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REVIEW

Gastrointestinal Stromal Tumors of the Small Intestine: Progress in Diagnosis and Treatment Research

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Abstract: In recent years, the diagnosis and treatment of gastrointestinal stromal tumors (GISTs) of the small intestine have been a hot topic due to their rarity and non-specific clinical manifestations. With the development of gene and imaging technology, surgery, and molecular targeted drugs, the diagnosis and treatment of GISTs have achieved great success. For a long time, radical resection was prioritized to treat GISTs of the small intestine. At present, preoperative tumor staging is a novel treatment for unresectable malignant tumors. In addition, karyokinesis exponent is the sole independent predictor of progression-free survival of GISTs. The DNA, miRNA, and protein of exosomes have also been found to be biomarkers with prognostic implications. The research on the treatment of GISTs has become a focus in the era of precision medicine, ushering in the use of standardized, normalized, and individualized treatment.

Keywords: gastrointestinal stromal tumors, GISTs, small intestine, novel treatment, preoperative tumor staging, karyokinesis exponent, exosomes

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that commonly exist in the gastrointestinal (GI) tract. They originate from the precursor cells of the Cajal mesenchymal cells in the muscle plexus. On the whole, sarcomas of the small intestine are identified as GISTs.[1–3] Small intestinal GISTs require a special and individualized diagnosis and treatment, given their heterogeneity. Clinically, tumor size, location, and karyokinesis exponent are the major elements affecting the prognosis. Due to the limitations of experimental techniques in the necessary sciences, such as molecular biology and immunohistochemistry, the diagnosis and treatment for GISTs face numerous constraints. In recent years, with the advancement of relevant technologies like genetic analysis, great advancement has been achieved in the field of GISTs diagnosis and treatment. Studies on the molecular subtypes of GISTs have direct implications on the development of novel diagnostic and therapeutic methods. Though considerable efforts are being made to address the aforementioned weaknesses, further development is needed to uncover more efficient and feasible approaches. Table 1 shows the summary of small intestine GISTs studies not included in the meta-analysis. This review discusses the present status of diagnosis and treatment for GISTs of the small intestine.

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Table 1 Summary of Studies of Small Intestinal GISTs Not Included in the Meta-Analysis

First Author	Study Design	Year	Age(Mean)	Sample	Study Period
Ihn et al[61]	Prospective study	2012	58(24–79)(Open) 57 (20–77)(Lap)	95	1993–2011
Wan et al[101]	Prospective study	2012	59(13–94)	91	2004–2010
Chen et al[42]	Retrospective study	2014	54 ± 12	25	2006–2013
Tabrizian et al[94]	Prospective study	2014	60.4	26	1999–2011
Sandvik et al[102]	Retrospective study	2015	63(15–86)	23	1980–2011
Liao et al[62]	Prospective study	2015	58.0±13.4	85	2005–2013
Güller et al[103]	Retrospective study	2015	62(18–101)	1603	1998–2008
Kukar et al[104]	Retrospective study	2015	60.6	1463	1990–2009
Ma et al[105]	Retrospective study	2015	64	1,765	2001–2011
Xing et al[9]	Retrospective study	2015	17–82(55.6 in jejunum and 55.3 in ileum)	197	2005–2015
Holmebakk et al[90]	Retrospective study	2016	63(27–86)	61	2000–2012
Giuliano et al[92]	Retrospective study	2016	62(51–71)	1848	2002–2012
Shinya et al[5]	Retrospective study	2016	62.59±12.246	76	2004–2015
Guller et al[74]	Retrospective study	2017	62(18–101)	1288	1998–2011
Nakano et al[4]	Retrospective study	2017	58.0(24–83)	25	2003–2015
Vasconcelos et al[34]	Retrospective study	2017	61.8±14	111	1998–2013
Verde et al[33]	Retrospective study	2017	54.4(23–86)	26	2000–2015
Giuliano et al[91]	Retrospective study	2018	62(52–72)	5683	2004–2014
Yan et al[106]	Retrospective study	2018	55(20–86)	213	2008–2016

