Int J Clin Exp Pathol 2010;3(5):461-471
www.ijcep.com /IJCEP1004005

Review Article

Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need for a standardized GIST reporting

Abbas Agaimy

Institute of Pathology, Friedrich-Alexander-University, Erlangen, Germany

Received April 21, 2010, accepted May 3, 2010, available online May 5, 2010

Abstract: Following the successful introduction of the receptor tyrosine kinase inhibitors (TKI) as the mainstay for the treatment of advanced and metastatic gastrointestinal stromal tumor (GIST), GIST has received a special attention in the recent literature. This resulted in major achievements on the surgical pathology diagnosis and improved our understanding of the molecular biology of the disease. Availability of the effective TKI therapy has emphasized the need for a more reliable and reproducible system for assessment of the malignant potential in GIST to allow for an optimal individualized patient treatment. All of the risk stratification systems proposed so far have emphasized the value of tumor size, mitotic count and anatomic site for risk estimation, at the same time appreciating the difficulty of classifying individual tumors as either benign or malignant. The newly proposed UICC TNM classification for GISTs represents the most recent hallmark on this topic; yet its usefulness remains to be tested in future clinical studies. This review briefly summarizes and discusses the most pertinent risk systems proposed for assessment of the malignant potential of GIST stressing their advantages and limitations and including some critical remarks on the newly proposed UICC TNM system for classifying GIST. Most importantly, an emphasis is made on the urgent need for a standardized approach for histopathological evaluation and reporting of GIST specimens to allow for a reproducible tumor size, mitotic count and tumor growth pattern, and hence for a better risk classification.

Keywords: GIST, risk classification, KIT, TNM, pediatric GIST, EGIST

Introduction

Gastrointestinal stromal tumors (GIST) are the most common primary mesenchymal neoplasms of the GI tract [1]. They are thought to derive from or differentiate similar to the gastrointestinal pacemaker cells, the interstitial cells of Cajal (ICCs) [2]. GISTs occur at any site along the tubular GI tract from the esophagus to the anorectum, but they are more common in the stomach (60-70%) and the small bowel (20-30%) [1]. In 1998, Hirota et al described the presence of oncogenic gain-of-function mutations involving the type III receptor tyrosine kinase KIT in a group of GIST [3]. This was followed by the demonstration of immunohistochemical expression of the KIT receptor protein detected by the antibody CD117 in the majority of GISTs [2]. In 2001, Joensuu et al reported on the first patient with advanced GIST treated by imatinib mesylate (STI571) with a dramatic tumor response [4]. Subsequently, imatinib mesylate (Glivec, Novartis, Basel, Switzerland) was established as the treatment of choice for patients with inoperable or metastatic disease [5]. In 2002, a consensus paper was published by a panel of experts recognizing GIST as a distinct clinicopathologic tumor entity that shows clinicopathologic, immunohistochemical and molecular profiles as well as clinical behavior distinct from true smooth muscle and neurogenic neoplasms of the gut and thus deserves different specialized treatment strategies [6]. Since publication of that consensus paper, several

studies assessing the usefulness of different prognostic factors in GIST have accumulated in the English literature; the consequence of them was the appearance of several alternative schemes proposed for the assessment of the malignant potential in GIST [7-9]. This review discusses briefly the usefulness and limitations of many of these risk stratification systems including short remarks on the newly proposed UICC TNM classification for GIST [10].

Historical assessment of the malignant potential in GISTs

Parallel to the controversy regarding their histogenetic derivation, the assessment of the malignant potential in GIST remained a major controversial issue for decades ending up to now. Initial suggestions for grading GISTs date back to the pre-KIT era; the most cited references in this context were the papers by Franquemont et al [11,12]. They have used tumor size (<5 cm vs. ≥5 cm), mitotic count (<5 vs. ≥5/10 HPFs) and PCNA proliferative index (<10% vs. ≥ 10%) to separate GISTs into low and high risk subgroups, respectively. However, the problem with the old grading systems was the fact that almost all studies preceding 1998 have lumped GISTs and true smooth muscle neoplasms together as *stromal/smooth muscle neoplasms*, thus making these studies non-comparable with each other and with current publications on prognostic parameters in GISTs.

