Why We Still Need the Better Risk Classification for GIST

Piotr Rutkowski, MD, PhD

Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

The fundamental treatment for primary, localized, resectable gastrointestinal stromal tumors (GIST) is radical resection with negative margins.¹ Nonetheless, virtually all GISTs are associated with some risk of recurrence.^{2–4} The identification of the risk factors for relapse after primary surgery is essential to establish a reliable prognosis and follow-up schedule, and the most importantly, to select the patients who may potentially benefit from the adjuvant therapy, aiming for a decrease in disease recurrences.

Currently, the main criteria for aggressiveness in GIST are based on primary tumor site, size and mitotic index (localized tumors) as well as the presence of metastases (overtly malignant cases).^{4,5} The staging system of the American Joint Committee on Cancer (AJCC) combines three crucial features (i.e., size, site, and mitotic index) and reflects the data showing that gastric GISTs demonstrate a much lower rate of aggressive behavior than jejunal and ileal GISTs of comparable size, mitotic rate, or both.^{5–8}

More recently, tumor rupture (spontaneous or iatrogenic) was established as an additional important risk factor strongly associated with the increased rates of relapses and was included in the modified National Institutes of Health criteria by Joensuu⁹ in 2008.¹⁰ Moreover, prognostic contour maps developed on non-linear modeling may be more appropriate for estimation of individualized outcomes.¹¹

In addition to these aforementioned clinicopathologic factors, accumulating data show that *KIT* and *PDGFRA* mutational status also may have a prognostic importance in

primary GIST. However, the kinase mutation status still is not incorporated into the risk stratification of primary tumors. Several studies have implied more favorable behavior after resection of primary tumors harboring exon 11 *KIT* point mutations or insertions and *PDGFRA* exon 18 mutations compared with tumors carrying exon 9 *KIT* duplications and exon 11 *KIT* deletions, especially those involving codons 557 and/or 558 or those in homozygous state.^{12–15}

Recent extended analysis of clinicopathologic and molecular data from 1844 patients with localized GIST who underwent surgery with curative-intent (R0/R1) and were registered in the European ConticaGIST database confirmed that specific tumor genotype (*KIT* exon 11 deletions involving Trp557/Lys558, including p.Trp557_Lys558del and *KIT* exon 9 duplications) is an independent molecular prognostic variable associated with GIST of gastric origin and should be included in prognostic classification to optimize adjuvant imatinib treatment of primary GIST patients.¹⁶ Population-based series of patients after resection of primary GIST have confirmed a more favorable prognosis for *PDGFRA* mutations and *KIT* exon 11 duplication mutation or deletion of one codon.^{17,18}

In the current *Annals of Surgical Oncology*, Hølmek et al.¹⁹ reports a retrospective study that analyzed a population-based cohort of 295 patients with primary gastric GIST and found a correlation of mutational status with anatomic distribution of tumor in the stomach. Specifically, the authors detected that *PDGFRA*-mutated tumors were located mainly in the lower two thirds of the stomach, in contrast to *KIT*-mutated GIST located in the upper part. Moreover, deletions 557 and 558 in the *KIT* gene are located in high prevalence in the upper part. This has clinical relevance because in this study, more than 90 % of the tumors located in the upper third of the stomach carried imatinib-sensitive mutations. On the other hand, they were related to a higher risk or recurrence than tumors in the

lower end. Moreover, the patients with exophytic or luminal tumors without rupture, irrespective of size, had an excellent prognosis, and such patients may not benefit from adjuvant therapy. In contrast, the transmural growth pattern was related to poor outcomes and correlated with increased mitotic index.

The recent work of Hølmekbakk et al.^{20,21} elegantly complements their previous study on the original and clinically meaningful classification of rupture in GIST.²² The authors for first time discovered the correlation between anatomic localization in the stomach and tumor extent in the layers of stomach wall, which may provide additional information and directions for adjuvant therapy.

Subsequently, the authors have tried to specify the risk criteria for stomach GIST. Further developments in molecular analysis (e.g., inclusion genomic index) may further optimize the individual risk assessment and inclusion criteria for adjuvant therapy after primary tumor resection.^{23,24} It definitively is the time to include mutational status in a prognostication system, at least for GIST of stomach origin. Nevertheless, for example, we still do not know the optimal management with adjuvant therapy for certain molecular subtypes of GIST. Findings show that *KIT* exon 11 mutations at codons 557 and 558 are related both to a high risk of recurrence and to pronounced sensitivity to imatinib. On the other hand, they may develop earlier resistance to imatinib, especially in the metastatic setting.²⁵ This implies that adjuvant imatinib therapy may be administered more than 3 years in the individualized setting.²⁶

DISCLOSURES Piotr Rutkowski has received honoraria for lectures and serves on the advisory boards of Novartis, BMS, MSD, Sanofi, Merck, Pierre Fabre, Pfizer, and Blueprint Medicines outside the scope of the manuscript.

