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INDIVIDUAL PROGNOSTICATION OF GASTROINTESTINAL STROMAL TUMORS BASED ON CLINICAL-MORPHOLOGICAL AND MOLECULAR-GENETIC MARKERS

Xoldarova Erkinoy

Andijan State Medical Institute
Department of Histology and Cytology

Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and are characterized by marked biological heterogeneity. Accurate prognosis cannot be based on tumor size alone because anatomic site, mitotic activity, tumor rupture, histological phenotype, immunohistochemical profile, and driver genotype materially modify recurrence risk and treatment sensitivity. The purpose of this review was to systematize clinically relevant prognostic markers and to formulate an integrated approach to individualized risk assessment. A structured narrative review of contemporary international guidelines, peer-reviewed studies, and Uzbekistan-based publications and clinical protocols was performed, with emphasis on evidence concerning KIT, PDGFRA, SDH-complex abnormalities, BRAF/NF1 alterations, DOG1/CD117 expression, mitotic index, tumor location, size, and rupture. The synthesis demonstrates that classical morphology remains the foundation of risk stratification, while molecular-genetic characterization refines both prognosis and therapeutic prediction. KIT exon 11 deletions involving codons 557/558, KIT exon 9 alterations, SDH-deficient status, and selected wild-type molecular subgroups may be associated with distinct clinical behavior; in contrast, PDGFRA-mutant gastric GISTs, particularly non-D842V variants, often show a more indolent phenotype, although genotype must always be interpreted together with morphology and stage. A practical individual prognostic model should therefore combine clinical stage, anatomic site, tumor size, mitotic count per 5 mm², rupture status, resection margin, immunophenotype, and mutational profile. Such integration provides a stronger basis for recurrence-risk estimation, selection of adjuvant tyrosine kinase inhibitor therapy, and personalized surveillance than any single marker used in isolation.

Keywords: gastrointestinal stromal tumor; GIST; prognosis; KIT; PDGFRA; DOG1; mitotic index; molecular markers; personalized medicine.

INTRODUCTION

Gastrointestinal stromal tumors represent a biologically distinct group of mesenchymal neoplasms that arise predominantly in the stomach and small intestine and show differentiation toward the interstitial cells of Cajal or related precursor cells. Although GISTs are rare in the general population, they constitute the most frequent mesenchymal tumor of the gastrointestinal tract and have become a paradigmatic model of precision oncology because their pathogenesis and treatment are closely linked to activating kinase mutations (1,2). The clinical course ranges from small, incidentally detected lesions with minimal metastatic potential to highly aggressive tumors that recur rapidly after apparently complete resection.

Modern prognostication is therefore based on a multidimensional assessment. Traditional systems use tumor size, mitotic activity, and anatomic site, while contemporary recommendations additionally emphasize tumor rupture and molecular genotype. The ESMO-EURACAN-GENTURIS guidance considers mutation testing a standard component of diagnostic work-up in patients who may require systemic therapy because genotype has both predictive and prognostic value (1). The 2025 Asian consensus update similarly highlights molecular classification as integral to therapeutic decision-making and risk assessment, especially in KIT/PDGFRA wild-type tumors and in cases with atypical clinical behavior (3).

The relevance of personalized prognostication is particularly high in settings where the decision to administer adjuvant imatinib must balance recurrence risk against treatment burden. A patient with a gastric, low-mitotic GIST may have a substantially different prognosis from a patient with a similarly sized jejunal tumor, and a KIT exon 11 deletion may carry different implications from a PDGFRA D842V mutation or an SDH-deficient phenotype. Uzbekistan-based clinical reports and national protocols also reflect the transition from purely morphologic diagnosis toward integrated immunohistochemical and targeted therapeutic approaches (8-10). The aim of this article is to summarize the clinical-morphological and molecular-genetic markers that determine GIST behavior and to propose a practical integrated model for individualized prognosis.

