Review article

Prognostic indicators for gastrointestinal stromal tumors: a review

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are potentially malignancies that can occur anywhere in the digestive tract. Tyrosine kinase inhibitors (TKIs) such as imatinib have proven effective since the discovery of KIT and PDGFRA. The current version of NCNN, ESMO and EURACAN guidelines recognized that the three main prognostic factors are the mitotic rate, tumor size and tumor site. In addition, tumor rupture is also recognized as an independent risk factor. However, recent evidence shows that various types of gene mutations are associated with prognosis, and influencing factors such as gastrointestinal bleeding and high Ki67 index have been associated with poor prognosis. It shows that the current risk classification is still insufficient and controversial. With the emergence of more and more lack mutation in KIT/PDGFRA GISTs (KIT/PDGFRA wild-type GISTs) or drug resistance genes, primary and secondary drug resistance problems are caused, which makes the treatment of late or metastatic GIST face challenges. Therefore, this article will review the clinicopathological characteristics of GIST, the special molecular subtypes and other factors that may affect prognosis. We will also explore reliable prognostic markers for better postoperative management and improve the prognosis of patients with GIST.

Contents

Introduction

GISTs were initially thought to originate from gastrointestinal stromal cells; however, it was found that these tumors eventually originated from interstitial cells of Cajal [1,2]. Current epidemiology shows that the overall incidence of GIST is 0.70 per 100 000 people per year in the United States, and there is an upward trend annually [3]. Most GISTs originate in the stomach (60%) or the small intestine including jejunum or ileum (30%). It also originates in duodenum (4%-5%), colon and appendix (1%-2%), and esophagus (1%) and occasionally outside the gastrointestinal tract [4,5].

Adjuvant therapy for patients with GIST after operation, especially using Imatinib or other TKIs, depends on it risk classifications; nevertheless,

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the risk classifications of GIST remain inadequate and controversial. The 2018 Version 2 NCCN guidelines [6] and the latest version of the ESMO/EURACAN guidelines [7], French Intergroup Clinical Practice guidelines [8] all regard the four most important known risk factors: mitotic rate, tumor size, tumor site and rupture. But other prognostic factors, including histological type, depth of invasion, grade, M-category are shown in ESMO/EURACAN guidelines. In addition, NCCN and French Intergroup Clinical Practice respectively introduced the use of nomogram and contour to evaluate prognosis. ESMO/EURACAN explains both. These guidelines also have different views on small GIST and surveillance.

In addition to the risk classifications, several gene molecular types of GIST have various clinical characteristics and outcomes, but KIT and PDGFRA mutation states have not been added to the risk classifications of GIST. Nevertheless, KIT and PDGFRA mutation types can predict the response of advanced or metastatic GIST to TKI drugs such as imatinib. For example, KIT exon 9 mutant requires increased doses of imatinib; another is mutation of PDGFRA exon 18 D842V gene subtype of primary drug resistance. These mutations can adjust the dose according to the type of mutation so as to improve the prognosis of patients [9,10].

Since the discovery of KIT gene mutation in 1998 [11] and the PDGFRA gene mutation in 2003 [12], TKIs such as imatinib have achieved great therapeutic effects [13]. Although most GISTs initially respond well to imatinib and can achieve great treatment results, unfortunately, almost all patients with GIST eventually become resistant to treatment. With the advent of new TKI such as avapritinib and ripretinib, the problem of drug resistance in GIST may be temporarily alleviated [14].

In recent years, several independent prognostic risk factors have been shown to be related to prognosis. For example, GIST patients with gastrointestinal bleeding or high Ki67 index may have a poor prognosis [15–18]. More evidence is needed to prove whether these prognostic parameters can be added to the risk classifications as new indicators.

