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GASTROINTESTINAL STROMAL TUMOR

Editors: Yong Li
Tatsuo Kanda
Seth M. Pollack

AME Medical Book 1A046

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We are pleased to announce that the "AME Research Time Medical Book Series" launched by AME Publishing Company have been published as scheduled.

Finishing my medical degree after 4 years and 3 months of study, I decided to quit going on to become a doctor only after 3 months of training. After that, I had been muddling through days and nights until I started engaging in medical academic publishing. Even 10 years after graduation, I had not totally lost the affection for being a doctor. Occasionally, that subconscious feeling would inadvertently arise from the bottom of my heart.

In April 2011, Mr. Tiantian Li, the founder of DXY.cn, and I had a business trip to Philadelphia, where we visited the Mütter Museum. As part of The College of Physicians of Philadelphia, the museum was founded in 1858 and has now become an exhibition hall of various diseases, injuries, deformities, as well as ancient medical instruments and the development of biology. It displays more than 20,000 pieces of items including pictures of wounded bodies at sites of battle, remains of conjoined twins, skeletons of dwarfs, and colons with pathological changes. They even exhibited several exclusive collections such as a soap-like female body and the skull of a two-headed child. This museum is widely known as "BIRTHPLACE OF AMERICAN MEDICINE". Entering an auditorium, we were introduced by the narrator that the inauguration ceremony of the Perelman School of Medicine at the University of Pennsylvania would take place there every year. I asked Mr. Li, "If it was at this auditorium that you had the inauguration ceremony, would you give up being a doctor?" "No," he answered.

In May 2013, we attended a meeting of British Medical Journal (BMJ) and afterwards a gala dinner was held to present awards to a number of outstanding medical teams. The event was hosted annually by the Editor-in-Chief of BMJ and a famous BBC host. Surprisingly, during the award presentation, the speeches made by BMJ never mentioned any high impact papers the teams had published in whichever prestigious journals over the past years. Instead, they laid emphasis on the contributions they had made on improving medical services in certain fields, alleviating the suffering of patients, and reducing the medical expenses.

Many friends of mine wondered what AME means.

AME is an acronym of "Academic Made Easy, Excellent and Enthusiastic". On September 3, 2014, I posted three pictures to social media feeds and asked my friends to select their favourite version of the AME promotional leaflet. Unexpectedly we obtained a perfect translation of "AME" from Dr. Yaxing Shen, Department of Thoracic Surgery, Zhongshan Hospital, Shanghai, who wrote: enjoy a grander sight by devoting to academia (in Chinese, it was adapted from the verse of a famous Chinese poem).

AME is a young company with a pure dream. Whilst having a clear focus on research, we have been adhering to the core value "Patients come first". On April 24, 2014, we developed a public account on WeChat (a popular Chinese social media) and named it "Research Time". With a passion for clinical work, scientific research and the stories of science, "Research Time" disseminates cutting-edge breakthroughs in scientific research, provides moment-to-moment coverage of academic activities and shares rarely known behind-the-scene stories. With global vision, together we keep abreast of the advances in clinical research; together we meet and join our hands at the Research Time. We are committed to continue developing the AME platform to aid in the continual forward development and dissemination of medical science.

It is said that how one tastes wine indicates one's personality. We would say how one reads gives a better insight to it. The "AME Research Time Medical Books Series" brings together clinical work, scientific research and humanism. Like making a fine dinner, we hope to cook the most delicate cuisine with all the great tastes and aromas that everyone will enjoy.

Stephen Wang
Founder & CEO,
AME Publishing Company

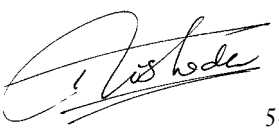
It is my great pleasure to publish a special book on gastrointestinal stromal tumor (GIST) in both English and Chinese as a one of the authors as well as a co-honorary Editor-in-Chief. The book has collected from the articles published in AME journals systematically, and covers the latest topics on the pathogenesis, diagnosis and treatment of GIST. Furthermore, the book contains concrete case reports, from which the readers could share medical knowledge and experience important for their clinical practice in near future.

The practice of medicine is an art, based on science (1). On boundary of the Century, the concept of GIST and its diagnosis and treatment were tremendously changed (2). For example, based on the molecular mechanism of tumor cell proliferation, molecular-targeted drugs of imatinib, sunitinib, and regorafenib, have been developed and the clinical practice guidelines have been published since 2004 (3). GIST is, however, rare cancer. There are a few specialists. Most general surgeons and physicians, who may occasionally take care of GIST patients, may have limited experiences and restricted, and sometimes outdated, information due to drastic changes in clinical practice and due to rapid increase in medical information. So, physicians and surgeons should always update their skills and medical knowledge in the field of oncology developing very rapidly, like GIST. Nevertheless, rare cancer sometimes lacks disease information, especially well-organized information, covering wide-range of clinical practice and science. To be timely, here, we publish a brand new book with latest information of GIST from the pathogenesis to the diagnosis and treatment.

Finally, Sir William Osler, the greatest and respectable physician in the end of the 19th century, once said "To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all" (1). A good book is a guide for students and doctors in terms of medical education and development, and is indispensable for nurturing a good doctor. I sincerely hope that this book may have potential to make a doctor an excellent and talented physician or surgeon who treats GIST. Thus, it is my expectation that the book will provide effective learning chances and referenced resource for medical professionals caring GIST patients in the clinical practice, resulting in improved patient care and outcomes. I also gratefully appreciate the editors and authors contributing the book by accepting their manuscripts to publish in this book.

References

1. Stone MJ. The wisdom of Sir William Osler. Am J Cardiol 1995;75:269-76.
2. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer 2016;19:3-14.
3. Demetri GD, Benjamin R, Blanke CD, et al. NCCN Task Force report: optimal management of patients with gastrointestinal stromal tumor (GIST)--expansion and update of NCCN clinical practice guidelines. J Natl Compr Canc Netw. 2004 May;2 Suppl 1:S-1-26; quiz 27-30.



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Gastrointestinal stromal tumor (GIST) is an uncommon tumor that occurs in the wall of the gastrointestinal (GI) tract and it can be malignant or benign. GIST can be found anywhere along the GI tract but up to 50% of GIST occur in stomach while the others occur in small intestine and other areas near GI tract. Though GIST has a long history of discovery, the prevalence of GIST is still not available and it is believed that the prevalence of it must be higher than people thought (between 6.5 and 14.5 per million per year) (1). In order to increase the knowledge of GIST, this new book, *Gastrointestinal Stromal Tumor*, begins with the introduction of GIST. Specially, a paper regarding the disparities between the clinical practice and profiles of malignancies in Asia and those in Europe & North America was included to review the global guidelines for GIST in order to help physicians better understand the global diagnosis and treatment of GIST.

GIST was once appeared as a poorly understood pathologic entity, but in the past few decades we have witnessed an explosion of research into the pathogenesis of GIST since the late 1990s (2). The recognition of KIT-activating mutations or the platelet-derived growth factor receptor alpha gene (PDGFRA) in GIST has led to better understanding of tumorigenesis. The second chapter of the book gives a detailed review on the molecular pathogenesis of GIST, including KIT mutations, PDGFRA mutations, familial GIST, SDH-deficient GIST, RAS signaling gene mutations, tumor suppressor genes, chromosomal alterations, epigenetic abnormalities and noncoding RNAs in GIST (3).

There is no effective way to detect GIST at its early stage and it is usually found unexpectedly when one is checking for other physical problems. To differentiate it from other diseases, the most common ways to diagnose GIST are computed tomography (CT), fecal occult blood test, MR Imaging scan, endoscopic ultrasound and biopsy. In recent years, the rapid development of CT technique and TKI target therapy for GIST has brought the significance of CT scan and pre-treatment histopathological and immunocytochemical diagnosis of GIST (4). Therefore, the third chapter of the book describes CT and MRI of GIST and compares the diagnostic accuracy of conventional ultrasound (US)—guided *vs.* contrast-enhanced ultrasound (CEUS)-guided core needle biopsy for GIST (4).

It is well known that surgical resection is the first-line treatment for GIST, but there is a chance that tumor may recur after the surgery or other treatments like chemotherapy and radiation. With this regard, neoadjuvant therapy and targeted therapy are playing a more and more important role. In the last two chapters of the book, we give a comprehensive review on the treatment options for GIST and presents eight case reports to further introduce the diagnosis and treatment of GIST.

Hopefully this book will be available to oncologists and gastroenterologists as it provides a reliable way for physicians to learn the cutting-edge researches in this field.

References

1. Zhao X, Yue C. Gastrointestinal stromal tumor. J Gastrointest Oncol 2012;3(3):189-208.
2. Sleijfer S, Wiemer E, Verweij J. Drug Insight: gastrointestinal stromal tumors (GIST)--the solid tumor model for cancer-specific treatment. Nat Clin Pract Oncol 2008;5(2):102-11.
3. Niinuma T, Suzuki H, Sugai T. Molecular characterization and pathogenesis of gastrointestinal stromal tumor. Transl Gastroenterol Hepatol 2018;3;2.
4. Cui NY, Liu JY, Wang Y, Cai JQ, Zou SM, Wang YX. Contrast enhanced ultrasound guided biopsy shows higher positive sampling rate than conventional ultrasound guided biopsy for gastrointestinal stromal tumors diagnosis. Transl Cancer Res 2016;5(2):152-159.

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"*There is new ammunition in the war against CANCER. These are the bullets.*" This appeared on the cover of the May 28, 2001 issue of TIME. This global weekly news magazine featured molecularly targeted therapy in that issue and declared that we are entering an era where a new concept of cancer therapy based on molecular biology may lead to substantial conquest in the war against cancer.

Imatinib mesylate, an orally available tyrosine kinase inhibitor (TKI), has shown unexpectedly high clinical efficacy against chronic myelogenous leukemia, a notorious disease that is refractory to classical chemotherapies. Joensuu *et al.* were inspired by the discovery of gain-of-function mutations in gastrointestinal stromal tumors (GISTs) by Hirota *et al.* and alternatively used TKI in a patient with far advanced GIST. They showed that imatinib exerted a dramatic effect on this gastrointestinal (GI) malignancy as well. Their astounding revelation triggered the explosive development of molecularly targeted therapy. Since then, GISTs, which are rare GI tract tumors, have captured the interest of oncologists as an experimental bench to explore new cancer therapies. The concept of gain-of-function mutations in GISTs has led to the identification of driver gene mutations in lung cancers and the success of TKIs in GISTs has resulted in the propensity for molecularly targeted therapy in medical oncology. Meanwhile, the acquisition of a deep understanding of GISTs has also fueled the emergence of new challenging clinical issues: whether or not we can overcome secondary resistance to TKIs, how we should manage potentially malignant small GISTs, whether or not secondary surgery is effective for metastatic GISTs, and how we should demonstrate that. Although researchers have addressed these issues and many GIST-related papers have been published, a platform to systemically discuss and learn state-of-the art therapy for GISTs remains lacking.

The editors considered that it was time to organize current knowledge of the diagnosis and treatment of GISTs as a step toward the next stage because more than 15 years have passed since imatinib therapy was introduced clinically.

This book aims to deliver an update of progress in GIST research and clinics. The contents include a selection of excellent articles from GIST-related ones that were recently published in AME journals, including *Chinese Clinical Oncology* and *Translational Gastroenterology and Hepatology*. Readers will be able to integrally advance their knowledge of GISTs and easily understand the current status of GIST research because the book contains reviews that concisely summarize accumulated evidence from GIST studies ranging from basic science to clinical practice and from endoscopic treatment to multimodality treatment of metastatic GISTs. Reviews and case reports of rare GISTs may serve as a helpful guide to clinicians in treatment decision-making for rare diseases. Furthermore, young researchers will be able to use this book as an example for writing papers with utilization of the PDF search engine.

I hope that this book will be an indispensable material for all clinicians and researchers who are involved in GISTs.

Tatsuo Kanda, MD, PhD
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This book is a collection of articles regarding the biology, pathogenesis and treatment of patients with gastrointestinal stromal tumor (GIST). While GIST is a devastating cancer that unfortunately remains fatal for far too many patients, the field of GIST has also undergone many advancements and patient outcomes have dramatically improved. One reason for this success is that the clinicians and researchers treating GIST are highly collaborative and come from many different medical disciplines including surgical oncology, interventional radiology, as well as gastrointestinal and sarcoma medical oncology. I was therefore thrilled to learn that the AME publishing company was preparing this unique volume reflecting the true diversity of perspectives and approaches towards this terrible disease. These articles do not have a singular perspective as often happens when a single editor invites multiple chapters. Instead, this book is a compilation of high quality articles published in AME journals and therefore the book was developed organically to represent the many different perspectives and practices held by clinicians and researchers who study and treat GIST.

The book is organized into five major sections: Introduction, Pathogenesis, Diagnosis, Treatment and Rare GIST sections. The introduction section begins with a truly definitive review by Zhao and Yue describing the state of the field as a whole. While the review touches upon nearly every topic relative to the diagnosis and treatment of GIST, I think everyone with an interest in GIST should take a look at the "Historic Overview" which puts the field as a whole into perspective. GIST is fundamentally a mesenchymal neoplasm of the gastrointestinal track that was "just another" sarcoma subtype as recently as the early 1990's. However, unlike other sarcoma subtypes where multiple disheartening failures have sometimes made the field feel stagnant in spite of some isolated successes, our understanding of GIST keeps moving forward, leading to more treatment options and better patient outcomes. The success of this research has remains a source of hope for patients with other mesenchymal tumors.

The Introduction section also includes overviews describing therapeutic approaches to esophageal and rectal GIST – two anatomic locations which have been sadly under-discussed by the academic GIST community. The section concludes with a review of the Asian consensus guidelines for GIST, comparing and contrasting key elements of these guidelines with other guidelines from around the world ultimately demonstrating that there is more agreement than disagreement in the international community but also identifying some interesting controversies and areas for further discussion. This article is highly relevant as the progress made in the treatment of GIST has been a truly international effort. This is reflected by the authors and editors of this book itself who are from all over the world, particularly from China and the United States but also from Brazil, Russia, India, Canada, Turkey, Italy and others.

The pathogenesis section consists of a comprehensive review by Niinuma *et al.* discussing not only *KIT* sequencing but also *PDGFR*α and SDH-deficient disease as well as clinically relevant situations, such as the cohorts of patients with familial GIST, that have shed light on our understanding of this biology. The review goes on to discuss a number of critical but under-discussed topics related to the pathogenesis of GIST such as the importance of RAS signaling mutations for some patients as well as tumor suppressor genes like *NF1* and the epigenetic changes that result from these various mutations and are likely responsible for much of GIST's clinical behavior.

The Diagnosis section begins with an article regarding ultrasound guided biopsy collection in GIST patients (Cui *et al.*). Decisions regarding when and how to biopsy a tumor that is potentially GIST are often controversial and can be very relevant therapeutically. The discussion in this article is balanced while also offering a unique perspective. Similarly, proper imaging is critical for diagnosis, staging and surveillance of GIST patients. The pictorial overview by Gong *et al.* present a comprehensive overview of imaging for GIST in the stomach demonstrated through striking images as well as commentary and an approach that is relevant for imaging of GIST elsewhere in the gastrointestinal tract.

The Treatment section includes comprehensive overviews regarding both surgical and systemic approaches to treatment. This section is notable for its particular attention to the many unique issues related to resection of gastric GIST, opening with a review on surgical management of GIST tumors of the stomach by Lim *et al.* providing detailed discussion of all major studies focused on this subset of GIST tumors. This articles pairs well with accompanying articles by Tan *et al.* and Koh *et al.* reviewing the major advances in minimally invasive approaches for these patients as well as endoscopic resection. The paper by Mitsui *et al.* goes on to discuss the role of endoscopic approaches for non-gastric as well as gastric tumors and work by Gluzman *et al.* presents a wide ranging Russian experience on surgical management of GIST tumors generally from through out the gastrointestinal track.

The role of surgery in the metastatic setting is another controversial topic but is very important for many patients. The

decision to resect metastatic disease may be the key to long-term disease free survival in some patients while for others, it can add unnecessary pain and morbidity with little benefit. The review by Kikuchi *et al.*, gives excellent guidance to clinician trying to weigh the potential advantages and disadvantages for their individual patient in the context of modern systemic therapy.

The use of adjuvant and neoadjuvant imatinib is absolutely critical for the success of definitive surgery in the high-risk population. The review by Ishikawa *et al.* clarifies the critical role that neoadjuvant imatinib can have in the right patients while the review by Shetty *et al.* discusses the use of imatinib and other tyrosine kinase inhibitors in the adjuvant and metastatic setting where they have been truly revolutionary. However, the review by Zeichner *et al.*, makes the point that while tyrosine kinase inhibitors are life-saving and invaluable medicines, they are also quite expensive and therefore need to be used selectively in the patients who are likely to benefit. While radiation is not standard for patients with GIST there are certainly settings where its use is appropriate and this is discussed in a convincing review by Halpern *et al.*

The Rare GIST section discusses a number of unusual GIST locations (for example, the prostate) and patterns of metastatic spread as well as unusual situations such as coexistence of GIST with a colorectal adenocarcinoma and treatment of GIST in a patient with neurofibromatosis. Like all great case reports, these articles highlight general issues related to biology and treatment that relate to the field as a whole.

In summary the book's editors, in collaboration with the AME publishing company, have put together a truly remarkable compilation of outstanding articles that I believe will be indispensible reading for physicians and researchers around the world. I am honored to be a part of it and hope that you enjoy. Most of all, I hope that this volume helps to further unite the community of GIST experts across the globe to push the field further forward, improving treatments and allowing our patients to live longer and better lives.

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At the end of the 20th century, the biological features of gastrointestinal stromal tumor (GIST) were reported. Imatinib mesylate, a selective inhibitor of driver mutation for GIST such as KIT and PDGFRA, entered the clinical stage. As we move further into the 21st century, we have acknowledged the clinical effects of increasing overall survival time with imatinib therapy from 1.5 years to more than 5 years. Nevertheless, surgery remains a mainstay for the curative treatment of this tumor. A new understanding of a multidisciplinary approach for GIST is necessary for the best clinical decision.

This book presents a comprehensive, state-of-the art review of this field. It covers all aspects of GIST from epidemiology, pathological classification and evaluation, and molecular biology through to diagnosis, minimal invasive or aggressive surgery, radiotherapy, management, and therapeutic options including the latest molecular targeted agents.

This subject is addressed in five sections. The first section of the book presents the overview, the management of rectal and esophageal GIST, and Asian consensus guidelines. The overview covers its unique biologic behavior, clinicopathological features, molecular mechanisms, and treatment implications. Most cases of GIST arise in the stomach and small intestine, although esophageal and rectal GISTs are rare. Accurate diagnosis and combined surgery with imatinib therapy are recommended for both advanced esophageal and rectal GISTs. So many published guidelines exist: National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), Asian consensus, Australia, United Kingdom, Canada, Japan, and Republic of Korea. Differences between Asia and other global guidelines are presented in this chapter. The second section addresses the general molecular character and pathogenesis of GIST. This section also explains that most GISTs harbor KIT or PDGFRA gain-of-function mutations and that a small number of GISTs exhibit mutation of NF1, RAS or RAF, and succinate dehydrogenase deficiency. The third section explains pathological diagnosis using endoscopic ultrasound guided fine needle aspiration biopsy, as well as radiology related to conventional computed tomography and magnetic resonance image. The fourth section describes surgical treatment for primary or metastatic lesions, and minimal invasive surgery using endoscopy. This section also describes molecular targeted therapy and radiotherapy. Several landmark trials have been published about imatinib, sunitinib, and regorafenib for metastatic GIST, and about imatinib for primary GIST after and before curative resection. Finally, the fifth section of the book presents examination of case reports of rare GIST. The various rare types of GIST are discussed individually, including extra-gastrointestinal GIST originated from the prostate, omentum, and peritoneum.

Every section provides a comprehensive summary of the current status of this field, which will help guide patient management and stimulate investigative efforts. All chapters were composed by experts in their fields, including the most up-to-date scientific and clinical information. We are thankful to all contributing authors for the time they devoted to sharing their knowledge and experience. This book constitutes an invaluable source of information for practicing medical oncologists, surgeons, radiologist, endoscopists, gastroenterologists, pathologists, and also trainees.

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Gastrointestinal stromal tumor

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Abstract: Gastrointestinal stromal tumor has received a lot of attention over the last 10 years due to its unique biologic behavior, clinicopathological features, molecular mechanisms, and treatment implications. GIST is the most common mesenchymal neoplasm in the gastrointestinal tract and has emerged from a poorly understood and treatment resistant neoplasm to a well-defined tumor entity since the discovery of particular molecular abnormalities, *KIT* and *PDGFRA* gene mutations. The understanding of GIST biology at the molecular level promised the development of novel treatment modalities. Diagnosis of GIST depends on the integrity of histology, immunohistochemistry and molecular analysis. The risk assessment of the tumor behavior relies heavily on pathological evaluation and significantly impacts clinical management. In this review, historic review, epidemiology, pathogenesis and genetics, diagnosis, role of molecular analysis, prognostic factor and treatment strategies have been discussed.

KeyWords: Gastrointestinal stromal tumor; GIST; KIT mutation; imatinib

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common (80%) mesenchymal tumor of the alimentary cannel (1-3). It accounts for less than 1% of all gastrointestinal tumors and about 5% all sarcomas (2-4). It represents a wide clinical spectrum of tumors with different clinical presentations, locations, histology and prognosis. GIST can occur throughout the entire gastrointestinal (GI) tract and may have extragastrointestinal involvement as well. The clinical relevance of this tumor was generated by the discovery of its molecular biology and, consequently, of a drug effective in treating the tumor. The following review will discuss the GISTs in all aspects including history, epidemiology, clinical presentation, diagnosis, prognosis and treatment and emphasize on those relevant to diagnosis.

Historic overview

Stromal tumors arising from the GI tract were initially classified as smooth muscle neoplasms including leiomyomas (5), leiomyoblastomas or sarcomas (6), following description by Stout and colleagues in 1940 (7). These descriptions were widely used until the 1970s when electron microscope found little evidence of the smooth muscle origin of these tumors (8,9). With the advent of immunohistochemistry during the 1980's it was soon appreciated that a large number of these tumors did not have immunophenotypic features of smooth muscle, and conversely, expressed antigens related to neural crest cells (10).

The term of "stromal tumors" was first described as a separate entity by Mazur and Clark (11) in 1983 and Schaldenbrand and Appleman in 1984 (12). However, this term was not widely accepted. In 1989, a distinctive subset of these stromal tumors revealing autonomic neural features was recognized and named "plexosarcoma" (13) and subsequently as gastrointestinal autonomic nerve tumor (GANT) (14). There was considerable confusion regarding the origin, differentiation and even clinical behavior of these tumors. In 1994, it was discovered that a significant proportion of GANTs were immunopositive for CD34 (15,16), which was the first relatively specific

marker of GISTs during the mid-1990s. Based on the CD34 immunopositivity the possibility that GIST might be related to the interstitial cells of Cajal was raised by investigators (17). Interstitial cells of Cajal, also known as pacemaker cells for peristaltic contraction, are a group of cells found in the muscularis propria and around the myenteric plexus along the GI tract and have the immunophenotypic and ultrastructural characteristics of both the neural and smooth muscle elements. Meantime, additional studies found that interstitial cells of Cajal express *KIT* and are developmentally dependent on stem cell factor which is regulated through the *KIT* kinase (17,18). However, the following critical issues were not resolved: the exact origin of GIST, the best way to diagnose GIST, and differentiation of benign from malignant GIST. As the developments in studies of GISTs, describing gain-of-function mutations and consequently, constitutive activation of *KIT* receptors in several human tumor cell lines was reported in the mid-1990s (19,20).

Finally in 1998, Hirota and colleagues (21) discovered a specific mutation in the intracellular domain of the *c-KIT* protooncogene in GISTs as well as a near-universal expression of *KIT* protein in GISTs by immunohistochemistry. In the same year, Kindblom and colleagues (22) corroborated findings from Hirota and colleagues by showing the immunoreactivity for *KIT* in 78 of 78 GISTs studied and GISTs shared striking ultrastructural and immunophenotypic similarities with interstitial cells of Cajal. Both studies supported the hypothesis that GIST may indeed derive from stem cells that differentiated toward interstitial Cajal phenotype and confirmed *KIT* as a diagnostic tool for GIST (23). The *KIT* mutation implied a gain-of function linked to the activation of the kinase even in the absence of the binding of the ligand. The identification of the *KIT* mutation was a major breakthrough in the biology of GIST and overall, in cancer biology.

The identification of the biologic driver, activating mutations in *KIT* provided a therapeutic target for the treatment of GIST. One patient with metastatic GIST refractory to multiple types of therapies was treated with STI-571 (Imatinib mesylate- Gleevec; Novartis, Basel, Switzerland), which is a small molecule tryosine kinase inhibitor (TKI) with potent activity against the transmembrane receptor *KIT*, *ABL* kinase and chimeric *BCR-ABL* fusion oncoprotein product of chronic myeloid leukemia. The treatment yielded an early, rapid, and sustained response (24) with supportive preclinical data (25,26). This case provided proof of principle that inhibition of *KIT* by drug therapy was associated with improvement in the disease and brought phenomenal growth in the understanding of GIST biology and therapeutics. Imatinib occupies the ATP binding pocket of *KIT*, thereby preventing substrate phosphorylation, downstream signaling, and thereby inhibiting cell proliferation and survival (23). The remarkable therapeutic efficacy of imatinib in patients with GIST along with accurate diagnoses using CD117 expression (a marker of *KIT* receptor tryosine kinase) resulted in subsequent approval of imatinib in this indication by the US Food and Drug Administration in February 2002 (27). In 2003, Heinrich and colleagues (28) and Hirota and colleagues (29) all found platelet-derived growth factor receptor alpha *(PDGFRA)* gene mutations as an alternative pathogenesis in GISTs without *KIT* gene mutation. In January 26, 2006, Sunitinib, a multitargeted TKI with activity against *KIT*, *PDGFR*, vascular endothelial growth factor (*VEGF*) receptor (*VEGFR*), and *FLT-1/KDR*, also received FDA approval for the management of patients who are refractory or intolerant to imatinib (30).

