Current treatment strategies and future perspectives for gastrointestinal stromal tumors

Yoichi Sugiyama, Masaru Sasaki, Mohei Kouyama, Tatsuya Tazaki, Shinya Takahashi, Atsushi Nakamitsu

ORCID number: Sugiyama Yoichi 0000-0002-8063-3961; Masaru Sassaki 0000-0002-9115-3381; Mohei Kouyama 0000-0002-7774-9541; Tatsuya Tazaki 0000-0002-9327-9749; Shinya Takahashi 0000-0002-5339-6534; Atsushi Nakamitsu 0000-0003-3538-6129.

Yoichi Sugiyama, Masaru Sasaki, Mohei Kouyama, Tatsuya Tazaki, Atsushi Nakamitsu, Department of Gastrointestinal Surgery, JA Hiroshima General Hospital, Hatsukaichi 738-8503, Hiroshima, Japan

Shinya Takahashi, Department of Surgery, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima 734-8551, Japan

Corresponding author: Yoichi Sugiyama, MD, PhD, Doctor, Surgeon, Surgical Oncologist, Department of Gastrointestinal Surgery, JA Hiroshima General Hospital, Jigozen 1-3-3, Hatsukaichi 738-8503, Hiroshima, Japan. sugiyama0113@gmail.com

Abstract

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that originate from the gastrointestinal tract, mostly from the stomach. GISTs are derived from the myenteric interstitial cells of Cajal and are caused by several mutations in the c-kit and platelet-derived growth factor receptor genes. Clinically, GISTs are detected by endoscopic and imaging findings and are diagnosed by immunostaining. Surgery is the first line of treatment, and if the tumor is relatively small, minimally invasive surgery such as laparoscopy is performed. In recent years, neoadjuvant therapy has been administered to patients with GISTs that are suspected of having a large size or infiltration to other organs. Postoperative adjuvant imatinib is the standard therapy for high-risk GISTs. It is important to assess the risk of recurrence after GIST resection. However, the effect of tyrosine kinase inhibitor use will vary by the mutation of c-kit genes and the site of mutation. Furthermore, information regarding gene mutation is indispensable when considering the treatment policy for recurrent GISTs. This article reviews the clinicopathological characteristics of GISTs along with the minimally invasive and multidisciplinary treatment options available for these tumors. The future perspectives for diagnostic and treatment approaches for these tumors have also been discussed.

Key Words: Gastrointestinal stromal tumor; Minimally invasive surgery; Laparoscopic surgery; Imatinib; Neoadjuvant therapy; Risk assessment

Core Tip: Radical resection is the most effective treatment for gastrointestinal stromal tumors, but there are other options including minimally invasive surgery and multidisciplinary treatment, which involves the use of neoadjuvant therapy in consideration of tumor size and location. Combination with tyrosine kinase inhibitors is important for maximizing the therapeutic effect of surgery. To predict the effect, it is important to examine the presence of tumor mutations, including type, location of the mutation, and molecular subtype. We herein discuss the current treatment strategies for gastrointestinal stromal tumors and promising treatments based on clinical trials.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare tumors that account for 3% of all gastrointestinal tumors. GISTs originate from spindle-shaped cells known as Cajal cells, which behave as pacemakers and are normally found in the proximal muscles surrounding the intermuscular plexus of the gastrointestinal tract[1]. Hirota *et al*[2] reported that receptor tyrosine kinase KIT expression was observed in most GISTs; they also suggested that GISTs usually exhibit gain-of-function mutations in the c-kit gene encoding KIT and may be caused by a specific genetic abnormality[2].

The standard treatment for GISTs is radical resection; for tumors classified as high-risk, the standard treatment includes the administration of adjuvant imatinib for at least 3 years post-surgery[3]. This is because it is difficult to determine whether a GIST is benign or malignant even by pathological examination. For adjuvant therapy, the risk of GIST recurrence has been stratified by assessing the mitotic index, tumor size, and tumor location.

In addition, surgical approaches have been diversified according to the size and location of the tumor. Less invasive surgical procedures such as laparoscopy and laparoscopic and endoscopic cooperative surgery (LECS) have been performed for small GISTs, while preoperative chemotherapy is used to improve the probability of complete resection and prognosis for giant GISTs. Furthermore, when considering the selection of preoperative and postoperative drug treatment, genetic analyses have made it possible to predict, to some extent, the therapeutic effect, recurrence risk, and prognosis.

The purpose of this review is to provide an overview of the clinical features, its diverse treatment modalities, and strategies for genetically informed drug therapy of GISTs.

MANAGEMENT OF GIST

The National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2021 was published on October 30, 2020, with the aim of describing basic treatment strategies for GIST[4]. If GISTs are suspected on endoscopy, imaging, and endoscopic ultrasound (EUS), then an EUS-guided puncture can be performed to confirm the diagnosis. An abdominal/pelvic contrast computed tomography (CT) or abdominal/pelvic contrast magnetic resonance imaging is recommended for every patient. In the case of submucosal tumors (SMTs) measuring less than 2 cm, the clinician should consider performing periodic endoscopic and radiographic surveillance. If there is a trend towards increase or high-risk features on EUS (unclear borders, cystic degeneration, ulceration, hemorrhage, and heterogeneity), curative surgery must be considered whenever possible[5]. For SMTs measuring over 2 cm, surgery is recommended if findings on imaging are suspicious of GIST, if there is a trend towards increase, or high-risk features. For SMTs measuring over 5 cm or if symptoms are observed (bleeding and pain, among others), surgery is recommended even if the diagnosis is

not confirmed.

When GIST is suspected, the treatment strategy differs depending on whether complete resection is possible. For resectable tumors with minimum morbidity, surgery is recommended; resection should be accomplished with histologically negative margins. For tumors that are not resectable without significant morbidity, administration of neoadjuvant therapy is the appropriate approach. In these cases, a biopsy is needed for confirming the diagnosis of GIST and for genetic examination. If the tumor is unresectable or if there is metastatic disease, tyrosine kinase inhibitor (TKI) treatment should be initiated.

SURGERY

For primary, non-metastatic GISTs, radical resection is the main treatment. Securing a margin at the time of excision is critical, as clean margins will affect the prognosis. For GISTs that have invaded or adhered to surrounding organs or viscera, *en bloc* resection including surrounding tissues is necessary to achieve R0 resection.