Clinicopathological features and prognosis evaluation

According to the latest version of clinical guidelines, including NCCN, ESMO/EURACAN, French Intergroup Clinical Practice guidelines, the widely recognized prognostic factors are mitotic rate, tumor size and tumor site, which also include tumor rupture. However, these four recognized prognostic factors have been continuously studied and improved in recent years. In 2002, Fletcher and colleagues first created the NIH risk classification, the first risk classification for prognosis. It divides patients into very low-risk, low-risk, medium-risk and high-risk groups according to tumor size and mitotic index [19]. Miettinen et al. evaluated 1765 GIST patients and found that tumors of the same size and mitotic index had a higher risk of recurrence in extra-gastric than tumors in gastric; they suggested that the primary location of the tumor was also an important prognostic risk factor, and proposed a new risk classification, called the Armed Forces Institute of Pathology (AFIP) criteria [20]. The prognosis of gastric GIST is the best, and various guidelines suggest that small GIST can be observed. The prognosis of the duodenum is slightly different from that of the small intestine because of its special anatomical position. But overall, their prognosis was relatively better

except for gastric GISTs. The 5-year DFS and OS of colorectal GIST were 33-57% and 46-63% [21], while the 5-year OS of esophageal GIST was 60% [22]. As for the extra-gastrointestinal GISTs, majority of them are metastases from GI, so it is relatively difficult to evaluate the prognosis [4,23]. Joensuu et al. made some improvements to previous risk classification. They found that if the size of tumor >10cm, no matter what the state of mitotic rate is, or the size of tumor >5 cm with a mitotic rate >5/50 HPF should be counted as a high-risk classification. Their study also found that if the tumor ruptures, it also needs to be included in the high-risk classification [24]. The differences between these risk classifications are listed in Table 1. The AFIP classification and the Modified-NIH (M-NIH) classification are still the most commonly used in clinical practice.

Gold et al. established the first line map, a prognostic nomogram for recurrence-free survival (RFS) after complete surgical resection of localized tumors to assess the risk of recurrence after GIST [25]. This nomogram was based on the tumor size, site, and mitotic rate. The final score determines the risk of postoperative recurrence and RFS. It may be an indication for patients who need adjuvant therapy after operation. The Memorial Sloan-Kettering Cancer Center, the Spanish Group for Research in Sarcomas and the Mayo Clinic all use this nomogram to compare with the NIH, AFIP and M-NIH risk classification. This nomogram was shown to be more accurate than that of NIH risk classification. Nevertheless, there was no significant difference with the other two evaluation methods [25–27]. In 2012, Joensuu proposed a new GIST risk classification, that is, the contour map approach [26]. The results of contour map study showed that the value of this method in prognostic risk classification of primary GIST patients who had been resected was better than that of AFIP or M-NIH classification.

Although nomogram and contour map may be more accurate in predicting the prognosis of GISTs, it is not widely used because of the complexity of its practical application. But they are recommended for personalized risk assessment in various versions of the guidelines. Unfortunately, these risk classifications were analyzed retrospectively for patients who had not been treated with imatinib after operation. Because of the extensive use of imatinib or other TKIs, few patients with moderate risk undergo surgery without TKIs treatment. It's difficult to conduct such a large sample prospective study in the future [28,29].

Prognostic factors of GIST genotypes

Background

Researchers first discovered the functional mutation of KIT in 1998, and confirmed that about 80% of GISTs accord with these mutations [11]. Platelet-derived growth factor receptor alpha (PDGFRA) mutations found in 2003 accounts for about 5% to 10% of GIST patients [12]. Interestingly, mutations in KIT or PDGFRA are mutually exclusive, leading to the activation of ligand-independence, which in turn activates intracellular signaling pathways to control cell differentiation, survival and proliferation [30]. Other GISTs without KIT or PDGFRA mutations are called KIT/PDGFRA wild-type GISTs. They can be divided into succinate dehydrogenase (SDH) deficient group and non-SDH deficient group. The SDH deficiency group includes Carney triad and Carney Stratakis syndrome. The non-SDH deficient group

Table 1
The differences between the versions of the guidelines for assessing malignant potential