Overall, about 85% of GISTs are reported to have activating mutation in *KIT* or *PDGFRA* (28,31,32). CD117 (c-*Kit*) immunohistochemistry has proven to be a reliable and sensitive diagnostic tool (22,33,34). With the TKI therapies against *KIT* and *PDGFRA* (imatinib and sunitinib), inoperable or metastatic GISTs are now treatable, and a number of additional alternative drugs are in clinical trials.

Epidemiology

Although the exact incidence of GISTs in the world is hard to determine since the entity was not uniformly defined until the late 1990s, a few estimates and studies indicate the incidences of approximately 14.5 cases/million/year in Sweden (35), 14.2 in Northern Italy (36), 13.7 in Taiwan (37), 12.7 in Holland (38), 11 in Iceland (39) and 6.5 in Norway (40). In a recent report, about 5,000 new cases of GISTs were diagnosed annually (41) and a incidence of 6.8/million from 1992 to 2000 (38) in the United States. The overall incidence rates of GIST, therefore, ranges between 6.5 and 14.5 per million per year. In general, little information on the prevalence of GIST was available. It is believed that the prevalence of GIST is higher, as many patients live with the disease for many years or develop small GISTs only detected at autopsy or if a gastrectomy is performed for other causes (42). A study performed in

Germany on consecutive autopsies revealed small (<10 mm) GISTs in 22.5% of individuals who were older than 50 years (43). Rubin and colleagues used the SEER (surveillance, epidemiology, and end results) cancer registry in US for patients with GIST from 1993-2002 to determine incidence, prevalence, and 3-year survival and found the overall incidence, prevalence, and 3-year-servival rate were 3.2/million, 16.2/million, and 73%, respectively (44).

GIST mainly affects middle aged to elderly adults, typically in their 60s (35,45) with no clear gender predilection (46) although some studies demonstrated a slight male predominance (39,47). GISTs are uncommonly seen in patients younger than 40, however, cases in children and young adults have been reported (46). The true incidence of GIST in children is unknown. An incidence rate of 0.06/million/year was reported among young adults (20-29 years of age) (37). Other large series studies showed the percentage of patients with GIST below the age of 21 years ranged from 0.5% to 2.7% (45,46,48). Data from the UK National Registry revealed an annual incidence of 0.02 per million children below the age of 14 years, which appears to be the most accurate epidemiological data to date on pediatric GIST (49). Pediatric GISTs are considered a rare entity that can be quite different from its adult counterpart and seen predominantly in the second decade (46,50,51) with a predilection for female patients (46).

Sporadic GISTs are most common and familial GISTs with germline mutation of the *KIT* gene are rare, but have been well described (52-55). These patients usually have multiple GISTs and cutaneous hyperpigmentation (53). In addition, GIST rarely occurs in association with other syndromes such as neurofibromatosis type I (56-59) or Carney's triad, a nonfamilial condition with gastric GIST, paraganglioma, and pulmonary chondroma (60,61). The latter should be distinguished from Carney-Stratakis syndrome, an inherited tumor syndrome comprising gastric GIST and paragangliomas (62).

GIST co-existing with other tumors has been reported mainly as case report (63) and mostly with colorectal carcinomas or adenomas, followed by gastric carcinomas (64,65). p53, one of the most common involved genes in colorectal carcinogenesis, has also been found to have a prognostic significance in GISTs, and mutations in this tumor suppressor gene are more often observed in the high-risk GISTs (66). GIST colliding with other tumors, mostly gastric adenocarcinomas, is rarely seen in literature (67-69). Only one case of gastric GIST colliding with angiosarcoma was reported (70).

Pathogenesis and genetics

In 1995 Huizinga and colleagues reported a knockout mice model of *KIT* failed to express in interstitial cells of Cajal cells (17). This finding led to the hypothesis that *KIT* was essential for the development of interstitial cells of Cajal cells. In 1998, Hirota and colleagues published a groundbreaking discovery of *KIT* mutations in GISTs (21) and 95% GISTs are immunohistochemically positive for the receptor tyrosine kinase *KIT* (also known as CD117) (21,22). It is now established that *KIT* mutations, which cause the constitutive activation of the kinase, are found in 70-80% of GISTs. CD117 becomes a crucial diagnostic marker for GIST, and mutant *KIT* provides an important therapeutic target clinically in GIST treatment.

Initially, GISTs lacking any evidence of *KIT* mutation were classified as "wild type" (WT). In 2003, novel mutations in *PDGFRA* were found in WT GIST by Heinrich and colleagues (28). Currently *PDGFRA* mutations account for 5-10% of known mutations in GIST. About 9-15% of all GISTs do not exhibit mutations in either *KIT* or *PDGFRA* and are now termed "wild type" (WT) (71).

KIT is a member of the type III transmembrane receptor tyrosine kinase (RTK) family that includes *PDGFRA* and *PDGFRB*, as well as macrophage colony-stimulating-factor receptor (*CSF1R*) and Fl cytokine receptor (*FLT1*) (72). Normally, binding of the *KIT* ligand, stem cell factor (SCF) to *KIT* results in receptor dimerization and kinase activation (73). In contrast, the presence of *KIT* receptor-activating mutations will bypass the ligand binding requirement for activation and therefore become oncogenic, which has been implicated in the pathogenesis of several human tumors in addition to GIST and chronic myelogenous leukemia (CML), including seminomas (74), mastocytosis (19), acute myelogenous leukemia (75) and, more recently, in melanomas (76).

KIT oncogenetic activation is the dominant pathogenetic mechanism in GIST (77). Although familial GIST with germline mutations have been reported (52,55), the majority of *KIT* mutations in GIST are somatic. The most common mutations in *KIT* are found in the juxtamembrane domain that is encoded by the 5' end of exon 11 of the *KIT* receptor (*Figure 1*). Mutations in exon 11 change the normal juxtamembrane secondary structure and cause the active conformation of the normal kinase activation loop (78). The mutations vary from in-frame deletions of variable sizes, point

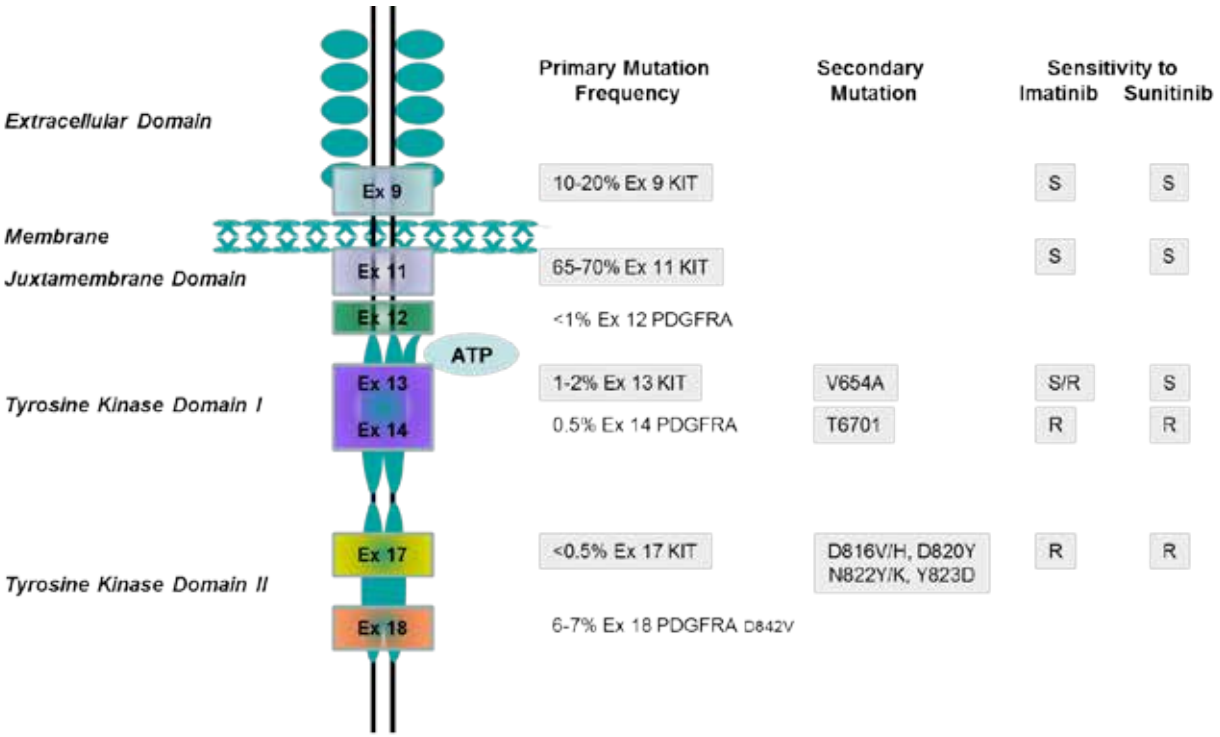

Figure 1 Schematic distribution of KIT or PDGFRA receptor mutations, frequency of mutations and TKI (Abbreviations: Ex, Exon; S, sensitive; R, resistant)

mutations to deletions preceded by substitutions (79). The deletions are associated with a more aggressive behavior in comparison to other exon 11 mutations (80-83). Particularly, deletions involving codon 557 and/or codon 558 are associated with malignant behavior (84,85). A less common mutant spot is located at the 3' end of exon 11, which includes mainly internal tandem duplications mutations (ITDs) (86). These ITD-type mutations are considered to have a more indolent clinical course and a predilection in GISTs located in the stomach (86). The second most common *KIT* mutation, between 10% and 15% of GISTs, is a mutation in an extracellular domain encoded by exon 9 (87). GISTs with *KIT* exon 9 mutations are characterized by small bowel location and aggressive clinical behavior (86).

A minority of GISTs that lack *KIT* gene mutations have high levels of phosphorylation of *PDGFRA* resulted from an activation by mutations or small deletions (28). *PDGFRA* is a close homologue of *KIT* (28). Mutations in *PDGFRA* and *KIT* in GIST are mutually exclusive and about one-third of GISTs without *KIT* mutations harbor a mutation of *PDGFRA*, within exons 12, 14 or 18 (28,88,89). In GIST, mutant forms of *PDGFRA* have constitutive kinase activity in the absence of their ligand-*PDGFRA* similar to those for *KIT* mutations, and the activated downstream pathways (28,29) are identical to those in *KIT*-mutant GISTs (28,90). In spite of the similarities in molecular aspect, most GISTs with mutated *PDGFRA* have distinct pathologic features, including gastric location, epithelioid morphology, variable/absent CD117 by immunohistochemistry and an indolent clinical course (88,91,92).

Recent studies indicate that a small portion of GIST wild-type for both *KIT* and *PDGFRA* genes may harbor mutations of the *BRAF* gene (93) and *KRAS* and *BRAF* mutations predict primary resistance to imatinib in GISTs (94).

Furthermore, GISTs demonstrate typical patterns of chromosomal gains and losses, including losses at 1p, 14q, 15q, and 22q. Tumor site appears to be associated with distinct chromosomal imbalances; for example, gastric GISTs show predominantly losses 14q, whereas intestinal GISTs more frequently exhibit losses of 15q (95).

Clinical presentation

Most GISTs remain 'silent' until reaching a large size.

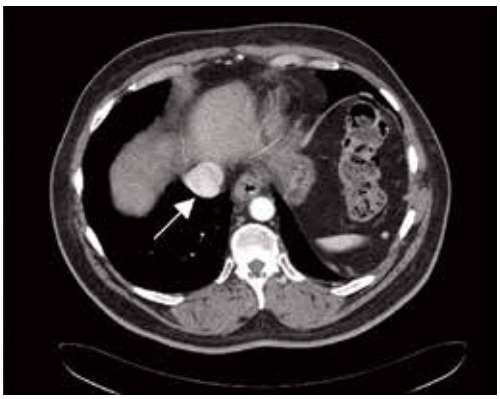

Figure 2 Computed tomography scan revealed a partially exophytic, dumbbell shaped solid mass (arrow) arising from the posterior aspect of the gastric fundus along the greater curvature, measuring approximately 6.7 cm × 4.5 cm

Symptoms vary according to location and size. Symptomatic GIST patients generally present with nonspecific symptoms including abdominal pain, fatigue, dyspepsia, nausea, anorexia, weight loss, fever and obstruction. Patients may present with chronic GI or overt bleeding due to mucosal ulceration or tumor rupture with life-threatening intraperitoneal hemorrhage. Some patients with large GISTs may have externally palpable masses (96,97). Aggressive GISTs have a defined pattern of metastasis to the liver and throughout the abdomen or both (45). Lymph node metastasis is not common. Spreading to the lung and bone in advanced cases has been reported (98). Metastasis often occurs 10-15 years after initial surgery (45).

More than 80% of GISTs are primarily located in GI tract and may occur throughout the GI tract with extra-GI tract GISTs reported in omentum, mesentery, retroperitoneum, gallbladder and urinary bladder (99-101). The majority of GISTs (60%) are seen in the stomach, usually in the fundus (35,39). The percentages of GISTs found in other portions of GI tract are reported as 30% in jejunum and ileum, 5% in duodenum, 4% in colorectum, and rarely in the esophagus and appendix (45,46,48,65). Reported tumor size in the stomach varies from a few millimeters to >40 cm with a mean size of 6 cm in the largest reported series (65). Apparently, the tumor size is one of the factors contributing to the clinical symptoms. A population-based study showed that the tumor size is 8.9 cm in patients with clinical symptoms, which is about 70% of GISTs studied, 2.7 cm in patients without clinical symptoms, 20%, and 3.4 cm in patients with GISTs detected at autopsy, 10% (35). Many smaller GISTs are detected incidentally during endoscopy, surgery, or computed tomography (CT) scans (35).

Diagnosis

The diagnostic evaluation of GISTs is based on imaging techniques (*Figure 2*), with a special role of endoscopic examination because it is usually accessible when tumors are in the stomach, esophagus and large intestine. In addition, endoscopic ultrasonography (EUS) also plays an important role in the diagnostic work-up of GISTs and is accurate and efficient in the diagnosis of GISTs (102). In general, externally bilging tumors are more common than intraluminal masses (103). Punch-out ulcer is the classical appearance of a submucosal tumor (104).

Macroscopy

Gastric GISTs are greyish-white sub-mucosal tumors with smooth contours and usually well-circumscribed and highly vascular tumors. They typically have a tan-white or fleshy pink cut surface often with hemorrhagic foci, central cystic degeneration, or necrosis (*Figure 3*). The overlying mucosa of large tumors is typically ulcerated (46).

Histopathology

Microscopically, GISTs have a broad morphological spectrum. Three main histological subtypes have been best widely accepted and they are spindle cell type (most common, 70%), epithelioid type (20-25%), and mixed spindle cell and epithelioid type (99,105,106) (*Figure 4*). In general, GISTs have a wide variation ranging from hypocellular to highly cellular with higher mitotic rates. Nuclear pleomorphism is relatively uncommon, and occurs more frequently in epithelioid type.

Spindle cell type of GIST is composed of cells in short fascicles and whorls. They have pale eosinophilic fibrillary cytoplasm, ovoid nuclei, and ill-defined cell borders. Gastric spindle cell GISTs often reveal extensive perinuclear vacuolization, a diagnostic feature formerly used for tumors of smooth muscle origin. The stroma sometimes demonstrates myxoid change or, rarely osseous metaplasia. Distinctive histological patterns among spindle cell GISTs including sclerosing type and palisading-vacuolated type (65). The sclerosing spindle cell GISTs have slender spindle cells with no nuclear atypia and low mitotic activity and are usually

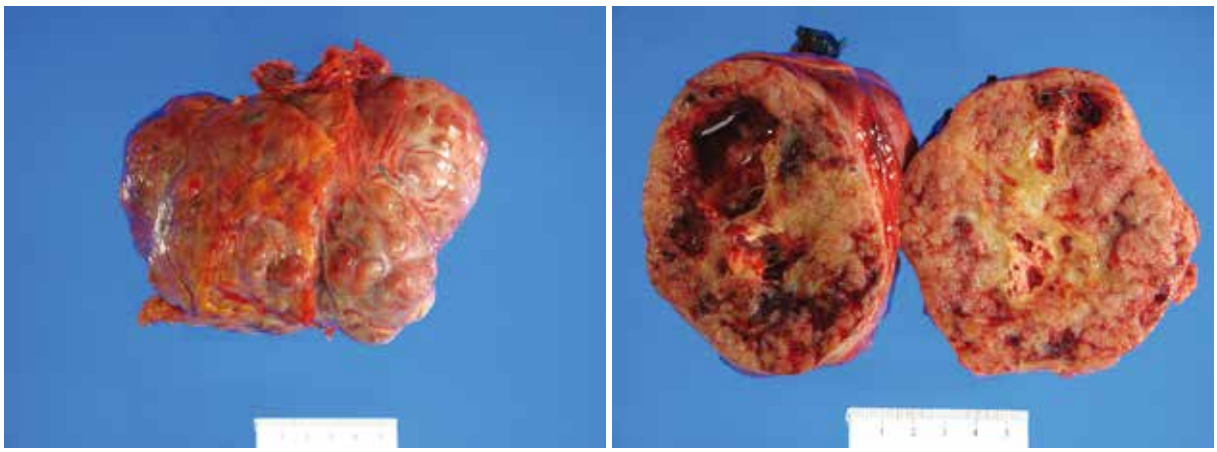

Figure 3 A gastric GIST with a nodulular surface and thin capusle. The cut surface reveals coarse granular and solid white tan suface with hemarrhage and cavities

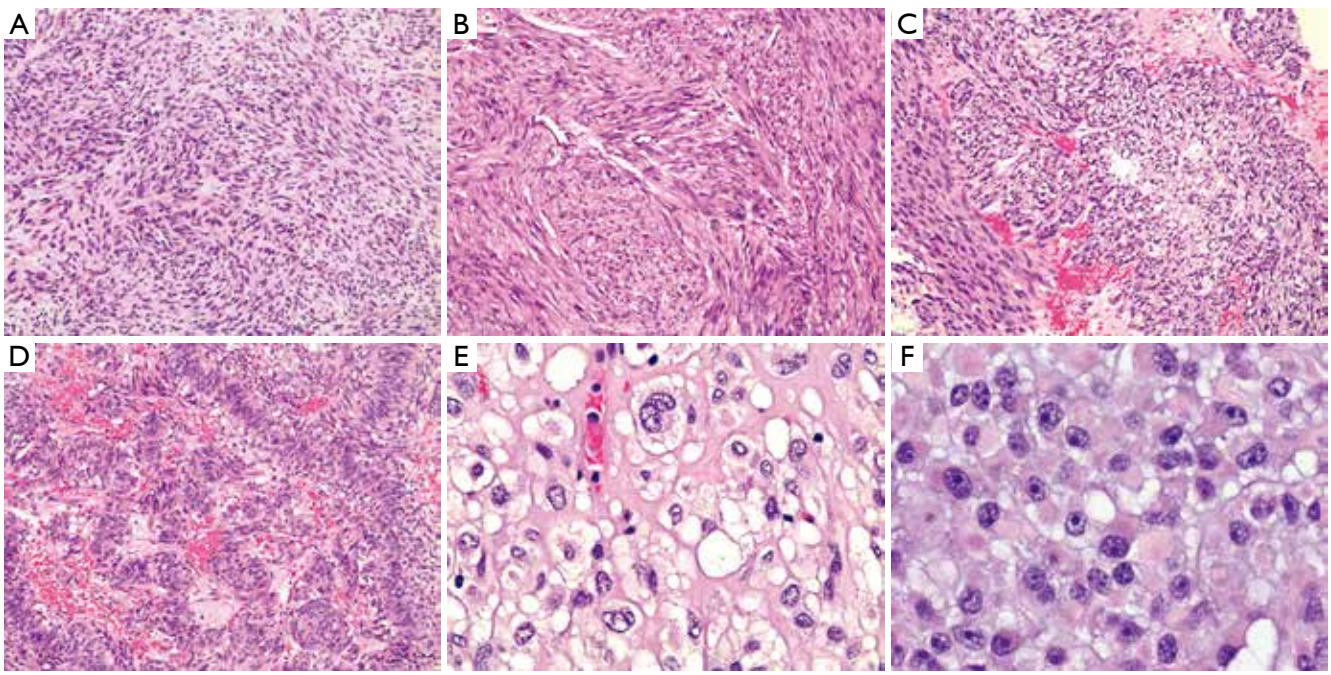

Figure 4 Common histologic al features of GISTs. A. Spindle cell GIST with short fascicles and whorls (×100); B. Spindle cell GIST with longer fascicles in bundles (×100); C. Spindle cell GIST with extensive perinuclear vacuolization (×100); D. Spindle cell GIST with prominent nuclear palisading (×100); E. Epithelioid cells GIST with pleomorphic nuclei and vacuolated cytoplasm (×400); F. Epithelioid cell GIST with rhabdoid features (×400)

paucicellular with extensive extracellular collagen. They are often small and contain calcifications. The palisading-vacuolated type is one of the most common gastric GISTs and usually cellular with plump and uniformed spindle cells. Nuclear palisading with perinuclear vacuolization is characteristic. There is usually limited atypia with mitotic activity rarely more than 10/50 high power fields (HPFs). However, some examples show diffuse hypercellular pattern, and others sarcomatoid features with significant nuclear atypia and mitotic activity (65,99,106).

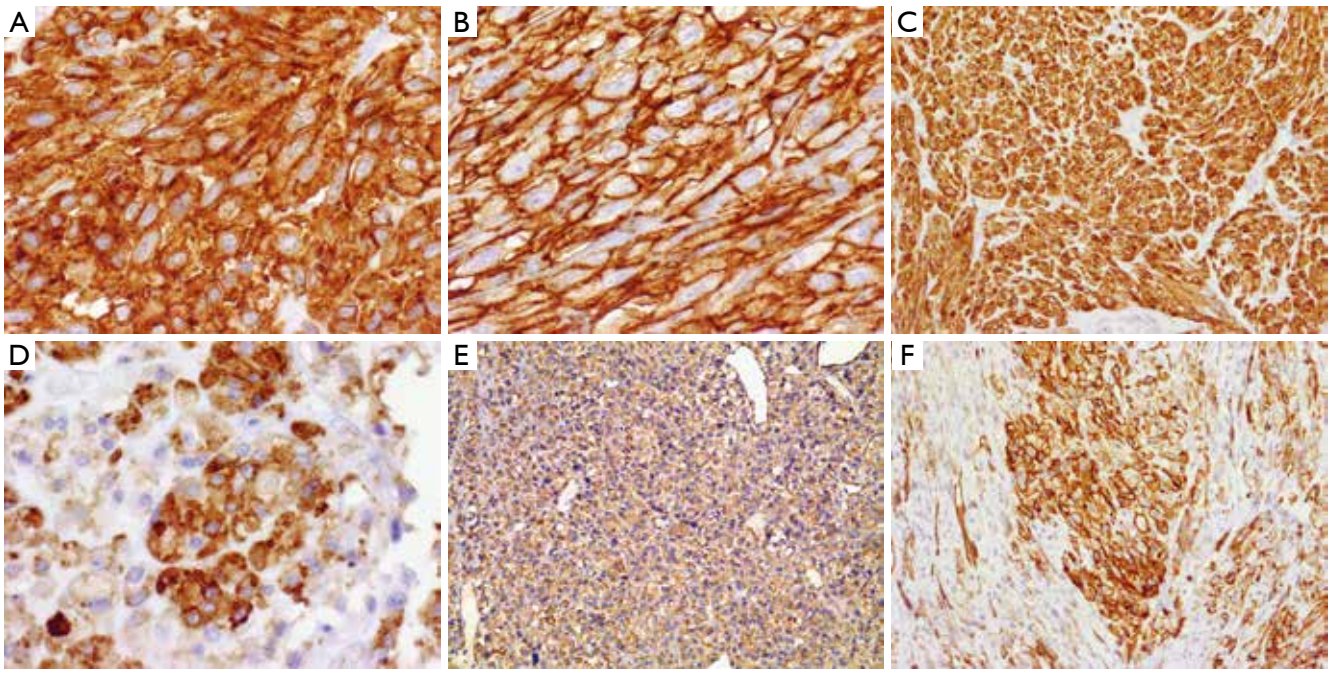

Figure 5 Immunohistochemical features of GIST. A. Spindle cell GIST with strong and diffuse cytoplasmic staining of CD117 (c-kit) (×400); B. Spindel cell GIST with strong and diffuse membrane staining of CD34 (×400); C. Epithelioid cell GIST with strong cytoplasmic staining of CD117 (×100); D. Epithelioid cell GIST with patchy and heterogeneous staining of CD34 (×400); E. Epithelioid cell GIST with punctate staining of h-Caldesmon (×100); F. Epithelioid cell GIST with patchy mambrane staining of h-Caldesmon (×400)

Epithelioid cell GISTs are characterized by round cells arranged in nests or sheets and with eosinophilic to clear cytoplasm. They also have spectrums from sclerosing and paucicellular to sarcomatous and mitotically inactive to mitotically highly active. However, the epithelioid GISTs with atypia, even with pleomorphism are sometimes benign (65,99,106).

Immunohistochemically, the vast majority of GISTs (95%) are strongly and diffusely positive for KIT (CD117), which makes the KIT to be a very specific and sensitive marker in the differentiating GIST from other mesenchyma tumors in the GI tract (21,22,34,107). The stain appears as cytoplasmic, membrane-associated or sometimes as perinuclear dots (34). Although KIT positivity appears to have significant therapeutic implications, the intensity, extent and patters of KIT staining neither correlates with the type of *KIT* mutation nor have therapeutic significance (34). It is important to note that negative KIT does not exclude the patient from being treated with TKI (imatinib or sunitinib) since some wild-type GISTs for both *KIT* and *PDGFRA* genes respond to treatment with TKI (42). In addition, CD34 is another common marker for GISTs but it is not as sensitive or specific. It is positive in about 80% of gastric GISTs, 50% of small intestine GISTs, and in 95% of esophageal and colorectal GISTs (48,108) (*Figure 5*). Other markers which can be expressed by GISTs include h-caldesmon, SMA, S100, desmin, Vimentin, and cytokeratins 8 and 18 (100). Recently other CD markers for GISTs are reported including CD10 (109), CD133, and CD44 (110).