However, due to anatomical constraints, especially when the tumor is located in the esophagus, duodenum, and rectum, invasive surgery is often required; high complication rates are a problem. Conversely, when minimally invasive local resections are performed, surgical margins and long-term outcomes are questionable. Wei *et al*[6] retrospectively evaluated the outcomes of pancreaticoduodenectomy (PD) versus local resection in duodenum GISTs. The short time results were better in the local resection group, and there was no difference in prognosis based on the surgical procedure. They reported that tumor size and location were independent prognostic factors[6]. Therefore, for GISTs located in the mesenteric side of the second portion of the duodenum, PD is generally recommended; however, enucleation is recommended if the tumor is less than 5 cm in size. Wang *et al*[7] reported that in rectal GISTs, local excision provided a higher rate of anorectal preservation, shorter operative times, and fewer postoperative complications than radical resection, and that the long term results were similar in terms of recurrence-free survival (RFS). Based on these results, local resection and minimally invasive surgery are recommended whenever possible for GISTs that occur in anatomically complex regions.

Since GISTs rarely metastasize to the lymph nodes, routine lymphadenectomy is not necessary unless the lymph nodes are enlarged. However, caution is required in the case of wild-type GISTs. Most GISTs that occur in adults are caused by mutations in the *KIT* or platelet derived growth factor receptor (*PDGFR*A) genes, but 10%-15% of GISTs in adults and 85% in children are wild-type GISTs. Wild-type GISTs primarily affect young females; the main site is generally gastric, and they are multifocal yet indolent[8]. The pathogenic mechanism of wild-type GISTs is unknown, but one possible cause is dysfunction of the succinate dehydrogenase (SDH) complex in tumor cells. Along with paragangliomas, this type of GIST, is a component of the Carney-Stratakis syndrome, characterized by germline mutations of the SDH subunit[9]. Wild-type GISTs are also associated with pediatric GISTs and non-familial tumors; this is known as the Carney triad (wild-type GISTs, paraganglioma, and pulmonary chondroma) that is not associated with *SDH* germline mutations[10]. In SDH-mutant GISTs, lymph node metastases are frequently observed. Boikos *et al*[11] reported that in SDH-mutant GISTs, the incidence of nodal lesions was as high as 65%; half of them had lymph node metastasis. Therefore, resection of enlarged lymph nodes should be considered in patients with SDH-mutant GIST.

Resectable GISTs with minimal morbidity

Laparoscopic and LECS: Laparoscopic surgery is considered for selected GISTs of small size located in easily accessible locations. Especially for tumors less than 5 cm, laparoscopic resection is acceptable[12]. In a systemic review and meta-analysis, laparoscopic surgery was recognized to be safe and feasible due to less intraoperative blood loss, early postoperative recovery, shortened hospital stay, and a lower rate of postoperative complications[13]. However, when performing laparoscopic resection, it is essential to obtain negative resection margins for complete resection of the localized tumor; in addition, great care should be taken to avoid capsule damage to prevent tumor spillage[14].

When the tumor is located near the cardia, partial gastrectomy should be considered instead of proximal gastrectomy. However, if the tumor is of luminal-growth type and close to the cardia, an extensive resection of the margins is often required. Minimum resection margins can be challenging and will often result in a proximal gastrectomy.

In such cases, the lesion can be resected to the minimum necessary extent by observing the tumor from the lumen with an endoscope and determining the excision line. Hiki *et al*[15] first established a technique for performing minimally invasive local excision using a laparoscope and an endoscope; this was the first report on LECS in 2008. Since then, many facilities have introduced LECS in Japan, and evidence on its usefulness has been reported. A method based on a similar concept attracted attention in the 2000s; it involved completion of endoscopic treatment with laparoscopic assistance as part of the Natural Orifice Transluminal Endoscopic Surgery (NOTES) and was reported as hybrid NOTES[16]. Notably, intraoperative endoscopy is becoming increasingly popular for laparoscopic GIST resection, especially when the tumor is less than 3 cm or the location is difficult to access[17]. In Japan, gastric GISTs are often found to be relatively small; many LECS procedures have therefore been performed. To date, five representative LECS techniques have been developed.

Classical LECS is an extremely efficient method, because each step is simple and clear, technically easy, and surgery can be completed in a relatively short time. In addition, since the lesion is collected *via* the abdominal wall, there is no restriction on the size of the tumor; this is one of the merits of this procedure. However, this procedure requires opening of the stomach wall; there is therefore a potential risk of leakage of gastric contents or tumor into the abdominal cavity. Thus, this procedure should be applied with caution in tumors where the mucosal surface is exposed, such as in SMT with ulcers. In such cases, the non-open technique described below should be selected.

Inverted LECS[18] is a technique that prevents the contents of the stomach from leaking into the abdominal cavity. The edge of the resected gastric wall is first stitched and lifted, and the tumor is inverted into the stomach cavity. After the tumor is dropped into the stomach and removed orally using an endoscope, the stomach dissection line is temporarily closed by hand suturing and completely closed with stapling. Inverted LECS can prevent gastric juice from leaking to some extent, but it may not be applicable for all sites such as posterior wall lesions, among others, as it is not an entirely non-open technique. Therefore, completely non-open techniques were developed, such as non-exposed endoscopic wall-inversion surgery (NEWS)[19-21], closed-LECS[22], and a combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique (CLEAN-NET)[23,24].

NEWS was first devised as a way to resect early gastric cancer without opening the stomach wall[19]. The first step is to place an incision in the seromuscular layer around the tumor using a laparoscope; after pushing the tumor into the luminal side of the stomach, the seromuscular layer is continuously sutured. The next step involves making an endoscopic incision in the submucosa surrounding the intruded tumor. The lesion is then dissected and retrieved orally. The advantage of this technique is that the incision can be made under direct visual observation with an endoscope or laparoscope, while the tumor resection is completely closed.

Kikuchi *et al*[22] reported on a similar closed LECS technique. After local injection of the submucosal layer, a mucosal incision is made with an endoscope; this is followed by suturing of the serosal muscular layer while inverting the lesion with a spacer. The seromuscular layer is incised again *via* an endoscope. The tumor is then retrieved orally, and the mucosal edge is closed using the same procedure as in NEWS. These procedures are excellent, especially for intraluminal GISTs; this is because they allow for an appropriate resection line. These techniques are very useful for small GISTs. However, one limitation is that the diameter of the tumor can only be up to 3 cm, because the resected tumor needs to be removed orally.