Predicted malignant potential	NIH classification (2002)	AFIP classification(2006)	M-NIH classification(2008)
Very low	<2 cm and <5 mitotic index	Gastric, <2-5 cm and ≤5 mitotic index	Any, <2 cm and ≤5 mitotic index
Low	2-5 cm and <5 mitotic index	Gastric, >5-10 cm and ≤5 mitotic index Extra-gastric, >2-5 cm and ≤5 mitotic index	Any, >2-5 cm and ≤5 mitotic index
Moderate	<5 cm and 6-10 mitotic index	Gastric, >10 cm and ≤5 mitotic index or >2-5 cm and >5 mitotic index Extra-gastric, >5-10 cm and ≤5 mitotic index	Gastric, ≤5 cm and >6-10 mitotic index or >5-10 cm and ≤5 mitotic index
High	5-10 cm and <5 mitotic index or >5 cm and >5 mitotic index or >10 cm or >10 mitotic index	Extra-gastric, >10 cm and ≤5 mitotic index or <2 cm and >5 mitotic index or >2-5 cm and >5 mitotic index Any, >5-10 cm and >5 mitotic index or >10 cm and >5 mitotic index	Extra-gastric, <5 cm and >5 mitotic index or >5-10 cm and ≤5 mitotic index Any, >5 cm and >5 mitotic index or >10 cm or >10 mitotic index or tumor rupture

included neurofibromatosis type 1 (NF1) and GISTs with BRAF, KRAS, PIK3CA mutation and fusion gene. There are differences in clinical manifestations and pathological features among the GISTs [31]. Recent studies have shown that mutations including KIT, PDGFRA and other DNA (such as BRAF, SDH) are associated with imatinib sensitivity and prognosis [32]. These common mutations have become an integral part of the treatment and management of GISTs [33]. It is suggested that molecular biomarkers can provide guidelines for postoperative treatment of GISTs and may improve the prognosis of the patients. The data of GIST mutation types, prognosis and treatment are listed in Table 2. Although the genotypes of GIST are not included in any version of the guidelines, some of the genotypes will be related to imatinib resistance and affect the prognosis.

KIT/PDGFRA mutations and prognosis

KIT mutations localized within exon 11 (70%), exon 9 (10%), exon 13 (1%), or exon 17 (1%), whereas PDGFRA mutations localized within exons 18 (5%), 12 (1%), or 14 (<1%) [34]. There are also about 10% of KIT/PDGFRA wild-type GISTs. However, KIT/PDGFRA wild-type GISTs and most PDGFRA mutation GISTs generally have a lower potential for malignancy [35].

The deletions of codons 557-558 in exon 11 of C-KIT was 23.2-27.7% in all GISTs; they are lost either as specific isolated p.W557_K558 deletions in 6.3% to 7.5% of GISTs or as part of larger deletions in 15.7% to 21.4% of the GISTs [9]. Recent retrospective studies have confirmed that, deletions of KIT exon 11, especially codon 557 or 558(KITdel-inc557/558), is associated with the malignant behavior of tumors [35,36]. Compared with other KIT exon 11, KIT exon 9 and PDGFRA exon 18 mutations, the adverse prognostic effects of KIT del-inc557/558 on survival were only significant in GISTs limited to the stomach ($P < .001$); however, they were not significant in non-gastric GISTs ($P < .26$). A study from Poland also found that patients with KITdel-inc557/558 had larger tumor diameter (88% >5 cm) and higher mitotic index (MI; 75% with >5/50 HPF). The 5-year RFS was lower than that of other exon mutations, only 23.8% [37]. By contrast, single nucleotide substitutions of exon 11 had better 5-year RFS and duplications of exon 11 showed better clinical outcomes. Nevertheless, homo/hemizygous KIT exon 11 mutants were associated with risk of early tumor metastasis and intraperitoneal spread [35,37–39]. Fortunately, current studies have confirmed that GISTs mutated in exon 11 are sensitive to imatinib.

