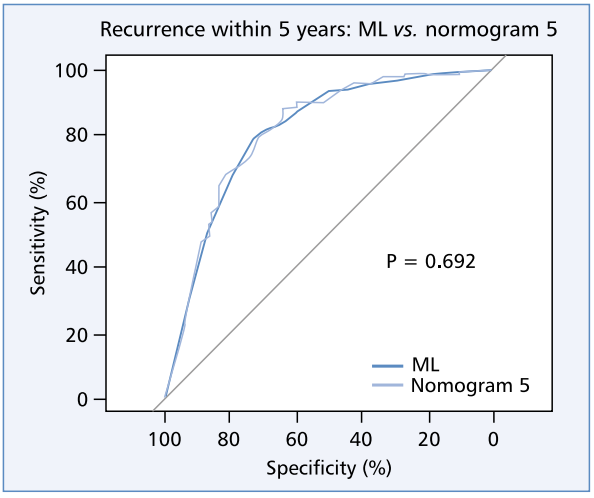

Figure 2. The prognostic value of the Miettinen and Lasota AFIP-NCCN (ML) classification in comparison to Nomogram 5 in comparing recurrence risk within 5 years

Moreover, the addition of the mutation status was the most significant in groups with intermediate risk in individual classifications (Figures 4–9).

In groups with intermediate risk a model taking into consideration sex, age and additionally the type of mutation is the closest to reality (Figures 7–9).

Discussion

The evaluation of recurrence risk after surgical treatment of GIST is very important in the context of adjuvant treatment and planning control examinations during observation after surgery [49]. The present clas-

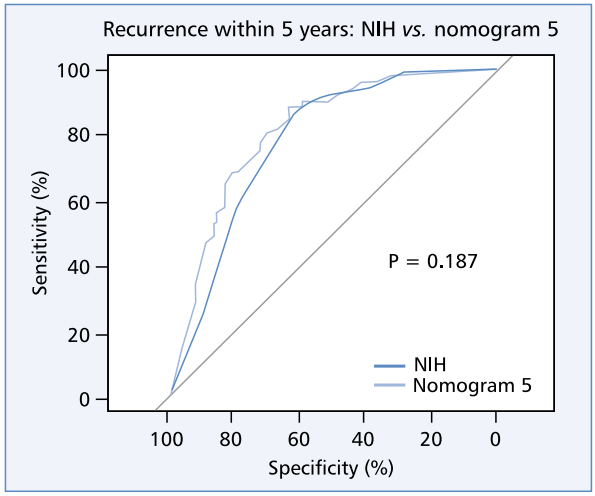

Figure 3. The prognostic value of the National Institutes of Health (NIH) classification in comparison to Nomogram 5 in comparing recurrence risk within 5 years

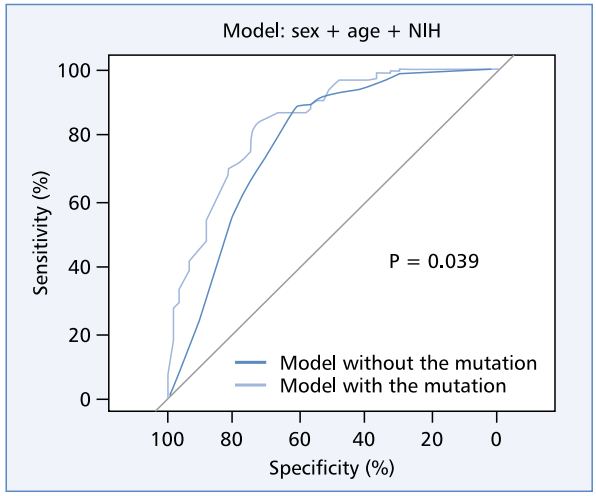

Figure 5. Model taking into consideration: sex, age and classification according to NIH

