



## Original research

## Significance of surgery for prognosis of gist in cohort from transitional healthcare settings



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## HIGHLIGHTS

- Transitional economies face economic boundaries in rehearsing optimal level of care.
- Surgery bears relatively important position in treatment of GIST.
- Limited availability of chemotherapy influenced prognostic significance of surgery.
- Ki-67 being greater than 9% showed association with overall survival.

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## ABSTRACT

**Objective:** Despite significant improvement in survival of gastrointestinal stromal tumors (GIST) due to use of tyrosine kinase inhibitors, surgery still represents the important part of clinical management. The aim of our study was to retrospectively analyze prognosis of GIST depending on the success of surgical treatments and utilization of chemotherapy in transitional country with relatively limited resources.

**Methods:** cohort of consecutive patients operated for GIST in tertiary medical center, within time frame 1999–2012. **Results:** 54 patients, in age range 20–85 years ( $63.3 \pm 14.7$ ), male to female ratio 28 (51.9%):26 (48.1%), respectively. Complete excision with clean resection margins (R0) was obtained in 44 (81.5%) of total patients i.e. 44/47 (93.6%) of localized GISTs. Mean follow up was  $3.9 \pm 3.3$  years and 19 patients (35.2%) received imatinib. Rate of overall survival was 40 (74.1%), disease-free survival 31 (57.4%) and 20 (37.0%) experienced recidivism. Follow-up parameters showed significant difference in connection with utilization of imatinib, completeness of resection and existence of metastatic disease (all  $p < 0.05$ ). ROC analyzes revealed critical value of Ki-67  $> 9\%$  as significant predictor of long-term mortality; sensitivity 64.3% [95%CI = 35.1–87.2]; specificity 75.0% [58.8–87.3]; (AUC = 0.693;  $p = 0.049$ ). **Conclusion:** Rate of complete resections in studied sample of patients from transitional background was overall peer comparable with reports from the developed countries. On the other hand, relatively dominant prognostic position of surgical treatments might be consequence of limited utilization of adjuvant treatment with tyrosine kinase inhibitors.

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*List of abbreviations:* GIST, gastrointestinal stromal tumor; TNM, classification of malignant tumors (tumor size, lymph nodes, metastases); Ki-67, "Kiel 67" proliferative index; R1, resection with unclear pathohistologic tumor margins.

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## 1. Introduction

Gastrointestinal stromal tumors (GIST) are rare cancerous diseases with incidence of around 10 cases per million [1]. GIST makes 1–3% of total cancer burden in gastrointestinal tract, however, at the same time it is the most common gastrointestinal mesenchymal tumor [2,3]. Important changes in natural course and

prognosis of GIST happened in connection with discovery of c-kit proto-oncogene [4]. C-kit encodes type III receptor of tyrosine kinase, which mediates regulation of cell cycle and differentiation. In case of GIST, gain of function mutation causes that c-kit becomes constitutively activated, without binding of ligand and necessity of dimerization [4]. Important role of c-kit in pathophysiology of neoplastic growth finally led to clinical use of exceedingly efficient chemotherapy with tyrosine kinase inhibitors [5]. Due to a concealed malignant potential and lacking of connection with traditional TNM-staging several specific prognostic systems were developed. The most notable parameters of GIST's malignant behavior occur in dependence with size of tumor, number of mitoses, localization within gastrointestinal tract and existence of metastases [6–8]. In addition, nuclear protein Ki-67 that is expressed during the course of cancerous growth offers relatively solid representation of the link existing between mitoses and tumor dimensions [9]. Ki-67 was actually found to be in correlation with prognosis of GIST and for that reason is being frequently applied as supplementary diagnostic tool [10].

Combination of surgical treatments and use of tyrosine kinase inhibitors became resourceful and efficient armamentarium for treatment of GIST, depending on clinical stage and extent of disease [11,12]. Although the role and position of surgical treatment has been evaluated in the most developed Western countries, only limited number of studies offered thorough prognostic analyzes in concern to economically, organizationally and technically less developed health systems. In those circumstances one could reasonably expect that limited health budgets experience the non-negligible challenges for rehearsing optimal level of cancer screening, early detection, having sufficient availability and competences of surgical treatments, along with presumable underutilization of chemotherapy. The aim of our study was to analyze temporal effects of surgery and targeted chemotherapy in tertiary medical center from transitional country. Assessment of surgical treatment and utilization of tyrosine kinase inhibitors was studied in connection with known prognostic parameters in cohort of patients with long-term postoperative follow up.