KIT exon 9 mutations in account for 7% to 15% of all GISTs. KIT exon 9 mutations characterized by A502_Y503 codon repetition are almost only found in intestinal GISTs. This type of mutation often leads to a more aggressive clinical phenotype, and has a male predominance [40]. Meta-analysis showed that the response rate and OS of patients with exon 11 mutations of KIT to imatinib were better than the patients with exon 9 mutations [41]. The KIT exon 9 mutations mainly occur in the non-gastric site, the

clinical prognosis is worse, and a higher dose of imatinib is needed for adjuvant therapy. However, the worse prognosis of KIT exon 9 mutations is related to the location of the tumor, rather than to the intrinsically invasive biological nature of the mutation [4,35,42]. As for KIT exon 13 and exon 17, a multicenter study found that these two types of mutations were more likely to occur in the small intestine than other types of mutations; however, there was no significant difference in terms of clinical prognosis [43].

GISTs with PDGFRA mutations are mostly originated in the stomach (90%-93%) [35,44,45]. In PDGFRA mutations, exon 18 accounted for a higher proportion, and the most common genotype was the replacement of p.D842V. In a Polish study, mutations in exon 18 of PDGFRA were shown to confer a lower risk of 5-year RFS [37], and there was no significant difference between PDGFRA p.D842V and other PDGFRA exon 18 mutations in DFS. Although there is primary imatinib resistance in GIST patients with D842V mutation. Therefore, GIST patients with exon 18 mutations of PDGFRA had lower tumor invasiveness and better OS and RFS [35,46]. The most common exon 14 mutation in PDGFRA is the N659K mutation, although this mutation is relatively rare compared with other exon 14 mutation types. This type of mutation is also sensitive to imatinib and usually shows better clinical outcomes [47].

KIT/PDGFRA wild-type GISTs and prognosis

In an epidemiological study from Northern Norway, KIT/PDGFRA wild-type GISTs accounted for about 15.7% of all GISTs [48], and data from the North American Intergroup were similar [49]. The wild type GISTs are classified into succinate dehydrogenase (SDH)-deficient and non SDH- deficient and SDH-deficient group. The risk of recurrence of these wild-type GISTs cannot be assessed by the current risk classifications because these wild type GISTs are not sensitive for TKIs and their biological characteristics are very different [31].

SDH-deficient GISTs. The inactivation mutation of SDH, which is composed of four subunits (SDHA, SDHB, SDHC and SDHD) was discovered in 2011 [50]. Tumors with SDH gene mutation or hypermethylation are collectively referred to as SDH-deficient GIST [51]. SDH-deficient GISTs may be associated with other neoplastic diseases including Carney triad and Carney Stratakis syndrome. GISTs with SDH-deficient are particularly common in childhood and adolescence, with about 1% to 2% of GISTs occurring in childhood [52–54]. The disease is characterized by gastric GIST, with a high incidence in female, usually showing a multi-lobed/multi-nodular growth pattern, and often metastasizes to lymph nodes. The prognosis of the patients was quite different, and about 15% to 20% of patients die of metastatic tumors [52,55]. But a recent study found that most patients survive the progression of the disease, indicating that SDH-deficient GIST is an overall indolent disease [56]. In addition, SDH-deficient GISTs are often accompanied by

Table 2

Common GIST mutation types, and the prognosis and adjuvant therapy

Genes mutation	Proportion	Common mutation	Prognosis	Treatment
KIT exon 11	65%	del-inc557/558 p. W557_K558del	Often a high mitotic count; a high risk of recurrence	Typical mutation type, sensitive to imatinib
KIT exon 9	10%	A502-Y503Dup	Usually intestinal location; often unfavorable prognosis	Imatinib sensitive, but a high dose required (800 mg daily)
KIT exon 13	1%	Lys642Glu	Often larger and more aggressive in gastric GISTs, whereas not differ from small intestinal GISTs	It is usually a secondary mutation resistant to imatinib but responds to sunitinib
KIT exon 17	1%	Asn822Lys	Often larger and more aggressive in gastric GISTs, whereas not differ from small intestinal GISTs	The secondary mutations were cross-resistant to imatinib and sunitinib, but may respond to regorafenib.
PDGFRA exon 18	6%	p. D842V	Usually gastric; low mitotic count; favorable prognosis	Imatinib resistance and cross resistance to most TKIs, but may respond to avapritinib
PDGFRA exon 14	1.5%	p.N659K	There seems to be a better prognosis	Typical mutation type, sensitive to imatinib
Other mutations	10-15%	SDH-deficient NF1 BRAF KRAS	Great differences in biological behavior□difficult to judge the prognosis	No benefit from imatinib; may benefit reported for sunitinib, regorafenib or other TKIs. Genetic counseling recommended