CLEAN-NET was developed by Inoue *et al*[23]; it is a non-exposed excision technique that involves incision of the serosa and muscularis, while preserving the continuity of the mucosa[23]. Unlike a normal laparoscopic local resection, this procedure allows for minimal local excision by first incising the serosa and muscularis, stretching the mucosa, and then pulling the lesion outward. The tumor is collected trans-abdominally, allowing for a relatively large GIST of up to 5 cm to be retrieved. However, this method tends to provide a slightly larger margin, because all sections are performed from the abdominal cavity. It is therefore not suitable for areas where a large surgical margin cannot be obtained, such as near the cardia.

The features of each LECS are summarized in Table 1. The choice of each technique depends on the size, location, and growth pattern of GISTs. Especially for ulcerated GISTs, the non-open techniques of NEWS, closed LECS, and CLEAN-NET are good options. In addition, NEWS and closed LECS are good alternatives for intraluminal type GIST and closed LECS for the extraluminal type[25,26].

Table 1 Various laparoscopic and endoscopic cooperative surgery procedures for gastrointestinal stromal tumors

Procedure	Yr	Author	Indication	Non-exposure	First approach	Preferred type and location	Extraction site	Suturing
Classical LECS	2008	Hiki	< 5 cm ulcer (-)	No	Endoscopic	Intraluminal > extraluminal; Anterior wall	Trans abdominal	Hand or mechanical
Inverted LECS	2012	Nunobe	< 5 cm ulcer (±)	No	Endoscopic	Intraluminal > extraluminal; Anterior wall	Either site	Hand or mechanical
Closed-LECS	2017	Kikuchi	< 3 cm ulcer (+)	Yes[1]	Endoscopic	Intraluminal < extraluminal; Anterior wall	Trans oral	Hand
NEWS	2011	Goto	< 3 cm ulcer (+)	Yes	Laparoscopic	Intraluminal < extraluminal; Anterior wall	Trans oral	Hand
CLEAN-NET	2012	Inoue	< 3 cm ulcer (+)	Yes	Laparoscopic	Intraluminal < extraluminal; Anterior wall	Trans abdominal	Mechanical
PEIGS	1995	Ohashi	< 3 cm ulcer (+)	No	Laparoscopic	Intraluminal > extraluminal; Posterior wall	Either site	Hand or mechanical

[1]Open the gastric wall.

LECS: Laparoscopic endoscopic cooperative surgery; NEWS: Non-exposed endoscopic wall-inversion surgery; CLEAN-NET: Combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique; PEIGS: Percutaneous endoscopic intragastric surgery.

Percutaneous endoscopic intragastric surgery: The percutaneous endoscopic intragastric surgery (PEIGS) technique was first reported by Ohashi *et al*[27]. A method using three indwelling intragastric ports had been devised; since then, intragastric surgery by various methods such as single incision and needlescopic PEIGS has been reported [25]. PEIGS is a surgical procedure in which an endoscope and forceps are inserted into the stomach lumen through the abdominal and anterior gastric walls. This procedure is useful for intraluminal gastric SMT. In this case, determining an adequate resection margin is not easy because of the difficulty in confirming the tumor location from outside the gastric wall. Especially for lesions on the posterior wall of the cardia, the laparoscopic approach is complicated and relatively time-consuming. In contrast, intragastric surgery can obtain an easy approach and good operative view; PEIGS is therefore suitable for such cases. The problem with this procedure is the risk of surgical site infection secondary to pseudo-perforation. However, Kanehira *et al*[28] reported the incidence of surgical site infection to be approximately 2%, which was well within the acceptable range.

Endoscopic resection: There are various reports on the removal of intraluminal SMTs with an endoscope alone[29-31]. In these procedures, endoscopic full-thickness resection may be performed for intraluminal SMT originating in the muscularis propria (MP) layer. This procedure involves incising the MP layer around the SMT first; the serosal layer is then incised to generate perforation. The SMT with surrounding tissue is then removed using a snare, and the perforated gastric wall is closed using an endoscopic clip and an endloop[31]. However, this procedure involves the risk of leakage of the gastric contents due to pseudo perforation. To solve this problem, over-the-scope-clip and snaring are being developed as a full-layer suture device[32]. In this procedure, the over-the-scope-clip is first placed in the lesion, and the base of the lesion is completely resected by the snare to prevent pseudo-perforation. This technique is especially useful for small SMTs of 2 cm or less.

Newer therapies, such as endoscopic ultrasound alcohol ablation, have shown promising results. EUS-guided injection of 1.5 mL of 95% ethanol was performed for primary or metastatic GISTs without technical incidents[33]. While long-term follow-up is required to ascertain its efficacy and safety, it may be considered for high-risk patients.

Resectable GISTs with significant morbidity

Neoadjuvant therapy: Surgical resection is the mainstream for GIST treatment, and

complete resection without damage caused by pseudo-capsule resection is essential. If the tumor is large and is suspected to have infiltrated to other organs, the complete resection rate may decrease and the recurrence rate due to intraoperative tumor rupture may be higher. Additionally, even if complete resection of a larger tumor is achieved, the risk of recurrence increases with tumor size[34]. For such cases, the rate of extensive surgery is increased; this is associated with significant morbidity. Preoperative treatment with imatinib is therefore attempted in such cases, as tumor shrinkage is essential for ensuring a negative surgical margin and avoiding the risk of rupture from subsequent surgical procedures.

Function-preserving surgery is another aim of preoperative administration of imatinib. When considering function preservation by avoiding extended surgery, the effect of neoadjuvant therapy is greatly influenced by the location of the tumor. Tumor shrinkage at the esophagogastric junction can convert a total gastrectomy into a local resection. In duodenal GISTs close to the pancreatic head, PD may be avoided by neoadjuvant therapy. Neoadjuvant imatinib allows for preservation of the anal sphincter in certain rectal GISTs. Indeed, neoadjuvant imatinib has been commonly administered in retrospective series for GISTs located in such locations.

Based on two large-scale clinical databases, the BFR14 trial[35] and the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group[36] from four Dutch institutions[37], several studies have reported on neoadjuvant imatinib for GISTs. Tielen *et al*[37] performed a cohort study on preoperative imatinib for locally advanced GISTs. All tumors were over 5 cm or ill-located for surgery. The response rate (RR) to preoperative treatment was 83%, and the R0 resection rate was 84%, with no tumor perforation occurring during the operation. The 5-year progression-free survival (PFS) and overall survival (OS) were 77% and 88%, respectively. The PFS tended to be better in the neoadjuvant imatinib group, but statistical significance was not detected. Among reports on neoadjuvant imatinib, the EORTG Soft Tissue and Bone Sarcoma Group study is the largest; the results of preoperative administration of imatinib at a dose of 400 mg for locally advanced GISTs have been reported. The average duration of imatinib administration was 40 wk. In this report, the RR was 80%, and the R0 resection rate was 83%. Five-year disease-free survival and disease-specific survival were 65% and 95%, respectively. The postoperative complication rate was 15%, although surgical re-intervention was required in only 3%. The authors concluded that preoperative imatinib administration appears safe, and it is a promising treatment for patients with locally advanced or marginally resectable primary GISTs.