National Institutes of Health (NIH) consensus criteria (so-called Fletcher's criteria)

Being based mainly on the personal experience of an expert panel, this risk stratification system represents the first and initial attempt to assess the malignancy in GIST in the light of current diagnostic criteria for this tumor entity [6]. Tumor size and mitotic activity were used as the sole parameters to define 8 prognostic categories that were further subdivided into four risk groups (**Table 1**) [6]. Based on this system, benign GISTs do not exist and instead the most harmless tumors have been assigned a "very low malignant potential". This system is the most popular among clinicians and also among many pathologists given its limited number of risk groups and its simple application. Although the size of 5 cm has been adopted as a cut-off value to define low vs. non-low risk tumors in a manner similar to soft tissue sarcomas, the observation that a majority of GISTs including those with malignant behavior may lack brisk mitotic activity lead to adoption of an area of 50 high power fields (HPFs) for mitotic counting instead of the traditional area of 10 HPFs applied for soft tissue neoplasia. However, tumors showing exactly 5 mitotic figures/ 50 HPFs have not been well defined. Also, it seems suboptimal for a subset of GIST that may be lumped together into the intermediate category solely based on the tumor size. Notably, the main shortage of this system lies in ignoring the anatomic site of the tumor and the presence of tumor rupture. As for the other risk systems discussed below, the macroscopic growth pattern of tumors including serosal penetration has not been considered and a clear-cut definition of the 50 HPFs area has not been stated. Nevertheless, the usefulness and sensitivity of the NIH risk system in predicting outcome in GISTs have been validated in several studies, but some authors have demonstrated a higher concordance for alternative risk stratification systems than for the NIH system [13,14,15].

Armed Forces Institute of Pathology (AFIP) criteria (Miettinen's criteria)

The criteria presented by Miettinen et al were based on a large series comprising more than 2.000 GISTs from different anatomic sites along the GI tract with long-term follow-up [1,7]. This risk system is distinguished from the NIH system by taking the anatomic site of the tumor into consideration. Initially defining 8 prognostic subgroups based on size and mitotic count, Miettinen et al used in addition the anatomic site to separate four risk groups (very low, low, moderate and high risk) similar to the 4 risk groups in the NIH system with addition of a new group of "benign tumors" that carry no risk of malignancy [1]. Being based on real data [1,7,16], the AFIP system has the advantage of delivering numerically calculated risk of tumor relapse and/ or progression, thus enabling clinicians to make solid therapeutic decisions more reliably. The prognostic significance of anatomic site was confirmed in other studies as well [15]. The single major drawback in the eye of some clinicians and/ or general pathologists is the presumable complexity of the AFIP system being composed of 8 prognostic subgroups and that the excessive subdivision of the different subgroups might reduce the prognostic sensitivity and specificity of recurrence [13]. The current

Table 1. Comparison of the different risk stratification systems and the proposed UICC TNM classification for GIST [1,6,8,10]

Tumor Size (cm)	Mitoses /50HPFs	Risk/Progression % AFIP, 2006 Stomach	Risk/ Progression % AFIP, 2006 Jejunum/ Ileum	Risk/ Progression % AFIP, 2006 Duodenum	Risk/ Progression % AFIP, 2006 Rectum	Risk NIH Fletcher et al, 2002 All sites	Revised NIH Risk Joensuu, 2008 Gastric tumors	Revised NIH Risk Joensuu, 2008 Non-gastric
≤2 cm	≤ 5	None (0%); benign UICC IA	None (0%); benign UICC I	None (0%); benign UICC I	None (0%); benign UICC I	Very low	Very low	Very low
>2-≤5 cm	≤ 5	Very low (1,9%) UICC IA	Low (4,3%) UICC I	Low (8,3%) UICC I	Low (8,5%) UICC I	Low	Low	Low
>5-≤10 cm	≤ 5	Low (3,6%) UICC IB	Intermediate (24%) UICC II	High (34)[a] UICC II	High (57%)[a] UICC II	Intermediate	Intermediate	High
> 10 cm	≤ 5	Intermediate (12%) UICC II	High (52%) UICC IIIA	High (34%)[a] UICC IIIA	High (57%)[a] UICC IIIA	High	High	High
≤2 cm	> 5	0[b] UICC II	High (50%)[b] UICC IIIA	No cases UICC IIIA	High (54%) UICC IIIA	Intermediate or high†	Intermediate or high†	Intermediate or high†
>2-≤5 cm	> 5	Intermediate (16%) UICC II	High (73%) UICC IIIB	High (50%) UICC IIIB	High (52%) UICC IIIB	Intermediate or high†	Intermediate or high†	High
>5-≤10 cm	> 5	High (55%) UICC IIIA	High (85%) UICC IIIB	High (86%)[a] UICC IIIB	High (71%)[a] UICC IIIB	High	High	High
> 10 cm	> 5	High (86%) UICC IIIB	High (90%) UICC IIIB	High (86%)[a] UICC IIIB	High (71%)[a] UICC IIIB	High	High	High

[a] Two groups were analyzed together because of low case numbers.
[b] Low case number.
† depends on whether 6-10 or >10 mitoses per 50 HPFs are detectable.

European Society of Medical Oncology (ESMO) has stressed the advantages of this risk system [17]. Comparing the NIH and the AFIP systems, there is a general tendency for the NIH system to over-grade gastric tumors and down-grade a subset of non-gastric tumors (**Table 1**). Although the total area used for mitotic count varied among different case series from the AFIP (see below), the most recent review from the AFIP recommended the use of a total area of 5 mm^2 [1].