up-regulated expression of insulin-like growth factors 1 receptor (IGF1R), which may become a diagnostic marker or potential therapeutic target for SDH-deficient GISTs [57].

Neurofibromatosis type 1. NF1 is an autosomal dominant tumor syndrome caused by the biallelic loss or mutation of the NF1 gene. Approximately 7% of patients develop GISTs in their lifetime [58,59]. GISTs with NF1 gene mutation may also show multiple lesions, more common in the small intestine, low mitotic rates, and generally good prognosis [45,60]. In the study of Miettinen et al, only five out of 35 patients dying of metastatic disease [61]. Although NF-1-related GIST is not sensitive to Imatinib, it has been reported that responses to sunitinib [62,63]. Unfortunately, due to the limitation of the number of cases, both treatment and prognosis are small-sample studies, so it is still controversial.

BRAF, KRAS, PIK3CA mutations and fusion gene. BRAF mutation in GIST is very rare, mostly in older adults, often in the small intestine, and most of the mutations are V600E in exon 15 [64,65], which can affect the function of PI3K. The progress of this mutation is slow [66]. A large sample multivariate analysis of 451 cases of GIST showed that the OS of GIST patients with BRAF mutation was longer and the prognosis was relatively good [67]. Clinicopathological features of KRAS mutated GIST are not fully elucidated. PIK3CA mutated GIST is usually invasive and the tumor can grow rapidly with high mitotic rate. Some studies suggest that the prognosis of this type of mutation may be poor [68,69], but it also needs to be confirmed by a large sample of study.

The prognosis of some extremely rare GIST cases with ETV6-NTRK3, FGFR1-HOOK3, FGFR1-TACC1 fusion gene is still unclear, and only some case reports have been reported. A case report describes a 44-year-old male rectal GIST patient with ETV6-NTRK3 fusion gene who had no recurrence 44 months after resection [70]. FGFR1-HOOK3 and FGFR1-TACC1 fusion genes were also accidentally found in wild-type GIST [71].

Imatinib resistance and prognosis

Primary imatinib resistance and prognosis

Imatinib plays an important role in the first-line treatment of GISTs, because most of the mutation types of GISTs are responsive to imatinib, and the prognosis of these GISTs is usually good. Compared with other mutation types, the prognosis of GISTs with KIT exon 11 mutations is the best. By contrast, GISTs with KIT exon 9 mutation need to be increased to 800mg/d because of the low responding to imatinib. However, the dose for exon 9 mutation is still controversial [36,72]. Patients with Imatinib trough concentration (Cmin) below 1100 ng/ml showed a lower rate of clinical benefit [72]. The decrease of trough concentration of imatinib may lead to decreased therapeutic effect and lead to recurrence. Another study found that KIT exon 9 mutations cause receptor dimerization in the absence of ligand in a conformation that may sterically hinder imatinib binding [73,74].

In clinical trials, about 30%-66% of the PDGFRA mutant GISTs responded to imatinib, but PDGFRA D842V subtype with D842 codon in exon 18 is generally thought to cause primary imatinib resistance [75,76]. Studies have shown that the D842V mutation reduces accessibility of imatinib's binding site to PDGFRA [77]. Moreover, studies have shown that almost all PDGFRA subtypes containing D842 codon in exon 18 are resistant to imatinib [39,77]. It is worth noting that the D842V mutation is cross-resistant to most TKIs. Although PDGFRA D842V mutations (about 8%) did not respond to imatinib and other TKIs, most of them responded to avapritnib [78–80]. A study shows that patients with D842V substitution have less median PFS (2.8 mouths) and median OS (14.7 mouths) than the patients with other PDGFRA mutations [10]. For example, the GISTs in PDGFRA exon 12 mutations respond to imatinib [81].

