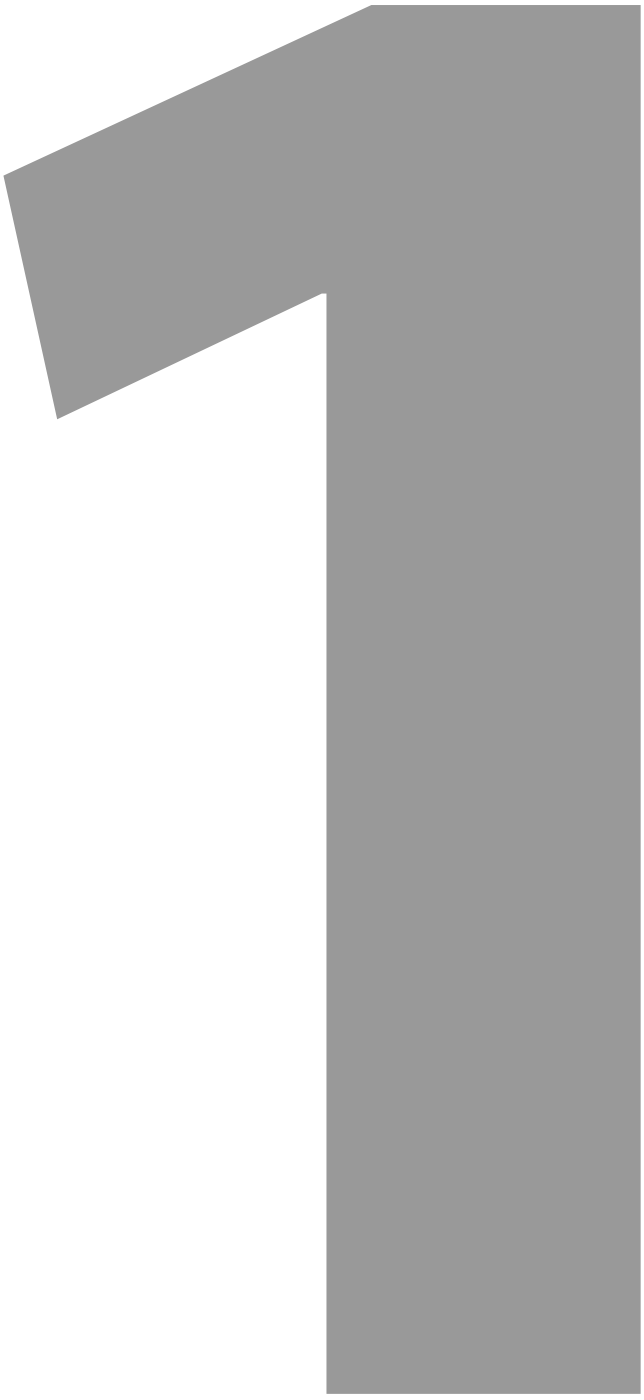
Improving diagnosis and treatment of gastrointestinal stromal tumor (GIST) patients: Results from the Dutch GIST Registry

Farag-Kal, S.



Chapter 1

General introduction and thesis outline

General Introduction

GIST diagnosis and pathogenesis

Gastrointestinal stromal tumor (GIST) is a rare mesenchymal malignancy in the gastrointestinal tract and arises from the interstitial cells of Cajal.(1) GIST can occur anywhere in the gastrointestinal tract, but predominantly arises in the stomach (60%) and small intestine (25%).(1) Worldwide, the annual incidence is between 11 and 19.6 per million. In the Netherlands the incidence is estimated at 250 patients per year. The highest incidence is found in the age group of 60-74 years. Clinical symptoms are mostly nonspecific and involve satiety, dysphagia, fatigue, abdominal pain, and obstruction.(2) Anemia is often revealed during workup and is mostly related to intratumoral hemorrhage or mucosal bleeding. However, GIST can also be detected in asymptomatic patients during diagnostics for other purposes.

In 1998 Hirota et al. published their discovery about the expression of KIT (CD117) in over 95% of GISTs.(3) They found that an activating mutation involving the *KIT* gene is important to their tumorigenesis. KIT is a type III tyrosine kinase receptor (TKR) and binding of stem cell factor (SCF) (the ligand of KIT) results in homodimerization and kinase activation. An oncogenic mutation in *KIT* causes ligand-independent activation. In 75% of GISTs an activating mutation in *KIT* is found and in 10% an activating mutation involving the platelet-derived growth factor receptor alpha (*PDGFRA*), another type III TKR,is found. Over 65% of GISTs harbor a mutation in *KIT* exon 11, in the juxtamembrane domain. *PDGFRA* mutations mostly involve exon 18, in the activation loop.(1) (Figure 1)