Nomogram for GIST assessment

Recently, Gold et al proposed a nomogram for estimating the risk of tumor progression [9]. Each tumor was assigned points on a scale based on tumor site (gastric, vs. small intestine vs. colon/rectum vs. extragstrointestinal), size (in a continuous non-linear fashion), and mitotic index (<5 vs. ≥5 per 50 HPFs). The total of points should determine the 2- and 5-yr recurrence free survival probabilities. The nomogram showed concordance probability of 0.78, a value comparable to that achieved by the AFIP system and higher than that of the NIH system in the same study. Notably, this system confirmed the significance of the anatomic site for predicting the tumor behavior in GIST, similar to the AFIP series. However, it remains to be further analyzed, whether the nomogram would predict the long-term disease-free survival in GISTs with an indolent course and late progress [9].

Revised NIH consensus criteria

Several investigators have presented a revised version of the NIH risk stratification system by inclusion of additional prognostic factors. Rutkowski et al showed that non-radical resection (R1) and tumor rupture are both associated with adverse outcome [18], both factors have not been included in any of the aforementioned risk classification systems. Furthermore, Takahashi et al suggested the inclusion of a "clinically malignant group" to include patients with peritoneal dissemination, metastasis, and invasion into adjacent organs or tumor rupture [19]. It is conceivable that patients within this group have overtly malignant tumors that do not need be included into any risk classification system. In this context, it should be emphasized that tumors within this "clinically malignant group" may lack histological features of overt malignancy and instead show a bland histology [20]. A recent proposal by Joensuu used the NIH system as a base to include in addition to the tumor size and mitotic count the presence of tumor rupture as a high risk factor irrespective of size and mitotic count [8]. Further modification in the Joensuu's criteria was the removal of non-gastric tumors in the NIH intermediate category to be placed into the high risk group, a step that reflect the influence of the AFIP system. Also, the "forgotten" tumors with exactly 5 mitoses have been included accordingly in the Joensuu´s revised NIH risk system. Other features remained as in the original NIH scheme.

The problematic mitosis counting: technical notes

Counting mitotic figures represents a highly significant issue in surgical pathology practice. The mitotic rates are often necessary, either for primary assessment of malignancy (particularly in soft tissue tumors), for grading malignant neoplasms (sarcomas and some carcinomas) or both. To date, there are no standardized data concerning the appropriate methods for mitotic counting in GIST. In our experience with referral materials, General pathologists tend to overcount mitoses, most likely because of the common sprinkling of irregular-shaped lymphocytes and other inflammatory cells between tumor cells and presence of apoptotic bodies in GIST (Agaimy, unpublished data). Generally, GISTs show a low to moderate mitotic activity distributed throughout the tumor. However, there exists a subset of GIST with a high intratumoral heterogeneity leading to a great discrepancy in mitotic rates based on the area used for this purpose [21]. The three major questions: where to count, how to count and how large the 50 HPFs area should be, are still open. In the studies from the pre KIT era, Franquemont et al examined five sets of 10 HPFs and the highest number of unequivocal mitotic figures in one set was used as the final mitotic count [11]. The calculated 50 HPFs area in their studies corresponded to 7.95 mm^2. Review of the recent literature revealed remarkable variation in the methods used to count mitosis in GIST, even by the same investigators. Miettinen et al counted mitoses in consecutive 50 HPFs from the most mitotically active area or the most cellular area, or until >100 mitoses were found [7]. Other authors counted in randomly selected 50 HPFs [15]. The 50 HPFs area varied from 5 mm^2 to

Table 2. The new TNM classification for GIST[a] [10]

Tumor size (cm)	Mitoses/ 50HPFs	T-stage gastric	T-stage non-gastric	UICC gastric	UICC non-gastric
≤2 cm	≤ 5	T1	T1	IA	I
>2-5 cm	≤ 5	T2	T2	IA	I
>5-10 cm	≤ 5	T3	T3	IB	II
> 10 cm	≤ 5	T4	T4	II	IIIA
≤2 cm	> 5	T1	T1	II	IIIA
>2-5 cm	> 5	T2	T2	II	IIIB
>5-10 cm	> 5	T3	T3	IIIA	IIIB
> 10 cm	> 5	T4	T4	IIIB	IIIB

[a] The above UICC stages are valid for N0 M0 tumors. All tumors with lymph node or other metastasis are considered UICC stage IV.