KIT/PDGFRA wild-type GISTs tend to be resistant to imatinib. Alternate signaling pathway mutations may be potential alternative mechanisms for GIST patients lack of PDGFRA or KIT mutations, explaining their frequent primary resistance to imatinib [73,82]. About half of the KIT/PDGFRA wild-type GISTs showed SDH deficient [83]. GISTs with SDH deficient showed specific pathological and clinical features, including lack of KIT/PDGFRA mutations, and is unlikely to benefit from imatinib. But SDH deficient GISTs may have a higher probability of response to sunitinib [6].

Secondary imatinib resistance and prognosis

Although imatinib and other TKIs have a great therapeutic effect on GIST patients. Unfortunately, acquired resistance to imatinib occurs in a median treatment period of less than 2 years [84,85]. Secondary imatinib resistance is a serious problem in patients with advanced or metastatic GIST. Although several new TKIs have been shown to be effective in the treatment of imatinib resistance patients, high cost of treatment and uncertain adverse effects remain serious problems.

Secondary mutations in KIT are the most common mechanism of imatinib resistance in GISTs [86]. Secondary mutations clustered in the KIT ATP-binding pocket (exon 13) and kinase activation loop (exon 17) [9]. Heinrich and his team compared the gene profiles of tumor samples from 78 metastatic GIST patients before and after imatinib treatment and found that 33 patients had secondary mutations [39]. Gramza and his team reported a clinical study of patients treated with imatinib. They found that about 70% of patients with acquired drug resistance have tumor clones with one or more secondary kinase mutations [73]. Wang et al. discovered the molecular mechanism of stabilizing the ring-opening active conformation. They found secondary KIT mutations in 40% of imatinib-resistant GIST patients. They also reported the molecular mechanism of stabilize the open active conformation of the A-loop. Each of these patients developed a secondary KIT mutation of the same type, especially exon 17 [87]. Another study reported that the secondary KIT mutation of A-loop was associated with sunitinib resistance [88]. Compared with secondary KIT mutations, secondary PDGFRA mutations are less common in imatinib resistance [89]. To sum up, the prognosis of secondary mutation after imatinib treatment is different because there are several factors. Nevertheless, the most important factor is the time and type of secondary mutation that determines the prognosis.

Other factors related to prognosis

At present, surgical resection is the first choice for the treatment of GIST, and about 45% to 60% of the GISTs can be R0 resection [90,91]. As the concept of preoperative adjuvant therapy for GIST is put forward, the proportion of R0 resection will increase. Although the optimal duration of preoperative treatment is controversial, it usually takes 6 to 12 months to shrink the tumor to an appropriate size [26]. During surgery, it is necessary to violate the pseudo-capsule of the tumor. Some studies and guidelines recommend that when the tumor originates from the stomach and is less than 5 cm in diameter, laparoscopic wedge resection can be considered [6,7,92].

As shown in Figure 1, according to the Oslo Sarcoma standard, the definition of "tumor rupture" is as follows: 1) tumor fracture or spillage; 2) blood-stained ascites; 3) gastrointestinal perforation at the tumor site; 4) microscopic infiltration of an adjacent organ; 5) intralesional dissection or piecemeal resection; or 6) incisional biopsy [93]. The common sites of GIST metastasis are liver (28%) and mesentery and omentum (30%) [94]. Omentum metastasis is mostly caused by tumor implantation, and the cause of tumor implantation is tumor rupture. A research shows that the rupture area of tumor pseudo-capsule has a different effect on the prognosis. Severe tumor rupture is more likely to lead to implant metastasis than slightly tumor rupture [95]. Other studies have also shown that tumor rupture often leads to tumor recurrence in the peritoneum and liver [96,97]. Nevertheless, the poor prognosis caused by tumor rupture is recognized, and it is an important factor to judge the prognosis of GIST.