The contribution of preoperative imatinib therapy varies depending on the location of the tumor and is considered particularly effective in the esophagogastric junction, duodenum, and rectum. Jakob *et al* showed that those who received neoadjuvant imatinib for rectal GISTs had a significantly higher rate of negative surgical margins than those who did not receive treatment. All patients with positive resection margins and postoperative recurrence had not received preoperative treatment. In patients undergoing preoperative imatinib therapy for locally advanced rectal GISTs, a complete resection rate was obtained in 77%, which is higher than that of patients not treated preoperatively[38]. These results suggest that preoperative imatinib was associated with an increased R0 resection rate and also allowed for surgery in anatomically difficult areas.

Three prospective multicenter phase II trials have evaluated the efficacy of neoadjuvant imatinib in locally advanced GISTs[39-42]. RTOG 0132 was the first trial and reported short- and long-term results. Eligible patients had GIST with primary disease greater than 5 cm or metastatic/recurrent disease greater than 2 cm. Thirty-one of the 53 patients had primary GIST and were evaluated as the preoperative imatinib group. Preoperative imatinib was administered at a dose of 600 mg for 8–12 wk until surgery, and postoperative adjuvant therapy was planned for 2 years. In this report, the RR was 7%, and R0 resection rate was 68%. The lower RR compared to other reports was attributed to the shorter duration of neoadjuvant imatinib therapy. The 5-year PFS and OS were 57% and 77%, respectively. This trial has proved to be feasible and was not associated with significant postoperative complications.

The results of a phase II trial on preoperative imatinib therapy for large gastric GISTs in Japan and South Korea have been reported recently. For patients with large gastric GIST (> 10 cm), imatinib was administered at a dose of 400 mg for 6-9 mo until surgery. The primary endpoint was the R0 resection rate, and the secondary end points were RR, PFS, and OS. The RR was 62%, and R0 resection rate was 91%. At a median follow-up of 32 mo, the 2-year PFS was 89% and OS was 98%. These results suggest that neoadjuvant imatinib administered at a dose of 400 mg for 6-9 mo would be a promising treatment for patients with high-risk GISTs. Long-term follow-up is

expected to prove the contribution of neoadjuvant imatinib to survival in high-risk GISTs.

These advanced treatments are expected to improve the prognosis, and many studies have reported such results (Table 2). Neoadjuvant therapy is expected to preserve organ function, avoid tumor rupture, reduce complications, and ultimately prolong overall survival; however, the evidence of efficacy remains to be established.

Important aspects for neoadjuvant therapy: The NCCN and European Society for Medical Oncology guidelines recommend that GIST must be diagnosed pathologically if neoadjuvant therapy is to be considered[4,43]. Tissue sampling can be obtained by endoscopic or bowling biopsy, but sometimes this is not sufficient for confirming the diagnosis. Percutaneous biopsy and tissue collection by laparotomy are contraindicated due to the risk of peritoneal dissemination. However, Eriksson *et al*[44] reported that percutaneous biopsy of GISTs collects sufficient tissue and does not increase the risk of recurrence in patients who receive imatinib preoperatively[44]. In addition to GIST diagnosis, it is recommended to check for genetic mutations before starting preoperative treatment to ascertain whether the treatment is likely to be effective. KIT exon 11 and 9 mutants will respond to imatinib, but higher doses of imatinib are required for response in cases of KIT 9 mutations[45].

Nilotinib is a selective TKI with a potency similar to that of imatinib[46]. A randomized phase III trial on the efficacy and safety of nilotinib as a first-line treatment was conducted[47]. In this study, the PFS was higher with imatinib in the KIT exon 9 group but similar in the KIT 11 group. Thus, for patients with KIT exon 11 mutations who cannot receive imatinib, nilotinib is a promising preoperative agent.

It is also known imatinib has no therapeutic effect on GIST with the PDGFRA exon 18 D842V mutation, which has a poor prognosis. The NAVIGATOR study was a phase I trial to assess the efficacy and safety of avapritinib administration for unresectable GISTs patients, who tested positive for the PDGFRA exon 18 D842 V mutation[48]. In patients with PDGFRA exon 18 D842 V-mutant GIST, 88% had a response; 9% had complete responses, and 79% had partial responses. Based on the results of this trial, the Food and Drug Administration approved the use of avapritinib in adult patients with unresectable or metastatic GIST who have PDGFRA exon 18 mutations, including D842V mutations. Therefore, in patients with resectable GISTs associated with significant morbidity, and those having PDGFRA exon 18 mutations including the D842 mutation, neoadjuvant avapritinib is considered.

Evaluation of the response and treatment period: CT is the most used imaging modality to determine the effect of neoadjuvant imatinib; however, depending on the conditions, magnetic resonance imaging may be more useful for patients who are allergic to CT contrast media, those who have tumors located at specific sites such as the rectum, or those who require evaluation for liver metastases. CT can assess the change in both, tumor size and tumor viability. If imatinib has a therapeutic effect, the inside of the tumor is necrotic and degenerative, although the tumor size does not change at first. Evaluating metabolic rather than morphologic changes may therefore be more reliable for early treatment assessment. Therapeutic effect determination by the Response Evaluation Criteria In Solid Tumor criteria may also underestimate the response. The Choi Criteria[49], however, evaluates the size of the tumor and its density; it is therefore useful for evaluating the therapeutic effect of TKI. However, in order to measure changes in vascularization and to measure tumor density, CT should be obtained in arterial and portal phases[50]. Positron emission tomography (PET)/CT is highly sensitive for GISTs and can evaluate the effect of treatment earlier than tumor size changes. Previous studies have shown that PET/CT can predict imatinib response within 1-8 d[51]. Therefore international guidelines recommend early evaluation of response by PET/CT (within 2-4 wk) when neoadjuvant treatment with imatinib is administered, and rapid readout of activity is necessary[4].