10 mm^2 in the series from the AFIP [7,22,23]. In our previous study, the total area was 11.9 mm^2 [21]. The European (ESMO) guidelines 2010 recommended a total area of 10 mm^2 [24]. In their most recent review on the topic, Miettinen and Lasota have recommended using a total area of 5 mm^2 and the area should be limited to 25 HPFs if a modern microscope with wide-field eye-pieces is used [1]. A similar area (5 mm2) was recommended in the new TNM [10]. Thus, the area recommended by the AFIP and the TNM represents half of that recommended in Europe [24]. These facts underscore the urgent need for an international standardized mitotic counting method in which the spectrum of mitotic figures, the total field area of 50 HPFs and the best tumor area to be used for counting mitoses are clearly defined. Notably, recognition of mitoses and differentiating them from several mitosis mimics (inflammatory cells with irregular folded nuclei, apoptotic bodies, karyorrhexis and other simulators) in a clearly defined 50 HPFs-area are prerequisite for a reproducible and reliable mitotic index and would probably influence the ultimate risk stratification significantly, irrespective of the risk system used. In our experience, the practice of counting mitoses in 10 HPFs and then calculating the ratio in 50 HPFs is often misleading and obtains false results.

Proposed systems for clinical GIST staging

The SEER-based proposal (TGM system)

Woodall et al [25] have recently proposed a system for GIST staging based on a tumor-grade -metastasis (TGM) system. The authors used the Surveillance Epidemiology and End Results (SEER) database comprising 2537 cases. The author found a cut-off point for tumor size of 70 mm to be most effective in separating clinical behavior in GISTs compared to other tested values of 2 cm, 5 cm and 10 cm as in the previous risk stratification systems. However, as the authors stated in their paper, a fraction of the cases has been diagnosed before 2000 and the KIT status was not known in the cases included, thus applying such data for GISTs in general might not be really representative. Also, the method used to grade GISTs into four grades is unclear. Furthermore, it would be inconsistent to apply "tumor differentiation" as a criterion to grade GISTs in a manner similar to that of soft tissue sarcoma. Notably, small bowel GISTs with strong smooth muscle actin reactivity were considered differentiated tumors in previous pre-KIT studies and thus have been assigned a lower score value, although these tumors are likely to follow a more aggressive course because of their common localization in the small intestine. The presence of nodal and distant metastasis was considered advanced stage, similar to the current TNM system.

Major features of the proposed UICC system (TNM classification 2010)

The seventh edition of the international union against cancer (UICC) published at the beginning of this year included for the first time a classification and staging system for GIST [10].

This represents a major step towards a more standardized surgical and oncological treatment for patients with GIST and, most importantly, may facilitate the establishment of a uniformly applicable follow-up program based on tumor stage. As depicted in **Table 1** and **2**, The TNM system has applied the same criteria used for risk assessment to categorize tumors into four major T-categories and corresponding UICC stages. In particular and different from any previously proposed TNM classification for a malignant neoplasm, four T-categories have been separated solely on the basis of tumor size. The T-category was then combined with mitotic rate and tumor site to define a clinical UICC stage. Given the rarity of nodal metastasis in GISTs in general, pNx is not recommended and any patient without examined regional nodes is considered to have pN0. It is obvious that this UICC TNM classification generally recapitulate the 8 prognostic subgroups defined in the AFIP system [1]. The presence of either nodal or distant metastasis heralds a stage UICC IV.

Does the TNM system apply well to GIST?

The principal aim of the TNM system is to facilitate a uniform and standardized analysis of malignant tumors based on their stage of development/spread. Generally, all of the tumors considered for the TNM system possesses the ability of local invasiveness (hence are suitable for a T-categorization) and they have a potential for spread via the lymphatic and/or the blood stream (thus deserving the N- and M-categories). While the TNM system applies well to carcinoma and melanoma, its usefulness in soft tissue sarcoma was evidently limited and does not represent more than reformulation of the tumor size, grade and depth. For GISTs, features that were shown to correlate with prognosis and hence used for risk assessment are tumor size, anatomic site and mitotic count in addition to tumor rupture in the revised NIH criteria. Thus, one might argue that using the same risk criteria in combination to calculate a TNM stage would represent no more than renaming the existing risk groups established by several working groups within the last years as summarized in this article. Notably, the proposed TNM for GISTs seems to parallel the AFIP risk stratification system. Thus, the very low and low risk category is replaced by stage UICC IA for gastric and stage I for non-gastric tumors and so forth. The most remarkable aspect is the subdivisions of tumors in the high risk category into 2 or three sub-stages (II, IIIA or IIIB). The value of this subclassification of the high risk tumors remains to be validated in future studies. However, an issue of controversy would arise regarding whether subclassification of "high risk or malignant" tumors be better performed using the UICC staging system or preferably by applying/proposing a grading system that would facilitate separation of these "visceral sarcomas" into three malignancy grades as done for soft tissue sarcomas.

