

Gastrointestinal stromal tumors in Osijek-Baranja County (Eastern Croatia): a population-based incidence study (2004 – 2017)

*Gastrointestinalni stromalni tumori u Osječko-baranjskoj županiji, (istočna Hrvatska);
populacijsko istraživanje pojavnosti (2004. – 2017.)*

Andrea Milostić-Srb, Nikola Kraljik, Nika Srb, Stana Pačarić, Nikolina Farčić, Dunja Degmečić, Štefica Mikšić, Dubravka Holik, Ivana Jelinčić*

Summary

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The epidemiology of these tumors in Osijek-Baranja County is not known. The aim of this study is to determine the incidence of gastrointestinal stromal tumors (GIST) and anatomic localizations in Osijek-Baranja County patients. In this study, we show the incidence of gastrointestinal stromal tumors (GISTs) in Osijek-Baranja County. We studied 65 cases of GIST diagnosed in Osijek-Baranja County in the period from January 1, 2004 to December 31, 2017. In this period, we registered 65 cases of GIST from which 29 females (44.6%) and 36 males (55.4%). The mean age at diagnosis was 66.9 years ranging from 37 to 86. Only 1.5% of tumors occurred before the age of 40 years. The crude incidence rate of GISTs was 1.47/100,000 (1.26/100,000 for females and 1.70/100,000 for males). The age-standardized incidence rate was 0.76/100,000 (0.60/100,000 for females and 0.98/100,000 for males). The annual European age-standardized incidence rate was 1.10/100,000 (0.86/100,000 for females and 1.44/100,000 for males). GISTs were mostly localized in the stomach (33 cases) and small intestine (20 cases), followed by peritoneum and omentum (8 cases), two in the pancreas, 1 in the rectum and 1 in other locations. Gastrointestinal stromal tumors are rare, but more common in the older population. The incidence rate was higher among men. These results will serve as reference for studying the patterns of descriptive epidemiology of GISTs in Osijek-Baranja County and the surrounding region.

Key words: epidemiology, incidence, GIST, Osijek-Baranja County, Eastern Croatia

Sažetak

Gastrointestinalni stromalni tumori (GIST) najčešći su mezenhimalni tumori gastrointestinalnog trakta. Epidemiologija ovih tumora u Osječko-baranjskoj županiji nije poznata. Cilj ove studije je odrediti pojavnost GIST-a i anatomske lokalizacije kod oboljelih u Osječko-baranjskoj županiji. U ovoj studiji prikazujemo pojavnost gastrointestinalnih stromalnih tumora (GIST) u Osječko-baranjskoj županiji. Proučavali smo 65 slučajeva GIST-a dijagnosticiranih u Osječko-baranjskoj županiji u razdoblju od 1. 1. 2004. do 31. 12. 2017. U ovom razdoblju zabilježili smo 65 slučajeva GIST-a, od čega je 29 žena (44,6%) i 36 muškaraca (55,4%). Prosječna dob bila je 66,9 godina, u rasponu od 37 do 86 godina. Samo 1,5% tumora pojavilo se prije 40-te godine. Nestandardizirana ili gruba stopa pojavnosti GIST-a iznosila je 1,47/100.000 (1,26/100.000 za žene i 1,70/100.000 za muškarce). Dobno standardizirana stopa pojavnosti bila je 0,76/100.000 (0,60/100.000 za žene i 0,98/100.000 za muškarce). Godišnja europska dobno standardizirana stopa incidencije bila je 1,10/100.000 (0,86/100.000 za žene i 1,44/100.000 za muškarce). Većina GIST-ova lokalizirana je u želucu (33 slučaja) i