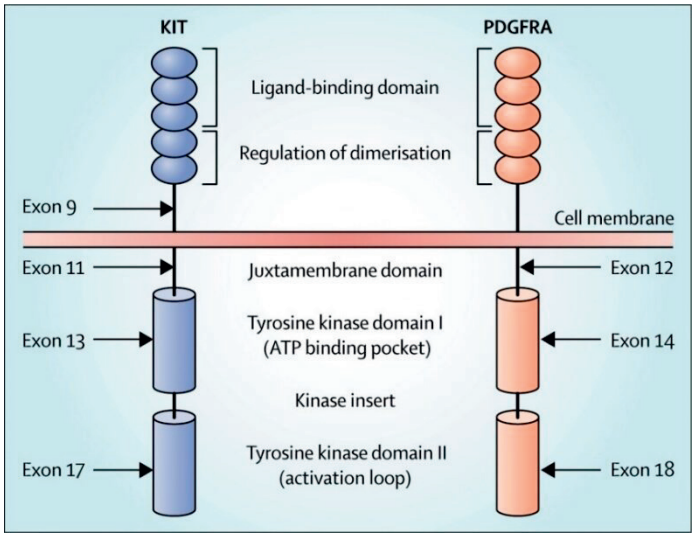


Figure 1: Structure of KIT and PDGFRA receptor kinases. *Adapted from Joensuu, Hohenberger, and Corless 2013* [7].

Approximately 15% of all GISTs are wild type for *PDGFRA* and *KIT*. This is a heterogeneous group and includes succinate dehydrogenase subunit (SDH)-deficient GISTs, neurofibromatosis type 1 (NF1) associated GISTs, and BRAF/RAS mutated GISTs.(4) SDH-deficient GISTs and NF1 associated GISTs can be related to familial syndromes. The Carney-Stratakis syndrome involves germline mutations of SDHA, -B, -C, and –D germline mutations leading to a dyad of GIST and paraganglioma.(5) The Carney triad on the other hand is found in non-familiar SDHB-deficient GISTs and involves gastric GIST, paraganglioma, and pulmonary chondroma.(5) Familial GISTs involving germline *KIT*- or *PDGFRA*-mutations are very rare and are associated with multiple and young onset GISTs.(6)

Treatment of GIST

Primary treatment of GIST consists of resection of the tumor. The aim of surgery is complete resection (R0) of the GIST without dissection of lymph nodes.(8) Despite surgery disease recurrence is seen in approximately 40% within 5 years.(9) Tumor site, mitotic count, and tumor size are important prognostic factors for recurrence.(10) In general, tumors originating from a non-gastric site have more malignant potential than gastric GISTs and larger tumors and tumors with high mitotic count are more likely to recur. In large tumors a laparoscopic approach is discouraged, because of the high risk of tumor rupture associated with high risk of recurrence. Table 1 shows the risk stratification as defined by the Armed Forces Institute of Pathology (AFIP). (Table 1) This stratification method is supported by 3 large retrospective studies on prognostic determinants of GIST. (10–12)

Table 1: Risk classification for primary GIST by mitotic index, size, and tumor site. *Adapted from Miettinen and Lasota 2006*.

Tumor Parameters		**Tumor Location**			
Tumor Size	**Mitotic Rate**	**Gastric**	**Jejunal and Ileal**	**Duodenal**	**Rectal**
≤2 cm	≤5/50 HPFs	0% None	0% None	0% None	0% None
>2 cm ≤5 cm	≤5/50 HPFs	1.9% Low	4.3% Low	8.3% Low	8.5% Low
>5 cm ≤10 cm	≤5/50 HPFs	3.6% Low	24% Moderate	34% High‡	57% High‡
>10 cm	≤5/50 HPFs	12% Moderate	52% High		
≤2 cm	>5/50 HPFs	0%†	50%†	§	54% High
>2 cm ≤5 cm	>5/50 HPFs	16% Moderate	73% High	50% High	52% High
>5 cm ≤10 cm	>5/50 HPFs	55% High	85% High	86% High	71% High‡
>10 cm	>5/50 HPFs	86% High	90% High		

† Tumor categories with very few cases; ‡ Combined in duodenal and rectal GISTs because of small number of cases; § No tumor of such category included in the study.