The optimal duration of preoperative administration of imatinib is still unclear, but the most suitable timing for maximum effect is before secondary resistance is acquired. The pharmacological effect of imatinib is rapid, but this drug acts as a cytostatic agent; tumor shrinkage therefore takes time. In unresectable GISTs it takes an average of 3 mo for the tumor to shrink with imatinib; a plateau is reached at 6 mo[52]. In a study on patients with metastatic or unresectable GISTs, the median time to tumor progression was 12 mo; tumor progression occurred in half of the patients within 2 years of starting imatinib[53]. Tirumani *et al*[54] reported that in a cohort receiving neoadjuvant with imatinib, best response was achieved at wk 28; thereafter, a plateau response continued until wk 34[54]. These results suggest that the appropriate duration of preoperative imatinib may be for 6-9 mo.

Table 2 Studies on neoadjuvant imatinib therapy for gastrointestinal stromal tumors

Ref.	Clinical trial	Yr	Design	Endpoint	Cases	Agent/Dose	Patients	Duration	RR	R0 rate	Adjuvant imatinib	PFS	OS
Prospective study													
Eisenberg *et al* [39]	RTOG0132 trial	2009	Phase II	RFS	30 (all; 52)	Imatinib/600 mg	GIST (> 5 cm)	8-12 wk	7%	77%	24 mo	2-yr PFS; 83%	2-yr OS; 93%
Wang *et al*[40]	RTOG0132 (long follow up)	2012			31 (all; 53)							5-yr PFS; 57%	5-yr OS; 77%
Doyon *et al*[41]		2012	Phase II	RR	14	Imatinib/400 mg	Locally advanced GIST	6 mo	43%	79%	12 mo	4-yr DFS; 64%	4-yr OS; 100%
Kurokawa *et al* [42]	Asia	2017	Phase II	PFS	53	Imatinib/400 mg	Gastric GIST (> 10 cm)	6-9 mo	62%	91%	36 mo	2-yr PFS; 89%	2-yr OS; 98%
Retrospective study													
Blesius *et al*[35]	BFR14 trial	2011	Subset phase III	-	25	Imatinib/400 mg	Locally advanced GIST	4.2 mo (median)	60%	32%	13-24 mo	3-yr PFS; 67%	3-yr OS; 89%
Rutkowski *et al* [36]	EORTC	2012	Database	-	161	Imatinib/400 mg	Locally advanced GIST	40 wk (median)	80%	83%	At least 1 yr (56%)	5-yr DFS; 65%	5-yr DSS; 95%
Tielen *et al*[37]		2013	Database	PFS/OS	57	Imatinib/400 mg	GIST (> 5 cm) and/or ill-located for surgery	8 mo (median)	83%	84%	1, 2 yr or lifelong (58%)	5-yr PFS; 77%	5-yr OS; 88%

RFS: Relapse-free survival; RR: Response rate; PFS: Progression-free survival; OS: Overall survival; DSS: Disease-specific survival.

Postoperative therapy: In GIST classified as high-risk after curative surgery, adjuvant imatinib therapy is standard treatment; the recommended period of therapy is at least 3 years[55]. However, there is no consensus on postoperative adjuvant therapy for patients treated with neoadjuvant imatinib. In the RTOG0132 trial; the 5-year disease-free survival in patients who received adjuvant imatinib was better than that in patients who did not receive the drug. However, recurrence occurred within 2 years of completion of adjuvant imatinib. Therefore, for patients treated with neoadjuvant imatinib, postoperative adjuvant therapy is required for 3 years, similar to the period of adjuvant therapy required for high-risk GIST.

Surgical intervention for metastatic GIST

The treatment of unresectable, advanced, and recurrent GISTs is mainly based on TKI administration; however, surgical intervention may be possible in some cases. If the response to imatinib is good and the disease is controlled, surgery may be indicated. This includes cases of initially unresectable GIST that has responded well to imatinib

and become resectable, locally progressed GIST due to secondary resistance, low-volume stage IV disease, or cases requiring palliative surgery for symptoms such as bleeding or obstruction. If complete resection can be achieved, surgical intervention in combination with imatinib is more effective[56,57]. A retrospective study reported that GIST patients who respond to imatinib therapy have significantly higher complete resection rates and better PFS and OS than those who do not respond to imatinib. Additionally, two randomized controlled trials evaluated the efficacy of multidisciplinary treatment combining imatinib with surgical intervention for recurrent or metastatic GISTs[56,58]. Xia *et al*[56] investigated the efficacy of surgery and pre-and post-operative imatinib administration for advanced GISTs with liver metastasis and reported that the OS was better with surgical intervention. Furthermore, surgical resection offered better OS in GIST patients who had a poor response to imatinib therapy in the 6 mo prior to surgery. These findings suggest that in some cases, patients with liver metastases from GIST may have a better prognosis with surgical intervention than with imatinib alone. However, the indication for and optimal timing of surgery are still unclear, and future consideration is awaited.

Surgery after second line treatment such as sunitinib is considerably rare; however, certain retrospective studies report on its efficacy. Yeh *et al*[59] reported on the benefit of surgical intervention in metastatic GIST with local progression while receiving sunitinib. They reported fewer complications (15.3%) and significantly prolonged PFS and OS. Surgery may contribute to the suppression of events such as bleeding and ileus caused by the growth of tumors that have acquired secondary resistance to sunitinib; it may also improve disease control by removing resistant lesions. The results of cytoreductive surgery for GIST with local progression during regorafenib treatment in the third line have also been reported[60]. Although there is a bias in the retrospective study, the PFS and OS were 12.9 mo and 32.2 mo, respectively; these were better than those of patients who did not undergo cytoreductive surgery. However, it is important to note that the complication rate was as high as 33%, although the surgery was performed on relatively young patients with good performance status.

Based on the above findings, cytoreductive surgery for selected GISTs that have acquired resistance in the second and third line may provide local control, serve as a bridge to drug therapy, and ultimately improve prognosis.

RISK ASSESSMENT AND ADJUVANT THERAPY

The tumor size and mitotic index are important in assessing the risk of recurrence of GISTs, but it is difficult to assess whether a tumor is a benign or malignant based on these features alone. Miettinen *et al*[61] reported that in GISTs with a diameter of more than 10 cm and a mitotic index of ≤ 5 mitoses/50 high power field, the recurrence rate of small intestinal GIST is considerably higher than that of gastric GIST[61]. Therefore, in addition to tumor size and mitotic index, tumor site is also included in their classification. The Joenssu classification, that includes tumor location and considers tumor capsule rupture cases where recurrence is almost inevitable, is useful in that it efficiently selects only the group at high risk of recurrence[62].