Epidemiology

Although GISTs are infrequent vascular tumors,[1] they are the most frequent mesenchymal tumors in the digestive tract, with an annually probability of occurrence of seven to 20 per million.[2,3] They can occur anywhere in the GI tract, with the stomach accounting for 50% to 60% of cases, the small intestine for 20% to 30%, the colon or rectum for 5% to 10%, the esophagus for <5%, and the peritoneum and mesentery for <1%.[4] The small intestine, which comprises most of the GI tract, is considered to be a relatively specialized organ. Because small intestinal neoplasms are usually rare, they are difficult to detect in early images. As a result, they are often overlooked and delayed in diagnosis.[5,6] GISTs of the small intestine are currently considered more invasive than GISTs of the same size in the stomach,[7] and their incidence has been rising in the past few years, a phenomenon that some scholars attribute to advances in radiology and endoscopy techniques, as well as improved physician awareness.[8] Small intestine GISTs predominantly affect people from 40 to 70 years of age.[8] In patients of different ages, the distribution of small intestine GISTs is roughly the same regardless of gender. In certain studies, males have a slight advantage, but this distinction is not well-defined.[9]

Clinical Presentation

GISTs result from incidental neoplastic disease usually found with non-specific clinical manifestations.[10] These clinical manifestations are primarily associated with the tumor diameter, presence or absence of tumor cracks, and the tumor's relationship with surrounding tissues, which cause symptoms such as abdominal pain, abdominal mass, and bleeding.[11] Other symptoms include abdominal distention and fullness, early abdominal distension, nausea and vomiting, and palpable swelling or pain.[12] Endoscopically, if there are no ulcers, the submucosal eminence will be consistent with overlying normal mucosa. If there are symptoms, the most common symptom will be GI bleeding, such as hematemesis or anemia, which can also cause intestinal obstruction or even perforation.[13] Intraperitoneal hemorrhage is often caused by necrosis and ulceration. The frequency of small intestine GISTs is slightly below that of gastric GISTs, whereas the major emergency manifestation of GISTs of the small intestine is intestinal obstruction.[14] It has been reported in the literature that intussusception caused by small intestine GISTs is quite rare in adults, and over 90% of the lesions are identifiable, comprising about 0.1% of all surgical approaches and 1–5% of mechanical ileus cases.[15] However, intussusception in adults is difficult to preoperatively diagnose due to its non-specificity, and

only about a third of cases are correctly diagnosed. In recent years, a few cases of GISTs of the small intestine with hepatic abscess have been reported. Rodrigues et al[16] reported a case of small intestine GISTs with suppurative liver abscess, suggesting that differential diagnosis of abscess and liver metastasis in small intestine GISTs patients is needed. For patients without a clear source of suppurative liver abscess, GI lesions may need to be examined. Previous studies have suggested that vascular infiltration is a strong indicator of liver metastasis in GISTs.[17]

Diagnosis of Small Intestine GISTs

The diagnosis of neoplasms of the small intestine is a continuous challenge that is often neglected clinically, characterized by low morbidity, common clinical symptoms, wide imaging manifestations, pleomorphic bowel, and overlapping of intestinal loops. Though the small intestine is an indispensable part of the GI tract, small intestine GISTs comprise merely 20% to 42% of GISTs. Accordingly, the diagnosis of small intestinal GISTs is a crucial task for clinicians. Clinical history, endoscopic examinations, and imaging examinations can greatly benefit diagnosis.[18]

Histopathology and Immunohistochemistry

According to histology, GISTs can be split into spindle cells, epithelioid cells, and mixed subtypes.[19,20] The spindle cell type consists of relatively homogeneous eosinophilic cells, as arranged in short bunches or spirals. The cytoplasm is moderately eosinophilic, with acidophilia shallower than that of the leiomyoma. The nuclei are uniformly distributed and variable in shape. Fragile parenchyma vessels may be prominent, resulting in a high risk for stromal hemorrhage. In contrast to the spindle cells, the cytoplasm of epithelioid cells is clear and eosinophilic, and hyaline degeneration or necrosis can be observed in the stroma. The nuclei are uniformly round or oval in shape. Due to the nested structure of the nuclei, they are likely to be presented as epithelial or melanocytic neoplasms. Mixed cell type lesions may be manifested as mutations between spindle cells and epithelioid cells, or as a mixture of both.[21] The technique of choice to achieve histological diagnosis is echoendoscopy-guided biopsy or a computed tomography (CT)-guided percutaneous biopsy. Because fine needle aspiration (FNA) endoscopy typically does not provide sufficient materials for definitive histological diagnosis and molecular analysis, biopsies are required.[22,23] If the biopsy becomes complicated, a laparoscopic incision or laparotomy will be required to make a diagnosis. Preoperative endoscopic biopsies are not necessary when a lesion is considered to be resectable. For patients with disseminated disease or carrying locally advanced cancer, neoadjuvant therapy should be adopted based on mutation analysis, which has predictive implications for sensitivity and prognosis of molecular-targeted therapy.[24] DOG1 refers to a monoclonal antibody against the chloride channel protein expressed in GISTs. Regardless of DOG1's mutation status, 95% of GISTs are immunoreactive.[25,26] However, peritoneal myomatosis and synovial sarcomas may also be DOG1 positive.[27] Pathologically speaking, the diagnosis of GISTs depends on morphology and immunohistochemistry, which usually means a positive test result for CD117 (KIT) or DOG1;[28] only a small number of GISTs are CD117 negative. GISTs are found positive for over 95% of the KIT of tyrosine kinase receptor protein measured with antibody CD117. CD117 immunoreactivity is not inevitably related to KIT gene mutation. Due to the lack of CD117 immunoreactivity, KIT mutations may also be present. It is suggested to combine CD117 and DOG1 for immunohistochemical staining for GISTs diagnosis, which can increase the diagnosis rate of GISTs.[29] However, in a few cases, both of them were not positively expressed at the same time.