## 2. Patients and methods

Study was performed in tertiary medical center and it included retrospective analyzes on consecutive sample of patients treated surgically for gastrointestinal stromal tumor in single center, during the time frame 1.1.1999–31.12.2012. The diagnosis of GIST was established by pathology and immunohistochemistry using c-kit, Ki-67, SMA, S-100 [13,14]. Tumors were classified as low, intermediate and high grade according to dimension, number of mitoses and localization [15].

Analyzes of surgical treatments included type of operation (elective vs. urgent surgery); completeness of resection (gross total resection verified by pathology, incomplete resection, and palliative tumor reduction); and early postoperative complications (wound dehiscence, infection, hemorrhage, renal failure, mortality). Data on oncological treatment and late postsurgical follow up were not available for 8 patients (14.8%).

## 3. Ethical issues

Study was approved by the ethical committee of University Hospital Center “Sestre Milosrdnice” in line with the good clinical practice guidelines. Patients were included upon signing of written informed consent by patient themselves or by legal representative i.e. family member in case patient's has deceased.

## 4. Statistical analyses

Population and studied groups were analyzed with descriptive statistic and presented as a percentage or means combined with standard deviations. Characteristics of treatments and GISTs were tested for differences with Chi square tests. Numeric data were tested for differences using Mann–Whitney *U* test or Kruskal Wallis. Correlation of studied parameters with clinical outcomes was done by Spearman Rho. Impact of Ki-67 on mortality was calculated with ROC analyzes. Analyzes of survival was performed using Kaplan–Meier estimator. *P* value less than 0.05 was considered significant. Statistical analyzes were done by experienced statistician using Statistica v.10 for Windows (StatSoft inc. USA) and MedCalc for Windows v. 12.2 (MedCalc Software, Belgium).

## 5. Results

Study population included 54 consecutive patients operated for GIST, in time frame 1999–2012. Forty one (75.9%) of patients were operated in the period 2005–2012. Mean age of patient was  $63.3 \pm 14.7$  years (range 20–85). There was a slight predominance of male patients over female; 28 (51.9%):26 (48.1%), respectively. The commonest tumor localization of GIST was in stomach, followed by small intestine, colon and extraintestinal/peritoneal. All cases were seropositive for c-kit. Characteristics of studied population are shown in Table 1.

Mean follow up lasted for  $3.9 \pm 3.3$  years, in range 1–13.5. Nineteen patients (35.2%) received imatinib chemotherapy, due to advanced clinical grade of tumor or recurrence of GIST. Metastatic disease was found in 10 (18.5%) of studied patients. Rate of overall survival was 40 (74.1%), disease-free survival 31 (57.4%) and 20 (37.0%) had recidivism of GIST during the study course. Follow-up parameters showed significant difference in connection with utilization of imatinib, completeness of resection and existence of metastatic disease (all  $p < 0.05$ ), Table 2.

There was 42 (77.8%) of elective procedures vs. 12 (22.2%) of urgent surgeries. Urgent procedures were performed due to acute abdominal pain ( $n = 8$ ), intractable gastrointestinal bleeding

**Table 1**  
Characteristics of patients, GISTs and treatments.

		<i>n</i> (%) or mean $\pm$ SD
Age (years)		$63.3 \pm 14.7$
Gender	Male	28 (51.9%)
	Female	26 (48.1%)
Localization	Stomach	29 (53.7%)
	Small intestine	17 (31.5%)
	Colon and rectum	5 (9.3%)
	Extraintestinal and peritoneal	3 (5.6%)
Maximal dimension (mm)		$63.9 \pm 52.5$
Ki67 (%)		$0.09 \pm 0.07$
Pathohistologic grade	Low grade	24 (45.3%)
	Intermediate grade	12 (22.6%)
	High grade	17 (32.1%)
Metastatic disease		10 (18.5%)
Cell type	Spindle	32 (59.3%)
	Mixed (including epitheloid)	22 (40.7%)
Level of resection	Gross total resection	44 (81.5%)
	Incomplete resection	6 (11.1%)
	Tumor reduction	4 (7.4%)
Type of surgery	Elective	42 (77.8%)
	Urgent	12 (22.2%)
Early postoperative complications		6 (11.1%)
Using Imatinib		19 (35.2%)
Mortality during follow up		12 (22.2%)

Data labels: *n* – number of patients; SD – standard deviations; Ki-67 – “Kiel 67” proliferative index.

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