As described previously, tumor size, mitotic count, and primary location are important in assessing the risk of GIST recurrence; however, measuring mitotic count on a slide is highly individualized and depends on the ability to distinguish the cells from other cells such as apoptotic bodies and pyknotic cells, among others. In SDH-deficient GISTs, mitotic count does not predict tumor behavior[63]. Therefore, at the basic research level, an attempt has been made to predict the risk of GIST recurrence by measuring gene expression related to DNA methylation; this has been shown to be an effective predictor[64].

Imatinib is administered as adjuvant therapy for the high-risk group after surgery, as GISTs generally harbor an imatinib-sensitive mutation. The most frequent *KIT* exon 11 mutations are sensitive to imatinib, whereas the PDGFRA exon 18 D842 V-mutation is considered to be imatinib-resistant. Tumor mutation analysis is important for estimating the therapeutic effect of imatinib; however, whether evaluation of tumor mutations is more useful than the above risk assessment is controversial. Under the circumstances, a study examined the indications for adjuvant therapy by gene mutation analysis. In GIST patients with *PDGFRA* mutations and *KIT* exon 11 duplication, mutation, or deletion of one codon, good RFS has been achieved with surgery alone. Therefore, this type of genetic variation is an independent factor that affects RFS beyond recurrence risk classification numbers. These results suggest that

adjuvant therapy is not necessary for these genetic mutations.

Three randomized phase III trials have reported on the efficacy of postoperative adjuvant imatinib (Table 3). The first trial was the ACOSOG Z9001 study by the American College of Surgeons Oncology Group. The major eligibility criterion was complete resection of the primary GIST, tumor diameter more than 3 cm, and positivity for KIT on immunostaining. In this study, imatinib administration for 1 year conferred significantly better RFS than placebo [98% *vs* 83%, hazard ratio (HR) = 0.35, *P* < 0.0001]. In the largest phase III trial, EORTC 62024 patients were randomly assigned to receive imatinib at a dose of 400 mg for 2 years or surgery alone. The high or intermediate-risk group with R0 or R1 surgical margins was eligible for inclusion. The 5-year imatinib failure-free survival was 87% in the imatinib administered group and 84% in the control group (HR = 0.79, *P* = 0.21); the primary endpoint was therefore not significant. However, when the high-risk subgroup was analyzed, there was a trend towards better imatinib failure-free survival in the imatinib group (79% *vs* 73%, *P* = 0.087). The results of these studies revealed that adjuvant imatinib improved RFS when administered to patients with operable GIST; however, its influence on OS remains uncertain.

In the open-label, multicenter, randomized phase III SSGXVIII/AIO trial, patients with GIST who underwent radical surgery but were at high-risk were enrolled; they received adjuvant imatinib therapy for 1 or 3 years after surgery. The primary endpoint was RFS; the secondary endpoints were OS and safety. The 5-year and 10-year RFS were 71.4% and 52.5%, respectively, in the 3-year group, and 53.0% and 41.8% in the 1-year group (HR = 0.66, *P* = 0.003). The 5-year and 10-year OS rates for the 3-year group were 92.0% and 79.0%, respectively; for the 1-year group, they were 85.5% and 65.3%, respectively. The difference was statistically significant (HR = 0.55, *P* = 0.004). Therefore, administration of adjuvant imatinib for at least three years is the standard treatment for patients in the high-risk group[3,55]. The cited article reported that approximately 50% of deaths may be avoided during the first 10 years after surgery with longer adjuvant imatinib treatment.

A study on long-term administration (5 years or more) has been reported in the phase II PERSIST trial[65]. The 5-year RFS was 90%, while the OS rate was 95%. Six of 7 patients who developed recurrence did so after completing adjuvant imatinib. Furthermore, among the patients with an imatinib-sensitive KIT exon 11 mutations, only 1 experienced recurrence, which occurred after imatinib was discontinued. This indicates that long-term imatinib administration in patients with imatinib-sensitive mutations is effective in preventing the recurrence of GIST. Two randomized trials on the effects of long-term adjuvant imatinib therapy, namely, sSGXXII and IMADGIST, are ongoing and their results are awaited.

SYSTEMIC THERAPY

Gene analysis

KIT mutations: Imatinib is expected to be more than 80% effective in patients with unresectable, advanced, and recurrent GIST; the median OS after treatment with imatinib is 50 mo[66]. However, the therapeutic effect depends on the sensitivity of the GIST to imatinib; this can be predicted to some extent by identifying gene mutations. The most frequent gene mutation is that of KIT exon 11 (65%), followed by that of exon 9 (10%). Approximately 90% of KIT exon 11 and 50% of KIT exon 9 mutation GISTs respond to imatinib; however, the therapeutic effect is different to a certain extent. In the EORTC study, GISTs with exon 11 mutations showed high efficiency to imatinib and increased PFS and OS than those with exon 9 mutations. However, the relationship between imatinib doses and therapeutic effects also differs by gene mutations. In GIST patients with KIT exon 9 mutations, increasing the dose of imatinib (800 mg/d) prolonged PFS. Conversely, in patients with KIT exon 11 mutations or wild-type GIST, imatinib dose escalation did not improve PFS. However, the contribution of imatinib dose increase to OS in exon 9 mutation cases was not clear even on meta-analysis; the finding has therefore remained controversial[45].

Mutations in exon 13 and 17 are very rare; compared to other mutations, they occur more frequently in the small intestine. Genetic mutations in secondary resistant GISTs are often found in exons 13 and 17; secondary mutations occur mostly in exon 13, which constitutes the adenosine triphosphate (ATP) binding domain, and in exon 17, which constitutes the activation loop[67]. Many secondary mutations in the ATP binding domain are sensitive to sunitinib even after imatinib resistance; however, most of the secondary mutations in the activation loop are resistant to both, imatinib and