Computed Tomography (CT)

CT is the prioritized method to diagnose GISTs. Contrast-enhanced computed tomography (CT) is capable of identifying tumors and assessing their range and metastasis. The study on multiphase threshold levels may stand a chance of enhancing the diagnostic ability of multidetector CT for small bowel neoplasms. The discovery of primary tumors by accident on multiphasic CT can provide an effective clue to diagnosing small intestinal neoplasms with metastatic malignancy of unknown source.[30] It was verified by surgery that all tumors have a clear anatomical location in the small intestine.[11] CT is superior over MRI in showing the thickness of the entire small intestine and in displaying the deep loops of the ileum and mesentery without superposition and evaluation of the surrounding mesentery.[31,32] The tumor size and the mitotic count suggests that there is no conspicuous difference in the risk categories between duodenal and jejunal GISTs that occur in different anatomical sites. Ileal GISTs lead to 66.0% of high-risk cases, higher than that of GISTs in the duodenum

and jejunum. The average size of ileal GISTs is 9.77 cm, larger than that of GISTs in the duodenum and jejunum. In brief, the clinicopathologic features and CT findings of small intestinal GISTs may vary depending on the primary anatomical site.

CT findings are associated with malignancy or karyokinesis exponent. On post-contrast multiphasic multidetector CT, the enhanced mode of GISTs refers to rapid and highly attenuated intravenous irrigation. Also, the attenuation peak is high, reaching the arterial stage, while the attenuation in the enteral and venous stages fluctuate less significantly. In CT images, the enhancement degree from the duodenum to the ileum during the portal phase is gradually upregulated, and the enhancement mode displays a trend of heterogeneity. The enhanced difference reflects underlying pathological changes, identified as necrotic. As tumors grow, they can outgrow the blood supply and turn necrotic, a process which is significantly associated with heterogeneous reinforcement, necrosis, and tumor enlargement. These cases reveal an imperative relation between the increased heterogeneity and non-low-risk small intestine GISTs. Also, tumor size is a determinant factor in disease progression risk. Small, uniformly-enhanced lesions have a lower risk of progression, while large uniformly-enhanced lesions have a higher risk of progression.[33] Besides routine abdominopelvic CT, multiphasic CT enterography is also feasible to identify patients with suspected intestinal bleeding. Also, it is more feasible than abdominopelvic CT or video capsule endoscopy for identifying small Intestinal neoplasms. Most small intestine GISTs examined by CT enterography are non-malignant, and the incidence of non-malignant small intestine GISTs has risen significantly. Such increased incidence is explained by the increased use of CT enterography to detect suspected small intestinal bleeding, leading to the discovery of small intestine GISTs with lower aggression.[34]

F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

PET-CT utilizes 18F-fluorodeoxyglucose (18F-FDG) to detect cancer based on tissue metabolic variations.[35] Although small intestine GISTs are fludeoxyglucose avid tumors, PET scans are typically employed only to assess indeterminate lesions on the CT, or to track the response to treatment in selected individuals. PET-CT imaging can be devoted to identifying lesions and necrotic areas as well as benign and malignant tumors.[36] Resembling a CT scan, a PET-CT scan is susceptive to ascertaining the availability of adjuvant therapy. In addition, PET-CT imaging is more likely to detect hepatic metastasis of GISTs, and is more accurate than CT imaging alone. Thus, PET combined with CT can facilitate the diagnosis of liver lesions. Studies have verified previously that the sensitivity and positive forecasted value of 18F-FDG PET reached 86% and 98% respectively, and it outperforms CT in predicting the early treatment response of recurrent or metastasized tumors.[37]