One other question seems to be justified: Does the growth pattern matter? Specifically, what is the relevance of the infiltration of subserosal fat or the omentum/mesentery, penetration of the visceral peritoneum by tumor cells/ tumor rupture and multiplicity of apparently primary tumors within the omentum/ mesentery? Would there be any difference regarding a predominantly extramural tumor localized to the omentum/mesentery (so-called EGIST) as opposed to a tumor of the same size completely surrounded by bundles of the muscularis propria or limited by an intact serosa? Most studies have shown a higher rate of peritoneal recurrence/ dissemination than true hematogenous metastasis to the liver [18]. However, reliable criteria for recognizing those patients at a higher risk for peritoneal recurrence are still lacking. Tumor rupture was correlated with a high risk for recurrence in the study by Rutkowski et al and was included as a high risk criterion in the revised NIH system [8,18]. Further questions concerning EGIST and pediatric GISTs are briefly discussed below.

Are all GISTs really potentially malignant?

The initial impression that all GISTs are potentially malignant was the consequence of lacking evidence-based demonstration of true benign tumors during the first few years following GIST definition. Accordingly, the NIH system used the term "very low risk" instead of "benign" to indicate a mostly benign clinical course, but at the same time to reflect the uncertainty and fear to designate a specific tumor as definitely benign [6]. However, the AFIP system could demonstrate that mitotically inactive small tumors (<2cm) carry no risk of progression and could thus be called benign, irrespective of their anatomic localization [1]. Thus, including such tumors within a classification/staging system

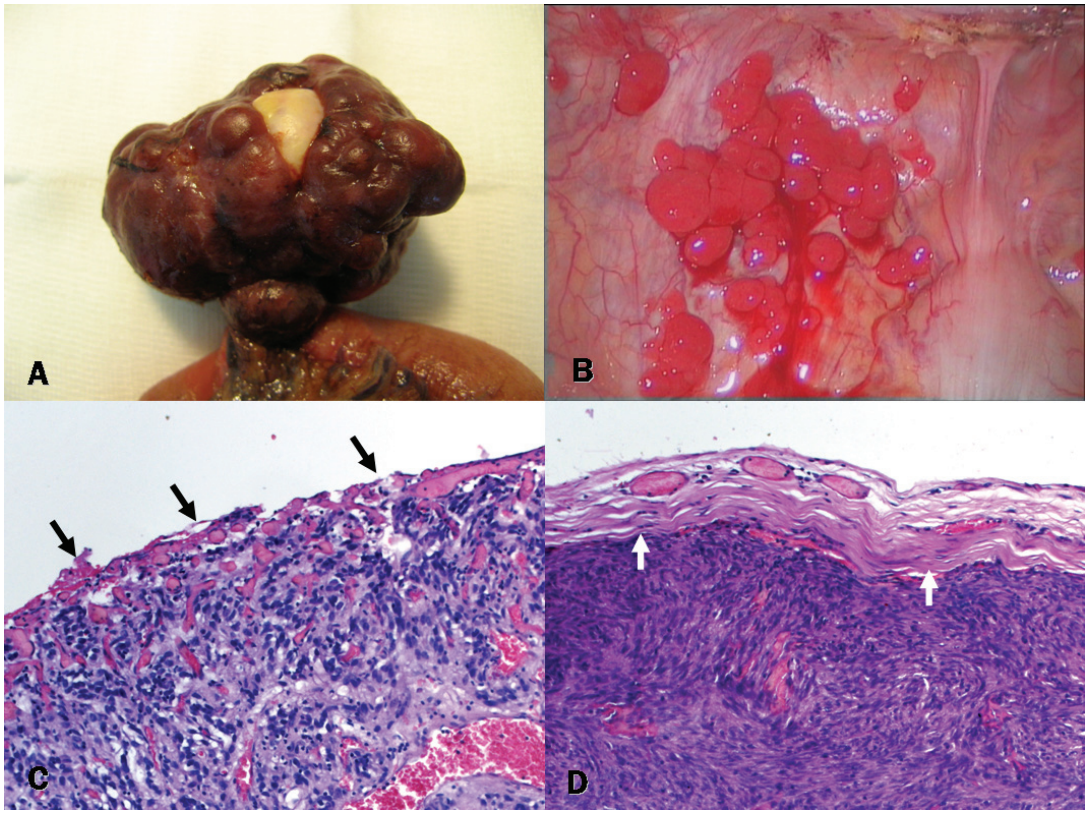

Figure 1. Examples of the serosal penetration/tumor rupture in GISTs. (A) Pedunculated GIST from the ileum showed a whitish plaque-like depressed serosal defect indicating an old perforation/tumor rupture. (B) Intra-operative image from the same patient showed extensive peritoneal sarcomatosis. (C) Microscopic serosal penetration from another patient with simultaneous peritoneal dissemination but no grossly obvious tumor rupture, note irregular microscopic defects at sites of penetrating tumor cells (arrows). (D) A gastric GIST with intact subserosal connective tissue layer forming a thick capsule. In our experience, such tumors carry a lower risk if any for peritoneal recurrence and would thus merit a different categorization as those with evidence of serosal penetration/rupture.