A small minority of GIST (<5%) are negative for KIT, or minimally, if any, positive for *KIT* by immunohistochemistry. These tumors appear to be either *KIT* wild-type or with mutant *PDGFRA*, have a predilection to stomach or omentum/peritoneum, and be usually epithelioid or mixed subtype (91,111). For the special interest in this subgroup of *KIT*-negative GISTs, several new antibodies for the diagnosis of GIST have been discovered based on the molecular studies. DOG1 (discovered on GIST1), known also as TMEM16A and ANO1, a transmembrane protein, has been found specifically in GISTs and has emerged as a promising biomarker for GISTs (112,113). Recent studies have shown that antibodies against DOG1 have even higher sensitivity and specificity than KIT (CD117) and CD34 with 75% to 100% overall sensitivity (113-116).

DOG1 is highly expressed in *KIT* mutant GISTs and also can detect up to one-third of *KIT*-negative GISTs, which mostly have *PDGFRA* mutation (113,116). In addition to GISTs, DOG1 is also positive in normal gastric epithelium, some carcinomas, germ cell tumors, melanomas, and some mesenchymal tumors (113,114), such as recently reported chondroblastoma (117). Like KIT, DOG1 is also expressed in interstitial cells of Cajal serving as an internal positive control. However, DOG1 does not stain mast cells which are usually positive for *KIT* (112,114).

Non-gastric gists and gists in specific populations

Non-gastric GISTs may vary in clinical presentation, histopathology, molecular profile, prognostic significance and management strategy compared with gastric GISTs. Small intestinal GISTs including the duodenal GISTs are more homogeneous histologically and have a significant tumor-related mortality if the tumor is >5 cm (48). They typically harbor *KIT* exon 11 mutations as seen in gastric GISTs and a small portion of small intestinal GISTs contain duplication of two codons in *KIT* exon 9 (86,118). Usually, small intestinal GISTs do not harbor *PDGFRA* mutations. The sigmoid colon is the most common segment involved by GISTs (39) in the colon. Histopathologic profile of colonic GISTs is similar to that of small intestinal GISTs.

Pediatric GISTs account for about 1-2% of GISTs. They are often misdiagnosed as having another acute or chronic abdominal condition and they are usually symptomatic and mostly located in the stomach with mainly epithelioid pattern (35,46,50,51). GIST occurs in children and young adults as a component of two distinct syndromes: Carney triad and Carney-Stratakis syndrome. Carney triad is composed of co-occurrence of GIST, pulmonary chondroma, and paraganglioma. Carney triad can be diagnosed when any of the two tumors are present in a patient. However, if only GIST and paraganglioma are present, it is considered to be Carney-Stratakis syndrome. GIST in patients with Carney triad tends to be multifocal and have high local recurrence rate and/or metastatic rate. However, the clinical course of GIST in Carney triad is usually indolent (61). Although pediatric GISTs express KIT protein, the majorities lack *KIT* or *PDGFRA* mutations (46,50,51). In 2002, a germline-inactivating mutation in the hereditary paraganglioma gene was found to be unique for Carbey-Stratakis (119,120). This germline mutation results in a cancer predisposition syndrome including GIST.

Patients with neurofibromatosis type 1 (NF1) have a high risk for GIST. Some autopsy studies have demonstrated as many as one of three NF1 patients to have GISTs (121). NF-associated GIST typically occur in duodenum or small intestine and often multifocal and small. They commonly have low risk parameters and are clinically indolent (57,121). In contrast to sporadic adults GISTs, NF1-associated GISTs lack *KIT* and *PDGFRA* mutations (57,121,122).

Familial GISTs were reported and account for a very small portion of GISTs (<0.1%). They have typically activated germline *KIT* or *PDGFRA* mutations with an autosomal dominant inheritance and high penetrance (52,55,123,124). They occur usually in middle age of life and typical multifocal or diffuse in the GI tract. Most of these GISTs have a benign course.

Differential diagnosis

Although GISTs are the most common mesenchymal tumor of the GI tract, a variety of other tumors should be included in the differential diagnosis. Accurate recognition of GIST is obviously important as the treatment differs according to the tumor type. The main differential diagnoses include smooth muscle tumors, schwannoma, desmoid fibromatosis, inflammatory myofibroblastic tumor, inflammatory fibroid polyp, solitary fibrous tumor, synovial sarcoma, follicular dendritic cell sarcoma, glomus tumor, and melanoma. Kirsch and colleagues have published extensive review of diagnostic challenges and practical approach to differential diagnosis of GISTs (125).

Anatomic location may be helpful in differential diagnosis. Intramural leiomyomas most commonly locate in the esophagus and are rare in the stomach and small intestine (126). Morphologically, leiomyomas have brightly eosinophilic cytoplasm with distinct cell borders whereas GISTs usually reveal syncytial cell morphology. Immunohistochemically, GISTs and leiomyomas share some markers, such as SMA and h-caldesmon, but spindle cell GISTs are rarely positive for desmin which is more specific for leiomyomas. Rare epithelioid GISTs that lack KIT expression do stain positive for desmin (116). Leiomyomas are negative for CD117.

Although gastric schwannomas are not commonly seen, they can be morphologically very similar to certain spindle cell GISTs. Distinct peripheral cuffing of lymphocytes and strong reactivity with S-100 and GFAP readily differentiate them from GIST in addition to the negativities of CD117 and CD34 (127).

Mesenteric fibrous lesions can be very challenging in

Table 1 Immunophenotypic features of gastrointestinal mesenchymal tumors

Diagnosis	KIT	DOG1	Desmin	SMA	h-Cal	S100	CD34	HMB45	EMA	β-Cat	Clusterin	Keratin	Other
GIST	+++	+++	-	++ (40)*	++	-	+++	-	-	-	-	-	
Leiomyoma	-	-	+++	+++	+++	-	-	-	-	-	-	-	
Leiomyosarcoma	-	-	+ to ++	+++	++	-	+ (10)	-	-	-	-	-	
Schwannoma	-	-	-	-	-	+++	-	-	-	-	-	-	GFAP
Fibromatosis	-	-	-	++	-	±	-	-	-	++	-	-	
Synovial sarcoma	-	-	-	-	-	++ (30)	-	-	++	-	-	±	
PEComa	-	-	++	++	-	-	-	+++	-	-	-	-	Melan-A
FDCS	-	-	-	-	-	±	-	-	±	-	+++	-	CD21/23/35
Dermatofibroma	-	-	-	+++	-	-	+++	-	-	++	-	-	
IFP	-	-	-	±	-	-	++	-	-	-	-	-	
IMT	-	-	-	++	-	-	±	-	-	-	-	-	ALK-1
SFT	-	-	-	+	-	-	+++	-	-	-	-	-	

*Parenthetical numbers represent approximate percentage of cases that are positive. Abbreviations: SMA, smooth muscle actin; h-Cal, h-Caldesmon; -Cat, -Catenin; PEComa, Perivascular epithelioid cell tumour; FDCS, Follicular dendritic cell sarcoma; IFP, Inflammatory fibroid polyp; IMT, Inflammatory myofibroblastic tumor; SFT, Solitary fibrous tumor; -, negative stain; ±, sometimes positive and sometimes negative stain; +, <25% of cases positive; ++, 25-50% of cases positive; +++, >50% of cases positive

terms of diagnosis of itself and confusion with GIST due to the location and gross appearance. Microscopically, intraabdominal desmoid fibromatosis usually display long sweeping fascicles of spindle cells embedded within a collagen matrix with an infiltrating patter at peripheral of the tumor. Immunohistochemical stain of beta-catenin is positive in about 75% of cases (128-130). Inflammatory myofibroblastic tumors are commonly seen in pediatric or young adult patients and recognized as a mesenteric mass. Microscopically, this tumor has cellular fascicular fibroblastic/myofibroblastic proliferation with a prominent mixed inflammatory components including significant number of plasma cells. About 50% of tumors express ALK-1 (131), which is essentially negative in GIST. Inflammatory fibroid polyp is a polypoid lesion of mucosa with collagenous or myxoid stroma admixed with fibroblasts. It can be CD34 positive but should be negative for CD117 and DOG1 (113,114,132). Interestingly, same *PDGFRA* mutations as seen in GISTs are also discovered in inflammatory fibroid polyps (133).

Histologically, epithelioid GISTs need to be distinguished from other epithelial or epithelioid tumors including carcinoma, melanoma, glomus tumor, germ cell tumor and clear cell sarcoma. Immunohistochemical studies play a major rule on the differential diagnosis and the evaluation of appropriate immunophenotypic markers in context with morphology in most cases allows an accurate classification (*Table 1*).

Role of molecular analysis

Mutational analysis of the *KIT* gene including exons 11, 9, 13, and 17, and *PDGFRA* gene including exons 12, 14, and 18 can be helpful in confirming the diagnosis of GISTs if immunohistochemical studies fail to support the diagnosis (particularly in CD117/DOG1-negative spindle cell suspect cases). Corless and colleagues (134) summarized the mutations of GISTs and classified GISTs based on the molecular findings (*Table 2*). Furthermore, mutational analysis probably has more clinical significance in therapeutic aspect as it has predictive value for sensitivity to molecular-targeted therapy (including dosage) and prognostic value. It is strongly recommended that it should be included in the diagnostic work-up of all GISTs (135). The correlation between *KIT* and *PDGFRA* mutational status and the response to tyrosine kinase inhibitors and their role in primary and secondary resistance has been widely investigated (31,136). Tumors harboring *KIT* exon 11 mutations have a better outcome

Table 2 Molecular classification of GISTs (134)*

Genetic type	Relative frequency	Anatomic distribution
KIT mutation (relative frequency 75-80%)		
Exon 8	Rare	Small intestine
Exon 9 insertion AY502-503	10%	Small intestine and colon
Exon 11 (deletion, single nucleotide substitution and insertions	67%	All sites
Exon 13 K642E	1%	All sites
Exon 17 D820Y, N822K and Y823D	1%	All sites
PDGFRA mutation (relative frequency 5-8%)		
Exon 12 (such as V561D)	1%	All sites
Exon 14 N659K	<1%	Stomach
Exon 18 D842V	5%	Stomach, mesentery and momentum
Exon 18 (such as deletion of amino acids IMHD 842-846	1%	All sites
KIT and PDGFRA wild-type (relative frequency 12-15%		
BRAF V600E	~7-15%	
SDHA, SDHB, SDHC and *SDHD* mutations	~2%	Stomach and small intestine
HRAS and *NRAS* mutation	<1%	
Sporadic pediatric GISTs	~1%	Stomach
GISTs as part of the Carney triad	~1%	Stomach
NF1-related	Rare	Small intestine

Adopted from Corless and colleagues [ref (134) Table 1]. Abbreviation: GIST, gastrointestinal stromal tumor; NF1, neurofibromatosis type I; PDGFRA, platelet-derived growth factor receptor- ; SDH, succinate dehydrogenase

under imatinib treatment than tumors harboring different mutation, whereas tumors with *PDGFRA* exon 18 mutations (D842V) have primary resistance to imatinib both *in vivo* and *in vitro* (27,71,137). Therefore, GIST mutational analysis is strongly recommended in current NCCN (National Comprehensive Cancer Network) clinical practice guidelines (*Figure 6*) and in ESMO (European Society for Medical Oncology) clinical recommendations (138,139).

Prognostic factors, grade and stage

The risk of relapse of GISTs is estimated based on mitotic rate, tumor size, tumor site, surgical margins and the status of tumor rupture. Tumor size and mitotic count are considered to be the most useful and best studied prognostic factors by the 2002 Consensus risk classification (*Table 3*) (99). It is believed that indicating a risk level of GIST (low, intermediate, or high) is more appropriate than definitively labeling the tumor as benign or malignant. This risk classification was based on the cumulative experience of the authors in the committee. The most important cut-offs as indicators of aggressive clinical behavior were tumor size of 5 cm and 5 mitoses/50 HPF. This consensus guideline indicated that all GISTs may have malignant potential (99). Based on long-term follow-up of more than 1,600 GISTs (1,055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal), Miettinen and colleagues proposed risk classification incorporates primary tumor site in addition to the mitotic count and tumor size (*Table 4*) (140). It demonstrates the fact that gastric GISTs have a better prognosis than small intestine or rectal GISTs. The more recently updated consensus NCCN guidelines from 2007 (141) includes anatomic site as an additional parameter in risk assessment for GIST. Based on those guidelines, GISTs that are smaller than 2 cm are considered to be essentially benign. Recently, Gold and colleagues proposed a nomogram for estimating the risk of tumor progression (142), in which each GIST was assigned points on a scale based on tumor site, size, and mitotic index. The total points of a tumor should determine the 2- and 5-year recurrence free survival probabilities. From a clinical point of view, additional prognostic factors including non-radical resection and tumor rupture, whether spontaneous or at the time of surgical resection, are both associated with adverse outcome independent of any

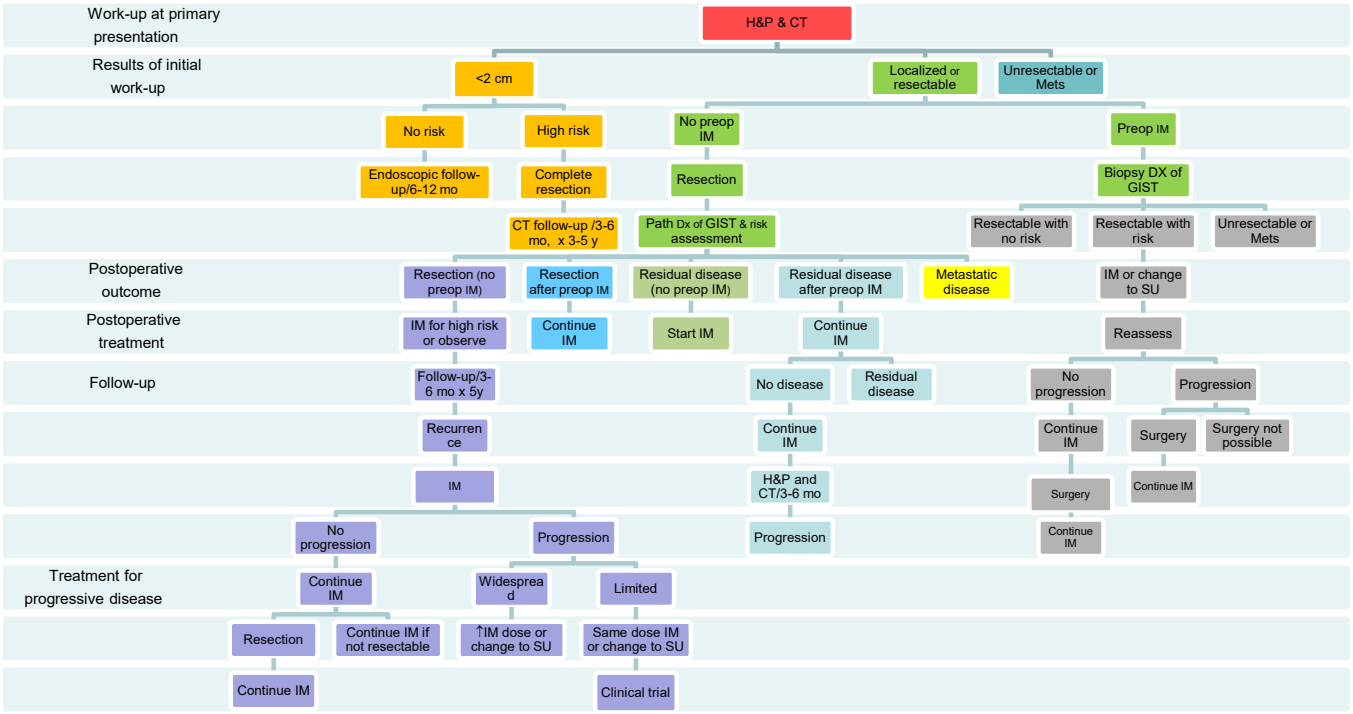

Figure 6 NCCN Guidelines Version 1.2012, Gastrointestinal Stromal Tumors (GIST) (Abbreviations: H&P, history & physical examination; Mets, metastatic disease; IM, imatinib; Preop, preoperative; DX, diagnosis; SU; sunitinib; mo, month; y, year)

Table 3 Risk assessment of GIST, 2002 by NIH

Risk category	Size (cm)	Mitotic count (50 HPF)
Very low risk	<2	<5
Low risk	2-5	5
Intermediate risk	5	6-10
	5-10	5
High risk	>5	>5
	>10	Any mitotic rate
	Any size	>10

Adopted from Fletcher and colleagues [ref (99) Table 2]. Abbreviations: HPF, high-power field

other prognostic factors (143). Furthermore, Takahashi and colleagues suggested the inclusion of a "clinically malignancy group" to include patients with peritoneal dissemination, metastasis, and invasion into adjacent organs or tumor rupture (144). In 2008, a proposal by Joensuu based on the NIH system included the presence of tumor rupture as a high risk factor irrespective of size and mitotic count (145). The Joensuu's revised NIH risk system is shown in *Table 5*.

In the TNM staging (AJCC, 7th edition, 2010) (146), grading of GISTs is based on mitotic rate. Mitotic rate less than 5/50 HPFs is considered to be low (grade 1) and greater than 5/50 HPFs is considered to be high (grade 2). Please note that the staging criteria are different for gastric GISTs and small intestinal GISTs to emphasize the more aggressive clinical course of small intestinal GISTs even with similar tumor parameters (147). The seventh edition of the international union against cancer (UICC) published at the beginning of 2010 included for the first time a classification and staging system for GIST (148). This represents a significant step towards a more standardized surgical and oncological treatment for patients with GIST and, more importantly, may facilitate the establishment of a uniformed follow-up system based on tumor stage (*Table 6*) (149).

Treatment

Treatment of localized disease

Surgery

The only potentially curative treatment of GISTs, still, is complete surgical resection if it is a locally resectable

Table 4 Risk assessment of GIST, 2006 by miettinen and lasota (ref 140)

Mitotic rate (50 HPF)	Tumor size (cm)	Stomach	Duodenum	Jejunum or ileum	Rectum
5	2	None	None	None	None
	>25	Very low	Low	Low	Low
	>510	Low	Moderate	Insufficient data	Insufficient data
	>10	Moderate	High	High	High
>5	2	None*	High*	Insufficient data	High
	>25	Moderate	High	High	High
	>510	High	High	Insufficient data	Insufficient data
	>10	High	High	High	High

Adopted from Miettinen and Lasota (ref 140). Abbreviation: HPF, high-power field; *Very small number of cases

Table 5 Risk Assessment of GIST, 2008 by Joensuu (ref 145)

Risk category	Tumor size (cm)	Mitotic rate	Duodenum
(50 HPF)	Primary tumor site	None	None
Very low risk	<2	5	Any
Low risk	2.1-5.0	5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	5	Gastric
High risk	Any	Any	Tumor rupture
	>10.0	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Nongastric
	5.1-10.0	5	Nongastric

Adopted from Joensuu [ref (145) Table 4]. Abbreviation: HPF, high-power field

Table 6 UICC TNM classification for GIST, 7th Edition, 2010

Mitotic rate (50HPFs)	Tumor size (cm)	T		N	M	UICC stage	
		Gastric	Non-gastric			Gastric GIST	Non-gastric GIST
5	2	T1	T1	N0	M0	IA	I
	2-5	T2	T2	N0	M0	IA	I
	5-10	T3	T3	N0	M0	IB	II
	>10	T4	T4	N0	M0	II	IIIA
>5	2	T1	T1	N0	M0	II	IIIA
	2-5	T2	T2	N0	M0	II	IIIB
	5-10	T3	T3	N0	M0	IIIA	IIIB
	>10	T4	T4	N0	M0	IIIB	IIIB
Any	Any	Any	Any	N1	M0	IV	IV
		Any	Any	Any	M1	IV	IV

Abbreviation: UICC, the international union against cancer; GIST, gastrointestinal stromal tumor; HPF, high-power field

or marginally resectable tumor (141,150). GISTs rarely metastasize to lymph node (142,151) and therefore regional lymph node dissection is generally not needed. In addition, organ-sparing resection (segmental resection) is also appropriate oncologically. However, about 40-90% of surgically treated patients experience disease recurrence (152). A recent study of 127 patients with localized GISTs who underwent complete resection demonstrated a 5-year recurrence-free survival (RFS) rate of 63% (153). This study concludes tumor size 10 cm, mitotic rate 5/50HPFs, and tumor location in the small intestine were all independently associated with an increased risk of recurrence. In addition, intraperitoneal rupture or bleeding is also associated with a high risk of postoperative recurrence of nearly 100% (143,154,155).

Adjuvant therapy

Understanding the molecular changes of GISTs along with target treatments resulted in a considerable transformation in the management of GISTs. The remarkable efficacy of imatinib in treating metastatic GISTs has prompted interest in developing an adjuvant after complete resection of GISTs. Resent phase III randomized trial involved 778 patients with localized GISTs who underwent complete surgical resection followed by 1 year of imatinib (400 mg/day) and revealed that adjuvant imatinib significantly improved the 1-year RFS rate (98%) compared with the placebo (83%) (P<0.0001) (156). Based on the results of this trial, FDA approved imatinib as adjuvant therapy for GISTs (157). The most recent management guidelines in US (NCCN) (138) and Europe (ESMO) (139) recommended adjuvant imatinib for at least 1 year following complete surgical resection in patients with intermediate- to high-risk GIST. However, the optimal duration of adjuvant therapy has not been established yet.

Treatment of localized unresectable or metastatic gists

Although surgical intervention was applied to patients with metastases prior to the imatinib era, it was unlikely to completely resect the tumor and consequently with earlier recurrence than localized disease (45). Nunoby and colleagues (158) in Japan studied the outcome of surgical resection in 18 patients with liver metastases of GISTs and showed 83% complete resection of liver metastases with 64% 3-year postoperative overall survival (OS) rate and 34% 5-year postoperative OS rate. However, the recurrence rate in the remnant liver and in other organs reached 94% in this study. Surgical treatment alone for metastatic GISTs, therefore, is only palliative (158).

The application of imatinib for patients with advanced and non-resectable GISTs was first evaluated in the palliative setting in 2000 (24). A recent large clinical study of imatinib for unresectable or metastatic GISTs revealed up to 57 months of median OS rate (159), which is almost a threefold increase in OS from about 20 months (45) prior to the application of imatinib. Based on the clinical practice guidelines (NCCN & ESMO), treatment with imatinib (400 mg/day) now is the standard of care for patients with locally advanced, recurrent, or metastatic disease (138,139). Multiple phase III clinical trials have confirmed the effectiveness of imatinib with standard-dose (400 mg/day) or high-dose (800 mg/day) (159,160). Furthermore, the efficacy of imatinib certainly also depends on the mutant profile of GISTs. *KIT* exon 11 mutations show the greatest benefit from imatinib treatment (400 mg/day) (*Figure 1*) (135,161). *KIT* exon 11 codon 557/558 deletion/insertion mutations have a more aggressive clinical behavior (162). *KIT* exon 9 mutant GIST requires a higher imatinib dosage to reach a better response (135,163). In addition, sunitinib, another TKI, is beneficial for exon 9 mutated-GIST (30). Although wild-type patients are not likely to benefit from imatinib (161), some *in vivo* and *in vivo* studies on sunitinib (164), nilotinib, and dasatinib (165) are promising. Regarding *PDGFRA*-mutated GISTs, *PDGFRA* exon 18 mutations have better response to imatinib therapy but not with PDFGRA exon 18 *D842V*-mutation (71).

According to the NCCN guidelines, patients with progressive disease after imatinib treatment are allowed to be re-assessed for surgery. Surgical resection has been achieved in those cases (166-168). However, the timing of the surgical intervention is very important and was recommended as the time at which patients reached maximum benefit from imatinib but before tumor progression occurs (139,169). In addition, neoadjuvant therapy with TKI should be considered to facilitate complete resection and allow for a less morbid operation, especially in duodenal GIST which can be sometimes hardly resected completely (170,171). With a short neoadjuvant imatinib therapy, tumor blood flow was decreased and apoptosis was increased within 3-7 days of starting therapy compared with pre-imatinib tumor tissue, although minimal size reduction was observed (171).

Assessment of treatment response

According to the NCCN guidelines, imaging study of contrast-enhanced CT scan is the technique of choice to detect

recurrence or progression of GISTs (138,139,172). In rectal GIST, MRI should be used or additional PET or PET-CT/MRI may be useful for early detection of tumor response to neoadjuvant therapy (172). Choi and colleagues (173) proposed modified response evaluation criteria which is considered to predict response more accurately than previously proposed Response Evaluation Criteria in Solid Tumor (RECIST) (174) and has a better correlation with time to progression (175).

Resistant disease and alterative treatments

Although TKIs, especially imatinib, have resulted in disease-free survival for patients following surgical resection of their primary tumors and increased response rates and survival for patients with metastatic disease, some patients will eventually develop resistance to imatinib (176). Several potential mechanisms of resistance were proposed and include specific types of mutations (*KIT* exon 9, *KIT* wild-type or *PDGFRA* exon 18) (31,135), acquisition of secondary mutations within the *KIT* gene, *KIT* gene amplification, loss of the wild-type allele, or inadequate imatinib plasma levels (176-179). Sunitinib is the only second-line TKI approved for use after imatinib failure due to its inhibitory function on multi-kinases receptors (136). It has also been shown to be effective against secondary mutations *in vitro* and *in vivo* studies (136,161). However, as with imatinib, resistance has recently been documented in patients with prolonged exposure to sunitinib (180,181). In addition, it has been shown that sunitinib can cause serious, life-threatening adverse effects, including hypertension, cardiotoxicity, and hypothyroidism (30,182,183). According to the NCCN and ESMO guidelines, sunitinib is recommended as a second-line therapy in patients who experience disease progression after high-dose imatinib or who have life-threatening side effects. If further progression occurs with sunitinib, patients should be considered for clinical trials of new agents or new combinations or discontinuation of anti-cancer therapy.

The role of newer generation *KIT* and *PDGFRA* kinase inhibitors, e.g., nilotinib, remains to be determined in GIST patients with multiple resistants after imatinib and sunitinib therapies. Nilotinib has demonstrated activity against imatinib- and sunitinib resistant GISTs (184) and displays, by an ongoing pilot study (185), substantial clinical benefit and is safe in the first-line treatment of advanced GIST. Other agents, such as dasitinib (186), sorafenib (187), and masitinib (188), target multiple oncogenic receptor tyrosine kinases that have been implicated in the development and growth of GIST. These newer agents and a wide number of others (189) are currently under clinical trials for the management of advanced and resistant GISTs and likely to change the treatment of this disease soon.