Magnetic Resonance Imaging (MRI)

Thus far, MRI has been used in imaging diagnosis of various systems throughout the body. MRI is especially applicable to the diagnosis of large tumors as an auxiliary examination of CT,[38] whereas it is limited in representing the skeleton and GI. MRI may be conducive to assessing tumors with stereotype structures, such as primary rectal GISTs or liver metastases. MRI is to some extent similar to the CT imaging of small intestine GISTs, while also providing information about perforation, metastasis, tumor infiltration, and tumor relationship to main blood vessels.

However, MRI is prioritized in the differentiation of liver metastasis, hemorrhage, and tumor necrosis. MRI findings verified that the small GISTs are round with strong homogeneity of arterial enhancement, while the large GISTs are lobulated and often exhibit mild, heterogeneous, and progressive enhancement accompanied by intracellular cystic variations.[39] Diffusion-weighted MRI (DWI) is particularly sensitive to the microscopic movement of properties of water. Several studies showed the application of DWI combined with the apparent diffusion coefficient (ADC) in the antidiastole of uterine fibroids and leiomyosarcoma.[40,41] DWI combined with ADC may act as a novel method to diagnose small intestine GISTs. Intratumor cystic variations and low ADC values have advantages in predicting the highly malignant potential of GISTs on an MRI.

Interventional Digital Subtraction Angiography (Interventional DSA)

DSA is primarily used for the observation of vascular lesions, the positioning and measurement of vascular stenosis, as well as the provision of real stereoscopic images for interventional treatment. It is a necessary condition for all types of interventional treatment, applicable to the examination of cardiovascular and cerebrovascular peripheral

vascular tumors and minimally invasive interventional treatment. In the study with the largest sample size to date, Chen et al[42] concluded that emergency DSA was a useful option when other auxiliary examinations failed to detect bleeding diseases in a timely manner. DSA intervention therapy is tolerated even in patients with severe anemia. Small intestine GISTs exhibited some common DSA characteristics, which can clearly show the exact location, range, blood supply, and complications of the tumors. The researchers consider that interventional DSA is a feasible imaging pattern to diagnose and locate small intestinal GISTs in patients with hemorrhage, as well as an effective therapeutic modality.

Endoscopic Ultrasonography (EUS)

According to the research results of Hedenström et al,[43] EUS-guided biopsy is a reliable and accurate method for further analysis of GISTs. Few prospective studies have assessed the accuracy of EUS-guided sampling in GISTs. EUS can reveal tumors, including GISTs. Sekine et al[44] concluded that EUS-guided fine needle aspiration (EUS-FNA) biopsy can significantly increase the detection rate of GISTs. However, during upper endoscopy, a GIST presents as a submucosal mass with smooth edges. Upper endoscopy with endoscopic biopsy, even with laminated or bite biopsy, exhibits a low diagnostic rate of nearly 17.42%.[45] Due to the risk of perforation, endoscopic submucosal resection is not advised for patients with small intestine GISTs. EUS showed hypoechoic round or oval lesions. It can distinguish GISTs from other submucosal lesions, but the diagnostic accuracy is affected by the difference between observers, and some studies reported the diagnostic accuracy as 43%.[46,47] The relationship between tumor size and irregular boundaries is well consistent with malignant behavior, and the presence of echogenic cystic space, ulcer lesions, and heterogeneity in EUS acts as a weak indicator of malignancy.

EUS-guided sampling is recommended for endoscopic lesions.[48] Under EUS guidance, FNA exhibits a high diagnostic rate. According to the results from earlier studies, the diagnostic sensitivity of EUS-FNA was approximately 50%.[49] The sensitivity to exclude small tumors (<20 mm) was 80%,[50] whereas EUS-FNA cannot detect the malignant potential in cytology. In some previous preliminary studies, the diagnostic accuracy of EUS-guided puncture biopsy with a 19-gauge core needle was higher than EUS-FNA.[51] However, these results are difficult to repeat in future in-depth studies or larger studies.[52] Importantly, because of the limited angle of endoscopic ultrasonography, it can only be performed when jejunal or ileal GISTs are visible from the stomach or duodenum. Accordingly, its application is limited to esophageal, gastric, and rectal lesions. For lesions not suitable for endoscopic biopsies, such as the small intestine, laparoscopic or open biopsy may be required.