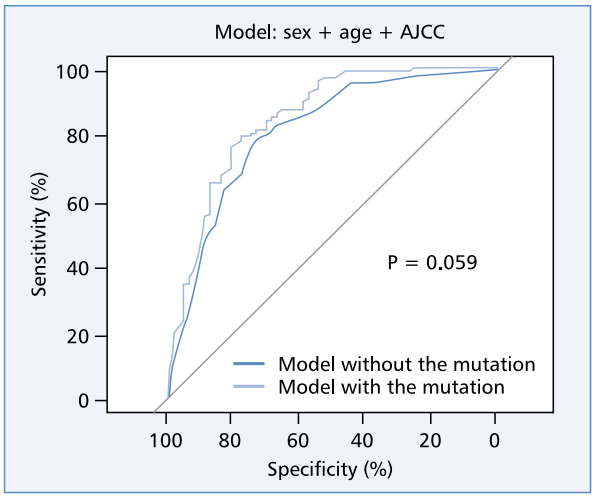

Figure 4. Model taking into consideration: sex, age and classification according to AJCC

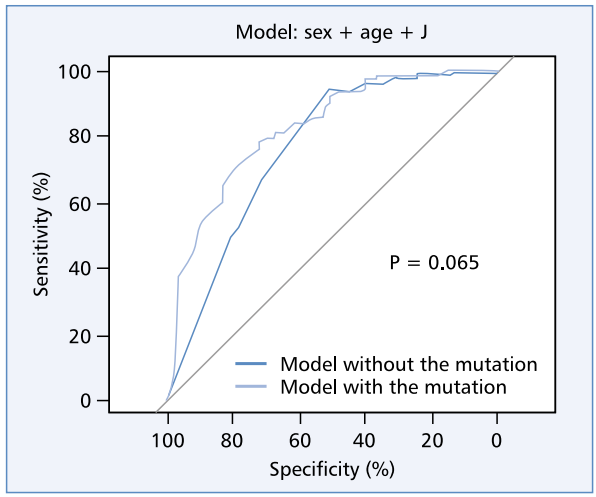

Figure 6. Model taking into consideration: sex, age and classification according to Joensuu (J)

sifications of recurrence risk based on such factors as tumor size, localization, mitotic index and tumor rupture allow reliable estimation of recurrence risk and are used in clinical practice [50, 51]. In recent years mutation status as a factor affecting recurrence risk has also been discussed [49, 51, 52].

In the presented group of patients, the basic evaluated parameter was disease-free survival DFS. During the observations, 265 (38.3%) of disease recurrences were observed. It should be stressed that the analyzed group consisted of patients not receiving imatinib adjuvant therapy after tumor resection, thus DFS represents the natural course of the disease. Median disease-free survival was 76 months. Other authors obtained similar results [17, 53, 54]. The following prognostic factors were found to be statistically significant in the present analysis: mitotic index 5–10/50 HPF and > 10/50 HPF ($P < 0.001$), size 5–10 cm and >10 cm ($P < 0.001$), MI > 5/50 HPF and tumor size > 5 cm are associated with a much shorter disease-free survival, which has also been demonstrated in all previous analyses [55–58]. The results of the analysis also confirm the effect of the tumor location for prognosis in GIST, which is in agreement with the results of other investigations [31, 32, 55–57, 59]. Localization of GIST outside the stomach (mainly in the intestine) gives a much worse prognosis than GIST localized in the stomach which has been reflected in the classification modified by Mietinnenn and Lasota [57, 59]. At present these factors are the basis of existing classifications, including the TNM staging

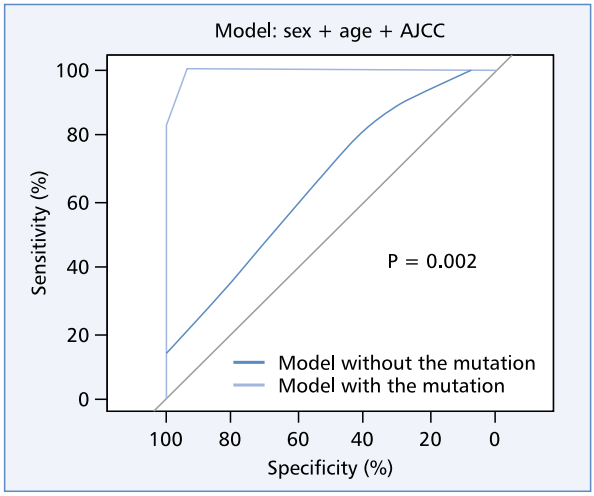

Figure 7. Model taking into consideration: sex, age and classification according to AJCC in an intermediate risk group