Conclusions

GISTs have received much attention for many reasons. The rapid expansion of molecular and clinicopathological knowledge of GIST has given this disease a promising future. The molecular targets for therapeutic interventions are not only of importance for the treatment of GIST patients, but also in the development of novel drugs and new strategies in basic cancer therapy. Pathologists need to know their role as the diagnostic information they provided impacts on the choice of treatment as well as on estimation of its efficacy. Molecular testing of GISTs should be performed for treatment selection and assessment of disease progression. The cause of GIST is still unknown; therefore, little has been done preventively. However, with gradual understanding the molecular mechanisms of GIST, the etiology will be elucidated eventually.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Joensuu H, Fletcher C, Dimitrijevic S, et al. Management of malignant gastrointestinal stromal tumours. Lancet Oncol 2002;3:655-64.
2. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. Lancet 2007;369:1731-41.
3. Steigen SE, Eide TJ. Gastrointestinal stromal tumors (GISTs): a review. APMIS 2009;117:73-86.
4. Katz SC, DeMatteo RP. Gastrointestinal stromal tumors and leiomyosarcomas. J Surg Oncol 2008;97:350-9.
5. Appleman HD, Helwig EB. Gastric epithelioid leiomyoma and leiomyosarcoma (leiomyoblastoma). Cancer 1976;38:708-28.
6. Akwari OE, Dozois RR, Weiland LH, et al. Leiomyosarcoma of the small and large bowel. Cancer

1978;42:1375-84.
7. Stout AP. Bizarre smooth muscle tumors of the stomach. Cancer 1962;15:400-9.
8. Welsh RA, Meyer AT. Ultrastructure of gastric leiomyoma. Arch Pathol 1969;87:71-81.
9. Weiss RA, Mackay B. Malignant smooth muscle tumors of the gastrointestinal tract: an ultrastructural study of 20 cases. Ultrastruct Pathol 1981;2:231-40.
10. Yagihashi S, Kimura M, Kurotaki H, et al. Gastric submucosal tumours of neurogenic origin with neuroaxonal and Schwann cell elements. J Pathol 1987;153:41-50.
11. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 1983;7:507-19.
12. Schaldenbrand JD, Appelman HD. Solitary solid stromal gastrointestinal tumors in von Recklinghausen's disease with minimal smooth muscle differentiation. Hum Pathol 1984;15:229-32.
13. Herrera GA, Cerezo L, Jones JE, et al. Gastrointestinal autonomic nerve tumors. 'Plexosarcomas'. Arch Pathol Lab Med 1989;113:846-53.
14. Lauwers GY, Erlandson RA, Casper ES, et al. Gastrointestinal autonomic nerve tumors. A clinicopathological, immunohistochemical, and ultrastructural study of 12 cases. Am J Surg Pathol 1993;17:887-97.
15. Miettinen M, Virolainen M, Maarit Sarlomo R. Gastrointestinal stromal tumors--value of CD34 antigen in their identification and separation from true leiomyomas and schwannomas. Am J Surg Pathol 1995;19:207-16.
16. Mikhael AT, Bacchi CE, Zarbo RJ, et al. CD34-expression in stromal tumors of the gastrointestinal tract. Appl Immunohistochem 1994;2:89-93.
17. Huizinga JD, Thuneberg L, Kluppel M, et al. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. Nature 1995;373:347-9.
18. Isozaki K, Hirota S, Nakama A, et al. Disturbed intestinal movement, bile reflux to the stomach, and deficiency of c-kit-expressing cells in Ws/Ws mutant rats. Gastroenterology 1995;109:456-64.
19. Nagata H, Worobec AS, Oh CK, et al. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci USA 1995;92:10560-4.
20. Longley BJ, Tyrrell L, Lu SZ, et al. Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. Nat Genet 1996;12:312-4.
21. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
22. Kindblom LG, Remotti HE, Aldenborg F, et al. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998;152:1259-69.
23. Quek R, George S. Gastrointestinal stromal tumor: a clinical overview. Hematol Oncol Clin North Am 2009;23:69-78. viii.
24. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001;344:1052-6.
25. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 2000;295:139-45.
26. Heinrich MC, Griffith DJ, Druker BJ, et al. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000;96:925-32.
27. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
28. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708-10.
29. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660-7.
30. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38.
31. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
32. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004;22:3813-25.
33. Hornick JL, Fletcher CD. Immunohistochemical staining for KIT (CD117) in soft tissue sarcomas is very limited in distribution. Am J Clin Pathol 2002;117:188-193.
34. Hornick JL, Fletcher CD. The role of KIT in the

management of patients with gastrointestinal stromal tumors. Hum Pathol 2007;38:679-87.
35. Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer 2005;103:821-9.
36. Mucciarini C, Rossi G, Bertolini F, et al. Incidence and clinicopathologic features of gastrointestinal stromal tumors. A population-based study. BMC Cancer 2007;7:230.
37. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100:162-8.
38. Goettsch WG, Bos SD, Breekveldt-Postma N, et al. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. Eur J Cancer 2005;41:2868-72.
39. Tryggvason G, Gislason HG, Magnusson MK, et al. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer 2005;117:289-93.
40. Sandvik OM, Soreide K, Kvaloy JT, et al. Epidemiology of gastrointestinal stromal tumours: single-institution experience and clinical presentation over three decades. Cancer Epidemiol 2011;35:515-20.
41. Pisters PW, Blanke CD, von Mehren M, et al. A USA registry of gastrointestinal stromal tumor patients: changes in practice over time and differences between community and academic practices. Ann Oncol 2011;22:2523-9.
42. Liegl-Atzwanger B, Fletcher JA, Fletcher CD. Gastrointestinal stromal tumors. Virchows Arch 2010;456:111-27.
43. Agaimy A, Wunsch PH, Hofstaedter F, et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol 2007;31:113-20.
44. Rubin JL, Sanon M, Taylor DC, et al. Epidemiology, survival, and costs of localized gastrointestinal stromal tumors. Int J Gen Med 2011;4:121-30.
45. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51-8.
46. Miettinen M, Lasota J, Sobin LH. Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol 2005;29:1373-81.
47. Kawanowa K, Sakuma Y, Sakurai S, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006;37:1527-35.
48. Miettinen M, Makhlouf H, Sobin LH, et al. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006;30:477-89.
49. Stiller C. Childhood cancer in Britain: incidence, survival, mortality. Oxford University Press Oxford. 2007.
50. Janeway KA, Liegl B, Harlow A, et al. Pediatric KIT wild-type and platelet-derived growth factor receptor alpha-wild-type gastrointestinal stromal tumors share KIT activation but not mechanisms of genetic progression with adult gastrointestinal stromal tumors. Cancer Res 2007;67:9084-8.
51. Prakash S, Sarran L, Socci N, et al. Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. J Pediatr Hematol Oncol 2005;27:179-87.
52. Nishida T, Hirota S, Taniguchi M, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet 1998;19:323-4.
53. Maeyama H, Hidaka E, Ota H, et al. Familial gastrointestinal stromal tumor with hyperpigmentation: association with a germline mutation of the c-kit gene. Gastroenterology 2001;120:210-5.
54. Beghini A, Tibiletti MG, Roversi G, et al. Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and urticaria pigmentosa. Cancer 2001;92:657-62.
55. Li FP, Fletcher JA, Heinrich MC, et al. Familial gastrointestinal stromal tumor syndrome: phenotypic and molecular features in a kindred. J Clin Oncol 2005;23:2735-43.
56. Takazawa Y, Sakurai S, Sakuma Y, et al. Gastrointestinal stromal tumors of neurofibromatosis type I (von Recklinghausen's disease). Am J Surg Pathol 2005;29:755-63.
57. Miettinen M, Fetsch JF, Sobin LH, et al. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol 2006;30:90-6.
58. Kang DY, Park CK, Choi JS, et al. Multiple gastrointestinal stromal tumors: Clinicopathologic and genetic analysis of 12 patients. Am J Surg Pathol

2007;31:224-32.
59. Maertens O, Prenen H, Debiec-Rychter M, et al. Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. Hum Mol Genet 2006;15:1015-23.
60. Carney JA, Sheps SG, Go VL, et al. The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med 1977;296:1517-8.
61. Carney JA. Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney Triad): natural history, adrenocortical component, and possible familial occurrence. Mayo Clinic proceedings Mayo Clinic 1999;74:543-52.
62. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002;108:132-9.
63. Melis M, Choi EA, Anders R, et al. Synchronous colorectal adenocarcinoma and gastrointestinal stromal tumor (GIST). Int J Colorectal Dis 2007;22:109-14.
64. Liszka Ł, Zielińska-Pajak E, Pajak J, et al. Coexistence of gastrointestinal stromal tumors with other neoplasms. J Gastroenterol 2007;42:641-9.
65. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29:52-68.
66. Ryu MH, Kang YK, Jang SJ, et al. Prognostic significance of p53 gene mutations and protein overexpression in localized gastrointestinal stromal tumours. Histopathology 2007;51:379-89.
67. Liu SW, Chen GH, Hsieh PP. Collision tumor of the stomach: a case report of mixed gastrointestinal stromal tumor and adenocarcinoma. J Clin Gastroenterol 2002;35:332-4.
68. Katsoulis IE, Bossi M, Richman PI, et al. Collision of adenocarcinoma and gastrointestinal stromal tumour (GIST) in the stomach: report of a case. Int Semin Surg Oncol 2007;4:2.
69. Toyoda A, Komaba A, Yoshizumi H, et al. Collision of advanced gastric adenocarcinoma and gastrointestinal stromal tumour: a case report. BMJ case reports 2009;2009.
70. Adhikari M, Wu ML, Zhao X. Gastrointestinal stromal tumor colliding with angiosarcoma. Int J Surg Pathol 2006;14:252-6.
71. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357-64.
72. Hanks SK, Quinn AM, Hunter T. The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. Science 1988;241:42-52.
73. Lev S, Yarden Y, Givol D. Dimerization and activation of the kit receptor by monovalent and bivalent binding of the stem cell factor. J Biol Chem 1992;267:15970-7.
74. Tian Q, Frierson HF Jr, Krystal GW, et al. Activating c-kit gene mutations in human germ cell tumors. Am J Pathol 1999;154:1643-7.
75. Gari M, Goodeve A, Wilson G, et al. c-kit proto-oncogene exon 8 in-frame deletion plus insertion mutations in acute myeloid leukaemia. Br J Haematol 1999;105:894-900.
76. Curtin JA, Busam K, Pinkel D, et al. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24:4340-6.
77. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci USA 2009;106:1542-7.
78. Mol CD, Dougan DR, Schneider TR, et al. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. J Biol Chem 2004;279:31655-63.
79. Corless CL, McGreevey L, Town A, et al. KIT gene deletions at the intron 10-exon 11 boundary in GI stromal tumors. J Mol Diagn 2004;6:366-70.
80. Ernst SI, Hubbs AE, Przygodzki RM, et al. KIT mutation portends poor prognosis in gastrointestinal stromal/smooth muscle tumors. Lab Invest 1998;78:1633-6.
81. Lasota J, Jasinski M, Sarlomo-Rikala M, et al. Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. Am J Pathol 1999;154:53-60.
82. Taniguchi M, Nishida T, Hirota S, et al. Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. Cancer Res 1999;59:4297-300.
83. Andersson J, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors with KIT exon 11 deletions are associated with poor prognosis. Gastroenterology 2006;130:1573-81.
84. Wardelmann E, Losen I, Hans V, et al. Deletion of Trp-557 and Lys-558 in the juxtamembrane domain of the c-kit protooncogene is associated with metastatic behavior of gastrointestinal stromal tumors. Int J Cancer 2003;106:887-95.
85. Martín J, Poveda A, Llombart-Bosch A, et al. Deletions affecting codons 557-558 of the c-KIT gene indicate

a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). J Clin Oncol 2005;23:6190-8.
86. Antonescu CR, Sommer G, Sarran L, et al. Association of KIT exon 9 mutations with nongastric primary site and aggressive behavior: KIT mutation analysis and clinical correlates of 120 gastrointestinal stromal tumors. Clin Cancer Res 2003;9:3329-37.
87. Lux ML, Rubin BP, Biase TL, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. Am J Pathol 2000;156:791-5.
88. Lasota J, Dansonka-Mieszkowska A, Sobin LH, et al. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. Lab Invest 2004;84:874-83.
89. Pauls K, Merkelbach-Bruse S, Thal D, et al. PDGFRalpha- and c-kit-mutated gastrointestinal stromal tumours (GISTs) are characterized by distinctive histological and immunohistochemical features. Histopathology 2005;46:166-75.
90. Kang HJ, Nam SW, Kim H, et al. Correlation of KIT and platelet-derived growth factor receptor alpha mutations with gene activation and expression profiles in gastrointestinal stromal tumors. Oncogene 2005;24:1066-74.
91. Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. Am J Surg Pathol 2004;28:889-94.
92. Sakurai S, Hasegawa T, Sakuma Y, et al. Myxoid epithelioid gastrointestinal stromal tumor (GIST) with mast cell infiltrations: a subtype of GIST with mutations of platelet-derived growth factor receptor alpha gene. Hum Pathol 2004;35:1223-30.
93. Hostein I, Faur N, Primois C, et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol 2010;133:141-8.
94. Miranda C, Nucifora M, Molinari F, et al. KRAS and BRAF Mutations Predict Primary Resistance to Imatinib in Gastrointestinal Stromal Tumors. Clin Cancer Res 2012;18:1769-76.
95. Gunawan B, von Heydebreck A, Sander B, et al. An oncogenetic tree model in gastrointestinal stromal tumours (GISTs) identifies different pathways of cytogenetic evolution with prognostic implications. J Pathol 2007;211:463-70.
96. Ueyama T, Guo KJ, Hashimoto H, et al. A clinicopathologic and immunohistochemical study of gastrointestinal stromal tumors. Cancer 1992;69:947-55.
97. Miettinen M, Sarlomo-Rikala M, Sobin LH, et al. Gastrointestinal stromal tumors and leiomyosarcomas in the colon: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases. Am J Surg Pathol 2000;24:1339-52.
98. Miettinen M, Furlong M, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. Am J Surg Pathol 2001;25:1121-33.
99. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459-65.
100. Miettinen M, Monihan JM, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol 1999;23:1109-18.
101. Reith JD, Goldblum JR, Lyles RH, et al. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol 2000;13:577-85.
102. Gu M, Ghafari S, Nguyen PT, et al. Cytologic diagnosis of gastrointestinal stromal tumors of the stomach by endoscopic ultrasound-guided fine-needle aspiration biopsy: cytomorphologic and immunohistochemical study of 12 cases. Diagn Cytopathol 2001;25:343-50.
103. Levy AD, Remotti HE, Thompson WM, et al. Gastrointestinal stromal tumors: radiologic features with pathologic correlation. Radiographics 2003;23:283-304, 456; quiz 532.
104. Saleem TB, Ahmed I. Gastrointestinal stromal tumour--evolving concepts. Surgeon 2009;7:36-41.
105. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438:1-12.
106. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumor. J Surg Oncol 2011;104:865-73.
107. Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, et al. CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 1998;11:728-34.
108. Miettinen M, Lasota J. KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation. Appl Immunohistochem Mol Morphol 2005;13:205-20.

109. Wong NA, Melegh Z. Gastrointestinal stromal tumours can express CD10 and epithelial membrane antigen but not oestrogen receptor or HMB45. Histopathology 2011;59:781-5.
110. Chen J, Guo T, Zhang L, et al. CD133 and CD44 are universally overexpressed in GIST and do not represent cancer stem cell markers. Genes Chromosomes Cancer 2012;51:186-95.
111. Debiec-Rychter M, Wasag B, Stul M, et al. Gastrointestinal stromal tumours (GISTs) negative for KIT (CD117 antigen) immunoreactivity. J Pathol 2004;202:430-8.
112. West RB, Corless CL, Chen X, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol 2004;165:107-13.
113. Espinosa I, Lee CH, Kim MK, et al. A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. Am J Surg Pathol 2008;32:210-8.
114. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009;33:1401-8.
115. Ardeleanu C, Arsene D, Hinescu M, et al. Pancreatic expression of DOG1: a novel gastrointestinal stromal tumor (GIST) biomarker. Appl Immunohistochem Mol Morphol 2009;17:413-8.
116. Liegl B, Hornick JL, Corless CL, et al. Monoclonal antibody DOG1.1 shows higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors, including unusual subtypes. Am J Surg Pathol 2009;33:437-46.
117. Akpalo H, Lange C, Zustin J. Discovered on gastrointestinal stromal tumour 1 (DOG1): a useful immunohistochemical marker for diagnosing chondroblastoma. Histopathology 2012;60:1099-106.
118. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology 2008;53:245-66.
119. McWhinney SR, Pasini B, Stratakis CA. Familial gastrointestinal stromal tumors and germ-line mutations. N Engl J Med 2007;357:1054-6.
120. Pasini B, McWhinney SR, Bei T, et al. Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. Eur J Hum Genet 2008;16:79-88.
121. Andersson J, Sihto H, Meis-Kindblom JM, et al. NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. Am J Surg Pathol 2005;29:1170-6.
122. Kinoshita K, Hirota S, Isozaki K, et al. Absence of c-kit gene mutations in gastrointestinal stromal tumours from neurofibromatosis type 1 patients. J Pathol 2004;202:80-5.
123. Agarwal R, Robson M. Inherited predisposition to gastrointestinal stromal tumor. Hematol Oncol Clin North Am 2009;23:1-13. vii.
124. Chompret A, Kannengiesser C, Barrois M, et al. PDGFRA germline mutation in a family with multiple cases of gastrointestinal stromal tumor. Gastroenterology 2004;126:318-21.
125. Kirsch R, Gao ZH, Riddell R. Gastrointestinal stromal tumors: diagnostic challenges and practical approach to differential diagnosis. Adv Anat Pathol 2007;14:261-85.
126. Miettinen M, Sarlomo-Rikala M, Sobin LH, et al. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. Am J Surg Pathol 2000;24:211-22.
127. Sarlomo-Rikala M, Miettinen M. Gastric schwannoma--a clinicopathological analysis of six cases. Histopathology 1995;27:355-60.
128. Montgomery E, Torbenson MS, Kaushal M, et al. Beta-catenin immunohistochemistry separates mesenteric fibromatosis from gastrointestinal stromal tumor and sclerosing mesenteritis. Am J Surg Pathol 2002;26:1296-301.
129. Bhattacharya B, Dilworth HP, Iacobuzio-Donahue C, et al. Nuclear beta-catenin expression distinguishes deep fibromatosis from other benign and malignant fibroblastic and myofibroblastic lesions. Am J Surg Pathol 2005;29:653-9.
130. Carlson JW, Fletcher CD. Immunohistochemistry for beta-catenin in the differential diagnosis of spindle cell lesions: analysis of a series and review of the literature. Histopathology 2007;51:509-14.
131. Cessna MH, Zhou H, Sanger WG, et al. Expression of ALK1 and p80 in inflammatory myofibroblastic tumor and its mesenchymal mimics: a study of 135 cases. Mod Pathol 2002;15:931-8.
132. Ozolek JA, Sasatomi E, Swalsky PA, et al. Inflammatory fibroid polyps of the gastrointestinal tract: clinical, pathologic, and molecular characteristics. Appl Immunohistochem Mol Morphol 2004;12:59-66.
133. Lasota J, Wang ZF, Sobin LH, et al. Gain-of-function PDGFRA mutations, earlier reported in gastrointestinal stromal tumors, are common in small intestinal inflammatory fibroid polyps. A study of 60 cases. Mod

Pathol 2009;22:1049-56.
134. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer 2011;11:865-78.
135. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093-103.
136. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352-9.
137. Tamborini E, Pricl S, Negri T, et al. Functional analyses and molecular modeling of two c-Kit mutations responsible for imatinib secondary resistance in GIST patients. Oncogene 2006;25:6140-6.
138. NCCN. Clinical Practice Guidelines in Oncology, Soft tissue sarcoma. Available online: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 2012.
139. Casali PG, Blay JY. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:v98-102.
140. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
141. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007;5:S1-29; quiz S30.
142. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045-52.
143. Rutkowski P, Nowecki ZI, Michej W, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol 2007;14:2018-27.
144. Takahashi T, Nakajima K, Nishitani A, et al. An enhanced risk-group stratification system for more practical prognostication of clinically malignant gastrointestinal stromal tumors. Int J Clin Oncol 2007;12:369-74.
145. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.
146. Edge SB, American Cancer Society, American College of Surgeons, et al. AJCC cancer staging handbook from the AJCC cancer staging manual 16. Gastrointestinal Stromal Tumor Springer New York 2010:16-1-16-2.
147. Miettinen M, Fletcher CDM, Kindblom LG, et al. WHO classification of tumours of the digestive system: Mesenchymal tumor of the stomach Bosman FT World Health Organization classification of tumours. International Agency for Research on Cancer Lyon 2010; 74-79.
148. (UICC). IUaC. TNM classification of malignant tumours Sobin LH, Gospodarowicz MK and Wittekind C Wiley-Blackwell Chichester, West Sussex, UK ; Hoboken, NJ 2010.
149. Agaimy A. Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need for a standardized GIST reporting. Int J Clin Exp Pathol 2010;3:461-71.
150. Gervaz P, Huber O, Morel P. Surgical management of gastrointestinal stromal tumours. Br J Surg 2009;96:567-78.
151. Pierie JP, Choudry U, Muzikansky A, et al. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. Arch Surg 2001;136:383-9.
152. Rossi CR, Mocellin S, Mencarelli R, et al. Gastrointestinal stromal tumors: from a surgical to a molecular approach. Int J Cancer 2003;107:171-6.
153. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer 2008;112:608-15.
154. Hohenberger P, Ronellenfitsch U, Oladeji O, et al. Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. Br J Surg 2010;97:1854-9.
155. Demetri GD, Antonia S, Benjamin RS, et al. Soft tissue sarcoma. J Natl Compr Canc Netw 2010;8:630-74.
156. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-104.
157. Administration: USFaD. FDA approves Gleevec to prevent recurrence of rare gastrointestinal cancer. Available online: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129210.htm 2008
158. Nunobe S, Sano T, Shimada K, et al. Surgery including liver resection for metastatic gastrointestinal stromal tumors or gastrointestinal leiomyosarcomas. Jpn J Clin Oncol 2005;35:338-41.
159. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with

unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620-5.
160. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127-34.
161. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360-7.
162. Kontogianni-Katsarou K, Dimitriadis E, Lariou C, et al. KIT exon 11 codon 557/558 deletion/insertion mutations define a subset of gastrointestinal stromal tumors with malignant potential. World J Gastroenterol 2008;14:1891-7.
163. Patel S, Zalcberg JR. Optimizing the dose of imatinib for treatment of gastrointestinal stromal tumours: lessons from the phase 3 trials. Eur J Cancer 2008;44:501-9.
164. Janeway KA, Albritton KH, van Den Abbeele AD, et al. Sunitinib treatment in pediatric patients with advanced GIST following failure of imatinib. Pediatr Blood Cancer 2009;52:767-71.
165. Agaram NP, Laquaglia MP, Ustun B, et al. Molecular characterization of pediatric gastrointestinal stromal tumors. Clin Cancer Res 2008;14:3204-15.
166. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol 2007;14:14-24.
167. Bonvalot S, Eldweny H, Pechoux CL, et al. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. Ann Surg Oncol 2006;13:1596-603.
168. Rutkowski P, Nowecki Z, Nyckowski P, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. J Surg Oncol 2006;93:304-11.
169. Pisters PW, Patel SR. Gastrointestinal stromal tumors: current management. J Surg Oncol 2010;102:530-8.
170. Lopes LF, Bacchi CE. Imatinib treatment for gastrointestinal stromal tumour (GIST). J Cell Mol Med 2010;14:42-50.
171. McAuliffe JC, Hunt KK, Lazar AJ, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol 2009;16:910-9.
172. Reichardt P, Blay JY, Mehren M. Towards global consensus in the treatment of gastrointestinal stromal tumor. Expert Rev Anticancer Ther 2010;10:221-32.
173. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007;25:1753-9.
174. Benjamin RS, Choi H, Macapinlac HA, et al. We should desist using RECIST, at least in GIST. J Clin Oncol 2007;25:1760-4.
175. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
176. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764-74.
177. Debiec-Rychter M, Cools J, Dumez H, et al. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology 2005;128:270-9.
178. Liegl B, Kepten I, Le C, et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J Pathol 2008;216:64-74.
179. Bauer S, Yu LK, Demetri GD, et al. Heat shock protein 90 inhibition in imatinib-resistant gastrointestinal stromal tumor. Cancer Res 2006;66:9153-61.
180. Guo T, Hajdu M, Agaram NP, et al. Mechanisms of sunitinib resistance in gastrointestinal stromal tumors harboring KITAY502-3ins mutation: an in vitro mutagenesis screen for drug resistance. Clin Cancer Res 2009;15:6862-70.
181. Nishida T, Takahashi T, Nishitani A, et al. Sunitinib-resistant gastrointestinal stromal tumors harbor cis-mutations in the activation loop of the KIT gene. Int J Clin Oncol 2009;14:143-9.
182. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011-9.
183. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 2006;145:660-4.
184. Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293-7.
185. Reichardt P, Montemurro M. Clinical experience to date

with nilotinib in gastrointestinal stromal tumors. Semin Oncol 2011;38:S20-7.
186. Dewaele B, Wasag B, Cools J, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. Clin Cancer Res 2008;14:5749-58.
187. Guo T, Agaram NP, Wong GC, et al. Sorafenib inhibits the imatinib-resistant KITT670I gatekeeper mutation in gastrointestinal stromal tumor. Clin Cancer Res 2007;13:4874-81.
188. Soria JC, Massard C, Magne N, et al. Phase 1 dose-escalation study of oral tyrosine kinase inhibitor masitinib in advanced and/or metastatic solid cancers. Eur J Cancer 2009;45:2333-41.
189. NIH. Clinical Trial Database. Available online: http://clinicaltrials.gov/ 2012

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Introduction

Management of rectal gastrointestinal stromal tumor

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Abstract: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. However, rectal GIST is rare, the incident rate of it is approximately 5% of all GISTs. Rectal GIST symptoms generally include bleeding and/or pain and occasionally, urinary symptoms. Immunohistochemical evaluation finds that most rectal GIST tumors are CD117 (KIT) positive, and are sometimes CD34, platelet-derived growth factor receptor alpha (PDGFRA), smooth muscle actin, S-100, or vimentin positive. The National Institutes of Health (NIH) classifies rectal GIST as very-low risk, low risk, intermediate risk, or high risk, and the frequencies have been estimated as 0–23.8% for very-low risk, 0–45% for low risk, 0–34% for intermediate risk, and 21–100% for high risk tumors. The first-line treatment for localized GIST is curative resection, but is difficult in rectal GIST because of anatomical characteristics such as the deep, narrow pelvis and proximity to the sphincter muscle or other organs. Several studies noted the efficacy of the minimally invasive surgery, such as trans-anal, trans-sacral, trans-vaginal resection, or laparoscopic resection. The appropriate surgical procedure should be selected depending on the case. Imatinib mesylate (IM) is indicated as first-line treatment of metastatic or unresectable GIST, and clinical outcomes are correlated with *KIT* mutation genotype. However, the *KIT* mutation genotypes in rectal GIST are not well known. In this review, as in other GISTs, a large proportion (59–100%) of rectal GISTs carry exon 11 mutations. Although curative resection is indicated for localized rectal GIST, a high rate of local recurrence is a problem. Multimodal therapy including perioperative IM may improve postoperative outcomes, contributing to anus-preserving surgery. Moreover, *KIT* mutation analysis before IM treatment is important. This review summarizes current treatment strategies for rectal GIST.