Genetic Analysis

Common sites of GIST gene mutations cover exons c-KIT 9, 11, 13, and 17, as well as exons 12, 14, and 18 of PDGFRA. The most common mutation of the c-KIT gene is the exon 11 mutation, which may exhibit point mutation, insertion mutation, fragment mutation, or substitution. Exon 9 mutations are most commonly expressed as ay502-3 repeat insertion mutations. Vadakara and von Mehren[53] reported that GISTs with c-KIT exon 11 point mutation and insertion mutation had a better prognosis; those with c-KIT exon 11 deletion mutation and exon 9 mutation had a worse prognosis. C-KIT exon 11 gene deletion may be an independent factor leading to poor prognosis in GIST patients, likely due to the different locations of Cajal mesenchymal cells from which the tumor originated. The mutation rate of c-KIT exon 13 is associated with imatinib resistance, and c-KIT exon 17 mutations are rare.[54] The biological behavior of PDGFRA mutations in GISTs is relatively inert.[55] Among the PDGFRA gene mutations, exon 18 mutations are the most common, and PDGFRA mutations are also common in patients with c-KIT negative mutations in GISTs.[56] The specific mutation type of KIT or PDGFRA gene is correlated with the phenotype of the GIST tumor. Certain del557/55827 activation that affects the possibility of tumor crack may be attributed to different KIT or PDGFRA mutations.[57] GISTs most commonly result from epitheliod tissue, in which D842V mutation can cause primary drug resistance. BRAF mutation is associated with secondary drug resistance.[58] According to another study, FGFR1 was detected as the major FGF receptor expression, and AKT was found to be phosphorylated, suggesting that an autocrine loop referring to FGF4-FGFR1 could induce a downstream signaling pathway of quadruple wild-type (WT) GISTs. Recent studies found that quadruple WT cases carry changes in FGFR1 activation, which strengthens the hypothesis that FGFR pathway dysregulation may be involved in quadruple WT GISTs, providing a theoretical basis for new treatment methods.[59] Relevant studies revealed that the activation of the PI3K-AKT-TSC-mTOR pathway is associated with the

diversity of genetic changes.[60] To summarize, molecular genotyping of GISTs can help to evaluate the prognosis of tumor patients and predict the efficacy of imatinib against tumors, especially for some specific and rare subtypes, including Carney-Stratakis syndrome (CSS) and Carney triad.

Therapy of Small Intestinal GISTs

At present, surgical resection and molecular-targeted drugs are the main therapeutic methods for treating small intestine GISTs. In recent years, with the research on the treatment of small intestine GISTs, preoperative systematic treatment and endoscopy have been used for the treatment of small intestine GISTs, which has greatly changed the treatment strategy and prognosis of small intestine GISTs.

Surgical Therapy

Radical resection is currently the preferred treatment for small intestinal GISTs. Sufficiency of radical resection is assessed by borderline status and by complete resection without tumor overflow or rupture.[61,62] Tumors with a diameter larger than or equal to 2 cm have the potential for malignancy. From an oncological perspective, limited resection of small intestinal GISTs is an ideal surgical approach.[63] Complete resection of the tumor with no large margins or lymph nodes, wide negative resection margins, and prevention of tumor rupture and hemorrhage are necessary. With the development of laparoscopic surgery (LS), the use of LS in small intestine GISTs has increased. Currently, studies have shown that there was no statistically significant difference in prognosis between LS and open surgery.[64] For GISTs of the small intestine, LS is comparable to open surgery and has numerous advantages, including low tumor crack rate, short operative time, early recovery time of intestinal function, and less postoperative pain.[65] Similar to previous studies on small intestinal GISTs,[66] the studies of Liao et al[62] successfully demonstrated that LS was superior over open surgery in postoperative recovery time. Currently, the NCCN guidelines recommend the use of LS for GISTs not exceeding five cm,[67] but the studies of Liao et al demonstrated that small intestine GISTs should be considered for LS when the tumor size was below 10 cm. Ihn et al[61] demonstrated that even a mass 10 cm in diameter can be taken out by an incision smaller than 6 cm. For patients with a postoperative positive resection margin (R1) after the complete resection of primary localized GISTs (R0 resection), the NCCN guidelines do not recommend reoperation, whereas the ESMO guidelines recommend reoperation to achieve R0 resection.[68] However, LS requires an anastomosis of the digestive tract, and Liao et al[69] addressed this problem using a wound protector, thereby not only preventing against tumor contamination, but also making the navel incision wider. Due to its mobility, the intestine can be placed under a subumbilical incision and anastomosed under direct vision or through an intraumbilical incision. This method is capable of shortening the operation time, reducing the surgery's learning curve, and making laparoscopic surgery easy for surgeons to learn. It also reduces the possibility of adhesion and incisional hernia.[70] The pathology of the tumor was the key factor for relapse, not the surgical technique. Thus, if patients do not have contraindications to LS, then LS may be a treatment option for small and medium-sized GISTs.[71]

