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A whole population study of gastrointestinal stromal tumors in the Czech Republic and Slovakia

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Due to problems with identification and an incomplete understanding on the gastrointestinal stromal tumors (GIST) before 2001, there has been a lack of comprehensive long-term population-based studies on GIST epidemiology at present date. We used data from the online registry of Czech and Slovak GIST patients (http://gist.registry.cz/), which has been compiled and maintained since 2006 and involves patients diagnosed from the year 2000. 278 patients were included in this study. Most of the tumors fell into the high-risk category (58.7%), followed by the intermediate (21.4%), low (16.6%) and very low (3.3%) categories.

Locations other than the small intestine and stomach had significantly higher contribution of high-risk tumors. The median time of overall survival was 93.2 months, 5-year relative survival was 78.3% overall, 71.9% for patients with high-risk tumors, 91.1% for intermediate patients, and 91.9% for patients from the low- and very low-risk category. The annual crude incidence between the years 2001-2005 was 0.52 cases per 100,000 inhabitants. The annual European ASR and World ASR were 0.44 and 0.31 per 100,000 inhabitants, respectively. Presented data generally correspond to the whole-population studies recently published, including actual data on epidemiology, clinical characteristics, and survival of patients. The registry helps in improving GIST diagnostics, knowledge about the properties and behaviour of tumors, communication among physicians, and, last but not least, therapeutical options and results.

Key words. Gastrointestinal stromal tumor, registry, epidemiology, incidence, survival, risk category

Although relatively rare, gastrointestinal stromal tumors (GIST) are the most common nonepithelial tumors of the gastrointestinal tract. They arise either from Interstitial cells of Cajal (ICC) or from less-differentiated stem or precursor cells that can develop into ICC. GIST mainly occur in the stomach (60-70%) followed by the duodenum and small intestine (20-30%), while GIST of the esophagus, rectum, and colon are relatively infrequent [1]. Exceptionally, they may occur in the omentum, mesentery, and retroperitoneum [2]. The most common symptoms are abdominal pain, intestinal bleeding, anemia, and dyspepsia. Approximately 20% to 25% of gastric and 40% to 50% of small intestinal GIST are clinically malignant. Metastases commonly develop in the abdominal cavity and liver; rarely do metastases develop in bones, soft tissues, skin, lymph nodes, and lungs [3].

A retrospective assessment of GIST incidence and other clinical aspects before 2000 is relatively difficult due to problems with identification and an incomplete understanding of its origin, which led to a highly variable nomenclature for the past several decades [4]. The group currently called GIST includes a majority of tumors previously diagnosed as GI leiomyoma, leiomyoblastoma, and leiomyosarcoma, as well as many tumors previously considered neurofibroma or schwannoma [3]. The situation has changed since the late 1990's with observations on the origin of GIST in ICC [5] and role of the activating Kit mutations, which can be detected immunohistochemically [6]. These findings also contributed to improved drug therapy based on imatinib mesylate, which targets and inhibits the activated KIT tyrosine kinase receptor [7].

Despite the problems described above, there have been several papers recently published that deal with long-term population-based studies on GIST incidence and survival [1, 4, 8–10]. Some of the papers emphasize the differences in GIST

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incidence before and after consensus on GIST detection and classification [11]. For example, Goettsch et al. [8] showed that the annual incidence of GIST in the Netherlands dramatically increased between the years 1995 and 2003 from 2.1 to 12.7 per million inhabitants, whereas the annual incidence of GIST-like tumors, mostly leiomyomas and leiomyosarcomas, decreased from 18.7 to 12.7 per million inhabitants. This was attributed to an improvement in the understanding of GIST pathobiology, detection, and identification.

In 2006, a GIST clinical registry was founded for patients from the Czech Republic and Slovakia (http://gist.registry.cz/). The project has focused on both a retrospective (patients diagnosed between 1st January 2000 and the registry initiation) and prospective (patients diagnosed after the registry initiation) collection of clinical data. This paper should contribute to the whole-population studies recently published, including actual data on epidemiology, clinical characteristics, and survival of patients.

Patients and methods

Centers involved in the registry project. The project covers the population of approximately 15 million inhabitants from the Czech Republic and Slovakia. Data have been collected from three Czech centers (University Hospital in Motol, Prague; Masaryk Memorial Cancer Institute, Brno; University Hospital, Hradec Králové) and five Slovak centers (National Oncological Institute, Bratislava; University Hospital, Martin; East Slovakian Cancer Institute, Košice; University Hospital, Banská Bystrica; St Elizabeth's Cancer Institute, Ltd., Bratislava). The technological base of the registry is provided by the Institute for Biostatistics and Analyses, Masaryk University, Brno, Czech Republic.