LITERATURE REVIEW

Risk stratification in GIST has evolved from simple size-based classification to systems that incorporate mitotic activity and tumor site. The modified NIH criteria and Armed Forces Institute of Pathology principles demonstrated that gastric tumors generally behave more favorably than small-intestinal or rectal tumors of comparable size and mitotic rate. More recent clinical practice has placed major emphasis on tumor rupture because rupture may result in peritoneal seeding and is associated with a very high risk of relapse (1,4). These variables remain clinically useful because they are inexpensive, reproducible when pathology reporting is standardized, and immediately available after resection.

At the molecular level, most GISTs harbor activating mutations in KIT, most commonly exon 11, followed by exon 9, whereas a smaller proportion contain PDGFRA mutations. A subset lacks both KIT and PDGFRA alterations and may instead demonstrate SDH-complex deficiency, BRAF mutation, NF1-associated biology, or rarer events (2,5). These molecular classes are not merely taxonomic. They influence tumor location, morphology, natural history, sensitivity to tyrosine kinase inhibitors, and patterns of acquired resistance. Genomic profiling studies have emphasized that the exact variant, rather than only the affected gene, may carry clinically meaningful information (5).

Immunohistochemistry continues to bridge morphology and molecular pathology. CD117 is positive in the large majority of GISTs, while DOG1 is highly useful, including in a proportion of KIT-negative tumors. CD34, SMA, S100, desmin, and SDHB staining can support differential diagnosis or help identify particular biological subgroups. Loss of SDHB expression is a practical surrogate for SDH-deficient GIST and should prompt consideration of syndromic associations and a distinct surveillance strategy. Thus, the current diagnostic paradigm is layered: histomorphology establishes the tumor pattern, immunohistochemistry confirms lineage, and genotyping defines the biologic and therapeutic subtype (1,2,5).

Regional experience from Uzbekistan is relevant because it demonstrates implementation of these principles in local oncologic practice. Yakubov, Khudayberdieva, and Khudoyorov described

clinical GIST observations from the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology in Tashkent, underlining the importance of histologic verification and modern treatment algorithms (8). Uzbek national oncology protocols recommend mutation-sensitive targeted treatment strategies, including genotype-dependent imatinib dosing in advanced disease, and thereby reinforce the practical importance of molecular testing (10).

MATERIALS AND METHODS

A structured narrative review was conducted using publications and guidance documents available up to October 2026. Priority was given to international clinical practice guidelines, major reviews of GIST molecular biology and prognostic classification, and publications originating from Uzbekistan. The analytic framework included four marker domains: (1) clinical markers - age, symptoms, primary site, stage, and tumor rupture; (2) morphologic markers - tumor size, mitotic count, spindle/epithelioid/mixed phenotype, necrosis, and resection status; (3) immunohistochemical markers - CD117, DOG1, CD34, and SDHB; and (4) molecular-genetic markers - KIT, PDGFRA, SDH-complex, BRAF, NF1 and other wild-type alterations. Evidence was synthesized qualitatively, with special attention to markers that influence recurrence risk, sensitivity to tyrosine kinase inhibitors, or surveillance intensity. No original patient-level data were generated; consequently, statistical hypothesis testing was not performed. The proposed prognostic algorithm is an evidence-based synthesis rather than a validated numerical score.

RESULTS

The literature synthesis identified tumor rupture, mitotic activity, tumor size, and non-gastric location as the most consistently adverse clinicopathological features. Among these, rupture has a particularly strong impact because it may convert a technically localized lesion into a biologically disseminated condition through intraperitoneal contamination. Mitotic count should be reported per 5 mm^2 rather than by an undefined number of high-power fields, because microscope field areas vary and can otherwise distort risk assignment (1). Large tumors with a high mitotic rate require the most intensive postoperative risk assessment, while small gastric tumors with low mitotic activity usually occupy the lowest-risk category.

Morphologic subtype alone is not sufficient for prognosis, but it may provide clues to genotype. Spindle-cell morphology is frequent in KIT-mutant GISTs, whereas epithelioid or mixed patterns are more common in some PDGFRA-mutant and SDH-deficient gastric tumors. Necrosis, marked cellularity, mucosal invasion, and high proliferative activity may support an aggressive interpretation but should not replace established risk variables. Complete resection remains an important clinical objective, although microscopic margin status must be interpreted in the context of tumor rupture, site, and feasibility of re-resection (1,4).