Adjuvant Therapy

Adjuvant therapy is an alternative treatment for inoperable small intestine GISTs. Imatinib mesylate (IM) is currently recognized as the first choice of adjuvant therapy for GISTs. Imatinib is a small molecule inhibitor of tyrosine-kinase (TKI), which can specifically inhibit KIT, PDGFRA, and BCL-al, significantly reducing the relapse rate, improving the survival rate, and slowing down the progression of the disease. Tumor size, site, karyokinesis exponent, and tumor crack are the most important free-standing prognostic indicators for GISTs relapse-free survival (RFS). All GISTs of 3 cm in size, small intestine location, and high karyokinesis exponent have been shown to do well out of adjuvant imatinib therapy.[72] In patients with early exon 11 mutations, low doses of imatinib are sufficient.[73] Adjuvant imatinib therapy for three years is currently standard for patients at high risk of relapse. Even after the completion of adjuvant imatinib therapy, imatinib is still effective for GIST relapse.[74] Although GISTs initially respond commendably to imatinib, almost all patients with GISTs eventually generate resistance to this treatment. The European Medicines Agency (EMA) and the FDA have approved sunitinib as a second-line therapy for GISTs, with patients taking 50 mg once per day for four weeks and taking two weeks off. Gronchi and colleagues concluded that adjuvant sunitinib therapy was the preferred treatment for CD117 exon 9 mutations and WT GISTs. Ramaswamy and colleagues found an overall survival rate of 38 months for exon 9 mutations of CD117

and 66 months for exon 11 mutations of CD117.[75] Sunitinib is used as adjuvant therapy for patients with exon 13 or 14 mutations, whereas ponatinib is applied to adjuvant therapy with exon 17 mutations. However, its side effects require further study.[76] Regorafenib is an oral inhibitor of multiple kinases authorized by the FDA and EMA to treat GIST patients who either cannot be resected, or metastasized after inefficiency or tolerance of imatinib and sunitinib.[77] In one existing study, it was found that ipilimumab and nivolumab could also treat patients with TKI-resistant or unresectable GISTs, and that these drugs may reduce tumor size by 40%.[78]

Preoperative Systemic Therapy

Preoperative systemic treatment of GISTs covers neoadjuvant treatment and preoperative tumor downstaging treatment. Tumor downstaging treatment is considered a novel treatment for unresectable malignant tumors. The combination of imatinib and surgical resection has become a vital approach to treat advanced GISTs. There has been rare clinical trial evidence for neoadjuvant imatinib treatment for GISTs.[79] The practicability of neoadjuvant imatinib treatment appears to be highly supported by the results of clinical trials. The NCCN guidelines propose neoadjuvant imatinib treatment to diminish the size of preoperative tumors in order to make surgical resection safer and more effectively negate the resection margin, especially for large primary tumors or inferiorly located tumors of patients who require extensive surgery or who must sacrifice a high quantity of healthy tissue. Fiore et al[80] concluded that the preoperative use of imatinib for high-risk patients or patients requiring extensive surgery led to improved results. PFS after three years was 77% of initial imatinib treatment.

Eisenberg et al[79] evaluated the reliability and effectiveness of neoadjuvant imatinib treatment in patients with KIT-positive primary GISTs or surgical metastasis/relapse of GISTs. The existing studies reported that imatinib is given preoperatively for anywhere from a few days to more than a year.[81] Tirumani et al[82] found that the optimal response of the neoadjuvant imatinib treatment occurred at 28 weeks, and the plateau reaction occurred at 34 weeks. They considered that two to three months of neoadjuvant treatment is too short to effectively reduce tumor size for the treatment of imatinib. For adequate efficacy, imatinib should be employed at least six months before surgery. Similarly, the studies of Demetri et al[83] have shown that the optimal duration of imatinib before surgery is six to 12 months for the best results.