Technological design and data safety. The registry is implemented online and uses internet and database technologies featuring a multilevel architecture (client – web server – database server). The online application is easily accessible via a standard internet browser. The system has been customized for the collection of specific clinical data for the project GIST.

Besides the complete registry operation, IBA further supports the software background of the project through an original, analytic tool called COBRA (Comprehensive Data Browser). COBRA communicates with the database of the project and returns standard statistical reports or user-specific analytic outcomes, all in forms of final tables and figures.

Special attention is paid to data security within the registry. Authorized users of the registry may access the system only after submitting a valid username and password. Users are assigned various levels of authorization to have access to selected functions or parts of the system. Apart from this, the system performs an automatic log-out after a predefined period of inactivity.

Any communication between the client and server is realized via secure protocol HTTPS using SSL (Secure Socket Layer) encryption to secure communication between the client and server (to prevent misuse of the user login and password, for example).

Identification and assessment of GIST. Identification of GIST was based on the immunohistochemical reaction with CD117 and morphological characteristics. Tumor risk was assessed according to size and mitotic rate, as defined at the National Institutes of Health GIST Workshop in 2001 [11].

Statistical evaluation. The Kaplan-Meier method was used for survival analysis. For a comparison of the survival of additional groups of patients, the Gehan-Wilcoxon test was used. Overall survival was calculated as the time from the patient's initial diagnosis until death.

Results

The GIST registry of Czech and Slovak patients covers a population of about 15 million inhabitants and contains GIST patients diagnosed after 1st January 2000. As of June 2008, the database contained 444 patients in total, for 278 of whom completed forms were available and could be included in this study.

Slightly more male patients (54.7%) were included than female. The mean and median age of diagnosis was 58.8 and 59.8 years, respectively. The most frequent sites of tumor primary occurrence were the small intestine (37%) and stomach (34.2%), followed by other locations (Table 1). 30.9% of tumors were metastatic. Metastases developed mostly in the liver (72.1% of patients with metastases) and peritoneum (46.5%).

77.7% of the tumors were detected due to symptoms, mainly abdominal pain (present in 67.1% of patients), anemia (34.3%), and intestinal bleeding (33.3%). The results and basic characteristics of the cohort are summarized in Table 1.

Among the GIST examined, larger tumors prevailed (38.9% larger than 10 cm, 32.4% between 5 and 10 cm). 45.4% of tumors had a mitotic rate lower than 5 per 50 HPF, while 35.4% had a higher rate than 10 per 50 HPF. Based on size and mitotic rate, the risk of individual GIST is defined [11]. According to these criteria, more than half of the patients fell into the high-risk category (58.7%), followed by the intermediate (21.4%), low (16.6%) and very low (3.3%) categories (summarized in Figure 1).

The stated proportion also applied to the tissues with the highest tumor occurrence (small intestine and stomach). In contrast, tumors found in the colon, peritoneum, retroperitoneum, and omentum were considered as high-risk in approximately 90% of the cases (Figure 2). However, the total numbers of tumors in these locations are much lower than in the small intestine and stomach (see Table 1) and are, therefore, rather less predicative.

Mitotic rate correlated significantly with tumor size (Pearson Chi-square test; Spearman's correlation coefficient $R=0.362$, $p<0.001$) (Figure 3). While 75% of the small tumors under 2 cm had a low mitotic rate (under 5 per 50 HPF), al-

Table 1. Basic characteristics of the cohort under study

Parameter	Value
Population	15 million
Number of GIST cases	278
Period examined	2000-2008
Age of diagnosis (years)	
Mean	58.8
Median	59.8
Gender (%)	
Male	54.7
Female	45.3
Symptoms (%)	
Yes	77.7
No	22.3
Abdominal pain	67.1
Anemia	34.3
Intestinal bleeding	33.3
Tumor localization (number, %)	
Small intestine	103 (37)
Stomach	95 (34.2)
Peritoneum, Retroperitoneum, Omentum	28 (10.1)
Rectum	13 (4.7)
Colon	9 (3.2)
Pancreas	4 (1.4)
Cecum and appendix	2 (0.7)
Liver	2 (0.7)
Gallblader	1 (0.4)
Other	13 (4.7)
Unknown	8 (2.9)
Incidence (no. of cases per 100,000 inhabitants)	
Crude rate	0.52
European ASR	0.44
World ASR	0.31
Median overall survival (months)	93.2
5-years survival (%, CI)	
All cases	78.3 (70.5-86.1)
Low + very low risk	91.1 (81.4-100)
Intermediate risk	91.9 (82.6-100)
High risk	73.0 (62.6-83.5)

most half (45.2%) of the tumors larger than 10 cm had a mitotic rate above 10 per 50 HPF.