Keywords: Gastrointestinal stromal tumor (GIST); rectal GIST; KIT mutation; imatinib mesylate (IM)

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Introduction

Gastrointestinal stromal tumors (GISTs) were first described by Mazur *et al.* in 1983 (1). GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract and can have spindle-cell or epithelioid histology; 80% express the KIT protein and 10% express platelet-derived growth factor receptor alpha (PDGFRA) (2,3). Gain-of-function mutations in the *KIT* proto-oncogene or *PDGFRA* are important in the genesis and classification of these tumors (3-6). These mutations are involved in GIST development, and result in the constitutive activation of KIT signaling (4). GISTs account for 0.1–3% of all malignant gastrointestinal neoplasms (7-9), and rectal GIST is rare, with an incidence of approximately 0.1% of all rectal neoplasms (10), and

Table 1 Clinical symptoms of rectal GIST

Authors	Year	No. of patients	Pain	Bleeding	Change of bowel habit	Constipation	Tumor	Urinary symptom	Others
Hamada (22)	2008	33	3.0%	30.3%	–	15.2%	12.1%	3.3%	36.1%
Agaimy (25)	2013	15	–	46.7%	–	–	53.3%	13.3%	–
Pai (23)	2015	13	38.5%	23.0%	–	–	–	–	38.5%
Shen (24)	2015	45	17.8%	28.9%	24.4%	–	–	6.7%	22.2%
Wilkinson (26)	2015	19	21.0%	36.8%	31.6%	–	–	–	31.6%

GIST, gastrointestinal stromal tumor.

comprises approximately 5% of all GISTs (11).

Curative resection is the first-line treatment for localized GISTs in all organs, but is difficult in rectal GIST because of anatomical features including the deep, narrow pelvis and proximity to the sphincter muscle or other organs. Several studies have reported the efficacy of multimodality therapy for rectal GIST, including perioperative imatinib mesylate (IM) treatment. Laparoscopic surgery or anus-preserving surgery for rectal GIST preserves patient quality of life (QOL). This review discusses the current treatment of rectal GIST.

Epidemiology

GIST may occur anywhere in the gastrointestinal tract, but its frequency is mostly in the stomach (60–70%) followed by small intestine (25–30%), rectum (5%), and colon (1%) (12). Furthermore, GIST may also occur as primary tumors outside of the gastrointestinal tract proper as intra-abdominal locations in the mesenteries, omentum, retroperitoneum, or pelvis (12-14). Colorectal GIST was reported to account for 6.3% of cases in western Sweden (15), and other studies reported that rectal GIST accounted for 3.5–5% of all cases (15-17). The annual incidence of GIST is approximately 1.1–1.45 per 100,000 population (15,17) and the overall incidence has been estimated as 10–20 per 100,000 population including incidental, minimal tumors (18). Rectal GIST accounts for 4% of all GISTs, or 800–1,000 new cases in the European Union each year (15,17,19). Hawkins *et al.* found that 333 anorectal GIST patients were registered in the National Cancer Database, that their mean age was 62.3 years, and that the median tumor size was 4.0 cm (20).

Rectal GISTs are also rare in eastern countries, accounting for approximately 0.1% of all rectal neoplasms in Republic of Korea (10). Yasui *et al.* reported that of 737 GIST patients evaluated between 2003 and 2007 in Japan, 24 (3.3%) were rectal GISTs (21). All were in the lower rectum, within a median of 2.5 cm from the anal verge (21). Hamada *et al.* reported 33 rectal GISTs in Japan before the era of IM. The mean age was 61.6 years, the maximum tumor size was 8.2 cm, and the mean distance from the anal verge was 4.2 cm (22).

Diagnosis

Baik *et al.* reported seven cases of rectal GIST in Republic of Korea with primary symptoms of hematochezia, constipation, and anal pain similar to those of other rectal tumors (10). In a case series in India, the main primary symptoms were pain (38.5%), bleeding (23.0%), and others (38.5%) (23). Shen *et al.* described bleeding (28.9%), pain (17.8%), difficulty with defecation (11.1%), urinary complaints (6.7%), and other symptoms (11.1%) in 45 cases of rectal GIST (24). In a patient series in Japan the chief complaints were anal bleeding (30.3%), constipation (15.2%), anal discomfort (12.1%), palpitation of tumor (12.1%), abdominal pain (3.0%), and ischuria (3.0%) (22). *Table 1* summarizes the most common symptoms of rectal GIST, which are primarily bleeding and/or pain; urinary symptoms may occur more frequently than in GISTs at other sites (22-26).

GISTs of the stomach, colon or rectum generally appear as a submucosal mass in endoscopy (27), and are diagnosed in biopsy tissue. In rectal GISTs, immunohistochemical analysis can be CD117 (KIT) positive dominantly, CD34, PDGFRA, smooth muscle actin, S-100, and vimentin positive occasionally (28). Rectal GISTs are classified as very-low risk, low risk, intermediate risk, or high risk tumors by National Institutes of Health (NIH) criteria (29), and the frequency of recurrence has been estimated as 21–100% for high risk, 0–34% for intermediate risk,

Table 2 The recurrent risk in rectal GIST by NIH criteria

Authors	Year	No. of patients	Very-low risk	Low risk	Intermediate risk	High risk
Farid (30)	2013	9	0%	0%	22.0%	78.0%
Liu (31)	2014	21	23.8%	23.8%	28.6%	23.8%
Zhou (28)	2014	67	0%	45.0%	34.0%	21.0%
Shen (24)	2015	45	8.9%	22.2%	2.2%	66.7%
Wilkinson (26)	2015	19	0%	0%	0%	100%
Yasui (21)	2017	24	20.8%	33.8%	0%	45.8%

GIST, gastrointestinal stromal tumor; NIH, National Institutes of Health.

0–45% for low risk, and 0–23.8% for very-low risk tumors (21,24,26,28,30,31) (*Table 2*). A diagnosis of GIST in the rectum was also considered to correlate with poor overall prognosis. However, Fletcher *et al.* reported that tumor site was not a reliable predictor of outcome (29). One reason for the poor prognosis of rectal GISTs is that the tumor rupture rate is more than four-fold higher than that of non-rectal GISTs (30).

GISTs are usually seen as an exophytic mass that heterogeneously enhances with intravenous contrast because of its high vascularization (32), and contrast enhanced computed tomography (CT) is the standard method of GIST imaging (33). Magnetic resonance imaging (MRI) is useful for liver-specific lesions or patients contraindicated for CT (33). Fluorodeoxyglucose positron emission tomography (FDG-PET) also has good specificity and sensitivity for evaluation of tumor response after IM treatment (32). However, FDG-PET cannot be used to evaluate treatment response if pretreatment FDG-PET was negative. Approximately 20% of lesions shown on CT do not display appreciable glucose uptake on pretreatment FDG-PET images (32). The imaging characteristics of rectal GISTs have been described by Jiang *et al.* (34). Enhanced MRI with direct multiplanar capability is useful in determining the exact origin tumor of pelvic tumors, which is often difficult to confirm. The imaging technology using MRI can detect invasion of adjacent organs in greater detail than possible with CT (34).

Treatment

Surgery

Surgical resection with curative intent is the standard treatment for localized GIST (35). Complete excision of the tumor is the most significant factor related to outcome, and can be accomplished in 40–60% of all GIST patients (36). The benefit of histologically negative margins in the surgical treatment of non-metastatic rectal GIST has been confirmed (19). Since GIST may occur anywhere in gastrointestinal tract, the surgical approach varies, with local excision by trans-anal, trans-sacral, or trans-vaginal procedures as the preferred treatments for early, lower rectal GISTs (37). On the other hand, the treatment of advanced rectal GISTs is controversial. Complete curative resection of rectal GISTs is difficult because of its anatomical features (35), and choice of the surgical procedure may be difficult in patients with large tumors close to the anal verge. Rectal GISTs have a high rate of local recurrence regardless of the surgical procedure (21). Surgical treatment is yet to be standardized (20), but local resection, low anterior resection, abdominoperineal resection (APR), and pelvic exenteration are performed. In each procedure, the objective is complete gross resection with negative microscopic margins and without bleeding or rupture of the pseudo capsule (38).

Trans-anal resection is one of the most minimally invasive approaches, but is limited by the distance from the dentate line (39). Trans-coccygeal excision is effective for the lower rectal GISTs, but has high postoperative morbidity, with fistulae occurring in 21% of patients (40). Matsushima *et al.* described a trans-coccygeal/trans-sacral approach that is relatively less invasive and recommended it as the treatment of choice for rectal GISTs because proper bowel preparation, prophylactic antibiotics, and adequate drainage reduce postoperative complications such as fistulae (41). Kinoshita *et al.* recommended a perineal approach as an option to preserve the anal function in patients with GISTs involving the anterior wall of the lower rectum (42). For small rectal GISTs, local resection may be safe (20). In a series of seven rectal GIST patients with curative

resection before the IM era (10), two (28.6%) experienced local recurrence. One patient had undergone Hartmann's procedure for a 12-cm tumor with local recurrence in the rectum. The second, with APR for a 6 cm tumor experienced local recurrence in the presacral area. Positive resection margins are associated with poorer survival (31), and margins free of tumor cells are most important regardless of the surgical procedure. The need for wide margins is controversial (36). McCarter *et al.* reported that there was no difference in recurrence-free survival between R0 and R1 margin surgery in GIST (43). Therefore, we should select appropriate surgical procedure from the anus preserving point of view, especially for rectal GIST's patients.

Laparoscopic surgery has been successful for resection of rectal GISTs (35,44-47), including anus-preserving surgery (46). Laparoscopic colorectal surgery is beneficial because of its minimal access trauma (35). Adequate visualization of deep pelvic lesions is possible. Although the data on laparoscopic surgery for rectal GISTs are limited, this approach seems feasible, especially for small tumors (48).

Prognostic factors of rectal GISTs have been identified. In a series of 21 patients, Xiao *et al.* reported a 5-year overall survival (OS) of 46%, with NIH high risk and hematochezia as independently associated with disease-free survival (DFS) (49). In another series, tumor size >5 cm was identified as the most important determinant of survival after surgery; age [hazard ratio (HR), 2.40; 95% confidence interval (CI), 1.77–3.25], tumor size (HR, 2.24; 95% CI, 1.35–3.73) were associated with increased mortality (20). Tumor size and mitotic index have also been identified as prognostic factors (50). Gold *et al.* developed a nomogram to predict 2- and 5-year recurrence-free survival after curative surgical resection of localized GISTs (48,50). Lymph node dissection is not considered necessary because lymph node metastasis of GISTs is very rare (10).

IM therapy for advanced/metastatic GIST

IM is a selective inhibitor of transmembrane receptor KIT protein tyrosine kinases. It acts by inhibiting the proliferation of GIST cells that are stimulated by activated KIT receptors (51,52). IM is indicated for the first-line treatment of metastatic or unresectable GIST. An international, large-scale phase II study (B2222) (6) demonstrated that IM was safe and highly effective for advanced GIST. Moreover, a phase II study (STI571B1202) in Japan also found that IM was generally safe for advanced GIST (53). Kanda *et al.* reported a 5-year OS of 60.9% and median survival of 70 months with a median follow-up of 68 months after IM therapy for advanced GIST, and IM treatment was also well tolerated in Japan (54). Several studies have assessed patients with rectal GIST and have reported that IM therapy showed antitumor effects for advanced rectal GIST and common-site GISTs (19-23).

GISTs share many phenotypic features associated with various *KIT* and *PDGFRA* mutations (55). Heinrich *et al.* described the correlations of kinase genotype and clinical outcome of IM treatment of GIST (CALGB 150105) (56). The objective response rate reported as complete response (CR)/partial response (PR) was 71.7% with tumors carrying exon 11 mutations, 44.4% with exon 9 mutations, and 44.6% with wild-type tumors (56). *KIT* mutations involving codons 557–558 were reported to have a poor prognosis (57). Andersson *et al.* found that 57% of GIST patients had *KIT* mutations of exon 11, and that approximately 60% were deletion and 40% were missense or duplication mutations (55).

The *KIT* mutation genotypes in rectal GIST are not well known, but have been described in several studies, which are listed in *Figure 1* (23-26,58). As seen in GISTs developing at other sites, a large proportion (59–100%) of rectal GISTs carried exon 11 mutations. We previously characterized the *KIT* mutations in nine of 12 rectal GIST patients (unpublished data), all of whom were found to have exon 11 mutations. Okamura *et al.* have confirmed that the exon 11 mutations in colonic GIST are like those present in stomach and small intestinal GIST (59). As exon 11 *KIT* mutations are the most frequent mutation genotype in rectal GIST, IM can be considered as a first-line treatment of advanced or metastatic rectal GISTs.

Figure 2 shows an enhanced CT image of our patient with rectal GIST. The patient was a 41-year-old woman with a locally advanced rectal GIST. Laparotomy revealed that the tumor was unresectable owing to tumor rupture. The patient underwent IM therapy as primary chemotherapy. The tumor markedly shrank with 18 months of treatment; the maximum diameter changed from 14 to 5 cm, which is a 64.3% reduction. The patient then underwent secondary surgery and finally achieved complete tumor resection. Histopathological examination of the resected tumor revealed viable tumor cells that accounted for only 20% of the residual tumor.

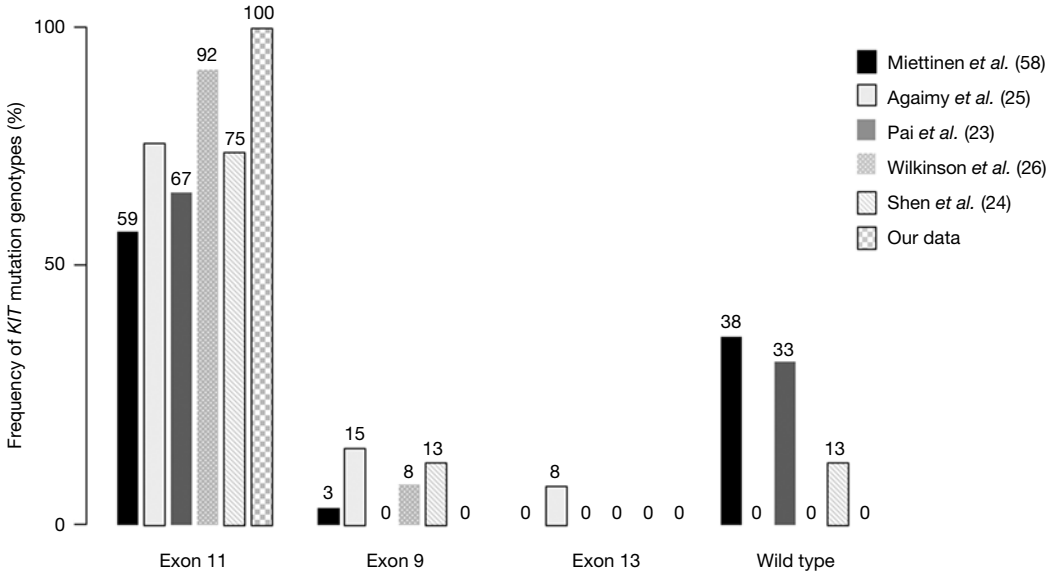

Figure 1 *KIT* mutation genotypes in rectal GISTs. A large proportion of patients have rectal GISTs with exon 11 mutations. GIST, gastrointestinal stromal tumor.

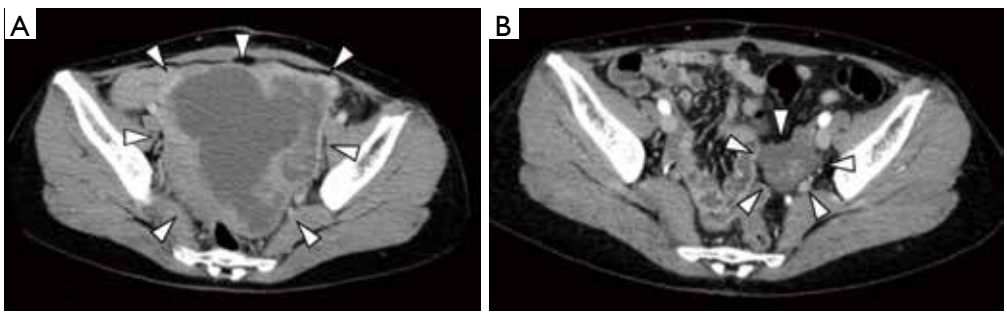

Figure 2 Enhanced pelvic CT scan of a large rectal GIST (A) with maximum diameter of 14 cm imatinib therapy and (B) 5.0 cm 18 months after initiation of the treatment (arrowheads). GIST, gastrointestinal stromal tumor; CT, computed tomography.

Combined modality therapy for rectal GIST

Curative resection is an appropriate treatment for rectal GIST, but the recurrent rate is 25% even in patients with low risk tumor (21). Perioperative treatment with IM may improve outcomes (19-23) and anus-preserving treatment is an important concern because a postoperative stoma decreases a patient's QOL. Tielen *et al.* reported that preoperative IM led to a decrease in the size of rectal GISTs, but did not lead to less extensive surgery (60). None in a series of seven rectal GIST patients with curative resection before the era of IM experienced anus-preserving surgery (10), and in another series, the anus-preserving rate was 33% in despite preoperative IM treatment (23). In *Table 3*, the anus-preserving rate with rectal GIST is summarized. Before IM treatment, the anus-preserving rate was 14.2%; after IM treatment, the rate was 33.0–94.9%. Perioperative IM treatment may be promising, but its benefit in anus-preserving surgery in rectal GIST is controversial, and requires further study.

Fujimoto *et al.* demonstrated the safety and successful use of laparoscopic intersphincteric resection of rectal GIST following IM treatment in a series of five patients (45). The benefits of laparoscopic surgery include an excellent, magnified view in the deep, confined space of the pelvic cavity that enables sphincter and continence conserving surgery (35,44). As there are few reports of the effectiveness

Table 3 Anus-preserving rate of the surgery for rectal GIST

Authors	Year	No. of patients	M/F	Age	Size (cm)	Distance from the anus (cm)	Neoadjuvant IM	Anus-preserving rate
Baik (10)	2007	7	2/5	54	6.6	4.1	0%	14.2%
Jakob (19)	2013	39	29/10	53	5.0	N/A	41.0%	94.9%
Tielen (60)	2013	32	22/10	60	9.3[†], 6.0[‡]	5.9[†], 5.3[‡]	68.8%	37.5%
Agaimy (25)	2013	15	8/7	55	4.8[§]	N/A	25.0%	75.0%
Shen (24)	2015	45	33/12	55	5.0	N/A	6.7%	71.1%
Pai (23)	2015	13	11/2	53	N/A	2.0	100%	33.0%
Wilkinson (26)	2015	19	11/8	57	7.6	N/A	78.9%	84.2%
Yasui (21)	2017	24	14/10	67	N/A	2.5	16.7%	50.0%

[†], data in patients with imatinib treatment; [‡], data in patients without imatinib treatment; [§], mean. GIST, gastrointestinal stromal tumor; IM, imatinib mesylate; N/A, not applicable.

of laparoscopic resection of rectal GIST following IM treatment, further studies are necessary.

Surgical resection combined with adjuvant IM is expected to improve not only surgical outcome but also survival one. The evidence from randomized trials supports 36 months of adjuvant IM in high risk GIST (61-63). It is important to evaluate the risk of recurrence because rectal GISTs, especially large tumors, have a high risk of recurrence, because of difficulty of curative resection. Tang *et al.* reported that IM treatment facilitated surgery for very large GISTs, avoided tumor rupture, and was associated with low surgical morbidity (64). In patients with tumors >5 cm, 5-year mortality in chemotherapy patients (79.2%) was better than that in patients without chemotherapy (51.2%, P=0.03). Hawkins *et al.* reported that preoperative IM treatment resulted in improved survival of patients with tumors >5 cm, treated with radical resection (20), but further study is necessary.

The resection with negative margins of rectal GISTs is most important; wide margins are not generally necessary if a non-residual tumor resection is obtained (36). Preoperative IM has been shown to significantly increase the achievement of negative margins and curative resection and to improve local DFS (19). In a series of 36 rectal GIST patients treated with surgery (19), five (13.9%) developed a local recurrence within a median of 12 months. The patients with local recurrence had not undergone curative resection, and had not received perioperative IM therapy. In another series of 45 patients, Shen *et al.* reported that DFS of patients with NIH high risk tumors was significantly improved by IM treatment (24), and found that risk category was the only prognostic factor independently associated with DFS (HR, 1.62; 95% CI, 1.034–2.551). Preoperative IM treatment has also been associated with an increased rate of curative resection, and may facilitate surgical procedures at critical anatomic sites, which have been associated with improved DFS (60) and improved prognosis in rectal GIST (19). The DFS benefit of perioperative IM treatment in patients with intermediate risk and high risk rectal GIST (P=0.030) was demonstrated by Liu *et al.* (31). On the other hand, when the preoperative treatment is done, there is a possibility that the preoperative treatment may affect the pathological evaluation of the tumor. In that case, we cannot make the risk evaluation appropriately.

In the era of IM, *KIT* mutation genotype analysis in pretreatment biopsy samples greatly assists the choice of treatment (19). Genotyping to identify likely non-responders is important to ensure that a window of opportunity is not missed by delaying surgery in patients who would not benefit from IM or who would benefit from dose escalation (26).

In general, radiotherapy is restricted to symptomatic palliation patient with GIST (65). However, the efficacy of radiotherapy in combination with tyrosine kinase inhibitors for metastatic or advanced GIST has been reported by some researchers (65,66). Ciresa *et al.* described that the introduction of molecularly targeted therapy combined with radiation therapy could improve the outcomes of patients with GIST (65), but the role of radiotherapy for GIST is controversial. Further studies are warranted to investigate combined modality therapy for rectal GIST patients.

Conclusions

Curative resection should be performed for localized rectal GIST. Combined modality therapy, including perioperative IM treatment, is recommended for advanced rectal GIST to facilitate anus-preserving surgery and improve the prognosis. *KIT* mutation genotype analysis before treatment is important. Further studies of perioperative treatment of patients with rectal GISTs are required to establish an appropriate treatment strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 1983;7:507-19.
2. Downs-Kelly E, Rubin BP. Gastrointestinal stromal tumors: molecular mechanisms and targeted therapies. Patholog Res Int 2011;2011:708596.
3. Joensuu H, Fletcher C, Dimitrijevic S, et al. Management of malignant gastrointestinal stromal tumours. Lancet Oncol 2002;3:655-64.
4. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
5. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660-7.
6. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
7. Lewis JJ, Brennan MF. Soft tissue sarcomas. Curr Probl Surg 1996;33:817-72.
8. Crosby JA, Catton CN, Davis A, et al. Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. Ann Surg Oncol 2001;8:50-9.
9. Varras M, Vlachakos N, Akrivis C, et al. Malignant gastrointestinal stromal tumor presenting with hemoperitoneum in puerperium: report of a case with review of the literature. World J Surg Oncol 2010;8:95.
10. Baik SH, Kim NK, Lee CH, et al. Gastrointestinal stromal tumor of the rectum: an analysis of seven cases. Surg Today 2007;37:455-9.
11. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100:162-8.
12. Miettinen M, Lasota J. Gastrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. Pol J Pathol 2003;54:3-24.
13. Miettinen M, Monihan JM, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol 1999;23:1109-18.
14. Sandrasegaran K, Rajesh A, Rydberg J, et al. Gastrointestinal stromal tumors: clinical, radiologic, and pathologic features. AJR Am J Roentgenol 2005;184:803-11.
15. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. A population-based study in western Sweden. Cancer 2005;103:821-9.
16. van der Zwan SM, DeMatteo RP. Gastrointestinal stromal tumor: 5 years later. Cancer 2005;104:1781-8.
17. Tryggvason G, Gíslason HG, Magnússon MK, et al. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer 2005;117:289-93.
18. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
19. Jakob J, Mussi C, Ronellenfitsch U, et al. Gastrointestinal stromal tumor of the rectum: results of surgical and multimodality therapy in the era of imatinib. Ann Surg Oncol 2013;20:586-92.
20. Hawkins AT, Wells KO, Krishnamurty DM, et al. Preoperative chemotherapy and survival for large anorectal gastrointestinal stromal tumors: A national analysis of 333 cases. Ann Surg Oncol 2017;24:1195-201.