However, there are risks associated with prolonged treatment that may lead to tumor necrosis, cystic changes, rupture, and hemorrhage Kang et al.[84] Provided the important information that neoadjuvant imatinib treatment could be considered with high karyokinesis exponents or large tumor sizes to decrease the hazard of intraoperative complications, including tumor crack. Imatinib is a cellular inhibitor that takes time to reduce tumor size. Accordingly, in order to be effective, imatinib is required to be given for a longer period of time than the usual neoadjuvant chemotherapy for cancers. The time of surgery for patients receiving imatinib should be consistent with the optimal clinical response. Surgery should be executed before patients developed resistance to it. In the B2222 trial, half of the patients developed tumor evolution within two years after initiating imatinib therapy.[85] Surgical treatment should be avoided if imatinib has been used for over one year. The operation is of high importance in controlling the disease during imatinib treatment. According to relevant reports, the median response time of patients with higher efficacy than partial response was 2.7 months, and the median response time of 75% of patients was 5.3 months.[82] However, the wide range of resection may lead to organ function loss and significantly affect the postoperative quality of life. For the applicable treatment period of neoadjuvant imatinib treatment for advanced GISTs, there has been insufficient evidence. Raut et al[86] showed that stable disease patients exhibited a PFS of 80% at 12 months, of which 33% showed limited progress and 0% showed extensive progress.

Endoscopic Ultrasonography

With the development of studies on small intestine GISTs, CT-guided radiofrequency ablation may be an option for patients whose tumors cannot be surgically removed in addition to surgery and targeted therapy. Though EUS alcohol ablation has room for improvement, it may be an effective treatment in cases of surgical contraindications. EUS alcohol injection can be used for the ablation of liver and adrenal or pelvic lymph node metastases[87] Gunter et al.[88] Reported that a middle-aged male patient diagnosed with GISTs with surgical contraindications underwent EUS-guided tumor ablation and demonstrated complete tumor remission after a two year follow-up. As EUS has been increasingly utilized for small intestine GISTs, more insights into the etiopathogenesis of GISTS have been gained, and the accurate differentiation

between small intestine GISTs and other submucosal tumors has been realized. Though surgery is preferred, an experienced endoscopist can work with the surgeon.

Clinical Outcome

Biological behavior of GISTs involves the general characteristics, histological morphology, and clinical situation of the tumors. NCCN adopts the maximum tumor diameter and karyokinesis exponent as classification indicators to predict the biological behavior of GISTs. In 2008, the NIH reported a high risk of intraperitoneal tumor rupture, regardless of the size or mitosis. The major purpose of tumor follow-up is to detect and treat relapse early. Table 2 shows a summary of recurrence studies and long-term survival. Staging procedures suggest that most tumor relapse is more likely to occur in the liver or peritoneum, and abdominal or pelvic CT-enhanced scanning is an option for studying stages and follow-up.[89] Karyokinesis exponent may affect the rate of relapse. Exposure rating on the strength of mitotic count, tumor size, and tumor location may help to standardize follow-up.[90] Patients with intestinal GISTs are

Table 2 Summary of Studies of Recurrence and Long-Term Survival

First Author	Surgery	N	Follow-Up (Month)	Recurrence	Survival (%)
Ihn et al[61]	Lap Open	41 54	24.7 51.6	3 13	NSD NSD
Wan et al[101]	Lap Open	43 38	40(4–96) 36(11–88)	3 1	3-year DFS: 91.1 3-year DFS: 93.8
Tabrizian et al[94]	Lap Open	10	56.4(0.1–162.4)	3	10-year-OS: 91.3 10-year-DFS: 71.6
Liao et al[62]	Lap Open	26 59	24.3 44.9	4 13	3-year DFS: 100, 5-year DFS: 88.5, 3-year OS: 100, 5-year OS: 100 3-year DFS: 78.2, 5-year DFS: 71.4, 3-year OS: 92.9, 5-year OS: 87.5
Ma et al[90]	Lap Open	- -	– –	– –	5 year-OS: 70% (68–73%); 5-year CSS: 82% (84–80%)
Sandvik et al[102]	Lap Open	23	– –	6	1-year DFS: 96; 5-year OS: 92; 1-year CSS: 100; 5-year CSS: 96; 1-year RFS: 96; 1-year DFS: 78; 5-year DFS: 78; 5-year OS: 80
Kukar et al[104]	Lap Open	1213	– –	– –	5-year DFS: 87
Güller et al[103]	Lap Open	4263	37	927	OS: 87(Unadjusted), 98(adjusted) CSS: 90(Unadjusted), 96(adjusted)
Giuliano et al[92]	Lap Open	1656	– –	– –	NR NR
Holmebakk et al[90]	Lap Open	71	58	27	5 year-RR: 39; 5 year-RR: 29
Guller et al[92]	Lap Open	9786	37	– –	3-year OS: 80.2 (77.8–82.7); 3-year CSS: 86.1 (84.0–88.3) 5-year OS: 72.1 (69.3–75.1); 5 year-CSS: 79.4 (76.7–82.1)
Nakano et al[4]	Lap Open	23	–	5	10- year OS: 89.6; 10-year PFS: 67.1; 10-year RFS: 65.0
Giuliano et al[91]	Lap Open	5208	–	–	5-year survival: 83.3(81.0–85.4)