91.4% of GIST were CD117 positive, 3.6% were negative and 5% were not stained or the result is unknown. For other antigens, such as CD34, vimentin, desmin and others, the percentage of positive samples was significantly lower (Figure 4).

The annual crude incidence between the years 2001-2005 was 0.52 cases per 100,000 inhabitants. The annual European ASR and World ASR were 0.44 and 0.31 per 100,000 inhabitants, respectively.

The median time of overall survival was 93.2 months, however for patients with high-risk tumors this was slightly lower (89.5 months). 5-year relative survival was 78.3% overall, 71.9% for patients with high-risk tumors, 91.1% for intermediate patients, and 91.9% for patients from the low- and very low-risk category.

Discussion

Due to identification and terminology discrepancies before 2001, there has been a lack of comprehensive GIST population-based studies for a long time. Even recent studies [1, 4, 8–10] contained a majority of cases from the 1980's and 1990's and were, therefore, subject to uncertainty associated with a retrospective assessment of non-uniform data. The Czech and Slovak GIST registry covers patients diagnosed from 2000 to 2008, i.e. predominantly those from the period "after the consensus".

A low mean and median age of diagnosis (both under 60 years) in comparison to other studies may be one of the consequences of the more recent set of data. The quality of tumor detection and identification has certainly improved over the decade, which may lead to detection in lower ages.

Most of the GIST in the Czech and Slovak registry falls into the "high-risk" category (57.2%). This is a combined effect of the relatively high occurrence of tumors larger than 10 cm and with a mitotic rate higher than 10 per 50 HPF. Although a direct comparison with other populations is not as simple due to the various number of samples with unknown size or mitotic rate (or both), we can conclude that the occurrence of high-risk tumors is comparable with Italy [1] and significantly higher than in the Netherlands, Sweden and Girona (Spain) [4, 8, 9]. However, it should be mentioned that the low number of small tumors (< 2 cm) may be underestimated due to the less significant symptoms and more difficult identification and diagnosis. This fact may be reflected in the higher number of larger tumors, and thus increased proportion in the high-risk category.

According to a statistical analysis carried out by Mucciarini et al. [1], tumor locations other than the small intestine and stomach are associated with an increased overall risk of recurrence (together with larger size and higher mitotic rate). Nilsson et al. [4] stated that patients with gastric GIST had a 10% lower estimated risk of dying compared with those who had small intestinal or colon GIST. Our results indicate that the contribution of high-risk tumors is significantly higher outside the small intestine and stomach (see Figure 2), which indirectly supports the conclusion of the Italian study.

CD117 positive staining is one of the primary characteristics of GIST. However, a certain amount (about 5%) of negative results is permissible due to sampling and processing errors or rarely-occurring c-kit negative tumors [12]. In our study, 3.6% of GIST were c-kit negative, which is in the accepted range and in agreement with previously published results (5.7% [8], 4.3% [9], 11.3% [1]). Other types of staining, except CD34, elicited a much lower number of positive results and generally correspond to data presented by Goettsch et al. [8].

Overall survival published in literature of patients with GIST ranges from 40.8 months [10] to 130.8 months [4], with 5-year relative survival from 53.9% [10] to 74.7% [9]. Our