Table 1. Integrated prognostic significance of major GIST markers

Marker domain	Key marker	Typical prognostic implication	Clinical use
Clinical	Tumor rupture	Very high recurrence risk; possible peritoneal dissemination	Escalates adjuvant and surveillance considerations
Morphologic	Size + mitotic count	Increasing size and mitoses correlate with recurrence	Core postoperative risk stratification
Anatomic	Primary site	Non-gastric tumors often have	Refines recurrence

		worse outcome at comparable size/mitoses	estimates
IHC	CD117/DOG1	Primarily diagnostic; loss/atypical profile may trigger expanded molecular testing	Confirms GIST lineage and supports differential diagnosis
IHC/molecular	SDHB loss	Suggests SDH-deficient GIST with distinct biology	Prompts SDH-focused genetic evaluation
Molecular	KIT exon 11 deletion, especially 557/558	Often associated with more aggressive biology than some other KIT variants	Prognostic refinement; predicts imatinib sensitivity
Molecular	KIT exon 9 mutation	Frequently intestinal; may require higher imatinib dose in advanced disease	Therapeutic prediction and risk context
Molecular	PDGFRA D842V	Primary resistance to imatinib; distinct targeted treatment implications	Avoids ineffective imatinib-based strategy

Molecular-genetic markers add a second level of prognostic precision. KIT exon 11 mutations constitute the largest molecular subgroup, but their prognostic behavior is heterogeneous. Deletions affecting codons 557/558 have repeatedly been linked to more aggressive clinicopathological features and higher recurrence risk, whereas some substitutions or duplications may behave more favorably (5,6). KIT exon 9 mutations are enriched in intestinal GIST and have both prognostic and predictive importance; in advanced disease, higher-dose imatinib is recommended in several guidelines for this genotype (1,10). Secondary KIT mutations that emerge during tyrosine kinase inhibitor therapy are major mechanisms of acquired resistance and are especially relevant when interpreting progression in metastatic disease.

PDGFRA-mutant GISTs are frequently gastric and may display epithelioid morphology. The PDGFRA D842V variant deserves separate consideration because it confers primary resistance to imatinib and changes the preferred targeted-treatment strategy. By contrast, many other PDGFRA-mutant tumors may show less aggressive natural history, although risk cannot be inferred from genotype alone (1,3). KIT/PDGFRA wild-type GISTs comprise several biologically distinct diseases rather than one uniform group. SDH-deficient GISTs often occur in the stomach, may arise in younger patients, can be multifocal, and may demonstrate lymph-node involvement more often than conventional KIT-mutant GIST. BRAF-mutant and NF1-associated tumors represent additional subgroups with distinct molecular pathways and limited expected benefit from standard imatinib when the relevant kinase target is absent (2,3,5).

The reviewed evidence supports a hierarchical individual prognostic model. First, the pathologist should establish GIST diagnosis and record size, site, mitotic count per 5 mm^2, rupture status, histologic type, necrosis, and margin status. Second, CD117 and DOG1 should be interpreted together with a focused immunohistochemical panel; SDHB staining is valuable when morphology, age, site, or genotype suggests an SDH-deficient tumor. Third, mutational testing should classify KIT/PDGFRA status and, in negative cases, guide expanded analysis according to available resources. Finally, the multidisciplinary team should integrate these variables with stage and treatment response to define the individual recurrence-risk level and follow-up schedule. This integrated approach is more informative than isolated reliance on either morphology or genotype.

DISCUSSION

The principal finding of this review is that individual prognosis in GIST is inherently composite. No single biomarker is sufficiently robust across all clinical settings. Tumor size and mitotic rate are powerful but context-dependent; molecular genotype is biologically informative but may not override a clearly high-risk phenotype; immunohistochemical markers are indispensable diagnostically but are not independent survival predictors in most routine settings. Consequently, the most clinically useful strategy is an integrated matrix in which established clinicopathologic risk factors define the baseline probability of recurrence and molecular features refine both prognosis and treatment sensitivity (1,3,5).