21. Yasui M, Tsujinaka T, Mori M, et al. Characteristics and prognosis of rectal gastrointestinal stromal tumors: an analysis of registry data. Surg Today 2017. [Epub ahead of print].
22. Hamada M, Ozaki K, Horimi T, et al. Recurrent rectal GIST resected successfully after preoperative chemotherapy with imatinib mesylate. Int J Clin Oncol 2008;13:355-60.
23. Pai VD, Demenezes JL, Patil PS, et al. Multimodality therapy of rectal gastrointestinal stromal tumors in the era of imatinib-an Indian series. J Gastrointest Oncol 2016;7:262-8.
24. Shen C, Chen H, Yin R, et al. Clinicopathologic, surgical characteristics and survival outcomes of rectal gastrointestinal stromal tumors. Neoplasma 2015;62:610-7.
25. Agaimy A, Vassos N, Märkl B, et al. Anorectal gastrointestinal stromal tumors: a retrospective multicenter analysis of 15 cases emphasizing their high local recurrence rate and the need for standardized therapeutic approach. Int J Colorectal Dis 2013;28:1057-64.
26. Wilkinson MJ, Fitzgerald JE, Strauss DC, et al. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. Br J Surg 2015;102:965-71.
27. Kramp KH, Omer MG, Schoffski P, et al. Sphincter sparing resection of a large obstructive distal rectal gastrointestinal stromal tumour after neoadjuvant therapy with imatinib (Glivec). BMJ Case Rep 2015;2015:bcr2014207775.
28. Zhou Z, Chen Z, Chen M, et al. Clinicopathologic factors predicting outcomes in patients with gastrointestinal stromal tumors of the rectum and colon. Tumour Biol 2014;35:4357-62.
29. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459-65.
30. Farid M, Lee MJ, Chew MH, et al. Localized gastrointestinal stromal tumor of the rectum: An uncommon primary site with prominent disease and treatment-related morbidities. Mol Clin Oncol 2013;1:190-4.
31. Liu H, Yan Z, Liao G, et al. Treatment strategy of rectal gastrointestinal stromal tumor (GIST). J Surg Oncol 2014;109:708-13.
32. Choi H, Charnsangavej C, de Castro Faria S, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol 2004;183:1619-28.
33. Kalkmann J, Zeile M, Antoch G, et al. Consensus report on the radiological management of patients with gastrointestinal stromal tumours (GIST): recommendations of the German GIST Imaging Working Group. Cancer Imaging 2012;12:126-35.
34. Jiang ZX, Zhang SJ, Peng WJ, et al. Rectal gastrointestinal stromal tumors: imaging features with clinical and pathological correlation. World J Gastroenterol 2013;19:3108-16.
35. Somu K, Dashore AR, Shah AR, et al. Laparoscopic excision of large lower rectal gastrointestinal stromal tumour (GIST): A case report. J Minim Access Surg 2016;12:283-5.
36. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol 2004;11:465-75.
37. Centonze D, Pulvirenti E, Pulvirenti D'Urso A, et al. Local excision with adjuvant imatinib therapy for anorectal gastrointestinal stromal tumors. Tech Coloproctol 2013;17:571-4.
38. Chaudhry UI, DeMatteo RP. Advances in the surgical management of gastrointestinal stromal tumor. Adv Surg 2011;45:197-209.
39. Tazawa H, Hirata Y, Kuga Y, et al. Sphincter-saving resection by cluneal arched skin incision for a gastrointestinal stromal tumor (GIST) of the lower rectum: a case report. Surg Case Rep 2017;3:8.
40. Christiansen J. Excision of mid-rectal lesions by the Kraske sacral approach. Br J Surg 1980;67:651-2.
41. Matsushima K, Kayo M. Transsacral approach to resect a gastrointestinal stromal tumor in the rectum: report of two cases. Surg Today 2007;37:698-701.
42. Kinoshita H, Sakata Y, Umano Y, et al. Perineal approach for a gastrointestinal stromal tumor on the anterior wall of the lower rectum. World J Surg Oncol 2014;12:62.
43. McCarter MD, Antonescu CR, Ballman KV, et al. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. J Am Coll Surg 2012;215:53-9.
44. Kyo K, Azuma M, Okamoto K, et al. Neoadjuvant imatinib treatment and laparoscopic anus-preserving surgery for a large gastrointestinal stromal tumor of the rectum. World J Surg Oncol 2016;14:68.
45. Fujimoto Y, Akiyoshi T, Konishi T, et al. Laparoscopic sphincter-preserving surgery (intersphincteric resection) after neoadjuvant imatinib treatment for gastrointestinal stromal tumor (GIST) of the rectum. Int J Colorectal Dis

2014;29:111-6.
46. Akiyoshi T, Ueno M, Fukunaga Y, et al. Laparoscopic local excision and rectoanal anastomosis for rectal gastrointestinal stromal tumor: modified laparoscopic intersphincteric resection technique. Dis Colon Rectum 2014;57:900-4.
47. Nakamura T, Ihara A, Mitomi H, et al. Gastrointestinal stromal tumor of the rectum resected by laparoscopic surgery: report of a case. Surg Today 2007;37:1004-8.
48. Theodoropoulos DG. Gastrointestinal tumors of the colon and rectum. Clin Colon Rectal Surg 2011;24:161-70.
49. Xiao CC, Zhang S, Wang MH, et al. Clinicopathological features and prognostic factors of rectal gastrointestinal stromal tumors. J Gastrointest Surg 2013;17:793-8.
50. Gold JS, Gönen M, Gutiérrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045-52.
51. Miettinen MM, Sarlomo-Rikala M, Kovatich AJ, et al. Calponin and h-caldesmon in soft tissue tumors: consistent h-caldesmon immunoreactivity in gastrointestinal stromal tumors indicates traits of smooth muscle differentiation. Mod Pathol 1999;12:756-62.
52. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
53. Nishida T, Shirao K, Sawaki A, et al. Efficacy and safety profile of imatinib mesylate (ST1571) in Japanese patients with advanced gastrointestinal stromal tumors: a phase II study (STI571B1202). Int J Clin Oncol 2008;13:244-51.
54. Kanda T, Ishikawa T, Hirota S, et al. Prospective observational study of imatinib therapy in Japanese patients with advanced gastrointestinal stromal tumors: long-term follow-up and second malignancy. Jpn J Clin Oncol 2012;42:578-85.
55. Andersson J, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors with KIT exon 11 deletions are associated with poor prognosis. Gastroenterology 2006;130:1573-81.
56. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360-7.
57. Hohenberger P, Ronellenfitsch U, Oladeji O, et al. Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. Br J Surg 2010;97:1854-9.
58. Miettinen M, Furlong M, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. Am J Surg Pathol 2001;25:1121-33.
59. Okamura T, Kanda T, Hirota S, et al. Imatinib therapy for a patient with metastasis of colonic gastrointestinal stromal tumor: report of a case. Clin J Gastroenterol 2013;6:116-21.
60. Tielen R, Verhoef C, van Coevorden F, et al. Surgical management of rectal gastrointestinal stromal tumors. J Surg Oncol 2013;107:320-3.
61. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-104.
62. Kanda T, Nishida T, Wada N, et al. Adjuvant therapy with imatinib mesylate after resection of primary high-risk gastrointestinal stromal tumors in Japanese patients. Int J Clin Oncol 2013;18:38-45.
63. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-72.
64. Tang S, Yin Y, Shen C, et al. Preoperative imatinib mesylate (IM) for huge gastrointestinal stromal tumors (GIST). World J Surg Oncol 2017;15:79.
65. Ciresa M, D'Angelillo RM, Ramella S, et al. Molecularly targeted therapy and radiotherapy in the management of localized gastrointestinal stromal tumor (GIST) of the rectum: a case report. Tumori 2009;95:236-9.
66. Gatto L, Nannini M, Saponara M, et al. Radiotherapy in the management of gist: state of the art and new potential scenarios. Clin Sarcoma Res 2017;7:1.

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Introduction

Gastrointestinal stromal tumor of the esophagus: current issues of diagnosis, surgery and drug therapy

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Abstract: Gastrointestinal stromal tumors (GISTs) often arise in the stomach and small intestine, while esophageal GISTs are rare. Due to their rarity, clinicopathological data on esophageal GISTs are extremely limited, and this results in a lack of clear recommendations concerning optimal surgical management for esophageal GISTs. It is difficult to distinguish esophageal GIST from leiomyoma, the most frequent esophageal mesenchymal tumor, prior to resection, because the two types of tumors appear similar on computed tomography (CT), endoscopic ultrasound (EUS), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). Fine-needle aspiration biopsy (FNAB) under EUS enables definitive diagnosis, but it is often avoided because scarring could make enucleation more difficult and increase the risk of tumor dissemination by capsule destruction. Esophageal segmental and wedge resections are not usually performed due to the anatomical peculiarity of the esophagus, and the surgical options are limited to the highly invasive esophagectomy or the much less invasive surgical tumor enucleation. The decision as to which surgical procedure should be performed for esophageal GISTs is still under debate. Tumor enucleation may be permitted for smaller tumors, and esophagectomy may be recommended for larger GISTs or high-risk tumors with a high mitotic rate. The purpose of neoadjuvant imatinib administration is downsizing of the GIST to reduce the extent of resection and to reduce the risk of intraoperative complications, including tumor rupture. The efficacy of neoadjuvant/adjuvant imatinib therapy for esophageal GISTs is poorly understood, because the reports are limited to case reports or case series with small numbers. More clinicopathological data and clinical trials for esophageal GIST are expected.

Keywords: Esophagus; enucleation; esophagectomy; gastrointestinal stromal tumor (GIST)

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms arising from the digestive tract, with an annual incidence of 7 to 20 per million (1-3). GISTs are positive for c-KIT (CD117) or CD34, and they account for less than 1% of all gastrointestinal tumors. Intestinal cells of Cajal (ICCs) are known to be precursors of GISTs (4). Surgical resection is considered to be the only potentially curative treatment for localized GISTs at present (5).

GISTs often arise in the stomach and small intestine, while esophageal GISTs are extremely rare (6-12). Due to their rarity, clinicopathological data on esophageal GISTs are extremely limited, with only individual case reports or case series with small numbers.

The rarity of esophageal GISTs results in a lack of clear recommendations concerning their optimal surgical management (13). As esophageal segmental and wedge resections are not usually performed due to the anatomical

peculiarity of the esophagus, the surgical options are limited to the highly invasive esophagectomy or the much less invasive surgical tumor enucleation (6,14).

When an esophageal submucosal tumor is found, it is sometimes difficult to determine preoperatively whether the tumor is benign or malignant by imaging examinations, such as endoscopic ultrasound (EUS), computed tomography (CT), and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). Fine-needle aspiration biopsy (FNAB) under EUS provides very important information preoperatively, but it is considered a controversial technique due to the risk of tumor rupture and seeding (15). The difficulty in preoperative diagnosis makes it difficult for surgeons to select the surgical method.

Imatinib, a Bcr-Abl tyrosine kinase inhibitor (TKI), has been shown to have high efficacy in the metastatic and adjuvant settings, and the use of imatinib in neoadjuvant setting has been attempted. However, due to the rarity of esophageal GISTs, there is limited literature available regarding neoadjuvant administration of imatinib in patients with esophageal GISTs (13,16-19). Since controlled clinical trials for esophageal GISTs are not available, the best surgical procedure and the impact of adjuvant or neoadjuvant imatinib therapy have not been established.

This article provides updates on esophageal GISTs, focusing particularly on preoperative diagnosis and surgical treatment.

Epidemiology and clinical presentation

GISTs occur predominantly in the stomach (60–70%), small intestine (20–30%), and colorectum (5–10%) (6-11). Esophageal GISTs are extremely uncommon, accounting for fewer than 5% of all GISTs (9,12).

Leiomyomas are the most common mesenchymal tumors of the esophagus, and GISTs account for about 25% of mesenchymal esophageal tumors (10).

The clinical features of esophageal GISTs are not well-known. Lott *et al.* summarized 55 cases of esophageal GIST and reported that in comparison to gastric GISTs, esophageal GISTs occurred significantly more frequently in men, as well as in patients younger than 60 years at diagnosis (2).

The most common location for esophageal GISTs is the lower esophagus, followed by the middle esophagus, and GISTs in the upper esophagus are rare (2,20,21). Radenkovic *et al.* found that ICCs were abundant in the lower esophagus, less numerous in the middle region, and rare in the upper part (22). The reported distribution of ICCs was in accordance with the distribution of esophageal GISTs (20).

Esophageal GISTs were often found accidentally on esophagoscopy or barium esophagography (15). As GISTs grow in the esophagus, patients present with various symptoms. Dysphagia (36–51%) is the most frequent symptom, followed by weight loss (20%), chest pain (8–15%), and bleeding (1–10%) (2,20,21).

Diagnosis of esophageal GISTs

When a submucosal tumor is found in the esophagus, the differential diagnosis of an esophageal GIST includes both malignant and benign tumors, including leiomyoma, hemangioma, schwannoma, leiomyosarcoma, and papillary epithelioma (1). It is unfortunately difficult to distinguish esophageal leiomyoma from GIST prior to resection, because the two types of tumors appear similar on CT and EUS (23).

FDG-PET

Recently, the use of FDG-PET for GISTs has been reported. The maximum standardized uptake value (SUVmax) on FDG-PET is considered to correlate with the degree of malignancy of GIST, but the definitive diagnosis is difficult (1,24,25). Dendy *et al.* reported that esophageal leiomyomas also showed a wide range of SUVmax values, from 3.8 to 13.4 (23). The PET-avidity of benign tumors limits the role of FDG-PET in the differential diagnosis of submucosal tumors of the esophagus. On the other hand, FDG-PET is known to be useful for evaluating postoperative recurrence and the response of GISTs to chemotherapy (1,24,25).

Magnetic resonance imaging (MRI)

Recent studies have shown the utility of diffusion-weighted imaging (DWI) with the apparent diffusion coefficient (ADC) in differential diagnosis between uterine leiomyomas and leiomyosarcomas (23,26,27). DWI with the ADC might be useful as a new modality in the preoperative diagnosis of esophageal submucosal tumors.

EUS and FNAB

The main purpose of EUS is to observe the size, shape, and

intratumoral character of tumors and their relationships within the layers of the bowel wall (28). Unfortunately, distinguishing GISTs from leiomyomas by EUS findings is not generally possible (23).

Pre-therapeutic histological and genetic diagnosis is essential for TKI treatment for GISTs (2). Ultrasound-guided FNAB or core biopsy is reported to be a secure procedure that enables differential diagnosis of mesenchymal tumors including GIST (14,29). In the preoperative situation, use of biopsy or FNAB is under debate (6). FNAB is often avoided with submucosal lesions because scarring could make enucleation more difficult, and there is a risk of tumor dissemination by capsule destruction (15,21,23). On the other hand, some have reported that the indications for preoperative biopsies are tumors above 2 cm in size with observed enlargement and/or intended neoadjuvant TKI treatment (2,6,14,29). In fact, FNAB seems to be performed frequently in clinical practice, especially for larger tumors. According to the NCCN Task Force Report, biopsy may not be necessary if the tumor is easily resectable and preoperative therapy is not required (3).

Pathological diagnosis and gene expression profiling

GISTs can be pathologically classified into three types: spindle cell, epithelioid cell, and mixed cell types (30). An immunohistochemical panel including KIT (CD117), DOG1, CD34, smooth muscle actin (SMA), desmin, and S100 protein is used for distinguishing GISTs from other tumors (31-33).

Frozen section examination is often used for intraoperative pathological diagnosis to guide the resection, but it may not be able to provide a definitive diagnosis because of the histologic similarities between GISTs and other spindle cell tumors (23).

The current risk stratification systems are based on tumor size, mitotic activity, tumor rupture, and tumor location (34-37). However, when these systems were established, only a few esophageal GISTs were included in risk assessment, and the accuracy of these systems for determining the prognosis of patients with esophageal GISTs is unknown (13).

Concerning the mutation status of esophageal GISTs, Kang *et al.* reported that most KIT mutations were detected in exon 11, the mutation spectrum of esophageal GISTs resembled that of gastric GISTs in their case series, and all cases with recurrent disease demonstrated KIT exon 11 deletions affecting codons 557 and/or 558 (31).

Surgical therapy for esophageal GISTs

The rarity of esophageal GISTs results in a lack of clear recommendations concerning their optimal surgical management (13). For localized GISTs, complete surgical resection is the treatment of choice (15). There have been a few reports regarding positive lymph node metastasis in esophageal GISTs, but GISTs rarely metastasize to lymph nodes, and routine lymphadenectomy is not recommended (38,39).

Although gastric and intestinal GISTs can be removed with segmental or wedge resections, resections for esophageal GISTs are essentially limited to enucleation or highly invasive esophagectomy due to the anatomical peculiarity of the esophagus (14). Which surgical procedure should be performed for esophageal GISTs is still under debate (2,6,40,41). With regard to postoperative morbidity and mortality, tumor enucleation seems a better option, particularly in patients with comorbidities (2,6,14,40). Generally, enucleation of esophageal GISTs is permitted for smaller tumors (2–5 cm in size), whereas esophagectomy is recommended for GISTs above 9 cm in size (2,6,14,42). The oncological outcomes of these two procedures are reported to be similar with proper patient selection (6,13,14,42-44).

Recently, thoracoscopic esophagectomy and enucleation have been successfully performed for esophageal GISTs (13,25,45). As minimally invasive esophagectomy has been performed widely for esophageal cancer, this technique can be applied for esophageal GISTs. The less invasive surgery might expand the indications for surgery, especially for smaller tumors and poor risk patients.

Neoadjuvant therapy for esophageal GISTs

There is only a little evidence based on clinical trials concerning neoadjuvant imatinib therapy for GISTs (46). In theory, downsizing of GIST by preoperative administration of imatinib seems attractive to reduce the extent of resection, especially in patients with GISTs of the esophagus, duodenum, and rectum, because wide resection may result in loss of function and greatly affect postoperative quality of life in these patients.

Concerning the duration of preoperative administration of imatinib, it has been reported to range from a few days to more than 1 year (13,47-49). The optimal duration of preoperative imatinib is considered to be as long as 6 to 12 months to obtain a maximal response prior to surgery (3).

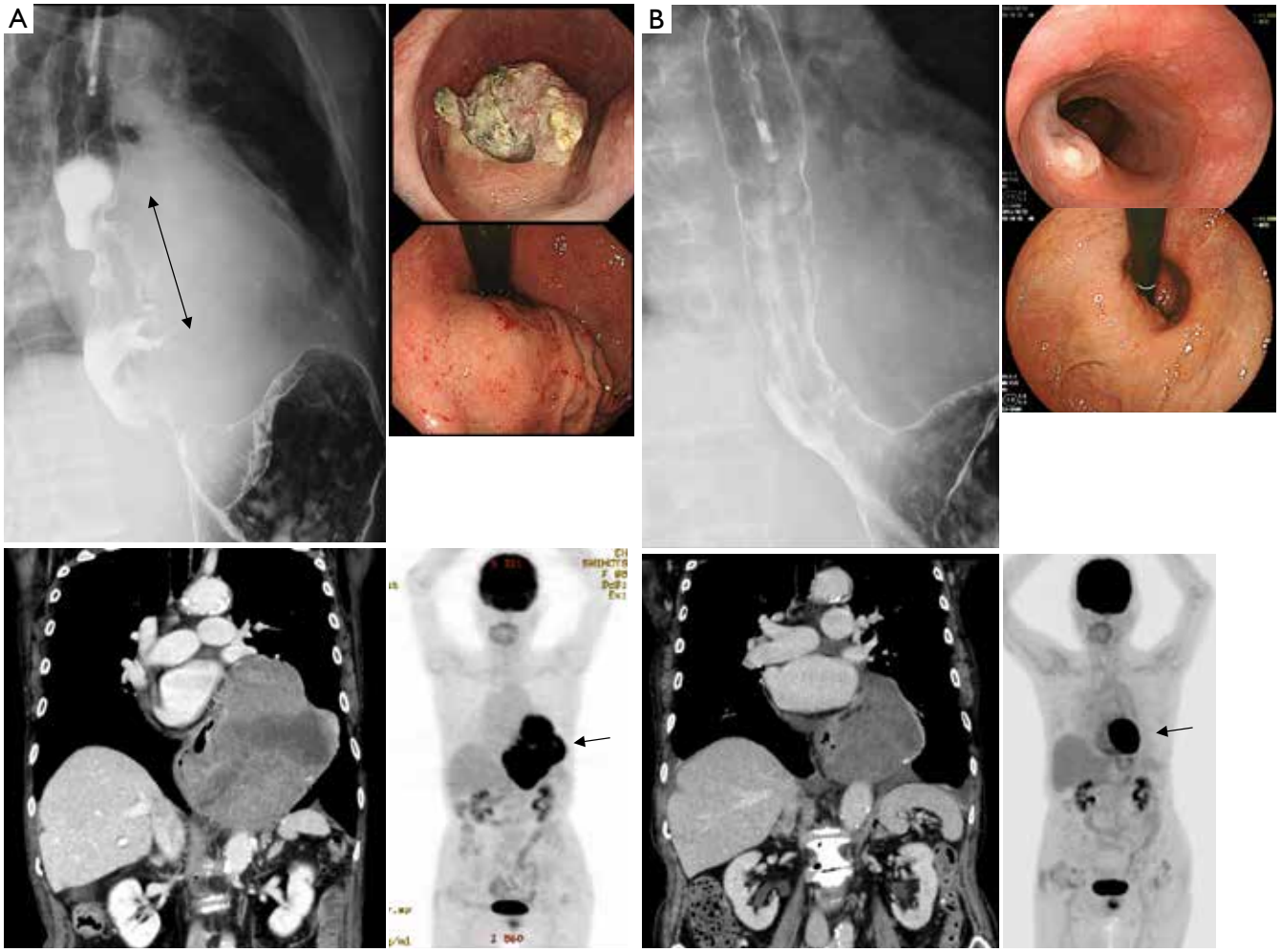

Figure 1 Esophagography, upper gastrointestinal endoscopy, CT, and FDG-PET before (A) and after (B) neoadjuvant imatinib therapy. Before imatinib treatment (A), a 10-cm-long defect in the lower esophagus is observed on esophagography. A submucosal tumor with ulceration is found in the lower esophagus by upper gastrointestinal endoscopy. CT shows a large tumor in the posterior mediastinum with a maximum diameter of 150 mm. SUVmax of the tumor is 9.9. After 3-month treatment with imatinib, the tumor is reduced, and the SUVmax has decreased to 2.0. (B). CT, computed tomography; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; SUVmax, maximum standardized uptake value.

However, caution is needed during preoperative imatinib therapy, because it has a risk of rupture or bleeding due to tumor necrosis and cystic changes (1,46).

Kang *et al.* suggested that neoadjuvant imatinib treatment can be considered in patients with high mitotic rates and/or larger tumor sizes to obtain negative microscopic margins (R0 resection) and to reduce the risk of intraoperative complications, including tumor rupture (31).

There is limited literature available regarding neoadjuvant administration of imatinib in patients with esophageal GISTs, and the usefulness of neoadjuvant imatinib has been reported (13,16,18,19,50,51).

We treated a patient with a large esophageal GIST with neoadjuvant imatinib followed by surgical resection (*Figures 1,2*). An 86-year-old woman was diagnosed with a submucosal tumor of the lower esophagus just above the esophagogastric junction by upper gastrointestinal endoscopy. The maximum diameter on CT was 150 mm, and EUS-FNAB showed a spindle cell tumor with c-KIT (++), CD34 (+++), SMA (+), and S-100 protein (–). Based on the pathological findings, GIST of the esophagus was diagnosed. Gene mutation analysis showed KIT exon

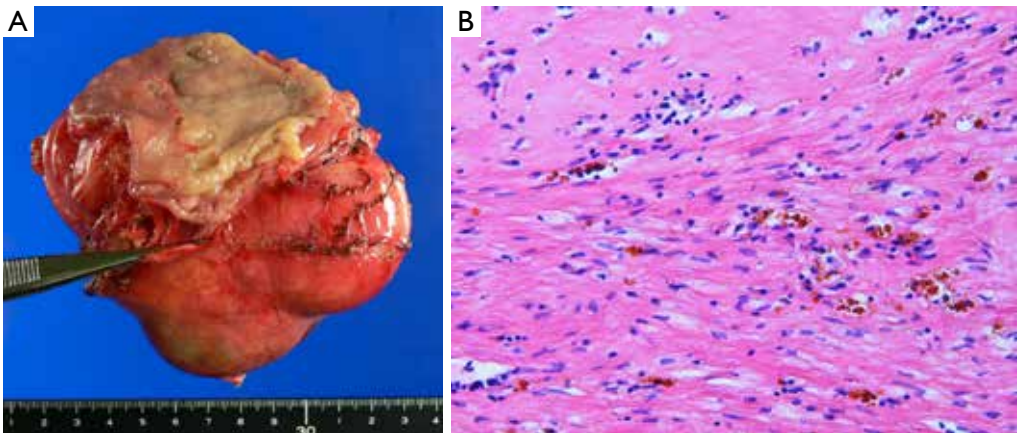

Figure 2 Gross and microscopic findings of the resected specimen. A solid tumor measuring 110×75×50 mm^3 in size has been resected (A); the pathological examination shows that preoperative imatinib therapy caused about 90% of the tumor to disappear (magnification, ×200) (B).

11 deletion. She received imatinib therapy (400 mg/day) because of her high age and because she did not want surgical resection. After 3 months of imatinib therapy, she developed severe edema of the lower extremities and an eruption as adverse effects of imatinib. The tumor decreased to 87 mm on CT, and the dysphagia disappeared. Since her general condition was such that she could tolerate surgery, she underwent lower esophagectomy and proximal gastrectomy by left thoracotomy and laparotomy. Esophagogastrostomy was performed in the posterior mediastinum. Her postoperative course was excellent, and she was discharged on the 18th postoperative day. Pathological examination showed that about 90% of the tumor had disappeared with preoperative imatinib therapy.

Adjuvant therapy for esophageal GISTs

Adjuvant imatinib therapy following resection of GISTs has been shown to prevent recurrences and prolong survival in many clinical studies (52,53). However, esophageal GISTs were not included in these studies, and more comparative studies are needed to determine the effectiveness of adjuvant imatinib therapy (1).

Clinical outcome of esophageal GISTs

Clinical outcomes of esophageal GISTs from large case series studies were summarized in *Table 1*.

Nakano *et al.* summarized the clinical outcomes of 153 patients with esophageal GISTs reported in the literature (21). Recurrence occurred in 23 of 139 patients (16.5%) after surgery, and metastatic disease was more common than local recurrence (18 *vs.* 5 patients). They also reported that the average time to recurrence was 40 months, and the 5-year disease-free survival (DFS) and overall survival (OS) were 57% and 89%, respectively. They emphasized the need for long-term follow-up, because recurrence occurred even 5 years after surgery, unlike esophageal cancer.