traditionally applied for malignant disease only (thus the name TNM classification for malignant tumors) looks contradictory. Furthermore, assigning a "pT1 or UICC IA" to a patient´s tumor detected incidentally at surgery for benign disease (ulcer, obesity, etc.) most likely would have several medicolegal consequences for individual patients and would at least have a negative impact on his/her payment for health insurance corporations. If one should compare the situation with colorectal carcinogenesis, it is well known that almost all colorectal adenomas possess a malignant potential and if left unremoved would ultimately progress to invasive colorectal cancer in a sense of adenoma-carcinoma-sequence. Nevertheless, colorectal adenomas are classified as definitely benign neoplasms and are not included in the TNM system. In comparison, minute incidental GIST (preferably referred to as *stromal tumorlets* [26]) are very common in the general population; their incidence in systematically examined stomachs removed at autopsy and surgically for gastric cancer was 22.5% and 35%, respectively [27,28]. It has been generally accepted that these minute lesions carry no malignant potential [1,8], although a minority of them would evolve into clinically meaningful GIST if left in situ [28].

Gross pattern, the concept of EGIST and the relevance of serosal penetration in the new TNM system

Retrospective critical analysis demonstrated that GISTs truly arising outside the GI tract are

exceptionally rare to non-existing [1,29]. Although the few published series pointed to a generally poor outcome in EGIST [29,30], the risk stratification of the "EGIST" has not been addressed separately. Notably, the same risk criteria as for their intramural and polypoid counterparts have been applied for EGIST. In a recent paper by Miettinen et al on a large series of omental GIST [23], 8% of the patients presented with tumor rupture which is a higher percentage compared to GIST in general. Most tumors in that study were large (>10 cm), but had a low mitotic count. Many of the patients with solitary tumors were long-term survivors (median, 129 months) indicating a generally indolent tumor behavior irrespective of the large tumor size. On the other hand, patients with multiple omental tumors had a poor median survival (8 months). Peritumoral fat invasion did not correlate with outcome in that study [23]. A recent study on a small series of cases has shown a correlation between serosal penetration and tumor progression [31]. However, the methods used and the extent of the histopathological assessment of serosal penetration have not been described in details. In our experience, the gross pattern in GIST, in particular the presence of no more than thin serosal covering on the surface of extramural tumors represents a significant predictor of peritoneal disease recurrence, probably as a result of undetected microscopic serosal penetration (Agaimy et al, unpublished data). Thus it would be of prognostic relevance to carefully assess the presence or absence of normal tissue on the peritoneal aspect of tumors and to check for any evidence of serosal tears or old sealed focal rupture both grossly and histologically (**Figure 1**). The negative impact of tumor rupture and R1-resection on the disease-free survival has been confirmed in several studies [18]. Notably, peritoneal dissemination represented the chief route of tumor spread in GIST in different series; disease recurrence involved the liver alone in 25%, the peritoneum alone in 33% and both in 28% in a large series published recently by Rutkowsky et al [18].

Do GISTs represent a single disease entity?

To date, all of the proposed risk systems have dealt with GIST as a uniform single disease entity. However, several recent observations argue to the contrary. Among neoplasms classified as GISTs are several groups with specific clinicopathologic and molecular features suggesting distinct disorders. Thus tumors arising in the stomach were thought initially to represent a uniform disease entity but later studies have demonstrated significant differences regarding their localization in the stomach (gastroesophageal junction and body versus distal antrum) [7], histology (pure spindled versus mixed/epithelioid) and molecular profile (KIT deletions versus point mutations versus PDGFRA mutations) [32], patient age (pediatric versus elderly) and occurrence in syndromic settings (Carney triad, NF1 versus sporadic) [33,34]. In brief, four major disease categories seem to exist: 1) KIT mutated GISTs arising at different anatomic sites seem to represent the bulk of the disease and most publications on GISTs actually describe this subgroup [1], 2) PDGFRA-mutants generally arise as epithelioid gastric tumors and may grow to a huge size, still possessing a favorable outcome [35,36]. 3) Pediatric-type (Carney-type) GISTs whether developing in pediatric or adult patients, irrespective of presence or absence of features of the Carney-triad seem to represent a clinicopathologically and molecularly distinct disorder [34,37,38], and 4) NF-1 associated GISTs which lack kinase mutations and tend to follow a more favorable clinical course [33]. These four major subgroups of GISTs differ not only in their histological appearance and clinical features but also in their prognosis, route of tumor spread and overall survival.