In 2002 the drug imatinib was introduced in the treatment of GIST. This is a tyrosine kinase inhibitor (TKI) that targets Bcr-Abl, *KIT* and *PDGFR*, which is orally administered. Consequently the prognosis of patients with advanced GIST has been spectacularly improved. Up to 85% of GIST patients with advanced disease derive clinical benefit from imatinib 400mg daily.(7) For patients with high-risk of recurrence (10 year recurrence rate >50%), adjuvant treatment with imatinib for a total of 3 years is recommended.(8,13) This increased progression-free survival (PFS) from 36% to 65.6%. Compared to 1 year of adjuvant imatinib treatment overall 5-year survival was also reported to improve with 3 years adjuvant imatinib treatment (92.0% vs 81.7%).(13)

Neo-adjuvant treatment with imatinib is recommended in patients with locally advanced disease when resection with positive margins or clear perioperative morbidity is expected.(8) Imatinib is used to downsize the tumor. Surgery is performed when maximum radiological response is achieved. In general, this is the case after 6 to 12 months of imatinib treatment.(14)

The effect of TKIs depends on the type of mutation. It is therefore important to assess *KIT* and *PDGFR* mutation status before the initiation of adjuvant or neoadjuvant therapy. (15,16) For instance, imatinib 400mg shows less benefit in GISTs harboring a mutation in *KIT* exon 9 and studies in advanced GISTs shows that the use of a 800mg imatinib in this case is more beneficial.(17) A D842V substitution in exon 18 of the *PDGFRA* gene, shows primary resistance to imatinib.(18) Furthermore, GISTs who are wild type for *KIT* and *PDGFRA* are less sensitive and even show primary resistance to imatinib treatment.

In metastatic disease, imatinib treatment with a standard dose of 400mg daily is used as first-line systemic palliative treatment. Therapy is continued until disease progression. Median progression-free survival in advanced disease is 20-24 months and overall survival is 5 years. Interestingly, around 20% of patients live longer than 10 years. (19) When the disease progresses this is often (80%) caused by a secondary mutation in the *KIT* gene. (20) In general these mutation occur in the ATP binding pocket of the *KIT* gene (exons 13 and 14).(21) Secondary mutations occur heterogeneously across different lesions, but can also vary within one lesion. Debate is still ongoing whether resection of the (single) progressive metastasis in case of limited progression is beneficial.(22) Some studies also advocate a dose escalation of imatinib to 800 mg daily.(17,23) This could be effective in case of secondary resistant mutations, but can also increase efficacy in patients with a low drug exposure as pharmacokinetic variability is high.(24)

Side effects of imatinib treatment are mostly mild and clinically manageable.(25,26) In general permanent discontinuation of treatment because of toxicity can be avoided. Most common side effects are edema (mostly periorbital), nausea, diarrhea, myalgia, fatigue, skin toxicity, headache and pain. Also, hematologic side effects are common with up to 90% of GIST patients having anemia and up to 40% having neutropenia.(25,26)

In case of progression or intolerance to imatinib, sunitinib has become a registered second line treatment. Sunitinib is a TKI that targets vascular endothelial growth factor

receptor (VEGFR), PDGFR, KIT and, and colony stimulating factor receptor (CSF-1R). It has been proven effective in a dose regimen of 50 mg daily '4-weeks on-2 weeks off'.(27) Median PFS was 27 weeks compared to 6 weeks in the placebo arm. Continuous dosing in a dose of 37.5 mg is reported to be equally effective with similar tolerance.(28) Regorafenib, a TKI targeting VEGFR, KIT, PDGFR, fibroblast growth factor receptor (FGFR), and RET has been registered in Europe in 2014 as an acknowledged third line treatment in progressive disease. In a dosing schedule of 160 mg daily every three of four weeks regorafenib has demonstrated to improve progression-free survival for up to 4 months.(29)

Response evaluations and follow-up

Computed tomography (CT) scans are considered standard in the response evaluation in routine clinical care.(8,30,31) On CT scan the anti-tumor activity does not only translate into decrease in size, but also in decrease in density. Prior research has shown that response evaluation using both tumor size and density (CHOI criteria) is better correlated with time to progression compared to standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The use of RECIST criteria might lead to underestimation of the effectiveness of TKI's in GIST.(32,33)

MRI usually provides better preoperative staging information in case of rectal GISTs. ^{18}F-flurodeoxyglucose (FDG)-positron emission tomography (PET) has proven to be an effective way for early response evaluation of systemic treatment.(34) There is still a lot of debate on the role of PET in routine clinical care.