*****, **University of Josip Juraj Strossmayer, Osijek, Croatia**, Faculty of dental medicine and health Osijek, (Assist. prof. Andrea Milostić-Srb, MSc in biology, PhD; Assist. prof. Stana Pačarić, RN, MSN, PhD; Nikolina Farčić, RN, MSN, PhD candidate; Assist. prof. Dunja Degmečić, MD, PhD; Assist. prof. Štefica Mikšić, RN, MSN, PhD; Ivana Jelinčić, RN, MSN); Faculty of medicine Osijek (Nika Srb, MD; Stana Pačarić, RN, MSN, PhD; Nikolina Farčić, RN, MSN, PhD candidate; Assist. prof. Dunja Degmečić, MD, PhD); **Institute of public health Osijek, Osijek, Croatia** (Nikola Kraljik, MD); **University hospital centre Osijek, Osijek, Croatia** (Stana Pačarić, RN, MSN, PhD; Nikolina Farčić, RN, MSN, PhD candidate; Assist. prof. Dunja Degmečić, MD, PhD; Ivana Jelinčić, RN, MSN)

Correspondence address / Adresa za dopisivanje: Andrea Milostić-Srb, Faculty of dental medicine and health Osijek, University of Osijek „Josip Juraj Strossmayer“, J.Huttlera 4. 31 000 Osijek. E-mail: amsrb@fdmz.hr

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tankom crijevu (20 slučajeva). Slijedi peritoneum i omentum (8 slučajeva), dva u pankreasu, jedan rektalni i jedan na drugim lokacijama. Gastrointestinalni stromalni tumori rijetki su i češći u starijoj populaciji. Stopa pojavnosti viša je među muškarcima. Dobiveni rezultati poslužiti će kao reference za proučavanje obrazaca opisne epidemiologije GIST-a na području Osječko-baranjske županije i okolice.

Ključne riječi: epidemiologija, pojavnost, GIST, Osječko-baranjska županija, istočna Hrvatska

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common non epithelial tumors of the gastrointestinal (GI) tract (1-3% of all gastrointestinal malignancies). They are mostly localized in the stomach (60-70%), followed by small intestine (20-30%), and colon and rectum (5-10%). GIST develops outside the digestive tube ($\leq 5\%$) in the mesentery, omentum or retroperitoneum. Most GISTs present asymptotically. They are best identified by computed tomography (CT), and most smears are positive for CD117 (C-Kit), CD34, and/ or DOG-1. There are many classification systems that calculate based on tumor size, mitotic rate, location, and perforation.^{1,2} Histological origin, classification, diagnostic criteria and their biological potential are still controversial. Today, the prevailing attitude is that GIST originate from Cajal cells (pacemaker cells of the GI tract), or from a less-differentiated stem or precursor cells that can develop into interstitial cells of Cajal (ICC). GISTs show a wide variety of clinical behavior ranging from benign to frankly malignant, making the outcome totally unpredictable. Metastases commonly develop in the abdominal cavity and liver; rarely do metastases develop in bones, soft tissues, lymph nodes, lungs and skin.³

GISTs usually occur in older adults, with a mean age of about 60-65 years and somewhat less frequently in diseases equal in men and women.⁴ Symptoms associated with GIST vary depending on the location and size of the lesion. Small GISTs often have no symptoms. An increase in the size of a GIST can develop mass-related symptoms, such as abdominal pain, discomfort in the digestive system, and a feeling of fullness in the abdomen.

In GIST, the most common clinical manifestation was GI bleeding resulting from mucosal ulceration, which occurs in almost half of GIST cases. GI bleeding can change the texture of the stool to dark red or black. In addition, bleeding leads to occasional vomiting of blood. Chronic blood loss can lead to anemia that causes fatigue and in some cases tachycardia. GI bleeding (58%) and abdominal pain (61%) are more common in gastric GISTs however other acute abdominal symptoms are more common in jejunal (40%) and ileal GIST (60%).⁵

The gold standard of GIST treatment is surgical resection by laparoscopy, however if the patient is unstable, then an open laparotomy method is the preferred method of treatment.