Feng *et al.* also summarized 135 cases of reported esophageal GISTs (20). They reported that 5-year DFS and disease-specific survival (DSS) were 65.1% and 65.9%, respectively. The most common site of distant metastasis was liver, followed by lung, thoracic cavity, pleura, peritoneum, and subcutaneous. On multivariate analysis, tumor size was the only independent predictor of the prognosis of esophageal GISTs. In addition, they compared the prognosis of esophageal GISTs with gastric GISTs after matching of tumor size, mitotic index, and adjuvant imatinib therapy. DFS and DSS were significantly lower for esophageal GISTs than for gastric GISTs.

Lott *et al.* analyzed 55 cases of esophageal GISTs and compared their prognosis with gastric GISTs (2). Esophageal GISTs were generally classified more frequently as high-risk GISTs, and 5-year DSS, DFS, and OS were 50.9%, 65.3%, and 48.3%, respectively. Esophageal GISTs showed a significantly worse prognosis than gastric GISTs.

Kukar *et al.* also compared 29 esophageal GISTs with 2,658 gastric GISTs from the SEER database (54). On univariate analysis, 5-year DSS was worse for esophageal GISTs (in both all patients and the resected group), but this was not significant when adjusted for covariates.

Table 1 Summary of the clinical outcomes of esophageal GISTs from large case series studies

Studies	N	Study design	Age (mean)	Size (cm) (mean ± SD)	Surgery (n)	Adjuvant TKI	Recurrence (n)	5-year-DFS (%)	5-year-DSS (%)	5-year-OS (%)
Nakano (21)	153	Literature review	61.0	7.3±4.1	139	–	23 of 139 (local 5, distant 18)	57.0%	–	88.7%
Feng (20)	135	Literature review	58.6	7.3±3.1	125	(+) 38, (–) 95	22 of 97	65.1%	65.9%	–
Lott (2)	55	Ulmer GIST registry, literature review	60.3	8.0±4.8	33 (enucleation 14, esophagectomy 19)	(+) 6, (–) 49	14 of 55	65.3%	50.9%	48.3%
Kukar (54)	29	SEER database	65.6	–	16	–	9 (disease specific death)	–	65.0%	88.7%
Kang (31)	27	Case series (multicenter)	56.0	5.6±3.1	25 (enucleation 15, esophagectomy 10)	No adjuvant TKI	9 of 22 (local 5, distant 4)	–	–	–

TKI, thymidine kinase inhibitor; DFS, disease free survival; DSS, disease specific survival; OS, overall survival.

Kang *et al.* performed clinicopathological and molecular analyses of 27 esophageal GIST cases (31). Surgery was performed in 25 patients (10 esophagectomy and 15 enucleation), and large tumor size (≥10 cm), high mitotic rate (>5/5 mm^2), presence of a deletion mutation in KIT exon11 involving codons 557–558, and a positive microscopic margin were associated with recurrence and metastasis.

Conclusions

Esophageal GISTs are rare (fewer than 5% of all GISTs), which results in a lack of evidence concerning their optimal management.

When esophageal submucosal tumors are found, distinguishing GIST from leiomyoma, hemangioma, schwannoma, leiomyosarcoma, and papillary epithelioma is important to select treatment. Unfortunately, the differential diagnosis of an esophageal GIST is not easy. FNAB under EUS-guidance gives a definite diagnosis, but there is a risk of tumor dissemination by capsule destruction and scarring of the esophageal mucosa, which might make enucleation difficult, in the preoperative situation. However, FNAB may be indicated in tumors above 2 cm in size with observed enlargement and for whom neoadjuvant TKI treatment is intended. FDG-PET is a useful modality because SUVmax is reported to correlate with the degree of malignancy of GISTs, but it seems difficult to distinguish GISTs from other esophageal mesenchymal tumors including leiomyomas, which also show a wide range of SUVmax values. MRI might be a promising modality for the differential diagnosis of esophageal mesenchymal tumors.

Surgical resection is the only potentially curative treatment for localized GISTs. Unlike for gastric and intestinal GISTs, the surgical methods for esophageal GISTs are essentially limited to enucleation or highly invasive esophagectomy. Routine lymphadenectomy is not recommended, because GISTs rarely metastasize to lymph nodes. It is difficult to choose between enucleation and esophagectomy in individual patients with esophageal GISTs; enucleation may be permitted for smaller tumors (2–5 cm in size) or poor risk patients with comorbidities, whereas esophagectomy may be recommended for larger GISTs above 5 cm in size and very high-risk lesions with a high mitotic rate.

Use of imatinib preoperatively and/or postoperatively is a promising strategy. The purpose of neoadjuvant imatinib administration is downsizing of the GIST to reduce the extent of resection and to reduce the risk of intraoperative complications, including tumor rupture. Since reports of the efficacy of neoadjuvant/adjuvant imatinib treatment for esophageal GISTs are limited to case series or case reports, evaluation of its efficacy still needs to be addressed.

In conclusion, as mentioned above, because of the rarity of esophageal GIST, its properties, malignancy, imaging

diagnosis, optimal surgical method, and the efficacy of neoadjuvant/adjuvant therapy are poorly understood. More clinicopathological data and clinical trials involving esophageal GISTs are expected.

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Footnote

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References

1. Zhang FB, Shi HC, Shu YS, et al. Diagnosis and surgical treatment of esophageal gastrointestinal stromal tumors. World J Gastroenterol 2015;21:5630-4.
2. Lott S, Schmieder M, Mayer B, et al. Gastrointestinal stromal tumors of the esophagus: evaluation of a pooled case series regarding clinicopathological features and clinical outcome. Am J Cancer Res 2014;5:333-43.
3. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41; quiz S42-4.
4. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
5. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii21-6.
6. Lee HJ, Park SI, Kim DK, et al. Surgical resection of esophageal gastrointestinal stromal tumors. Ann Thorac Surg 2009;87:1569-71.
7. Abraham SC, Krasinskas AM, Hofstetter WL, et al. "Seedling" mesenchymal tumors (gastrointestinal stromal tumors and leiomyomas) are common incidental tumors of the esophagogastric junction. Am J Surg Pathol 2007;31:1629-35.
8. Ji F, Wang ZW, Wang LJ, et al. Clinicopathological characteristics of gastrointestinal mesenchymal tumors and diagnostic value of endoscopic ultrasonography. J Gastroenterol Hepatol 2008;23:e318-24.
9. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130:1466-78.
10. Miettinen M, Sarlomo-Rikala M, Sobin LH, et al. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. Am J Surg Pathol 2000;24:211-22.
11. Søreide K, Sandvik OM, Søreide JA, et al. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. Cancer Epidemiol 2016;40:39-46.
12. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. Lancet 2007;369:1731-41.
13. Neofytou K, Costa Neves M, Giakoustidis A, et al. Effective Downsizing of a Large Oesophageal Gastrointestinal Stromal Tumour with Neoadjuvant Imatinib Enabling an Uncomplicated and without Tumour Rupture Laparoscopic-Assisted Ivor-Lewis Oesophagectomy. Case Rep Oncol Med 2015;2015:165736.
14. Blum MG, Bilimoria KY, Wayne JD, et al. Surgical considerations for the management and resection of esophageal gastrointestinal stromal tumors. Ann Thorac Surg 2007;84:1717-23.
15. Nemeth K, Williams C, Rashid M, et al. Oesophageal GIST-A rare breed case report and review of the literature. Int J Surg Case Rep 2015;10:256-9.
16. Yanagawa S, Tanabe K, Suzuki T, et al. A large esophageal gastrointestinal stromal tumor that was successfully resected after neoadjuvant imatinib treatment: case report. World J Surg Oncol 2014;12:47.
17. Tirumani SH, Shinagare AB, Jagannathan JP, et al. Radiologic assessment of earliest, best, and plateau response of gastrointestinal stromal tumors to neoadjuvant imatinib prior to successful surgical resection. Eur J Surg Oncol 2014;40:420-8.
18. Fiore M, Palassini E, Fumagalli E, et al. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). Eur J Surg Oncol 2009;35:739-45.
19. Shinagare AB, Zukotynski KA, Krajewski KM, et al. Esophageal gastrointestinal stromal tumor: report of 7 patients. Cancer Imaging 2012;12:100-8.
20. Feng F, Tian Y, Liu Z, et al. Clinicopathologic Features and Clinical Outcomes of Esophageal Gastrointestinal Stromal Tumor: Evaluation of a Pooled Case Series. Medicine (Baltimore) 2016;95:e2446.
21. Nakano A, Akutsu Y, Shuto K, et al. Giant esophageal

gastrointestinal stromal tumor: report of a case. Surg Today 2015;45:247-52.
22. Radenkovic G, Ilic I, Zivanovic D, et al. C-kit-immunopositive interstitial cells of Cajal in human embryonal and fetal oesophagus. Cell Tissue Res 2010;340:427-36.
23. Dendy M, Johnson K, Boffa DJ. Spectrum of FDG uptake in large (>10 cm) esophageal leiomyomas. J Thorac Dis 2015;7:E648-51.
24. Park JW, Cho CH, Jeong DS, et al. Role of F-fluoro-2-deoxyglucose Positron Emission Tomography in Gastric GIST: Predicting Malignant Potential Pre-operatively. J Gastric Cancer 2011;11:173-9.
25. Isaka T, Kanzaki M, Onuki T. Long-term survival after thoracoscopic enucleation of a gastrointestinal stromal tumor arising from the esophagus. J Surg Case Rep 2015;2015. pii: rju155.
26. Tasaki A, Asatani MO, Umezu H, et al. Differential diagnosis of uterine smooth muscle tumors using diffusion-weighted imaging: correlations with the apparent diffusion coefficient and cell density. Abdom Imaging 2015;40:1742-52.
27. Sato K, Yuasa N, Fujita M, et al. Clinical application of diffusion-weighted imaging for preoperative differentiation between uterine leiomyoma and leiomyosarcoma. Am J Obstet Gynecol 2014;210:368.e1-368.e8.
28. Săftoiu A. Endoscopic ultrasound-guided fine needle aspiration biopsy for the molecular diagnosis of gastrointestinal stromal tumors: shifting treatment options. J Gastrointestin Liver Dis 2008;17:131-3.
29. Stelow EB, Stanley MW, Mallery S, et al. Endoscopic ultrasound-guided fine-needle aspiration findings of gastrointestinal leiomyomas and gastrointestinal stromal tumors. Am J Clin Pathol 2003;119:703-8.
30. Dei Tos AP, Laurino L, Bearzi I, et al. Gastrointestinal stromal tumors: the histology report. Dig Liver Dis 2011;43 Suppl 4:S304-9.
31. Kang G, Kang Y, Kim KH, et al. Gastrointestinal stromal tumours of the oesophagus: a clinicopathological and molecular analysis of 27 cases. Histopathology 2017;71:805-12.
32. Yamaguchi U, Hasegawa T, Masuda T, et al. Differential diagnosis of gastrointestinal stromal tumor and other spindle cell tumors in the gastrointestinal tract based on immunohistochemical analysis. Virchows Arch 2004;445:142-50.
33. Kang GH, Srivastava A, Kim YE, et al. DOG1 and PKC-θ are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors. Mod Pathol 2011;24:866-75.
34. Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-74.
35. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.
36. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459-65.
37. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
38. Matsumoto S, Takayama T, Wakatsuki K, et al. An esophageal gastrointestinal stromal tumor with regional lymph node metastasis. Esophagus 2010;7:115-8.
39. Masuda T, Toh Y, Kabashima A, et al. Overt lymph node metastases from a gastrointestinal stromal tumor of the esophagus. J Thorac Cardiovasc Surg 2007;134:810-1.
40. Coccolini F, Catena F, Ansaloni L, et al. Esophagogastric junction gastrointestinal stromal tumor: resection vs enucleation. World J Gastroenterol 2010;16:4374-6.
41. Peparini N, Carbotta G, Chirletti P. Enucleation for gastrointestinal stromal tumors at the esophagogastric junction: is this an adequate solution? World J Gastroenterol 2011;17:2159-60.
42. Jiang P, Jiao Z, Han B, et al. Clinical characteristics and surgical treatment of oesophageal gastrointestinal stromal tumours. Eur J Cardiothorac Surg 2010;38:223-7.
43. Robb WB, Bruyere E, Amielh D, et al. Esophageal gastrointestinal stromal tumor: is tumoral enucleation a viable therapeutic option? Ann Surg 2015;261:117-24.
44. von Rahden BH, Stein HJ, Feussner H, et al. Enucleation of submucosal tumors of the esophagus: minimally invasive versus open approach. Surg Endosc 2004;18:924-30.
45. Koyanagi K, Nakagawa M, Ozawa S, et al. Thoracoscopic enucleation for small-sized gastrointestinal stromal tumor of the esophagus: report of two cases. Esophagus 2010;7:219-24.
46. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009;99:42-7.
47. Bednarski BK, Araujo DM, Yi M, et al. Analysis of prognostic factors impacting oncologic outcomes after neoadjuvant tyrosine kinase inhibitor therapy

for gastrointestinal stromal tumors. Ann Surg Oncol 2014;21:2499-505.
48. McAuliffe JC, Hunt KK, Lazar AJ, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol 2009;16:910-9.
49. Tielen R, Verhoef C, van Coevorden F, et al. Surgery after treatment with imatinib and/or sunitinib in patients with metastasized gastrointestinal stromal tumors: is it worthwhile? World J Surg Oncol 2012;10:111.
50. Kobayashi H, Kiguchi G, Miki A, et al. A case report of giant esophageal gastrointestinal stromal tumor surgically resected after preoperative imatinib treatment. Esophagus 2011;8:119-24.
51. Sato H, Kanda T, Hirota S, et al. Surgical resection of gastrointestinal stromal tumor of esophagus following preoperative imatinib treatment: a case report. Esophagus 2010;7:65-9.
52. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-104.
53. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-72.
54. Kukar M, Kapil A, Papenfuss W, et al. Gastrointestinal stromal tumors (GISTs) at uncommon locations: a large population based analysis. J Surg Oncol 2015;111:696-701.

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Introduction

Asian consensus guidelines for gastrointestinal stromal tumor: what is the same and what is different from global guidelines

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Abstract: There are some disparities between the clinical practice and profiles of cancer in Asia and those in Europe & North America. In Asia, surgical oncologists still have a major role in the multidisciplinary therapy of gastrointestinal stromal tumor (GIST), whereas medical oncologists hold this status in the West. Although the incidence of clinical GIST is considered similar between the two areas, small gastric GISTs are more frequently treated by surgery in East Asia compared with Europe & North America. The diagnosis and treatment of small submucosal tumors (SMTs), including GIST, is important in Asian clinical practice guidelines for GIST. Most items of Asian and Western GIST guidelines are very similar. There are slight differences between the two guidelines in the degree of recommendation, which may come from disparities of clinical practice and available medicines. Importantly, most clinical evidence in the GIST guidelines has been established by clinical trials conducted in Western countries, and the number of clinical trials is still limited in Asia, suggesting that Asian GIST patients may have limited access to investigational drugs after standard therapy. Finally, both Asian and Western GIST guidelines are well-harmonized in some parts, and their contents may reflect the medical circumstances of each region.

Keywords: Gastrointestinal stromal tumor (GIST); guidelines; evidence-based; submucosal tumor (SMT)

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Introduction

Gastrointestinal stromal tumor (GIST) is a potentially malignant tumor and the most frequent type of sarcoma in the gastrointestinal tract. The discovery of driver mutations in the *KIT* or *PDGFRA* (platelet-derived growth factor receptor alpha) gene and subsequent development of molecularly targeted therapy based on molecular mechanisms of tumor cell proliferation have revolutionized the diagnosis and treatment of GIST, which facilitates scientific research, as well as the publication of clinical guidelines (1,2). Today, a multidisciplinary approach with surgical and medical oncologists, pathologists, gastroenterologists, and radiologists is mandatory to provide optimal treatment for GIST patients. Evidence-based diagnosis and treatment according the guidelines has improved the prognosis of cancer patients (3,4). The clinical guidelines of GISTs were first published by the National Comprehensive Cancer Network (NCCN) in 2004 (5), and by the European Society of Medical Oncology (ESMO) in 2005 (6), followed by clinical practice guidelines in various countries around the world (7-12). Most evidence has been established in Western countries, and Asian patients have supplied limited data on the diagnosis and treatment of GIST. There still exist some differences in the clinical practice and disease spectrum between European & North American countries and Asian countries, especially East Asian countries (12). The GIST experts in Republic of Korea, China and Japan consider that some aspects of Western guidelines are not always applicable to Asian patients and that clinical practice in East Asia is somewhat different from that of Western countries. Thus, they have published the Asian consensus GIST guidelines (12).

In this review, we will summarize the clinical practice of both areas and then discuss the similarities and disparities

between Western and Asian GIST guidelines, although the fundamental approaches to the diagnostic and treatment strategy for GIST are very similar.

General considerations on clinical practice for GIST in Asia and Europe & North America

The oncological disease spectrum is different between Asia and the West (13,14). In Western countries, breast cancer, colon cancer and prostate cancer are frequent, whereas gastric cancer, esophageal cancer and hepatocellular carcinoma are dominant in East Asian countries. Even in colon cancer and gastric cancer, there still exist some differences in sub-location and histology; right colon cancer is relatively prevalent in the West vs left colon cancer and rectal cancer in the East; proximal gastric cancer with poorly differentiated adenocarcinoma is relatively common in the West vs distal gastric cancer with well differentiation in the East. This may lead to some differences in cancer screening. Gastric cancer screening is emphasized and flourishes in East Asia, while the same holds for health examinations for breast and colon cancer in Western countries. In clinical practice, medical oncologists are crucial and are widely involved in cancer treatment in the West, whereas in the East, surgical oncologists still cover a broad area of oncology because of the limited number of medical oncologists. Surgical oncologists may have a significant role in adjuvant therapy, neoadjuvant therapy and sometimes even imatinib therapy for advanced and/or metastatic GIST.

The true incidence of clinical GIST, which may be symptomatic GIST requiring immediate medical and/or surgical therapy, GIST with considerable recurrent-risk, or metastatic and/or recurrent disease, is considered to be no different between Asian and Western countries (1,15). It is estimated to be no more than 10/million people/year (1,2,6). There are, however, reports describing a high incidence of small GISTs, including mini-GISTs and micro-GISTs (16-21). Almost all these small GISTs show morphologically and clinically indolent features (20,21). Pathological examinations of the stomach and small intestine of middle-aged persons have revealed frequent findings (10% to 35%) of pathological GISTs (micro-GISTs) less than 1 cm in diameter (16-18). Others indicated that fewer than one in one thousand middle-aged adults may potentially have small GISTs less than 2 cm (mini-GISTs) (22). Most of them neither grow nor become clinical GISTs, although the distinction of potentially malignant GISTs from indolent ones appears to be extremely difficult even in pathological examinations. Thus, the true incidence of biological GIST is not known.

In East Asia, gastric cancer screening sometimes finds an asymptomatic submucosal tumor (SMT) less than 5 cm, which may be pathologically diagnosed as GIST after surgical resection. Thus, the incidence and relative frequency of gastric GIST are higher in East Asian countries compared with Western countries, especially for asymptomatic and small gastric GIST (2,9,22). These circumstances may result in the relatively good prognosis of Asian GIST patients (15). The frequent finding of small and asymptomatic SMTs may also facilitate endoscopic resection of these SMTs and GISTs in East Asia (23,24). Based on the above circumstances, GIST clinical guidelines may start from the diagnosis and treatment of SMT in Asia (*Figure 1*) (2,9). Small gastric SMTs less than 2 cm without malignant features could be followed by periodical endoscopic ultrasonography (EUS) until the tumors become symptomatic and/or show malignant features in endoscopy and/or EUS. Malignant features of SMT (or GIST) include ulcer formation, internal heterogeneity in EUS, irregular margin, and increase in size during follow-up (2,9,22). These approaches may be applicable for histologically proven gastric GISTs, although the decision should be shared with patients. These decision-making processes are similar to the NCCN guidelines but may be slightly different from the ESMO guidelines (6,8). When small gastric SMTs have malignant features, the guidelines recommend further examination, for example, histological diagnosis by EUS-guided fine-needle aspiration (EUS-FNA) or surgical removal (2,6,9). When EUS-FNA reveals histological GIST, surgery is recommended. For non-gastric GISTs, all guidelines recommend surgical resection regardless of tumor size because recurrence risk and disease progression may be high and frequent in non-gastric GIST, even if it is small (2,6,8,12).

Pathological diagnosis & genetic analysis

Pathological diagnosis is similar between Asia and the West. In Asian GIST guidelines, the algorithm of the pathological diagnosis is explicitly presented as shown in the upper panel of *Figure 2* (2,9,12). Asian GIST guidelines recommend KIT and DOG1 immunostaining and, in addition, genotyping, when required. The guidelines do not always recommend CD34 immunostaining because CD34 is not specific for GIST. In clinical practice, genotyping

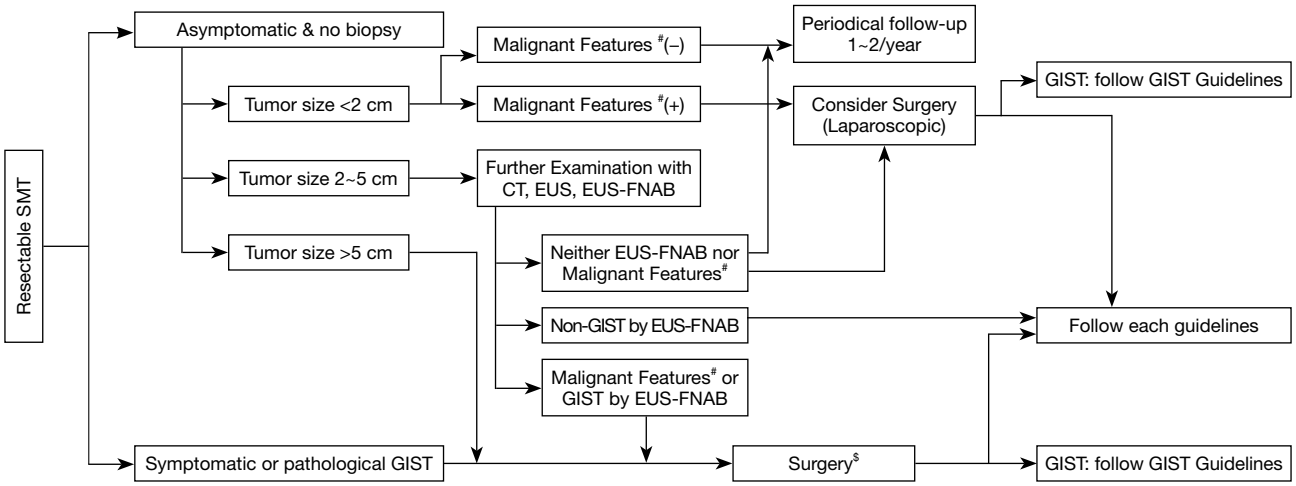

Figure 1 Diagnostic and therapeutic strategy for small submucosal tumors in the gastrointestinal tract. Small submucosal tumors (SMTs) may necessitate surgery when they produce symptoms or when they have malignant features. The strategy shows that the diagnosis and treatment of asymptomatic and pathologically undetermined SMTs are divided by size. A part of the algorithm is similar to the Japanese clinical practice guidelines for GIST (9). #, Malignant features include ulceration, irregular margins, inhomogeneous parenchyma in endoscopy and EUS and tumor growth during follow-up; $, in this situation, imatinib neoadjuvant therapy may be considered when a large tumor is preoperatively diagnosed as GIST. GIST, gastrointestinal stromal tumor; CT, computed tomography; EUS, endoscopic ultrasonography; EUS-FNAB, endoscopic ultrasonography-guided fine-needle aspiration biopsy.

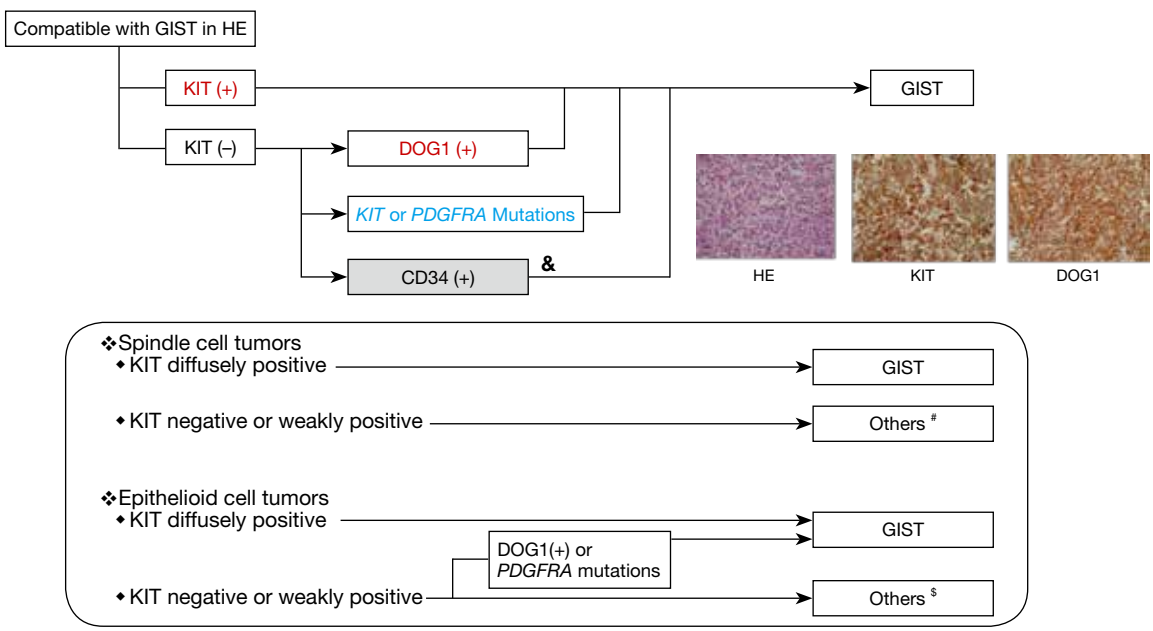

Figure 2 The algorithm of pathological diagnosis of GIST. &, CD34 is not specific for GIST; #, others include leiomyoma & leiomyosarcoma (desmin-positive), schwannoma (S-100-positive), solitary fibrous tumor (CD34-positive and nuclear STAT6-positive), desmoid (nuclear beta-catenin-positive), inflammatory myofibroblastic tumor (ALK-positive), PEComa (HMB45-positive) and others; $, others include PEComa (HMB45-positive), glomus tumor (smooth muscle actin-positive & vimentin-positive), solitary fibrous tumor (CD34-positive and nuclear STAT6-positive), malignant melanoma (S-100 positive, HMB45-positive), neuroendocrine tumor (several biomarkers), and others. GIST, gastrointestinal stromal tumor.