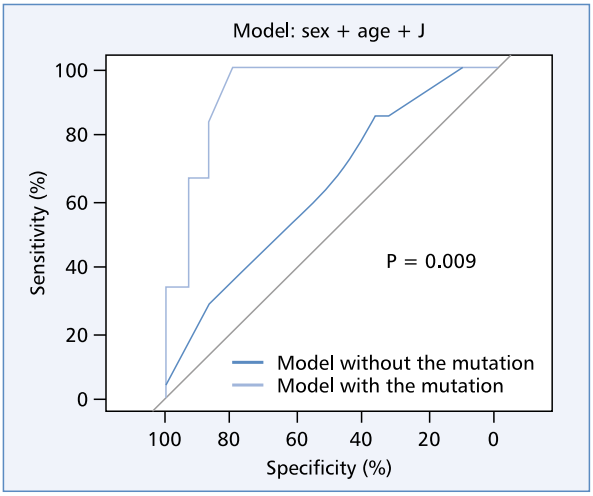

Figure 9. Model taking into consideration: sex, age and classification according to Joensuu (J) in an intermediate risk group

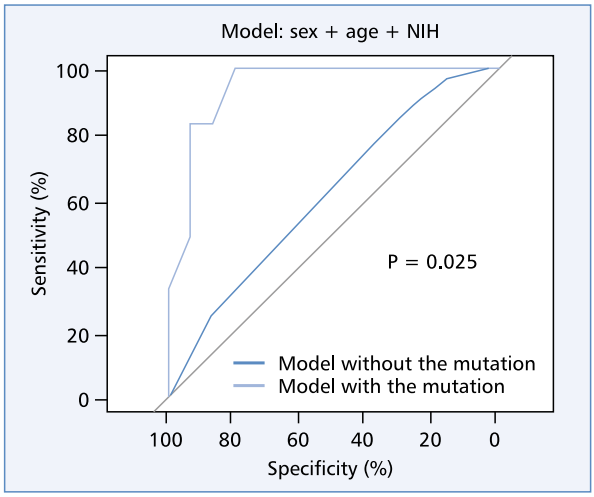

Figure 8. Model taking into consideration: sex, age and classification according to NIH in an intermediate risk group

according to AJCC. The presented relationships also confirm that the group of patients with primary GIST is representative. Other factors which significantly increase GIST recurrence risk are the extent of resection R1 ($P < 0.001$), tumor rupture ($P < 0.001$), male sex ($P = 0.02$). Radical resection (R0) in the microscopic evaluation and lack of tumor rupture regardless of whether spontaneous or linked to surgery, is extremely important during GIST surgery. Tumor rupture, regardless of tumor size and mitotic index, is a factor placing the patients in a high recurrence risk group according to the NIH classification modified according to Joensuu [33, 59–61]. The presented results also indicate an association between male sex and recurrence risk. Male sex in the analyzed group was a negative prognostic factor. Data from the literature concerning this factor are not as unequivocal as those presented above [56, 58]. All the above-mentioned factors (with the exception of resection R1) are statistically significant in uni- and multivariate analysis. So far only a few papers have analyzed the prognostic significance of the genotype of the primary tumor in patients with GIST, as many more were focused on the predictive role of mutations in response to treatment with tyrosine kinase inhibitors [62–64]. The next factor important for evaluation is the presence of a mutation in exon 11 of the *KIT* gene encompassing deletion 557–558, which turned out to be a factor associated with short disease-free survival time. In the light of available data, this mutation most commonly occurs in tumors originating outside the stomach, > 5 cm and with MI > 5/50 HPF, which automatically qualifies the patients for the high recurrence risk group and should be an additional factor in qualification for adjuvant treatment with imatinib [65], moreover, the present data unequivocally indicate that this is the mutation which is the most sensitive to imatinib [66–68]. The results of the univariate analysis indicate that the presence of an exon 9 mutation in the *KIT* gene also significantly shortens the time to disease recurrence. Summing up, the presence of a mutation in the *KIT* gene, regardless of whether it is in exon 11 encompassing deletion 557–558 or exon 9 ($P = 0.009$), is associated with a shorter DFS, comparing to a mutation in the *PDGFR* gene where the estimated 5-year disease-free survival with a mutation in exon 11 encompassing deletion 557–558 is 35.1% (95% CI: 23.8–51.8%) or exon 9 — 38.5% (95% CI: 21.2–69.95) *vs.* 83.6% (95% CI: 68.2–100.0) in the presence of a mutation in the *PDGFRA* gene. Longer DFS for GIST with a *PDGFRA* mutation has already been presented by other authors [69, 70]. The first papers at