Bloody ascites also suggests a ruptured tumor [98]. In recent years, some studies have found that gastrointestinal bleeding is an independent risk factor for poor prognosis in GISTs. If GIST patients have gastrointestinal bleeding, it should be equated with tumor rupture, and it should be included in the high-risk group for postoperative adjuvant therapy [15,16,99].
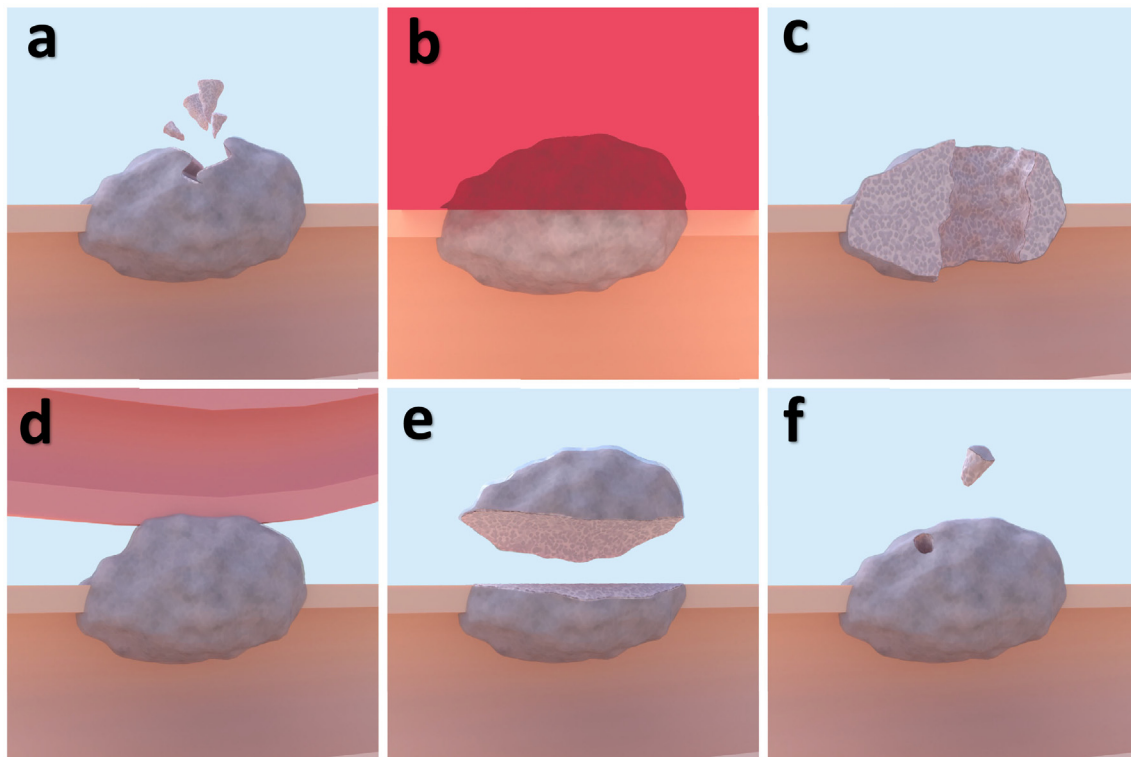
Figure 1. (A) Tumor fracture or tumor spillage. (B) Blood-stained ascites. (C) Gastrointestinal perforation on tumor. (D) Adjacent organ infiltration. (E) Piecemeal resection or intralesional dissection. (F) Tumor biopsy.

Ki67 can accurately reflect the proliferative activity of tumor cells and is related to the development, metastasis and prognosis of various tumors. In GIST, Ki67 is also an important indicator. Studies have shown that most patients with Ki67 >5% have a high risk of recurrence and are prone to metastasis ($P < .001$). Ki67 index positively correlated with risk classification (r = 0.558) and mitotic index (r = 0.619) [17]. Another meta-analysis showed that there were more GIST patients with high Ki67 index in the middle and high NIH group than in the low NIH group [100].