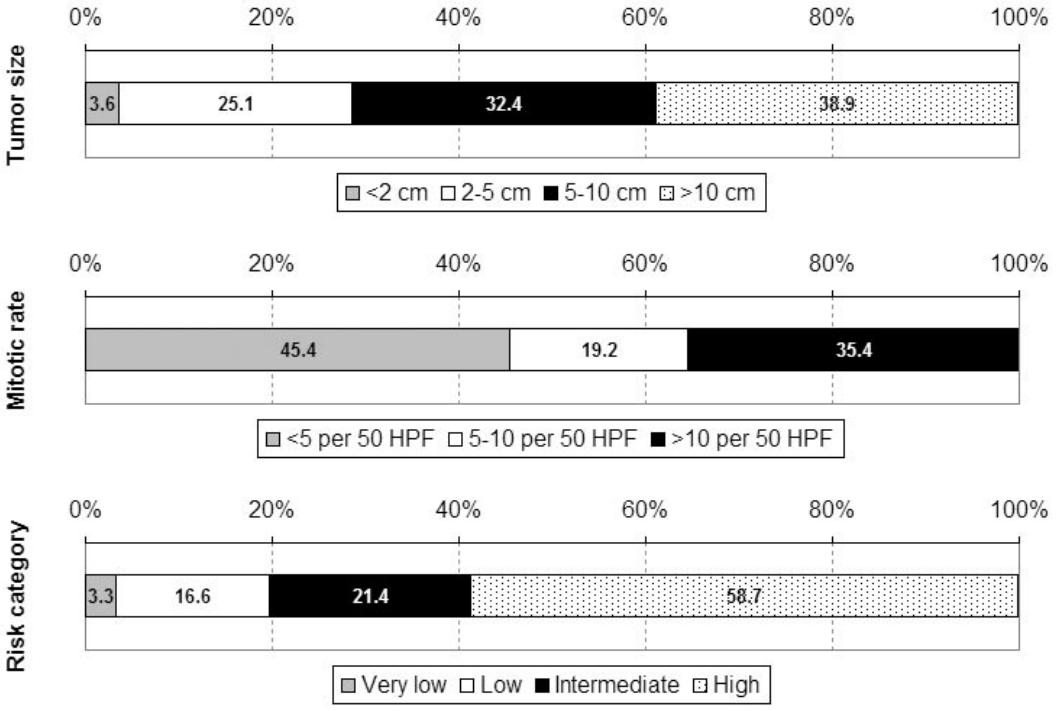

Figure 1. Tumor size, mitotic rate, and risk categories of tumors registered in the database