Pediatric GISTs and GISTs in young adults and the problem in the light of the TNM system

GISTs generally occur beyond the age of 50. However, ≤10% of reported GISTs affected patients who were ≤40 yrs of age at first diagnosis [7]. Review of the recent literature and our data indicates that GISTs in this age group are most commonly of the pediatric-wild-type GIST, tumors that closely resemble the "gastric stromal sarcoma" in patients with the Carney triad [34]. These tumors differ in many aspects from their adult counterparts. Regarding their biological behavior, pediatric GISTs in the setting of the Carney triad showed inconsistent risk stratification. In particular, the risk group showed no correlation with disease outcome and development of recurrence or metastasis [34,37]. Notably, 3 of 6 patients who died of Carney triad GISTs had low risk tumors compared to 2 with high risk tumors [34]. Likewise, metastasis occurred in

23% of very low/low risk pediatric and young adult GIST patients reported in the series by Miettinen et al [37]. This contrasts strikingly with a frequency of only 2.5 % metastatic disease in comparable risk groups in adult gastric GISTs reported by the same authors [7]. Furthermore, pediatric and Carney-triad GISTs showed a high rate of regional lymph node metastasis approaching 29% [34,38] compared to a nodal frequency of ~2% in GIST in general [1,7,15]. These observations clearly demonstrate that these two groups of tumors represent biologically distinct neoplasms and that their malignant potential might not be reliably assessed using the same risk criteria. However, based on the general rarity of nodal spread in sporadic GISTs (1-2%), the new TNM classification allowed assigning a pN0-status for a tumor without histologically examined lymph nodes [10]. On the other hand, presence of nodal metastasis was considered UICC stage IV in a manner similar to peripheral soft tissue sarcoma. It thus looks inappropriate to assign a pediatric GIST pN0 based on the current TNM if we know that the majority of nodal metastasis in this subset of GIST patients are detected histologically in grossly unremarkable lymph nodes in the surgical specimen [34,38]. However, the prognostic relevance of regional nodal metastasis commonly seen in pediatric GISTs and in rare adult GISTs remains currently unclear [34,39]. Thus, pediatric GISTs deserve a completely different approach regarding their diagnosis, treatment, risk assessment and staging stratification.

In summary, review of available literature and considering also our own data and our experience with this tumor type, it is obvious that we urgently need a standardized system for evaluating and reporting GIST tumors. Notably, the great heterogeneity of these disorders has to be taken into consideration when proposing risk stratification and classification systems. An important question to be addressed initially should be: which criteria would be suitable for which tumor? Future studies are needed to address several questions and hypotheses presented and discussed in this critical perspective review.

Please address correspondence to: Abbas Agaimy, MD, Institut für Pathologie, Universitätsklinikum, Krankenhausstrasse 12, 91054 Erlangen, Germany. Tel. +49-9131-8522288, Fax +49-9131-8524745, E-mail abbas.agaimy@uk-erlangen.de

References

[1] Miettinen M , Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.

[2] Kindblom L-G, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998;152:1259-1269.

[3] Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.

[4] Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B, Demetri GD. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001;344:1052-6.

[5] Heinrich MC, Blanke CD, Druker BJ, Corless CL. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. J Clin Oncol 2002;20:1692-703.

[6] Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002; 33:459-465.

[7] 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.

[8] Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.

[9] Gold JS, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, Smyrk TC, Maki RG, Singer S, Brennan MF, Antonescu CR, Donohue JH, DeMatteo RP. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045-52.

[10] International union against cancer (UICC). TNM classification of malignant tumours. 7th ed. Sobin LH, Wittekind Ch., eds. New York: Wiley; 2010.

[11] Franquemont DW, Frierson HF Jr. Muscle differentiation and clinicopathologic features of gastrointestinal stromal tumors. Am J Surg Pathol 1992;16:947-54.