Laparoscopic surgery (LSG) is recommended for GISTs smaller than 5 cm located in the stomach and small intestine.⁶ The European Society of Medical Oncology Clinical Practice Guidelines consider any GIST to be potentially malignant and recommend surgical treatment of all GISTs without metastases.⁷ However, not all patients are diagnosed at an early stage; 10%–25% of patients have metastatic disease. Tumors that have spread are more aggressive or have progressed locally may benefit from combined targeted therapies in combination with surgery.⁸ Survival after complete surgical resection ranges from 48% to 80% after 5 years. If resection is not completed, only 9% of patients survive an average of 12 months.^{9,10}

Retrospective assessment of GISTs incidence and other clinical characteristics prior to 2000 is relatively difficult because of problems with identification and an incomplete understanding of their origin. A large number of tumors previously diagnosed as GI leiomyoma, leiomyosarcoma and leiomyoblastoma, as many tumors that were previously considered neurofibromas or Schwannoma.¹¹ The situation has changed since the late 1990s with observations on the origin of GIST in the ICC and the role of c-Kit proto-oncogene mutations. More than 90% of malignant GISTs have aberrant signal transmission mediated by KIT.¹² In the past few years, GIST has become a prototype neoplasm that responds to therapy directed against the target molecule receptor tyrosine kinase Kit (CD117), which induce cell proliferation.¹³ New evidence-based treatment guidelines recommend imatinib as first-line therapy in cases of marginally respectable pathology-confirmed GISTs, with surgery and postoperative imatinib administration advised if imatinib response improves resectability.^{14,15} The epidemiology of these tumors in the Osijek-Baranja County has not been known.

The aim of this study was to determine the incidence of GIST and anatomic localizations in Osijek-Baranja County patients.

Materials and methods

In this study, we show the incidence of gastrointestinal stromal tumors (GISTs) in Osijek-Baranja County. We studied 65 cases of GIST diagnosed in Osijek-Baranja County in the period from January 1, 2004 to December 31, 2017. Data were also derived from hospital discharge notifications called “Onco Type Cards” and outpatient “Malignant Neoplasm Notification”, submitted to the Institute of Public Health for Osijek-Baranja County and the Croatian National Cancer Registry. All cases were verified by a histopathology and immunohistochemical examination, also confirming the previously established histological diagnosis of GIST. The approval of the Ethics Committee of the Clinical Hospital Center Osijek was obtained.

Statistical analysis

Data were encoded according to the International Classification of Diseases Tenth Revision (ICD-10) and ICD-O-3, i.e. code M8936/0-M8936/3.¹⁶ The crude rate of GIST incidence was calculated on the basis of the 2001 and 2011 Croatian census. Age-standardized incidence rates of GIST were calculated by the direct standardization method, using the World Standard Population and the European Standard Population.¹⁷

Statistical analysis was done by the use of SPSS 13.0 software.

Results

In Osijek-Baranja County, in a fourteen-year period from 2004 to 2017 there were 65 registered patients with GISTs. Of the total number of GIST 29 were females (44.6%) and 36 males (55.4%). The mean age at diagnosis was 66.9 years ranging from 37 to 86. Only 1.5% of tumors occurred before the age of 40 years. 98.5% of all GIST cases were over 40 years, more likely between 60-79 years of age (Figure 1).

In the considered period, in the Osijek-Baranja County crude incidence rate of GISTs was 1.47/100,000 (1.26/100,000 for females and 1.70/100,000 for males). The age-standardized (ASR World) incidence rate was 0.76/100,000 (0.60/100,000 for females and 0.98/100,000 for males). The annual European ASR was 1.10/100,000 (0.86/100,000 for females and 1.44/100,000 for males). The incidence rate was higher among men (Figure 2).

The most frequent sites of tumor primary occurrence were the stomach 33 (50.8%) and small intestine 20 (30.8%), followed peritoneum and omentum 8 (12.3%), 2 (3.1%) pancreas, 1 (1.5%) in the rectum and 1 (1.5%) by other locations of tumor, with almost similar distribution by female and male (Figure 3). Forty-nine (75.4%) of GISTs were registered as localized disease and sixteen (24.6%) as regional disease.