Table 3 Clinical studies on adjuvant imatinib

Trial	ACOSOG Z9001	SSG XVIII/AIO	EORTC 62024	PERSIST-5
Study/yr	Phase III/2009	Phase III/2012, 2020	Phase III/2015	Phase II/2018
Number	359 (total: 713)	397 (199 *vs* 198)	454 (total: 908)	91
Eligible criteria	Tumor size ≥ 3 cm	High risk group	Intermediate and high-risk group	Intermediate and high-risk group
Treatment dose	400 mg/d	400 mg/d	400 mg/d	400 mg/d
Duration	1 yr *vs* placebo	1 yr *vs* 3 yr	2 yr *vs* placebo	5 yr
Risk classification				
High risk	NA	178 (89%)	266 (58.6%)	67 (74%)
Intermediate risk		15 (8%)	186 (41%)	24 (26%)
Etc.		6 (3%)	2 (0.4%)	
Residual tumor				
R0	325 (90.5%)	169 (85%)	381 (83.9%)	90 (99%)
R1,2	34 (9.5%)	30 (15%)	73 (16.1%)	0 (0%) 1; unknown
Tumor rupture				
No	NA	164 (82%)	404 (89%)	NA
Yes		35 (18%)	50 (11%)	
End point				
Primary endpoint	RFS	RFS	IFFS	RFS
Secondary endpoint		OS, safety	RFS, OS, safety	OS
Results	1-yr RFS; 98% *vs* 83% (HR = 0.35, *P* < 0.0001); OS: Not significant	5-yr RFS; 71% *vs* 53% (HR = 0.66, *P* = 0.003); 5-yr OS; 92% *vs* 86%; 10-yr OS; 79% *vs* 65%	5-yr IFFS; 87% *vs* 84% (HR = 0.79, *P* = 0.21); 3-yr RFS; 84% *vs* 66%; 5-yr RFS; 69% *vs* 63%	5-yr RFS; 90%; 5-yr OS; 95%; 45 (49%) pts early discontinuation of imatinib

NA: Not associated; RFS: Relapse-free survival; OS: Overall survival; IFFS: Imatinib failure-free survival.

sunitinib.

Mutations in exon 8 are even rarer, with only a few cases reported in the past and an estimated frequency of approximately 0.3%. The most common genotype of exon 8 mutations is Del-Asp419; the others known are ThrTyrAsp (417-419) Tyr. In pediatric mastocytosis, the reported type of c-kit mutation in exon 8 is Del-Asp419. Hartmann *et al*[68] reported that GIST patients with Del-Asp419 mutations had mastocytosis as well as multiple GISTs, suggesting an association. The most common sites are the small intestine and duodenum, and it appears to arise from extragastric sites. Many GISTs with exon 8 mutations have metastases at the time of diagnosis or are classified in the high risk group; this indicates the possibility of aggressive behavior. Sensitivity to imatinib has been demonstrated *in vitro*. In clinical practice, it has been administered as adjuvant therapy to the intermediate to high-risk group, with no observed recurrence for 24 mo[69].

PDGFRA mutations: Mutations in the PDGFRA gene account for 5%-10% of all GISTs and are found mostly in the stomach. Mutations are present in exons 12, 14, and 18, with mutations in exon 18 being the most common; the most common genotype was D842V. D842V mutations are resistant to imatinib, but sensitive to avapritinib. In D842V mutant GISTs, avapritinib was found to be highly effective, with a response rate of 90% and a mean response duration of 34 mo[70]. Hence, the NCCN guidelines recommended avapritinib as first-line therapy for PDGFR D842V-mutant GIST. Among exon 12 and 14 mutants, V561D and N659K are the most common mutations, respectively; both types are sensitive to imatinib. Most GISTs with this mutation are of epithelioid morphology and have relatively good prognosis[71].

Wild-type GISTs: KIT/PDGFRA wild-type GISTs account for approximately 10%-15% of all GISTs. The pathogenesis of wild-type GISTs is unknown, but inactivation of neurofibromatosis type 1 (NF1) and SDH and gain-of-function mutations in genes downstream of KIT and PDGFRA (RAS and BRAF) have been suggested as a possible cause. Mutations in this alternate signaling pathway may lead to primary resistance to imatinib. SDH-deficient GISTs have a higher probability of responding to sunitinib and regorafenib[72], and are considered to have a good prognosis. NF1-related GISTs are multiple and most often located in the small intestine. Histologically, they are of the spindle cell type, contain many stained filamentous fibers and S100-positive cells, have few mitotic figures, and have a relatively good prognosis. NF1-related GISTs may result from related syndromes; up to 25% of NF-1 patients may develop GISTs over their lifetime[73].

BRAF mutations, which are mainly found in melanoma, thyroid papillary carcinoma, and colorectal carcinoma, are localized in exon 15, with valine at position 600 replaced by aspartic acid (V600E). V600E BRAF mutations destabilize the inactive conformation of the BRAF kinase; activated BRAF stimulates the activation of the mitogen-activated protein kinase pathway to induce atypical cell proliferation. This mutation accounts for 4%-13% of GISTs, and are found most frequently in the small intestine, followed by the stomach. The prognosis is relatively good, although they are not highly sensitive to imatinib. The growth of tumors with mutations in BRAF is inhibited by the use of BRAF inhibitors such as dabrafenib, which blocks kinase activity. Dabrafenib has also been reported to have a good therapeutic effect in GIST [74]. Conversely, reports suggest that approximately 50% of patients develop resistance to BRAF inhibitors within 6 mo of initiation of treatment with a single agent[75]. The mechanism of resistance to single-agent BRAF inhibitors is believed reactivation of mitogen-activated protein kinase kinase and extracellular signal-regulated kinase through a bypass pathway, that does not involve BRAF[76]. In malignant melanoma, the combination of BRAF and mitogen-activated protein kinase kinase inhibitors is believed to potently inhibit tumor growth and delay the development of resistance; the same therapeutic effect is expected for GISTs with BRAF mutations.

The impact of KIT, PDGFRA, and BRAF mutational status on the natural history of localized GISTs has been reviewed by Rossi *et al*[77]. They found that GIST patients with KIT mutations had a poorer prognosis than those with PDGFRA mutations or with triple negative (KIT, PDGFRA, and BRAF wild-type) tumors. In addition, they classified GISTs into three molecular risk groups using multivariable Cox regression models. Group I, including KIT exon 13, PDGFRA exon 12, and BRAF mutated GISTs, had the best prognosis. Group II, including KIT exon 17, PDGFRA exon 18 D842V, and PDGFRA exon 14 mutants and triple-negative mutation GISTs, had intermediate prognosis. Group III, including KIT exon 9, exon 11, and PDGFRA exon 18 mutations apart from D842V, had the worst prognosis. These results suggest that genetic mutations have prognostic value and that grouping by mutation is useful in determining the indications of adjuvant therapy; it also complements clinicopathological risk stratification. The features of KIT mutation types are shown in Table 4.