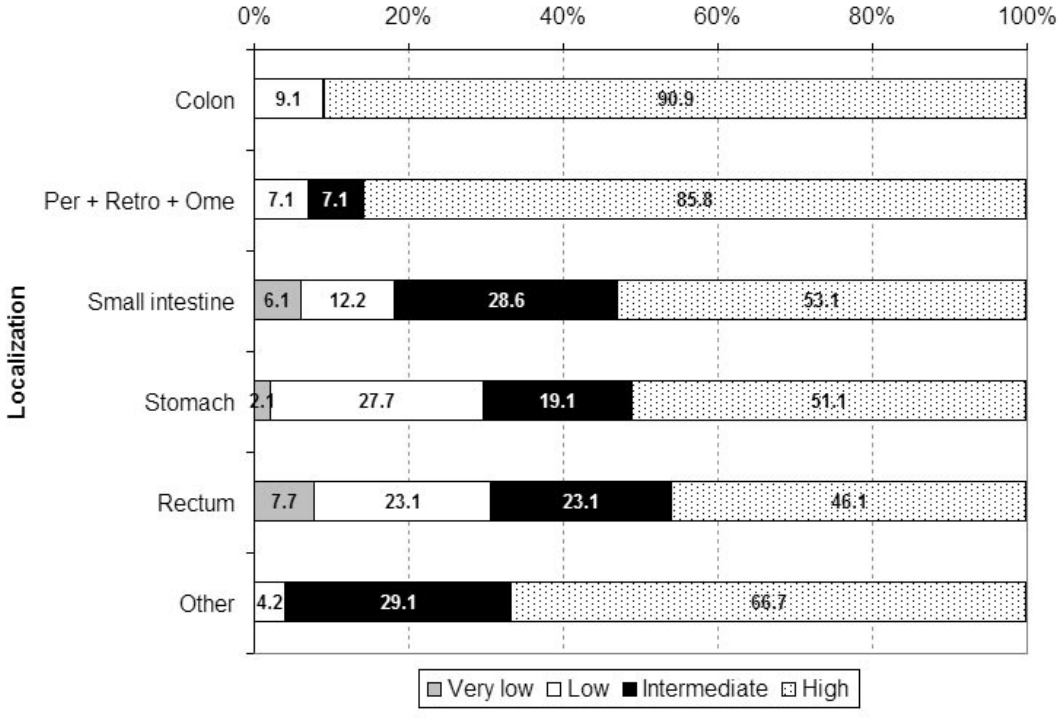

Figure 2. Tumor risk categories in individual locations

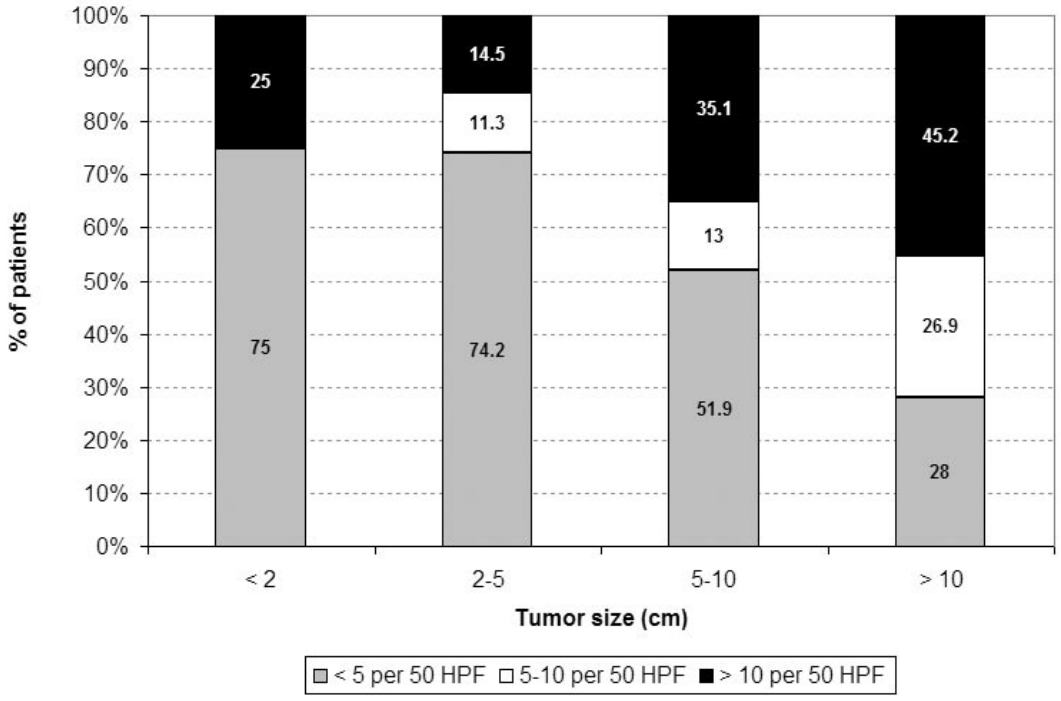

Figure 3. Relationship between tumor size and mitotic activity

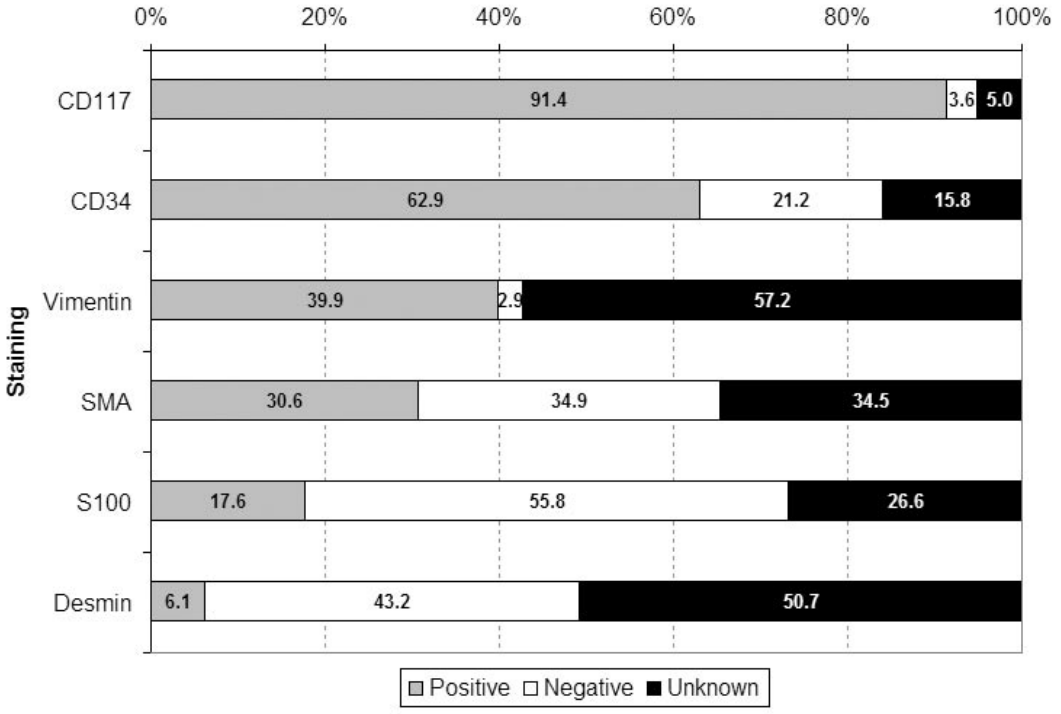

Figure 4. Immunohistochemical properties of GIST examined

median value of 93.2 months for overall survival is within the mentioned range, while the 5-year relative survival 78.3% is slightly above it. Authors do not usually find differences in 5-year relative survival within the very low-, low- and intermediate-risk categories, however the percentage rapidly decreases for high-risk tumors. This difference was also confirmed by our study (73% for high-risk and 91.1-91.9% for other categories). The survival of Czech and Slovak patients with high-risk tumors is comparable with the population study from Italy (61.5%) [1] and much better than in the Spanish study (21.4%) [9].

The GIST incidence data in the Czech Republic have been available from the Czech National Cancer Registry. The mean incidence in years 2001-2005 was relatively low in comparison to other studies, including the crude rate, European ASR, and World ASR. Even the lowest world population-standardized incidence rate, 0.65 cases per 100,000 inhabitants, recorded by Rubio et al. [9], is two times higher than that in the Czech Republic.

Identification of GIST in the Czech National Cancer Registry has been complicated by changes in classification codes and a subsequent delay in the processing of new registration rules in clinical praxis. Before the implementation of an explicit group of GIST in 2005, these tumors were identified as sarcoma, fibrosarcoma, liposarcoma, leiomyoma, leiomyoblastoma, histiocytoma etc. The mean crude incidence of such tumors is 0.52 cases per 100,000 inhabitants, which is approximately 36-48% of the crude incidence stated in literature [1,4,9]. We assume that the rest of GIST have fallen into the group of tumors without the stated morphology or localization, or incidentally have not been correctly registered. Furthermore, some patients (especially among the oldest ones) might not have been registered for oncological therapy. These circumstances have been the main impulses and reasons for building a specialized GIST registry capable of describing individual cases in detail, including tumor occurrence and properties, types of therapy, therapeutical responses etc. Such a registry may help in improving GIST diagnostics, knowledge about the properties and behavior of tumors, communication among physicians, and, last but not least, therapeutical options and results. The registry is still being developed and might be, in the future, extended to other European countries.