[12] Franquemont DW. Differentiation and risk assessment of gastrointestinal stromal tumors. Am J Clin Pathol 1995;103:41-7.
[13] Sanchez Hidalgo JM, Rufian Peña S, Ciria Bru R, Naranjo Torres A, Muñoz Casares C, Ruiz Rabelo J, Briceño Delgado J. Gastrointestinal stromal tumors (GIST): a prospective evaluation of risk factors and prognostic scores. J Gastrointest Cancer 2010;41:27-37.
[14] Vallböhmer D, Marcus HE, Baldus SE, Brabender J, Lurje G, Drebber U, Metzger R, Hölscher AH, Schneider PM. Comparative analysis of four histopathological classification systems to discriminate benign and malignant behaviour in gastrointestinal stromal tumors. Anticancer Res 2008;28:367-72.
[15] Dematteo RP, Gold JS, Saran L, Gönen M, Liau KH, Maki RG, Singer S, Besmer P, Brennan MF, Antonescu CR. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer 2008;112:608-15.
[16] Miettinen M , Makhlouf H, Sobin LH, Lasota J. 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;30:477-489.
[17] Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY; ESMO Guidelines Working Group. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:64-7.
[18] Rutkowski P, Nowecki ZI, Michej W, Debiec-Rychter M, Woźniak A, Limon J, Siedlecki J, Grzesiakowska U, Kakol M, Osuch C, Polkowski M, Głuszek S, Zurawski Z, Ruka W. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol 2007;14:2018-27.
[19] Takahashi T, Nakajima K, Nishitani A, Souma Y, Hirota S, Sawa Y, Nishida T. An enhanced risk-group stratification system for more practical prognostication of clinically malignant gastrointestinal stromal tumors. Int J Clin Oncol 2007;12:369-74.
[20] Elshenawy YM, Ganote CE, Al-Abbadi MA. Fatal abdominal sarcomatosis secondary to gastrointestinal stromal tumor with bland histology. Saudi Med J 2009;30:1469-72.
[21] Agaimy A, Haller F, Gunawan B, Wünsch PH, Füzesi L. Distinct biphasic histomorphological pattern in gastrointestinal stromal tumours (GISTs) with common primary mutations but divergent molecular cytogenetic progression. Histopathology 2009;54:295-302.
[22] Miettinen M, Kopczynski J, Makhlouf HR, Sarlomo-Rikala M, Gyorffy H, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. Am J Surg Pathol 2003;27:625-41.
[23] Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors presenting as omental masses--a clinicopathologic analysis of 95 cases. Am J Surg Pathol 2009;33:1267-75.
[24] Wardelmann E, Hohenberger P, Reichardt P, Merkelbach-Bruse S, Schildhaus HU, Büttner R. Gastrointestinale Stroma-tumoren des Magens. Neues und Besonderes im Vergleich zu anderen Lokalisationen Pathologe 2010 Epub. DOI10.1007/s00292-009-1270-9.
[25] Woodall CE 3rd, Brock GN, Fan J, Byam JA, Scoggins CR, McMasters KM, Martin RC 2nd. An evaluation of 2537 gastrointestinal stromal tumors for a proposed clinical staging system. Arch Surg 2009;144:670-8.
[26] Chetty R. Small and microscopically detected gastrointestinal stromal tumours: an overview. Pathology 2008;40:9-12.
[27] Kawanowa K, Sakuma Y, Sakurai S, Hishima T, Iwasaki Y, Saito K, Hosoya Y, Nakajima T, Funata N. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006;37:1527-1535.
[28] Agaimy A, Wünsch PH, Hofstaedter F, Blaszyk H, Rümmele P, Gaumann A, Dietmaier W and Hartmann A. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol 2007;31: 113-20.
[29] Agaimy A, Wünsch PH. Gastrointestinal stromal tumours: a regular origin in the muscularis propria, but an extremely diverse gross presentation. A review of 200 GISTs to critically re-evaluate the concept of so-called extra-gastrointestinal stromal tumours. Langenbecks Arch Surg 2006;391:322-29.
[30] Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrointestinal (soft tissue) stromal tumors: An analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol 2000;13:577-85.
[31] Vallböhmer D, Marcus HE, Baldus SE, Brabender J, Drebber U, Metzger R, Hölscher AH, Schneider PM. Serosal penetration is an important prognostic factor for gastrointestinal stromal tumors. Oncol Rep 2008;20:779-83.
[32] Kim TW, Lee H, Kang YK, et al. Prognostic significance of c-kit mutation in localized gastrointestinal stromal tumors. Clin Cancer Res 2004;10:3076-81.
[33] Miettinen M, Fetsch JF, Sobin LH, et al. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol 2006;30:90-96.
[34] Zhang L, Smyrk TC, Young WF Jr, et al. Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tu-

mors: findings in 104 cases. Am J Surg Pathol 2010;34:53-64.
[35] Heinrich MC, Corless CL, Duensing A, et al. PDGFRA Activating mutations in gastrointestinal stromal tumors. Science 2003;299:708-710.
[36] Lasota J, Miettinen M. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). Semin Diagn Pathol 2006;23:91-102.
[37] Miettinen M, Lasota J and Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults. A clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol 2005;29:1373-1381.
[38] Agaimy A and Wünsch PH. Lymph node metastasis in gastrointestinal stromal tumours (GIST) occurs preferentially in young patients ≤40 yrs: An overview based on our case material and the literature. Langenbecks Arch Surg 2009;394:375-381
[39] Valadão M, de Mello EL, Lourenço L, Vilhena B, Romano S, Castro Ldos S. What is the prognostic significance of metastatic lymph nodes in GIST? Hepatogastroenterology 2008;55:471-4.