Liquid biopsy

To confirm genetic mutations, and especially secondary mutations, it is necessary to collect tumor tissue. However, if the tumor is located deep in the abdominal cavity owing to recurrence after surgery or bone metastasis, obtaining tumor tissue is challenging. To solve this problem, a liquid biopsy method has been developed for detecting mutations in tumor-related genes using tumor-derived DNA (circulating tumor DNA: ctDNA)[78]. There is a risk of complications from tissue biopsy; in addition, even if a biopsy specimen is used, it is difficult to evaluate the fission image and MIB-1 labeling index of the entire tumor, as the tissue of GIST is not necessarily homogeneous. Liquid biopsy for detecting ctDNA is noninvasive and safe and provides a highly sensitive biomarker. Kang *et al*[79] reported a simple method for detecting primary and secondary mutations in ctDNA from liquid biopsy samples obtained from GIST patients. Additionally, they suggested that these gene mutations could serve as predictive markers for drug resistance. By identifying resistance mutations from plasma DNA, it is possible to increase the dose of imatinib or quickly switch to another drug. In order to apply this method clinically in the future, technical aspects such as reliability and detection sensitivity need to be established.

Drugs other than imatinib

In GIST patients who experience disease progression during imatinib administration, develop secondary resistance, or cannot tolerate imatinib administration, sunitinib and

Table 4 Clinical features of various molecular subtypes of gastrointestinal stromal tumors

Gene mutation	Exon	Proportion	Common mutation	Treatment	Characteristics
KIT	11	70%	Del-inc557/558	Sensitive to imatinib, secondary mutation resistant to sunitinib, some effect for regorafenib	High risk of recurrence
			p.W557_K558 del		Adverse prognosis effect in stomach
			SNSs and Dup		Relatively good prognosis
	9	10%	A502-'503 Dup	Need high dose of imatinib, effective for sunitinib	Mainly in small intestinal, worse prognosis
	13	1%	Lys642Glu	Secondary mutation resistant to imatinib	Mainly in small intestinal
	17	1%	Asn822Lys	Secondary mutation resistant to imatinib and sunitinib, but responding to regorafenib	Mainly in small intestinal
	8	0.30%	Del-Asp419	Sensitive to imatinib	Extragastric, metastatic prone nature
PDGFRA	18	5%	Asp842Val (D842V)	Responds to avapritinib, resistance to imatinib	Mainly in gastric and favorable prognosis
	14	1%	Apn659Lys	Sensitive to imatinib	Relatively good prognosis
	12		V561D	Sensitive to imatinib	Relatively good prognosis
Wild-type GIST		10%-15%	SDH-deficient	Not sensitive to imatinib, response to sunitinib, regorafenib	Overall indolent disease
			NF1	Not sensitive to imatinib, response to sunitinib	Mainly in the small intestine and good prognosis
	15	1%	BRAF	Not sensitive to imatinib, response to dabrafenib	Relatively good prognosis
			K-RAS	Not sensitive to imatinib	

PDGFRA: Platelet derived growth factor receptor; SNSs: Single-nucleotide substitutions; Dup: Duplication; SDH: Succinate dehydrogenase; NF1: Neurofibromatosis type 1.

regorafenib are recommended for second and third-line treatment, respectively. Sunitinib is a multi-targeted TKI inhibitor that targets c-kit, PDGFRA, and vascular endothelial growth factor receptor, thereby inhibiting angiogenesis and cell proliferation. The issue of secondary resistance as well as primary mutations should be taken into account when considering second-line treatment. Sunitinib is active in KIT exon 11 mutations but less effective against GISTs having secondary resistance after imatinib; it is more effective in treating GISTs with exon 9 mutations or of the wild-type. However, sunitinib shows high inhibitory activity against mutations in the ATP-binding site (exon 13); however, its activity is reduced by mutations in the activation-loop region (exons 17 and 18).

Regorafenib is also a multikinase inhibitor for vascular endothelial growth factor receptor 1/2, PDGFR, Kit, BRAF, and RAF and includes mediators that act on angiogenesis and the tumor microenvironment to promote tumor growth. Gene mutations have also been reported to impact the therapeutic effect of regorafenib, which in a genetic search of the primary tumor was found to be particularly effective in patients with metastatic GIST with KIT exon 11 mutations or SDH deficiency[80]. In another study, GIST patients with KIT exon 17 mutations, who had been previously treated with TKI, showed particularly good response to treatment and prolonged PFS[81].

Ripretinib has been recently included in the NCCN guidelines as a fourth-line drug for patients with GIST, whose disease has progressed on imatinib, sunitinib, and regorafenib. This drug is a KIT and PDGFRA inhibitor that blocks initiating KIT mutations 13, 14, 17 and 18; they include KIT D816V and PDGFRA D842V and are expected to show considerable therapeutic effect. Recently, a double-blind randomized placebo-controlled study was conducted in GIST patients with progression on at least imatinib, sunitinib, and regorafenib. In this trial, PFS improved significantly in the group administered ripretinib compared with placebo (6.3 *vs* 1.0 mo, HR = 0.15, *P* < 0.0001); the safety was acceptable[82].

Although TKIs are useful drugs for GIST, their expected effect may not be obtained due to the issue of primary and secondary resistance. Research is therefore ongoing to find new drugs. In recent years, immunotherapy for cancer is gaining popularity, and its therapeutic effect has been clinically proven. Immune checkpoint inhibitors, such as programmed death protein 1 and cytotoxic T-lymphocyte-associated antigen 4, block the transmission of inhibitory signals to maintain T-cell activation and restore anti-tumor effects. Basic research suggests that GISTs with the D842V mutation show immune cells with increased cytolytic activity, and more tumor cells express programmed death protein 1 and programmed death ligand 1[83]. In addition, regulatory T cells and CD8+ T-cells are overexpressed, while the proportion of CD4+ T-cells is low. These data imply that immunotherapy is effective for patients with GIST, especially for those with D842V mutant tumors. The results of several ongoing clinical trials, especially those evaluating combination therapy with other immune therapeutic agents and TKIs are awaited.

CONCLUSION

Laparoscopic surgery and LECS have not only made it possible to ensure complete curative resection in GIST but have also made it possible to perform less invasive surgery aimed at functional preservation. There is also a wider range of available surgical techniques, which may be selected depending on the location and growth pattern of the tumor. It is expected that multimodal treatment with TKIs and surgery will be an option for progressive GISTs and the results of several clinical trials are awaited. Treatment based on genetic information has been established; in the future, novel treatment strategies with newly developed TKIs, molecularly targeted drugs, and immunotherapy may therefore play important roles in the treatment of GIST.

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