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References

[1] Mucciarini C, Rossi G, Bertolini F et al. Incidence and clinicopathologic features of gastrointestinal stromal tumors. A population-based study. BMC Cancer 2007; 7: 230. doi:10.1186/1471-2407-7-230 PMid:18096058 PMCid:2241631

[2] Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004; 22: 3813–3825. doi:10.1200/JCO.2004.05.140 PMid:15365079

[3] Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006; 130: 1466–1478.

[4] Nilsson B, Bumming P, Meis-Kindblom JM et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. A population-based study in western Sweden. Cancer 2005; 103: 821–829.

[5] Kindblom LG, Remotti HE, Aldenborg F et al.Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152: 1259–1269.

[6] Hirota S, Isozaki K, Moriyama Y et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998; 279: 577–580. doi:10.1126/science.279.5350.577 PMid:9438854

[7] Heinrich MC, Blanke CD, Druker BJ et al. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. J Clin Oncol 2002; 20: 1692–1703. doi:10.1200/JCO.20.6.1692 PMid:11896121

[8] Goettsch WG, Bos SD, Breekveldt-Postma N et al. Incidence of gastrointestinal stromal tumors is underestimated: Results of a nation-wide study. Eur J Cancer 2005; 41: 2868–2872. doi:10.1016/j.ejca.2005.09.009 PMid:16293410

[9] Rubió J, Marcos-Gragera R, Ortiz MR et al. Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. Eur J Cancer 2007; 43: 144–148. doi:10.1016/j.ejca.2006.07.015 PMid:17055254

[10] Tryggvason G, Kristmundsson P, Orvar K et al. Clinical study on gastrointestinal stromal tumors (GIST) in Iceland, 1990–2003. Dig Dis Sci 2007; 52: 2249–2253. doi:10.1007/s10620-006-9248-4 PMid:17420941

[11] Fletcher CDM, Berman JJ, Corless C et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002; 33: 459–465. doi:10.1053/hupa.2002.123545 PMid:12094370

[12] Blay JY, Bonvalot S, Casali P et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20–21 March 2004, under the auspices of ESMO. Ann Oncol 2005; 16: 566–578 doi:10.1093/annonc/mdi127 PMid:15781488