This distinction between prognostic and predictive markers is important. A marker is prognostic when it relates to the natural course of the disease, whereas it is predictive when it identifies the likelihood of response to a specific therapy. KIT exon 9, KIT exon 11, and PDGFRA D842V alterations can have elements of both functions. For example, a KIT exon 9 mutation may occur in a biologically less favorable intestinal context while also influencing imatinib dose selection in advanced disease. PDGFRA D842V is especially important because recognition of this variant prevents the inappropriate expectation of benefit from imatinib and directs attention toward mutation-specific agents (1,3).

For postoperative management, individualized prognosis should directly inform adjuvant therapy. Patients with substantial recurrence risk and an imatinib-sensitive genotype are candidates for adjuvant treatment according to guideline-defined principles, whereas treatment should not be prescribed solely because a tumor expresses CD117. Conversely, patients with imatinib-insensitive molecular subtypes require a different strategy. This is precisely why molecular testing should be performed before committing a patient to prolonged targeted therapy. Regional protocols in Uzbekistan already incorporate genotype-dependent approaches for advanced GIST, creating a foundation for broader implementation of molecularly informed adjuvant decision-making (10).

Several limitations should be acknowledged. The available prognostic literature includes retrospective cohorts, different historical risk classifications, variable mutation-testing platforms, and heterogeneous follow-up durations. Rare molecular subgroups are underrepresented in prospective trials, and the precise independent prognostic contribution of individual variants may be difficult to separate from tumor site and morphology. In addition, access to next-generation sequencing is not uniform. For resource-conscious practice, a stepwise pathway is rational: standardized morphology and mitotic counting, CD117/DOG1 immunohistochemistry, KIT/PDGFRA testing, SDHB staining where indicated, and broader molecular analysis for unresolved wild-type cases. Such a strategy maximizes clinically actionable information without requiring comprehensive sequencing for every small low-risk lesion.

Future prognostic systems are likely to combine classical variables with quantitative genomics, circulating tumor DNA, radiomics, and treatment-response kinetics. Circulating tumor DNA is particularly attractive for monitoring molecular evolution under tyrosine kinase inhibitor pressure, although it is not yet a replacement for tissue-based diagnosis or routine postoperative risk classification (5). Prospective validation in Central Asian populations would be valuable, because local tumor biology, referral patterns, and availability of molecular testing may influence real-world outcomes.

CONCLUSION

Individual prognostication of gastrointestinal stromal tumors should be based on an integrated assessment of clinical, morphological, immunohistochemical, and molecular-genetic markers. Tumor size, mitotic count, primary site, and rupture status remain the core determinants of recurrence risk, while KIT, PDGFRA, SDH-related and other molecular alterations refine biologic interpretation and predict sensitivity to targeted therapy. CD117 and DOG1 are central diagnostic markers, and SDHB immunohistochemistry is useful for identifying a distinct molecular subgroup. The most clinically meaningful prognostic approach is therefore not a single-marker model, but a multidisciplinary algorithm that links morphology with genotype and treatment context. Wider access to standardized molecular testing and prospective regional validation would strengthen personalized GIST management in Uzbekistan and comparable healthcare systems.

Proposed practical prognostic sequence

1. Confirm the diagnosis morphologically and by CD117/DOG1 immunohistochemistry.
2. Record tumor site, maximum size, mitotic count per 5 mm², rupture status, histologic subtype, necrosis, and resection margins.
3. Assign baseline recurrence risk using an accepted clinicopathologic system.
4. Perform KIT and PDGFRA mutation analysis when systemic therapy or substantial recurrence risk is relevant.
5. In KIT/PDGFRA wild-type tumors, assess SDHB and consider expanded molecular testing (SDHx, BRAF, NF1 and other relevant pathways).
6. Integrate genotype with clinicopathologic risk to select adjuvant therapy, systemic treatment, and surveillance intensity.

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