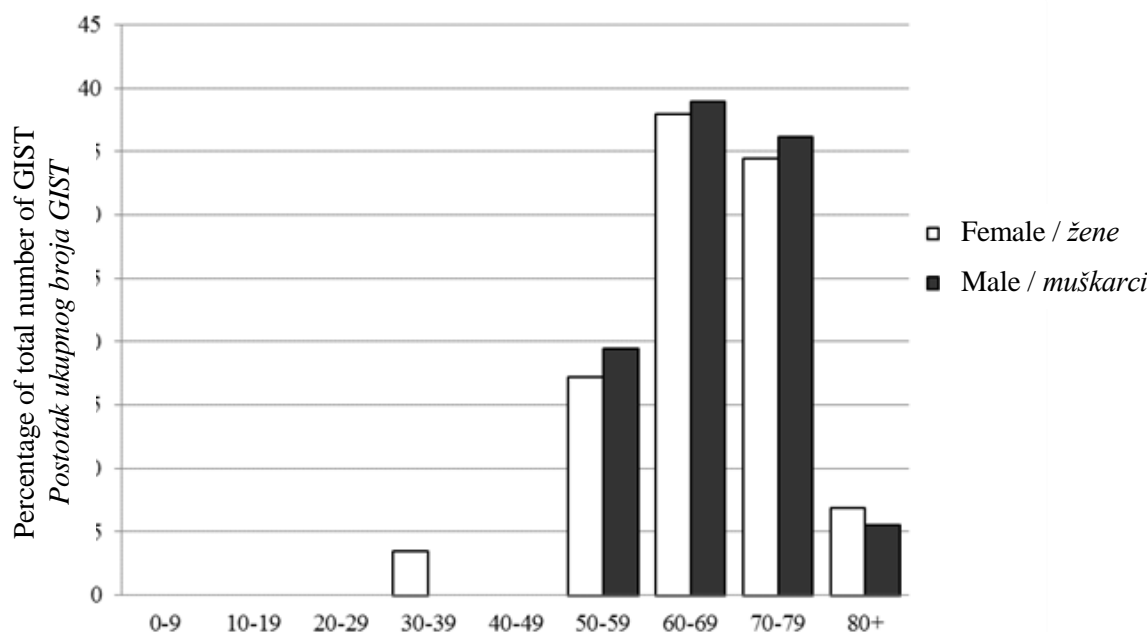


Figure 1 Distribution of GIST patients by age and sex in Osijek-Baranja County, 2004 - 2017
Slika 1. Distribucija GIST bolesnika po dobi i spolu u Osječko-Baranjskoj županiji, 2004. – 2017.