REFERENCES

- Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2018;29(Suppl 4):51–67. <https://doi.org/10.1093/annonc/mdy096>.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors: definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch*. 2001;438:1–12.
- DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000;231:51–8.
- Rutkowski P, Nowecki ZI, Michej W, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumors (GISTs). *Ann Surg Oncol*. 2007;14:2018–27.
- Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol*. 2006;23:70–83.
- Miettinen M, Sobin LH, 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;29:52–68.
- Miettinen M, Makhlof H, Sobin LH, et al. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol*. 2006;30:477–89.
- Rutkowski P, Wozniak A, Dębiec-Rychter M, et al. Clinical utility of the new American Joint Committee on Cancer staging system for gastrointestinal stromal tumors: current overall survival after primary tumor resection. *Cancer*. 2011;117:4916–24.
- Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol*. 2008;39:1411–9.
- Rutkowski P, Bylina E, Wozniak A, et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour: the impact of tumour rupture on patient outcomes. *Eur J Surg Oncol*. 2011;37:890–6.
- Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol*. 2012;13:265–74.
- Martin J, Poveda A, Llombart-Bosch A, et al. Spanish Group for sarcoma R: deletions affecting codons 557–558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). *J Clin Oncol*. 2005;23:6190–8.
- Wozniak A, Rutkowski P, Piskorz A, et al., on behalf of the Polish GIST Registry. Prognostic value of KIT/PDGFRA mutations in gastrointestinal stromal tumours (GIST): Polish Clinical GIST Registry experience. *Ann Oncol*. 2012;23:353–60.
- Wardelmann E, Losen I, Hans V, et al. Deletion of Trp-557 and Lys-558 in the juxtamembranedomain of the c-kit protooncogene is associated with metastatic behavior of gastrointestinal stromal tumors. *Int J Cancer*. 2003;106:887–95.
- Wozniak A, Rutkowski P, Schöffski P, et al. Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a European multicenter analysis based on ConticaGIST. *Clin Cancer Res*. 2014;20:6105–16. <https://doi.org/10.1158/1078-0432>.
- Wozniak A, Laenen A, Gutiérrez A et al. Extended ConticaGIST analysis adds to the amended prognostication in gastrointestinal stromal tumors (GIST) based on tumor KIT/PDGFRA genotype status. Connective Tissue Oncology Society Annual Meeting 2018, Poster 190.
- Joensuu H, Rutkowski P, Nishida T, et al. KIT and PDGFRA mutations and the risk of GI stromal tumor recurrence. *J Clin Oncol*. 2015;33:634–42.
- Bylina E, Osuch C, Rutkowski P. Analysis of reliability of different risk classifications for assessment of relapses of gastrointestinal stromal tumors (GIST): the impact of primary tumor genotyping. *Oncol Clin Pract*. 2020;16:276–94.
- Hølmekbakk T, Wiedswang AM, Meza-Zepeda LA, et al. Integrating anatomical, molecular, and clinical risk factors in gastrointestinal stromal tumor of the stomach. *Ann Surg Oncol*. 2021. <https://doi.org/10.1245/s10434-021-09605-8>.
- Hølmekbakk T, Bjerkehagen B, Boye K, et al. Definition and clinical significance of tumour rupture in gastrointestinal stromal tumours of the small intestine. *Br J Surg*. 2016;103:684–91.
- Hølmekbakk T, Hompland I, Bjerkehagen B, et al. Recurrence-free survival after resection of gastric gastrointestinal stromal tumors classified according to a strict definition of tumor rupture: a population-based study. *Ann Surg Oncol*. 2018;25:1133–9.
- Boye K, Berner JM, Hompland I, et al. Genotype and risk of tumour rupture in gastrointestinal stromal tumour. *Br J Surg*. 2018;105:e169–75.

23. Lartigue L, Neuville A, Lagarde P, et al. Genomic index predicts clinical outcome of intermediate-risk gastrointestinal stromal tumours, providing a new inclusion criterion for imatinib adjuvant therapy. *Eur J Cancer*. 2015;51:75–83.
24. Rutkowski P, Hompes D. Combined therapy of gastrointestinal stromal tumors. *Surg Oncol Clin North Am*. 2016;25:735–59.
25. Patrikidou A, Domont J, Chabaud S, et al. Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group. *Eur J Cancer*. 2016;52:173–80.
26. Raut CP, Espat NJ, Maki RG, Araujo DM, Trent J, Williams TF, et al. Efficacy and tolerability of 5-year adjuvant imatinib treatment for patients with resected intermediate- or high-risk primary gastrointestinal stromal tumor: the PERSIST-5 clinical trial. *JAMA Oncol*. 2018;4:e184060. <https://doi.org/10.1001/jamaoncol.2018.4060>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.