On CT imaging, GISTs with diameter less than 5 cm were symmetrical, with clear boundaries, and mostly showed intracavitary growth patterns. By contrast, GISTs of 5–10 cm showed poor symmetry, growing inside and outside the lumen and infiltrating into other organs. Finally, GISTs larger than 10 cm showed aggressive behavior of peritoneal or distant metastasis [101]. As many as 79% of the GISTs showed exogenous growth, while the frequency of endogenous or mixed growth was lower, and the appearance of clinical symptoms of exogenous growth occurred later, while endogenous growth of GISTs often led to gastrointestinal bleeding or obstruction [102,103].

In Table 3, some related factors that may lead to poor prognosis of GISTs are listed. For example, recent studies have shown that low systemic immune-inflammation index (SII) and high prognostic nutritional index (PNI) values are associated with longer PFS, and GISTs with high neutrophil to lymphocyte ratio (NLR), high SII and low PNI have poor OS [104]. Another study also showed that GISTs with high PNI ($P < .001$), low NLR ($P < .001$) and low PLR ($P = .002$) had better prognosis. PNI is an independent prognostic factor of RFS (HR = 1.967, 95% CI: 1.243–3.114, $P = .004$) [105]. These two articles also confirm the importance of PNI in GISTs. Tumor necrosis also indicates rapid tumor growth, accompanied by high mitotic index, indicating a poor prognosis [106–108]. The disease-specific-survival (DSS) of GIST patients older than 50 years old was significantly lower than young patients (HR = 0.307, 95% CI 0.113–0.834; $P = .021$), and in young patients, the prognosis of women was better than that of men ($P = .033$) [109].

Conclusions

Although there are controversies and deficiencies in the risk classifications of GIST, there are two kinds of evaluation methods: one is the threshold classification of pathological indicators, and the other is the judgment of continuous variables, including NIH, M-NIH, AFIP classification, nomogram, and contour maps. But the most commonly used in clinic is AFIP or M-NIH classification [4,25,78,110]. When the tumor diameter or mitotic count is close to the critical value, it is best to refer to another scheme, or to use a method that represents the size and mitotic count as continuous variables. Clinicopathological features combined with other indicators will make the prognosis of GIST more accurate.

The strategy to combat primary imatinib resistance caused by D842V mutation is to switch to another TKI. Whether exon 9 mutation increases the dose to 600 mg/d or 800 mg/d remains controversial; however, some studies show that the GIST patients will benefit if they can tolerate 800mg/d. [38]. The dose of 400 mg twice a day is determined as the maximum tolerable dose (MTD) [111]. However, considering adverse effects, economic and other factors, individualized treatment for GIST patients

Table 3
Some indicators related to prognosis

clinical features	Risk of recurrence	Overall survival	References
Gastrointestinal hemorrhage	Poor RFS in hemorrhage group	Poor OS in hemorrhage group	15,16
High Ki67 index	High risk of recurrence	No discussion	17,18,100
PNI	PNI-high group had a longer RFS	PNI-high group had a longer OS	104,105
Tumor necrosis	Low DFS in tumor necrosis group	Poor OS in tumor necrosis group	106-108
Age>50	DSS is lower than young people	OS is lower than young people	109

RFS, recurrence-free survival; OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; PNI, prognostic nutritional index.

will be more widely recognized. Of course, there are still some controversial issues that need to be discussed: if the patients underwent preoperative adjuvant therapy and R0 resection, adjuvant therapy is still needed after operation. But when the size of the tumor becomes smaller after adjuvant therapy, the mitotic index may also be reduced. How to assess the risk? Why do patients with different body weight and body surface area take the same dose of TKIs?

In recent years, many prognostic factors have been found, but lack of prospective, large sample, multicenter studies, the level of evidence is not particularly high, so they have not been added to the guidelines, with the continuous study, there will be some factors added to the risk classifications to guide the treatment of GIST patients and improve their prognosis.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contribution statement

Qi Liu: The conception and review of manuscripts, and the writing of manuscripts.

Haixin Zhang: Figures and tables production, literature inquiry, manuscript writing.

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