More important, there is no known optimal follow-up schedule for patients with GIST. ASCO and ESMO guidelines for the diagnosis and treatment of GIST patients do exist. However, routine follow-up schedules still differ across treatment centers and countries. (8,30)

The Dutch GIST Registry

In January 2014 the Dutch GIST Consortium (DGC) was established by the five leading GIST centers in the Netherlands, the Netherlands Cancer Institute/Antoni van Leeuwenhoek (NKI/AvL), Leiden University Medical Center (LUMC), Erasmus Medical Center (EMC), Radboud University Medical Center Nijmegen (Radboud UMC) and University Medical Center Groningen (UMCG). In January 2014 the DGC has initiated the Dutch GIST Registry The GIST registry includes a retrospective dataset as well as a prospective dataset. Retrospective data has been collected from all patients treated in five GIST centers in the Netherlands between 2009 and 2014. Prospectively, data is collected from patients diagnosed with GIST and treated in one of the GIST centers from January 2014 and onwards.

Approximately 200 variables per patient are entered in the registry. The variables include patients' demographics, tumor characteristics including pathological and genetic information, systemic therapies with their start and stop dates, adverse events with start

and stop dates, any GIST related surgery, medical history and co-medication. In addition, the data obtained during hospital visit are put in the database, containing physical examination, laboratory results, tumor measurements by any imaging technique (e.g. CT-scan, MRI, PET-CT), electrocardiography results and QOL results.

Outline of the thesis

The focus for this thesis will be on treatment strategies and follow-up in GIST patients and in particular subgroups of GIST patients in daily clinical practice. In the first part of this thesis (Chapter 2) clinical characteristics and treatment patterns of different subgroups of GIST patients will be assessed.

An important subgroup are the elderly GIST patients (> 75 years of age). Paragraph 2.1 will assess differences in local treatment and systemic treatment between elderly patients and younger patients treated in one of our 5 GIST centers.

A second important subgroup are the patients with a *PGFDRA* mutated GIST. *PDGFRA* mutated GISTS are very rare. A D842V substitution in exon 18 is the most common *PDGFRA* mutation. The specific mutation in exon 18 of *PDGFRA* is essential for their sensitivity to imatinib treatment. Paragraph 2.2 describes treatment response in a cohort of GIST patients harboring various *PDGFRA* exon 18 mutations.

A third important subgroup of GIST patients are the patients with underlying germline mutations. Although GISTs harboring a *KIT* mutation are almost always sporadic, familial GISTs associated with germline *KIT* or *PDGFRA* mutations do occur. Paragraph 2.3 reports the effects of imatinib on the tumor and on the cutaneous hyperpigmentation associated with this rare syndrome.

Despite the spectacular improvements in the treatment of GIST since the introduction of imatinib, disabling and even life-threatening adverse events can occur. In chapter 3 the occurrence and management of agranulocytosis is described.

Follow-up and assessment of treatment effects are described in chapter 4 and 5. In chapter 4 the value of ^{18}F-flurodeoxyglucose (FDG)-positron emission tomography (PET) in the management of GIST patients treated in neo-adjuvant (4.1) and palliative setting (4.2) is assessed. Chapter 5 describes the pharmacokinetics and occurrence of underexposure of imatinib in a large observational cohort of GIST patients with over 400 drug levels measured in more than 100 patients during routine outpatient care. Finally, in chapter 6 the content of this thesis and future prospects in the treatment of GIST are discussed.

References

1. Corless CL. Gastrointestinal stromal tumors: what do we know now? Mod Pathol [Internet]. Nature Publishing Group; 2014;27 Suppl 1(S1):S1–16.
2. Chou F, Eng H. Smooth muscle tumors of the gastrointestinal tract : Analysis of prognostic factors. 1996;171–7.
3. Hirota S, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, et al. Gain-of-function mutations of platelet-derived growth factor receptor 18 gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125(03):660–7.
4. Boikos SA, Stratakis CA. The genetic landscape of gastrointestinal stromal tumor lacking KIT and PDGFRA mutations. 2014;401–8.
5. Gist KITP, Pantaleo MA, Astolfi A, Urbini M, Nannini M, Paterini P, et al. Analysis of all subunits , SDHA , SDHB , SDHC , SDHD , of the succinate dehydrogenase complex in. Eur J Hum Genet [Internet]. Nature Publishing Group; 2013;22(1):32–9.
6. Ricci R. Syndromic gastrointestinal stromal tumors. Hered Cancer Clin Pract [Internet]. 2016 Dec 19;14(1):15.
7. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumor. Lancet [Internet]. Elsevier Ltd; 2013;382(9896):973–83.
8. Casali PG, Blay JY. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2014 Sep 1;25(suppl 3):iii21–6.
9. Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, et al. Risk of recurrence of gastrointestinal stromal tumor after surgery: an analysis of pooled population-based cohorts. Lancet Oncol [Internet]. 2012 Mar 10;13(3):265–74.
10. Miettinen M, Makhloof H, Sobin HL, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochmeical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol. 2006;30(4):477–89.
11. Miettinen M, Sobin L, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52–68.
12. Miettinen M, Lasota J. Gastrointestinal stromal tumors-definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch. 2001;438(1):1–12.
13. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: A randomized trial. Jama [Internet]. 2012;307(12):1265–72.
14. Yang T, Hou M, Chen P, Hsin I. Clinical Outcomes and Complications of Endoscopic Submucosal Dissection for Superficial Gastric Neoplasms in the Elderly. 2015;94(44):1–7.
15. Gramza AW, Corless CL, Heinrich MC. Resistance to tyrosine kinase inhibitors in gastrointestinal stromal tumors. Clin Cancer Res. 2009;15(24):7510–8.
16. Debiec-Rychter M, Dumez H, Judson I, Wasag B, Verweij J, Brown M, et al. Use of c-*KIT*/*PDGFRA* mutational analysis to predict the clinical response to imatinib in patients with advanced