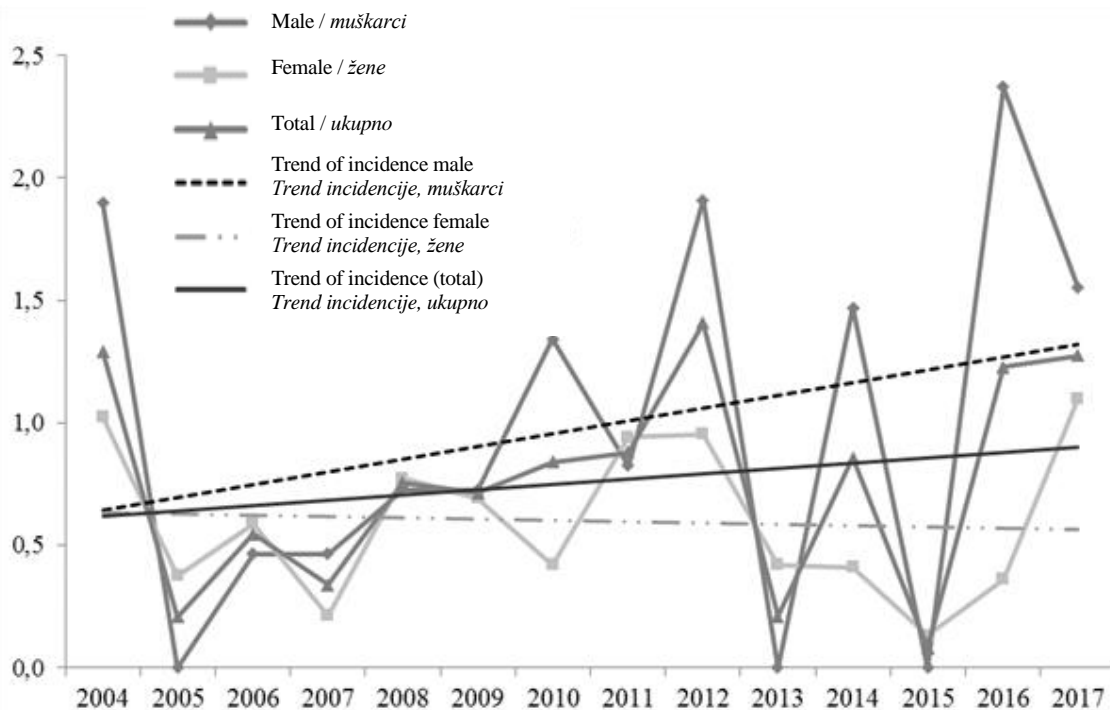


Figure 2 Age-standardized (ASR World) incidence rates of GIST by sex in Osijek-Baranja County, 2004 - 2017
 Slika 2. Dobna standardizirana stopa (ASR World) incidencije GIST-a po spolu u Osječko-Baranjskoj županiji, 2004. – 2017.

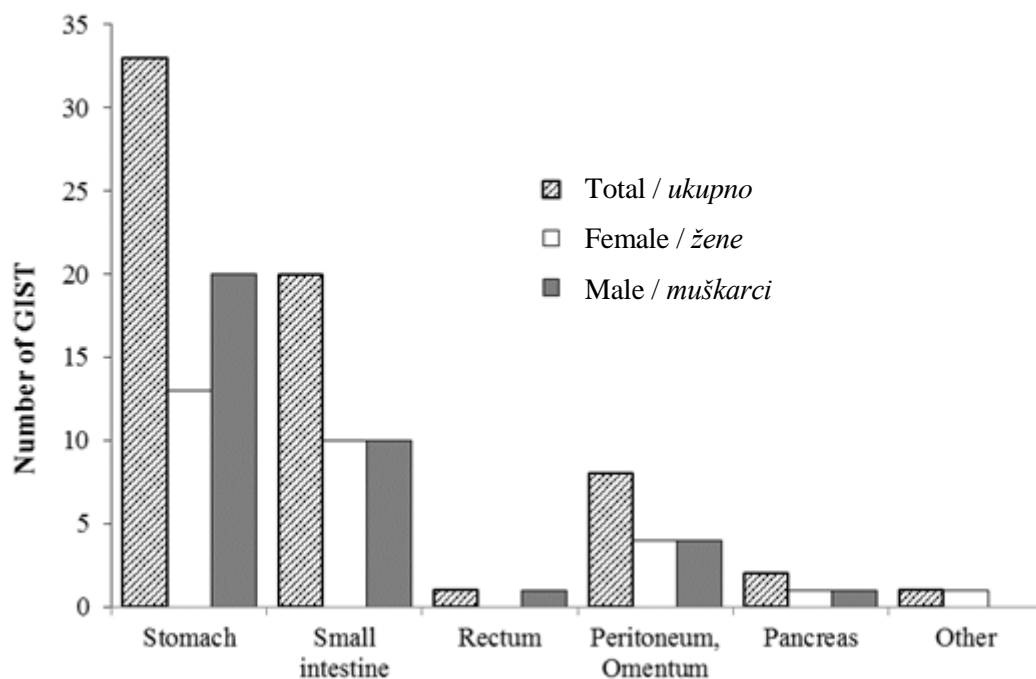


Figure 3 Localization of gastrointestinal stromal tumor (GIST) in female and male patients in Osijek-Baranja County, 2004 - 2017

Slika 3. Lokalizacija gastrointestinalnih stromalnih tumora (GIST) kod ženskih i muških bolesnika u Osječko-Baranjskoj županiji, 2004. – 2017.