the end of the 20th beginning of the 21st century only indicated that patients with GIST with a *KIT* mutation have more aggressive forms of the tumor than patients without the mutation, or with a mutation in the *PDGFRA* gene but the types of mutations were not analyzed in detail [38, 71, 72]. A Spanish group [73] was the first to observe the negative prognostic significance of a deletion encompassing codon 557 and/or 558 of the *KIT* gene. DeMatteo and co-authors also suggested that specific *KIT* mutations can have a prognostic value in univariate, but not multivariate analysis [68, 74] — indicating that GIST with a point mutation or a *KIT* insertion can have a better clinical course than exon 9 *KIT* mutations or deletions encompassing amino acids W557 and/or K558 of *KIT*, whereas tumors without *KIT* mutations are associated with an intermediate prognosis. The presented work is a confirmation of these factors as independent prognostic biomarkers for a much larger group of patients. The biological basis of these associations has not been explained but it is suggested that the mutated form of the KIT protein generated by substitution of proline for lysine in position 558 leads to ahigher constitutive phosphorylation of the receptor and greater cellular proliferation [75]. Several papers have also indicated a more favorable course of the disease in patients with primary GIST with a *PDGFRA* mutation (especially in exon 18, occurring mainly in tumors with a stomach localization and interestingly with a point mutation D842V characterized by resistance to used tyrosine kinase inhibitors in the case of nonresectable/metastatic tumors) [39, 46, 70, 76–78], this was also confirmed by the analysis of trial ACOSOG Z9001 in the placebo group [68].

On the basis of univariate analysis the following factors were found to have a negative effect on OS: the number of mitoses > 10/HPF ($P < 0.001$), size of primary tumor > 10 cm ($P < 0.001$). surgical margins R1 ($P = 0.004$), tumor rupture ($P < 0.001$) and age < 40 ($P = 0.045$). These factors, with the exception of surgical margins, were also found to be statistically significant in multivariate analysis. In the presented analysis no significant effect of mutation status on OS was observed. The analysis of factors affecting OS, after resection of the primary GIST, is one of the few in the literature and indicates significantly good survival even in high-risk groups which is associated with the high activity of imatinib and other tyrosine kinase inhibitors used to treat the recurrence of this disease [14, 79]. The currently used adjuvant therapy imatinib after resection of high-risk GIST can be expected to contribute to further improvement of the patients' survival.