Abbreviations: Lap, laparoscopic resection; Open, conventional open resection; DFS, disease-free survival; OS, overall survival; CSS, cancer-specific survival; RFS, relapse-free survival; RR, recurrence rate; PFS, progression-free survival; NR, not report; NSD, only reported no significant difference between two groups without specific survival rate.

more likely to have macro tumors with high karyokinesis exponent. In spite of these poor prognostic characteristics, the location of the tumor does not independently affect OS.[91,92]

A study by Zhang et al[93] revealed that karyokinesis exponent was the sole independent predictor of GIST PFS. However, in the analysis by Tabrizian et al[94] the microscopic margins (R1) and a high karyokinesis exponent did not predict poor outcomes. A significant defect in tumor integrity was a remarkable marker of poor prognosis, whereas there was a lack of association between minor defects and relapse. Serosal involvement is known as a negative prognostic factor. There is no published data to suggest the optimal routine follow-up policy for patients with GISTs of the intestine. NCCN's guidelines revealed that patients with low risk of relapse and no preoperative treatment were prioritized for follow-up. IM treatment is recommended for patients with severe risk of relapse (moderate or high stake of relapse) or radical resection who have undergone preoperative treatment. Once relapse is classified as non-resection, relapse, or metastasis, after radical surgery, patients should receive abdominal or pelvic CT examination approximately every three to six months, lasting for three to five years, and then once a year. For patients having undergone preoperative IM therapy and obtained radical resection, postoperative IM therapy should be continued for two years. In cases with a significant risk of relapse, postoperative treatment for at least 36 months is recommended.[95] It is feasible to reduce the frequency of follow-up for GISTs with a diameter <2 cm. In cases of non-radical resection or intraoperative detection of metastasis, abdominal or pelvic CT examination should be continued every three to six months.

The CT or MRI of abdomen or pelvic were used to evaluate curative effect after the treatment of advanced diseases, and PET-CT was only used when the above examination results were in doubt. According to the study by Joensuu et al[96] patients with postoperative low-risk GISTs were recommended to undergo abdominal and pelvic CT examinations per year for five years. Additionally, Benjamin and Casali[97] reported that patients at high risk of metastasis should be reexamined with continuous CT scans every three months for five years. Though it is still necessary to carefully consider whether neoadjuvant therapy is required for high-risk patients with GISTs, postoperative adjuvant imatinib therapy is the normative treatment for the prevention of relapse.[98,99] Thanks to in-depth studies of exosomes, their DNA, miRNA, and protein markers have been discovered and scientists are beginning to verify their expression and function. Thus, some scholars considered that exosome DNA, miRNA, and protein may also be promising prognostic biomarkers for GISTs.[100]

Conclusions

With the reform of surgical instruments and the advancement of minimally invasive techniques, the application of laparoscopy in the treatment of GISTs will continue to mature and be recommended to a greater extent. Furthermore, the development of precision medicine has enabled surgical treatment combined with molecularly targeted drugs to become a conventional treatment.

However, with the extensive use of molecularly targeted drugs in recent years, some problems have emerged, such as the correlation between genotyping and prognosis of GIST patients. The drug resistance phenomenon of GISTs and its specific mechanism still requires further study. Several ongoing prospective randomized controlled clinical studies will help answer these questions. GISTs have become a hot topic in the age of precision medicine. In recent years, new knowledge about the composition and properties of GISTs has been uncovered. The author concludes that a growing body of evidence-based medical research from clinical studies will continue to appear, which will better guide our clinical work and enable us to achieve standardized, normalized, and individualized diagnosis and treatment for GISTs.

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