gastrointestinal stromal tumors entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2004;40(5):689–95.

17. Debiec-Rychter M, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumors. Eur J Cancer. 2006;42(8):1093–103.
18. Corless CL. *PDGFRA* Mutations in Gastrointestinal Stromal Tumors: Frequency, Spectrum and In Vitro Sensitivity to Imatinib. J Clin Oncol [Internet]. 2005;23(23):5357–64.
19. Casali PG, Zalcberg J, Le Cesne A, Reichardt P, Blay J-Y, Lindner LH. Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Tr. J Clin Oncol. 2017;35(15):1713–20.
20. Nishida T, Kanda T, Nishitani A, Takahashi T, Nakajima K, Ishikawa T, et al. Secondary mutations in the kinase domain of the KIT gene are predominant in imatinib-resistant gastrointestinal stromal tumor. 2008;99(4):799–804.
21. Debiec-Rychter M, Cools J, Dumez H, Sciot R, Stul M, Mentens N, et al. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology [Internet]. 2005 Feb;128(2):270–9.
22. Bauer S, Rutkowski P, Hohenberger P, Miceli R. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib e Analysis of prognostic factors (EORTC-STBSG collaborative study) *. Eur J Surg Oncol [Internet]. Elsevier Ltd; 2014;40(4):412–9.
23. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the KIT receptor tyrosine kinase: S0033. J Clin Oncol. 2008 Feb;26(4):626–32.
24. Demetri GD, Wang Y, Wehrle E, Racine A, Nikolova Z, Blanke CD, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. J Clin Oncol. 2009 Jul;27(19):3141–7.
25. Joensuu H, Trent JC, Reichardt P. Practical management of tyrosine kinase inhibitor-associated side effects in GIST. Cancer Treat Rev. 2011;37(1):75–88.
26. Ami E Ben, Demetri GD. Expert Opinion on Drug Safety A safety evaluation of imatinib mesylate in the treatment of gastrointestinal stromal tumor. Expert Opin Drug Saf. 2016;15(4):571–8.
27. Reichardt P, Kang Y, Rutkowski P, Schuette J, Rosen LS, Seddon B, et al. Clinical Outcomes of Patients with Advanced Gastrointestinal Stromal Tumors: Safety and Efficacy in a Worldwide Treatmentuse Trial of Sunitinib. Cancer. 2015;121(9):1405–13.
28. George S, Blay JY, Casali PG, Cesne A Le, Stephenson P, Deprimo SE, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumor after imatinib failure. Eur J Cancer 2009;45(11):1959–68.
29. Demetri GD, Reichardt P, Kang Y, Blay J, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumors after failure of imatinib and

sunitinib: an international, multicentre, prospective, randomised, placebocontrolled phase 3 trial (GRID). Lancet. 2013;381(9863):1–17.

30. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw. 2010;8 Suppl 2(April):S1–41; quiz S42–4.
31. Judson I, Bulusu R, Seddon B, Dangoor A, Wong N, Mudan S. UK clinical practice guidelines for the management of gastrointestinal stromal tumors (GIST). Clin Sarcoma Res 2017;1–10.
32. Choi H, Charnsangavej C, de Castro Faria S, Tamm EP, Benjamin RS, Johnson MM, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol 2004 Dec;183(6):1619–28.
33. Choi H. Response evaluation of gastrointestinal stromal tumors. Oncologist [Internet]. 2008;13 Suppl 2:4–7.
34. Scott AM, Gunawardana DH, Kelley B, Stuckey JG, Byrne AJ, Ramshaw JE, et al. PET changes management and improves prognostic stratification in patients with recurrent colorectal cancer: results of a multicenter prospective study. J Nucl Med. 2008;49:1451–7.