Analysis of existing classifications of recurrence risk (expressed as ROC curves) for 5-year DFS and OS confirmed the prognostic significance of these classifications. The presented results demonstrate that the currently available and used classifications allow a reliable evaluation of recurrence risk, which is in agreement with the results from other authors [80–82]. No statistically significant differences were found when comparing particular classifications. This may be due to the fact that each of them encompasses two characteristics, tumor size and the number of mitoses, which as has also been demonstrated in the present analysis are the most important risk factors. Of course, each of the classifications has limitations, and the results of Goh et al. (2008) indicate that the AFIP classification of Miettinen and Lasota is better at predicting recurrence in comparison with NIH, which is due to the addition of the criterion of tumor localization, which as has been proved also in this analysis is an unfavorable prognostic factor for tumors localized outside the stomach. At the same time, the application of a division into low and very low recurrence risk appears to be insignificant in the context of deciding about adjuvant treatment and the planned scheme of control visits, which is also reflected in the present analysis where no statistically significant difference was found between low and very low recurrence risk both for DFS and OS. Similar results of analyses are also presented by other authors [51]. In the literature, it is difficult to find a comparison of all the current existing classifications. In the analysis performed by Yanagimoto et al. comparing NIH, AFIP, NIH according to Joensuu, AJCC and „Japanese modified NIH", where tumor rupture and/or organ infiltration were added in a group of 712 patients, the NIH classification according to Joensuu was found to be the most sensitive in predicting GIST recurrence. On the basis of this analysis, the NIH classification was selected for qualifying patients for adjuvant treatment [69]. However, this analysis did not take into consideration mutation analysis nor the nomogram according to Gold.

None of the papers published so far has attempted to include mutation analysis in the prognostic system after resection of primary GIST. The results presented in this paper unequivocally demonstrate an improvement in the prognostic accuracy of risk classification after including genotyping in addition to classical prognostic factors — this can affect the proper classification of patients with intermediate recurrence risk for adjuvant treatment with imatinib after resection of the primary tumor. The paper by Wozniak et al. encompassing multicenter clinical, pathological and molecular data of patients with localized GIST after resection collected in the database European ConticaGIST confirms the favorable prognostic significance of the exon 18 *PDGFRA* mutation and the negative effect of duplication in exon 9 of *KIT* (occurring mainly in the small intestine) and deletion 557–558 in exon 11 of *KIT*. Interestingly, according to the authors of that paper, the presence of a deletion encompassing codons 557 and/or 558 of *KIT*

was a significant, independent negative prognostic factor only for GIST originating in the stomach. The authors state that the presence of this genetic perturbation in patients with GIST derived from the stomach even with a theoretically lower risk evaluated on the basis of existing classifications should be an additional indication for adjuvant treatment with imatinib. In the presented work a statistical significance ($P < 0.001$) was also found for the presence of mutations in particular risk groups with an unfavorable indication for the high-risk group. Over 40% of all determined mutations are mutations determined in tumors which were evaluated as a high-risk group, moreover, an exon 11 deletion in *KIT* (W557–K558) is the most common mutation in the group with high recurrence risk. Because of the size of the examined group it was not possible to conduct such a detailed analysis of subgroups of patients depending on the localization as had been done by the ConticaGIST group. In the newest extended analysis by the ConticaGIST research team of a group of 1844 patients where the most common types of mutations were analyzed two prognostic classes were distinguished: class 1 (C1, good prognosis), this group included mutations of exon 11 of *KIT*, duplications, deletions with the exception of codons 557–558 and exon 18 of PDGFRA 18, whereas class 2 (C2, poor prognosis) encompassed deletions of codons 557–558 of *KIT* exon 11. When in a multivariate model the correlation between tumor localization and the mutation status were taken into consideration an unfavorable effect of tumor size > 10 cm, mitotic index 6–10 > 10/50 HPF, were observed but class 2 mutations gave a poorer prognosis only in the case of stomach tumors in contrast to GIST localized outside the stomach [83]. Even though the group analyzed in the present work is smaller and the evaluation of the mutation type was not as precise, similar conclusions can be drawn from the results — a tumor localized in the stomach and the presence of a *KIT* mutation in codons 557–588 is a poor prognostic factor and should be important in updating the current classifications of recurrence risk.