Discussion

This study included 65 patients (36 male and 29 female). Their mean age at diagnosis was 66.9 years (ranging from 37 to 86 years). In their research, Cavaliere and associates¹⁸ reported that GIST can occur at any age, peaking around age 60, and that it affects men and women equally. Miettinen and associates¹⁹ reported that GISTs were rare before the age of 40 years and very rare in children and were mildly predominant in men however other research reports did not show gender differences.²⁰

The incidence of GISTs is not known for all populations, most data refer to Caucasian industrialized populations, and prior studies in many countries often provide conflicting results. Some of the papers emphasize the differences in GIST incidence before and after the consensus on GIST detection and classification.²¹ It is primarily a disease of older adults, with the median age at diagnosis reported in the seventh decade of life.²² Despite the described problems, several studies have been published on the basis of long-term population studies on the incidence and survival on GIST. For example, Goettsch et al. 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.²³ A study in western Sweden showed that the annual incidence of GIST was about of 1.45/100,000 inhabitants.²⁴ Epidemiology data from the first population-based study in Iceland from 1990 to 2003 (300,000 inhabitants) estimated an overall world ASR of 1.1/100,000.²⁵ Recent population studies from the GIST Register in the Czech Republic and Slovakia evaluate the annual crude incidence between years 2001-2005 was 0.52/100,000 inhabitants. The annual European ASR and World ASR were 0.44 and 0.31/100,000 inhabitants.²⁶ A study based on pathology reports from 38 hospitals in Korea (2003-2004) reported that the incidence of GISTs was approximately 1.6-2.2/100,000 inhabitants.²⁷ The results of the first Asian nation-wide cancer registry-based study (1998-2008) of GISTs showed that the annual incidence of GISTs in Taiwan ranged from 1.13-1.97/100,000 inhabitants.²⁸ The incidence of these tumors is variable from as low as 4.3-6.8 per million to as high as 19-22 cases per million, with a high degree of variability between different geographic areas.²⁹ GIST showed a female predilection in

France.³⁰ Recent studies in the USA noted an increase in the incidence of the GIST with Ma et al. reporting a 42% increase in the diagnosis of GIST from 2001 to 2011.³¹⁻³³ The overall incidence of GISTs in the 50 states of the United States from 2001-2015 was 0.70 per 100,000 population per year with a slight upward trend noted annually.³⁴ Some reports do exist regarding the incidence of GIST in 3 different regions of China: 0.43 per 100,000 population in Shanxi,³⁵ 2.11 per 100,000 population in Shanghai,³⁶ and 1.55 per 100,000 population in Taiwan.³⁷ In addition, due to racial and weight differences between patients from Eastern and Western countries, there also may be differences regarding tolerance to the targeted agent therapy of the same dosage.³⁸ Given the different study time periods and the lack of confirmation by KIT immuno-histochemical staining in some studies, it is difficult to compare the incidence rates of GISTs across different countries; however, the published literature to date showed that the incidence rates of GISTs in different countries appeared to fall in a similar range.³⁹

GIST therapy is a prototype of treatment based on the "single target molecule" principle where the target enzyme is an abnormal protein of tyrosine kinase activity, the so-called KIT protein.⁴⁰

Osijek-Baranja County is situated in north-eastern Croatia and takes up a total area of 4,155 km², which is 7.3% of Croatia's territory. According to the 2011 census, Osijek-Baranja County has a population of 305,032; 158,141 (52%) are female and 146,891 (48%) are male.³⁹ This population-based study shows that the incidence of GIST in Osijek-Baranja County is comparable to that reported in other European countries. It is very similar to the rate of population based studies in the province of Modena in Italy (0.66/100,000),⁴¹ or in Girona in Spain (0.65-0.90/100,000),²⁸ and significantly higher than the rate that shows the registry for GIST in the Czech Republic and Slovakia.²⁶ The most common localization of the GISTs in our study was the stomach and small intestine, what is also observed in some other studies.^{41,42} Gender, race, and location distribution of GISTs are also uncertain.^{43,44}

In this study, the crude incidence rate of GISTs was 1.47/100,000 (1.26/100,000 for females and 1.70/100,000 for males). The age-standardized (ASR World) incidence rate was 0.76/100,000 (0.60/100,000 for females and 0.98/100,000 for males).

Gastrointestinal stromal tumors are rare, but more common in the older population. The incidence rate was higher among men. These results will serve as reference for studying the patterns of descriptive epidemiology of GISTs in the Osijek-Baranja County and the surrounding region.

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