Similar conclusions were reached by the authors on an analysis of a group of 451 patients, during which multivariate Cox regression models allowed three molecular risk groups to be identified: group I had the best result and encompassed mutations of exon 12 of *PDGFRA*, a *BRAF* mutation and exon 13 *KIT* mutations; group II, with an intermediate clinical phenotype (HR = 3.06), encompassed triple-negative cases, mutations in exon 17 of *KIT*, codon D842V in exon 18 of *PDGFRA* and in exon 14 *PDGFRA*; group III had the poorest result (HR = 4.52) and encompassed mutations in exon 9 of *KIT* and exon 11 of *KIT* and in exon 18 of *PDGFRA* other than *D842V*. The mutation was a significant prognostic factor for overall survival in localized GIST not subjected to systemic treatment ($P < 0.001$): in patients with a *KIT* mutation the results were worse than in the case of a *PDGFRA* mutation or triple-negative (wild type *KIT*, *PDGFRA*, *BRAF*). This analysis underlines the prognostic effect of mutation status on the natural course of GIST and suggests that molecular prognostic grouping can supplement clinical stratification criteria when making decisions on adjuvant treatment and responds to the question whether the mutation status affects the prognosis of localized untreated GIST [84].

The Scandinavian Sarcoma Group performed an analysis aimed at determining the effects of *KIT* and *PDGFRA* mutations on recurrence-free survival (RFS) in patients with GIST treated by surgery and with imantinib adjuvant treatment. 400 patients treated by resection in whom recurrence risk was evaluated as high were included in the analysis. They were divided into 2 groups receiving imatinib for one or 3 years. The end-point was disease-free survival. The mutations were grouped according to the gene and exon. Mutations in exon 11 of *KIT* were then grouped into deletion mutations or insertion-deletion mutations, substitution mutations, insertion or duplication mutations and mutations encompassing codons 557 and/or 558. Mutations in *PDGFRA* and insertion or duplication mutations in exon 11 of the *KIT* gene were linked with a favorable DFS, whereas mutations in exon 9 of the *KIT* gene were associated with an unfavorable outcome. Patients with a deletion in exon 11 of the *KIT* gene or an insertion/deletion mutation had a better DFS when they were assigned to a 3-year group in comparison with a one year group (5-year RFS 71.0% *vs.* 41.3%; $P < 0.001$), whereas a lack of positive effects of 3-year treatment was observed in other examined mutation subgroups. Deletion mutations in exon 11 of the *KIT* gene, deletions encompassing codons 557 and/or 558 were linked with short DFS in the one year group but not in the 3-year group. The results of the analysis presented above confirm that the benefits for patients from adjuvant treatment depend on the type of occurring mutation. Patients included in the analysis in whom deletion mutations in exon 11 of the *KIT* gene were confirmed profited the most from a longer duration of adjuvant treatment with imatinib. Thus the time of adjuvant treatment with imatinib modifies the risk of GIST recurrence linked to some *KIT* mutations including deletions, which affect the codons 557 and/or 558 [85] of exon 11.

Conclusions

In this analysis the most important prognostic factors linked to disease-free survival were found to be: tumor size, mitotic index, localization outside the stomach and the presence of a mutation in exon 11 of the *KIT* gene encompassing deletion 557–558 and in exon 9 of the

same gene. The factors which significantly affect overall survival are: number of mitoses > 10/HPF ($P < 0.001$), size of primary tumor > 10 cm ($P < 0.001$), surgical margins R1 ($P = 0.004$), tumor rupture ($P < 0.001$) and age < 40 ($P = 0.045$). Over 40% of all determined mutations were determined in tumors which were classified into the high-risk group, moreover, mutations encompassing deletion (557–558) in exon 11 of the *KIT* gene are most commonly present in the group with a high recurrence risk which should cause initiation of adjuvant therapy. The presence of a mutation in exon 18 of *PDGFRA* has a favorable prognostic significance in GIST after resection of the primary tumor. All presently used classifications of evaluation of GIST recurrence risk allow a reliable evaluation of this risk. The reliability of the existing classifications of GIST recurrence after resection can be improved by including the mutation status especially in groups with intermediate recurrence risk. The use of treatment molecularly directed at the presence of a specific mutation appears to be critical not only in the context of adjuvant treatment but also in the treatment of advanced and/or metastatic disease.

Conflict of interest

PR has received honoraria for Advisory Board from Novartis, Roche, MSD, BMS, Pierre Fabre, Amgen, Blueprint Medicine, Eli Lilly, and honoraria for lectures from Novartis, Roche, MSD, Pfizer, BMS, and travel grant from Orphan Drugs.

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