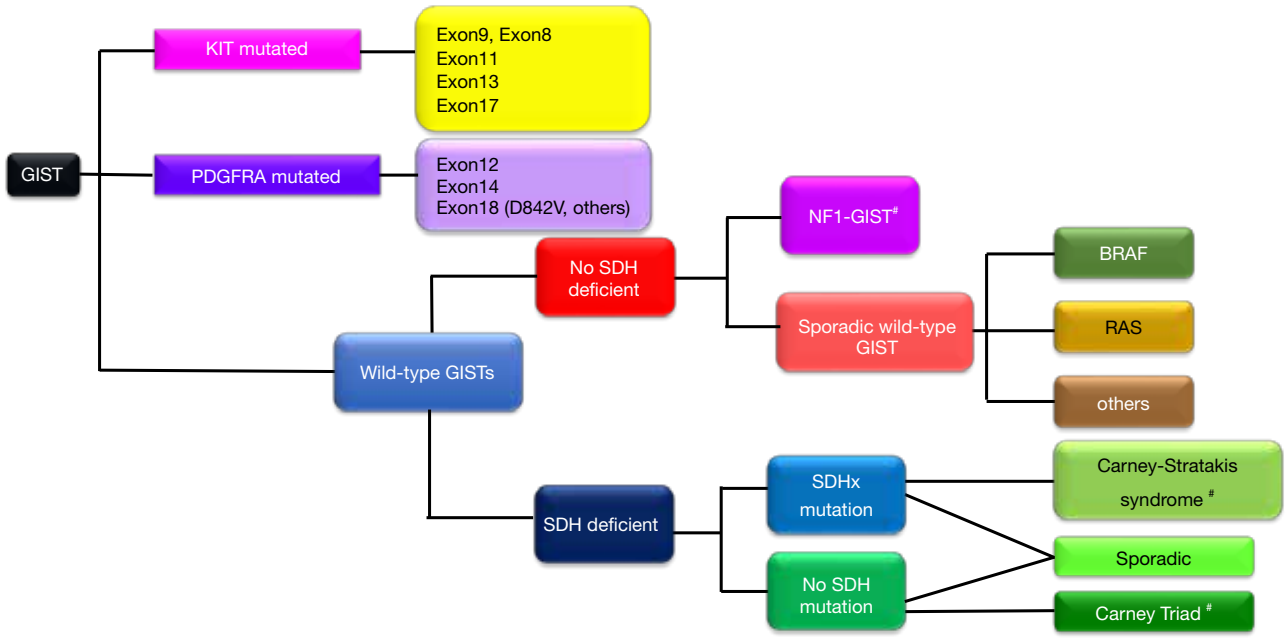

Figure 3 Genotypes of GIST. Carney-Stratakis syndrome is a dyad of paraganglioma and gastric GIST with autosomal dominance. Carney triad is characterized by three neoplasms of gastric GIST, pulmonary chondroma, and extra-adrenal paraganglioma. A part of the algorithm is similar to (25). #, indicates syndromic GIST. GIST, gastrointestinal stromal tumor; SDH, succinate dehydrogenase; NF1, neurofibromatosis type 1.

is not as commonly used in Asian countries compared with hospitals and institutes in Europe & North America. Thus, the Asian guidelines suggest the use of both KIT and DOG1 immunostaining, as well as immunostaining of other markers depending on the tumor (*Figure 2* in the lower panel). Both guidelines recommend that mitosis should be expressed with a denominator of 5 mm^2 because of different fields of view among microscopes. The Asian GIST guidelines suggest required items in a pathologic report form.

GIST is a heterogeneous disease composed of several genotypes (1,2). Ninety percent of primary GISTs may have mutations in either the *KIT* (80%) or *PDGFRA* genes (10%), and 10% have no mutation in either gene (*Figure 3*) (1,2,6). The latter type is called wild-type GIST. The most frequent *KIT* mutations are found in the juxtamembrane domain of exon 11, followed by exon 9, and *KIT* mutations in exons 8, 13 and 17 are rare. Contrary to *KIT*, kinase domain mutations, especially in exon 18, are most common in *PDGFRA*. Genotyping is considered to be primarily important as a predictive biomarker of clinical activities of tyrosine kinase inhibitors (TKIs) and secondarily important as a diagnostic biomarker of KIT-negative GIST in immunohistochemistry (1,2,6,8,9,12). For example, no guidelines recommend imatinib adjuvant therapy for high-risk GIST with *PDGFRA* D842V mutation because this type of mutation is considered to be resistant to all available TKIs, including imatinib, sunitinib, and regorafenib (6,8,9,12). Wild-type GIST may be divided into several genotypes, as shown in *Figure 3*, and the initial diagnostic step may be SDHB-immunostaining. The GIST experts may consider that wild-type GIST is insensitive to imatinib and do not always recommend imatinib adjuvant therapy for wild-type GIST. Details of wild-type GIST should be found in other reviews and original articles (25-27).

There are several risk stratifications and nomograms for GIST (28-33). Among the major risk stratifications and staging systems (*Tables 1-4*), the Armed Forces Institute of Pathology (AFIP) criteria are indicated to accurately predict recurrence after complete surgery and are recommended by the NCCN and ESMO guidelines (6,8,33-35). However, Asian guidelines recommend the modified NIH (National Institutes of Health) classification (Joensuu classification) because this stratification is suggested to be the most sensitive to select GIST patients who may have benefits from adjuvant therapy (12,36-38). Except for the modified

NIH (Joensuu) classification (15), all risk-stratifications and nomograms lack evidence for Asian GIST patients, and there have been few validation studies from Asian countries. Asian guidelines mention that further investigations are still required to find the best risk stratification for Asian GIST patients.

Surgical treatment

Surgery is still a mainstay for a potential permanent cure even in the era of tyrosine kinase inhibitors. Indications of multidisciplinary therapy of neoadjuvant and adjuvant therapy may be individualized. Before neoadjuvant therapy, pathological diagnosis using biopsy samples is mandatory (9,12). Asian guidelines recommend luminal biopsy, such as EUS-FNA (2,9,12), and Western guidelines recommend fine-needle biopsy through the abdominal wall based on the results from retrospective studies indicating that such biopsies did not increase recurrent risk when appropriate surgery and/or medical therapy were done after biopsy (6,8,39).

In surgical treatment, macroscopically and microscopically clear surgical margins are required for complete resection of GIST without injuring the pseudocapsule, even if it is small. Thus, Asian guidelines do not recommend endoscopic resection of small GIST because it has a potential risk of pseudocapsule damage, which may be predisposed to recurrence (9,12). The guidelines recommend laparoscopic surgery for small GIST less than 5 cm when it is in a favorable location (2,6,9,12). Laparoscopic surgery is less painful and less invasive and shows better cosmetic results, as well as earlier recovery, than open surgery (40-43). Furthermore, oncologic outcomes are similar between laparoscopic and open surgery.

The prognostic factors for recurrence after complete surgery have been rigorously investigated in both Western and Asian countries (5-12), and four factors are recognized as independent prognostic factors: tumor size (cm), mitosis (per 50 HPF or per 5 mm^2), tumor location (gastric vs non-gastric) and tumor rupture (15,28-32). Among the four factors, tumor rupture is the most ominous prognostic factor, and most ruptured GIST may have recurrences during follow-up (1,2,15). Thus, all guidelines suggest imatinib adjuvant therapy for GIST patients with tumor rupture, and some experts may consider that these patients should have adjuvant therapy for much longer than three years. The definition of "tumor rupture", however, has been subjective, and the diagnosis of tumor rupture may depend on the surgeon. Hence, the preliminary data indicate

Table 1 Risk classifications—National Institute of Health (NIH) consensus criteria

Risk categories	Tumor size (cm)	Mitosis/50 HPF
Very low	<2	<5
Low	2–5	<5
Intermediate	<5	6–10
	5–10	<5
High	>5	>5
	>10	Any
	Any	>10

HPF, high power field.

Table 2 Risk classifications—the Armed Forces Institute of Pathology (AFIP) criteria (with some modifications)

Group	Tumor size (cm)	Mitosis/50 HPF	Tumor site		
			Stomach	Small intestine	Large intestine and rectum
1	≤2	≤5	None	None	None
2	2–5		Very low	Low	Low
3a	5–10		Low	Moderate	High
3b	>10		Moderate	High	
4	≤2	>5	None	High	High
5	2–5		Moderate	High	High
6a	5–10		High	High	High
6b	>10		High	High	

HPF, high power field.

Table 3 Risk classifications—the modified NIH (Joensuu) classification

Risk category	Tumor size (cm)	Mitosis/50 HPF	Primary tumor site
Very low	≤2	≤5	Any
Low	2–5	≤5	Any
Intermediate	≤5	6–10	Gastric
	5–10	≤5	Gastric
High	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	≤5	>5	Non gastric
	>5–10	≤5	Non gastric

HPF, high power field.

Table 4 Risk classifications—American Joint Committee on Cancer (AJCC) staging

Stage	T	N	M	Mitotic index
Gastric				
Stage I	T1, T2, T3	N0	M0	Low
Stage II	T1, T2	N0	M0	High
	T4	N0	M0	Low
Stage III	T3, T4	N0	M0	High
Stage IV	Any T	N1	M0	Any
	Any T	Any N	M1	Any
Non-gastric				
Stage I	T1, T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage III	T4	N0	M0	Low
	T1, T2, T3, T4	N0	M0	High
Stage IV	Any T	N1	M0	Any
	Any T	Any N	M1	Any

T1, <2 cm; T2, 2–5 cm; T3, 5–10 cm; T4, >10 cm; N0, no lymph node metastasis; N1, regional lymph node metastasis; M0, no distant metastasis; M1, distant metastasis; mitotic index low: <5/50 HPF, high: >5/50 HPF. HPF, high power field.

different prognostic outcomes between intraoperative and preoperative rupture. Recently, Hølmebakk *et al.* (44) classified major and minor tumor ruptures. A major defect included tumor spillage, tumor fracture, piecemeal resection, bowel perforation at the tumor site with blood-tinged ascites at laparotomy, microscopic tumor invasion into neighboring structures, and surgical biopsy; and a minor defect included iatrogenic peritoneal laceration on the tumor (injury to the pseudocapsule) and serosal laceration at the tumor site. GISTs with major findings showed poorer prognosis than those with only minor findings. These criteria do not consider minor defects and fine-needle biopsies to be true "tumor rupture" (44,45). However, macroscopic injuries to the pseudocapsule exposing tumor cells were shown to have similarly poor prognosis as a major defect (37,46). Finally, we may consider that "tumor rupture" includes tumor perforation and tumor fracture with blood-tinged ascites, piecemeal resection during operation, microscopic tumor invasion into neighboring structures, and macroscopic injuries to the pseudocapsule exposing tumor cells into the peritoneal cavity.

The follow-up strategy after complete surgery also depends on risk classification, and the most careful follow-up is required for high-risk GIST patients. Patients with intermediate-risk GISTs may accept a more relaxed follow-up. In Western countries, patients with very low-risk GISTs may be considered to have no follow-up after complete surgery because they have had no relapse (6,8,47,48). The evidence for the follow-up strategy has been established in Western countries, and Asian GIST patients have not supplied their own data. Hence, Asian guidelines indicate that further investigations are required to establish an optimized surveillance schedule with CT for Asian GIST patients.

Multidisciplinary treatment

There is no large difference in adjuvant and/or neoadjuvant therapy recommended by GIST experts between the East and the West (*Figure 4*). In the ESMO guidelines, however, neoadjuvant therapy is concisely described, and the NCCN guidelines suggest that neoadjuvant treatment may be considered for patients who may require extensive surgery with resection of surrounding organs and/or surgery with significant risks (6,8). Both guidelines indicate that the decision to use neoadjuvant therapy may be made on an individual basis. In contrast, the Asian guidelines describe details of neoadjuvant therapy, including purpose, early evaluation, and duration of preoperative imatinib therapy (12,49). After preoperative imatinib, surgery is recommended at the time of best response or sufficient shrinkage, which

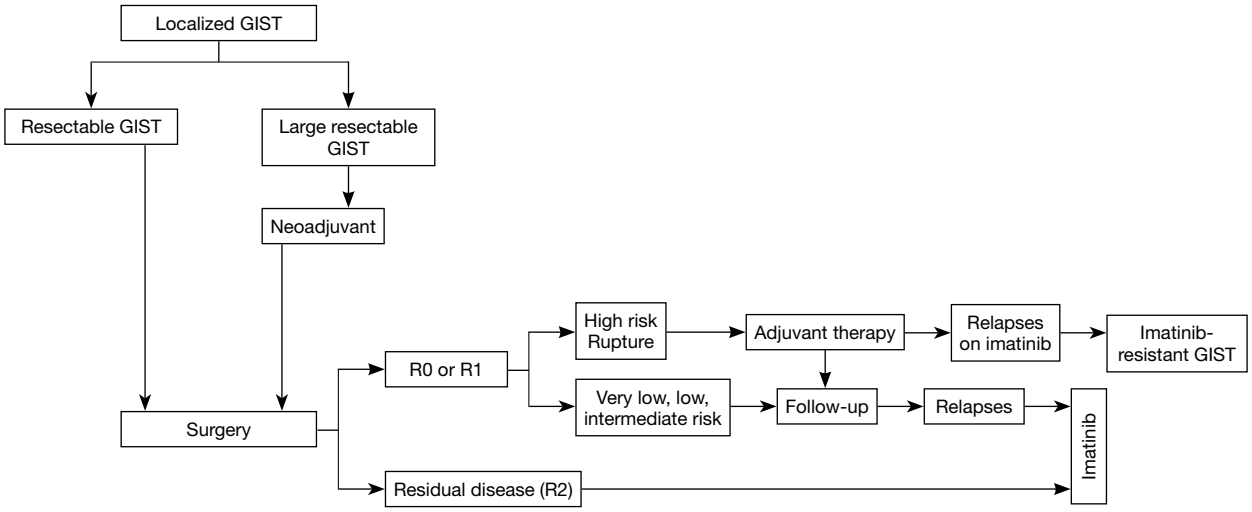

Figure 4 Treatment of localized GIST. R0, microscopically and macroscopically no residual disease; R1, microscopic-positive and macroscopic-negative margin; R2, macroscopically residual disease. GIST, gastrointestinal stromal tumor.

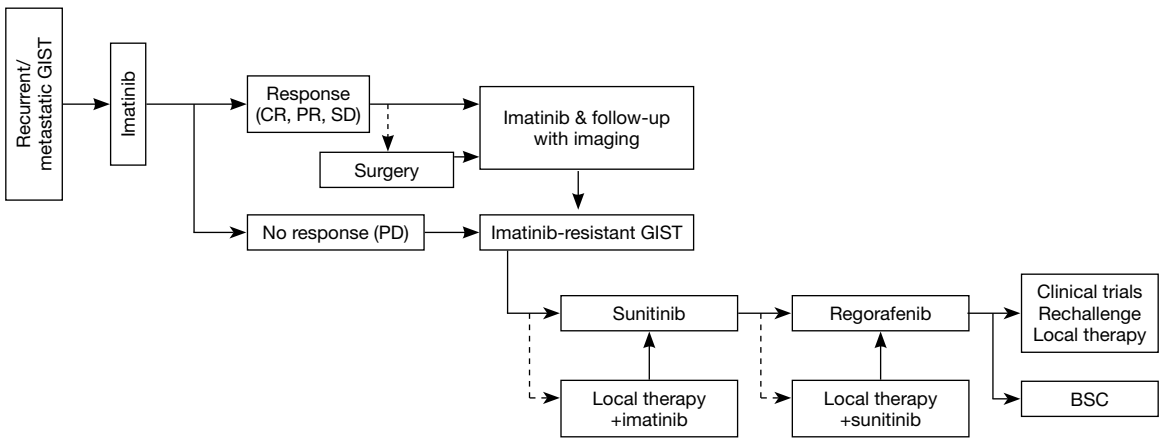

Figure 5 Treatment of recurrent/metastatic GIST. GIST, gastrointestinal stromal tumor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BSC, best supportive care.

usually takes 6 to 12 months of therapy (49). A preoperative drug holiday is not always required in the absence of significant drug-related adverse events. After complete resection, adjuvant therapy for three years or more is recommended for high-risk and/or ruptured GIST based on the disease evaluation before imatinib treatment. In adjuvant therapy, NCCN and ESMO guidelines consider that patients with significant risk of recurrence may have adjuvant therapy after discussion with experts from multiple disciplines and that shared decision with patients is important for adjuvant therapy (6,8). Both guidelines may allow some patients with intermediate-risk GISTs to have adjuvant therapy, depending on the patient's situation and point of view in addition to recurrence risk. In contrast, Asian guidelines describe that candidates for adjuvant therapy may be high-risk GISTs, and patients with intermediate-risk GISTs have no sufficient evidence at present (12).

Compared with the Western guidelines, the Asian consensus guidelines indicate a more aggressive approach for advanced GIST patients, such as *en bloc* resection of extra-gastrointestinal GIST, even if it requires multi-visceral resection, and surgery for resectable residual diseases of metastatic and/or recurrent GIST under imatinib therapy (*Figure 5*) (12). Based on retrospective analyses and sub-

analysis of discontinued clinical trials suggesting potential improvement of PFS and OS by surgical resection of residual tumors responding to imatinib, the Asian guidelines indicate *en bloc* resection of residual disease of advanced GIST patients after 4 to 12 months of imatinib therapy when applicable (12,50-53). The guidelines also suggest surgical resection or intervention by radiofrequency ablation (RFA) or by trans-arterial embolization (TAE) might be used when GIST patients show limited (or focal) progression of the disease in the presence of TKI (50-52,54). The primary approach to metastatic and/or recurrent GIST is imatinib, and the Asian guidelines tend to consider multidisciplinary therapy to improve the prognosis when applicable. Neither Asian nor Western guidelines suggest front-line debulking surgery for metastatic and/or recurrent disease (6,8,9,12).

Medical therapy

For medical treatment, Asian and Western guidelines are very similar in recommending 1st-line imatinib, 2nd-line sunitinib and 3rd-line regorafenib (6,8,9,12). However, most of the evidence supporting those recommendations has been established by clinical trials conducted in the Western countries (55-57), and Asian GIST patients may still require their own evidence for some aspects, such as dose optimization. Asian patients are generally smaller than Caucasians and may have a different profile of adverse events. For example, Asian patients may show relatively frequent and severe hand-foot syndrome and hematotoxicity of the decrease in platelet and neutrophil counts when they receive sunitinib or regorafenib, whereas diarrhea is more frequent in Caucasians (56-60). The NCCN guidelines describe the details of medical therapy, including dose optimization, management of drug toxicities, mechanisms of drug resistance and treatment strategy for refractory GISTs, including investigational agents. After standard treatment, the guidelines recommend clinical trials for investigational agents, but in Asia, these trials are limited (12). In these situations, the Asian guidelines encourage a repeated challenge of TKI or use of TKI beyond PD (progressive disease) if applicable (61).

Conclusions

Between Asian and Western countries, there are some disparities in the medical system, clinical practice and disease profiles in oncology. In Asia, surgical oncologists have a major role in the multidisciplinary therapy, whereas medical oncologists are more prominent in the West. Although the incidence of clinical GIST appears to be similar between the two, the number of small GISTs treated by surgery seems to be high in Asia. Thus, the diagnostic and treatment strategies for small SMTs and GISTs are important in clinical practice in East Asia. Major parts of GIST guidelines are very similar between Asia and the West. However, there exist slight differences between their guidelines in the degree of recommendation, which may come from disparities in clinical practice and available medicines. Importantly, most clinical evidence in the GIST clinical guidelines has been established by clinical trials conducted in Western countries, and the number of clinical trials is still limited in Asia. This indicates that Asian GIST patients may have limited evidence based on their own data and may have limited access to new drugs after standard therapy. Finally, we may conclude that the GIST guidelines are well harmonized and reflect the particular medical circumstances in each region.

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Footnote

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References

1. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumour. Lancet 2013;382:973-83.
2. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer 2016;19:3-14.
3. Rossi CR, Vecchiato A, Mastrangelo G, et al. Adherence to treatment guidelines for primary sarcomas affects patient survival: a side study of the European CONnective TIssue CAncer NETwork (CONTICANET). Ann Oncol 2013;24:1685-91.
4. Derbel O, Heudel PE, Cropet C, et al. Survival impact of centralization and clinical guidelines for soft tissue sarcoma

(A prospective and exhaustive population-based cohort). PLoS One 2017;12:e0158406.
5. Demetri GD, Benjamin R, Blanke CD, et al. NCCN GIST Task Force. NCCN Task Force report: optimal management of patients with gastrointestinal stromal tumor (GIST)--expansion and update of NCCN clinical practice guidelines. J Natl Compr Canc Netw 2004;2 Suppl 1:S1-26.
6. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41.
7. Blay JY, Bonvalot S, Casali P, et al. GIST consensus meeting panelists. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol 2005;16:566-78
8. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii21-6.
9. Nishida T, Hirota S, Yanagisawa A, et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. Int J Clin Oncol 2008;13:416-30.
10. Kang YK, Kang HJ, Kim KM, et al.; Korean GIST Study Group (KGSG). Clinical practice guideline for accurate diagnosis and effective treatment of gastrointestinal stromal tumor in Korea. Cancer Res Treat 2012;44:85-96.
11. Yeh CN, Hwang TL, Huang CS, et al.; Taiwan Surgical Society of Gastroenterology. Clinical practice guidelines for patients with gastrointestinal stromal tumor in Taiwan. World J Surg Oncol 2012;10:246.
12. Koo DH, Ryu MH, Kim KM, et al. Asian Consensus Guidelines for the diagnosis and management of gastrointestinal stromal tumor. Cancer Res Treat 2016;48:1155-66.
13. Allemani C, Weir HK, Carreira H, et al.; CONCORD Working Group. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015;385:977-1010.
14. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
15. Joensuu H, Vehtari A, Riihima¨ki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-74.
16. Kawanowa K, Sakuma Y, Sakurai S, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006;37:1527-35.
17. Abraham SC, Krasinskas AM, Hofstetter WL, et al. "Seedling" mesenchymal tumors (gastrointestinal stromal tumors and leiomyomas) are common incidental tumors of the esophagogastric junction. Am J Surg Pathol 2007;31:1629-35.
18. Agaimy A, Wünsch PH, Hofstaedter F, et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol 2007;31:113-20.
19. Agaimy A, Wünsch PH, Dirnhofer S, et al. Microscopic gastrointestinal stromal tumors in esophageal and intestinal surgical resection specimens: a clinicopathologic, immunohistochemical, and molecular study of 19 lesions. Am J Surg Pathol 2008;32:867-73.
20. Rossi S, Gasparotto D, Toffolatti L, et al. Molecular and clinicopathologic characterization of gastrointestinal stromal tumors (GISTs)of small size. Am J Surg Pathol 2010;34:1480-91.
21. Nishida T, Goto O, Raut CP, et al. Diagnostic and treatment strategy for small gastrointestinal stromal tumors. Cancer 2016;122:3110-8.
22. Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. Surg Endosc1991;5: 20-3.
23. Joo MK, Park JJ, Kim H, et al. Endoscopic versus surgical resection of GI stromal tumors in the upper GI tract. Gastrointest Endosc 2016;83:318-26.
24. An W, Sun PB, Gao J, et al. Endoscopic submucosal dissection for gastric gastrointestinal stromal tumors: a retrospective cohort study. Surg Endosc 2017;31:4522-31.
25. Nishida T. Therapeutic strategies for wild-type gastrointestinal stromal tumor: is it different from KIT or PDGFRA-mutated GISTs? Transl Gastroenterol Hepatol 2017;2:92.
26. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A 2011;108:314-8.
27. Boikos SA, Pappo AS, Killian JK, et al. Molecular Subtypes of KIT/PDGFRA Wild-Type gastrointestinal stromal tumors: a report from the national institutes of health gastrointestinal stromal tumor clinic. JAMA Oncol 2016;2:922-8.
28. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459-65.

29. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.
30. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
31. Edge SB, Byrd DR, Compton CC, et al. AJCC staging manual. 7th ed. New York: Springer; 2010.
32. Gold JS, Go¨nen M, Gutie´rrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 2009;10:1045-52.
33. Rossi S, Miceli R, Messerini L, et al. Natural history of imatinib-naive GISTs: a retrospective analysis of 929 cases with long-term follow-up and development of a survival nomogram based on mitotic index and size as continuous variables. Am J Surg Pathol 2011;35:1646-56.
34. Goh BK, Chow PK, Yap WM, et al. Which is the optimal risk stratification system for surgically treated localized primary GIST? Comparison of three contemporary prognostic criteria in 171 tumors and a proposal for a modified Armed Forces Institute of Pathology risk criteria. Ann Surg Oncol 2008;15:2153-63.
35. Bischof DA, Kim Y, Behman R, et al. A nomogram to predict disease-free survival after surgical resection of GIST. J Gastrointest Surg 2014;18:2123-9.
36. Rutkowski P, Bylina E, Wozniak A, et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour—the impact of tumour rupture on patient outcomes. Eur J Surg Oncol 2011;37: 890-6.
37. Yanagimoto Y, Takahashi T, Muguruma K, et al. Re-appraisal of risk classifications for primary gastrointestinal stromal tumors (GIST) after complete resection: indications for adjuvant therapy. Gastric Cancer 2015;18:426-33.
38. Joensuu H, Eriksson M, Hall KS, et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. Cancer 2014;120:2325-33.
39. Eriksson M, Reichardt P, Sundby Hall K, et al. Needle biopsy through the abdominal wall for the diagnosis of gastrointestinal stromal tumour - Does it increase the risk for tumour cell seeding and recurrence? Eur J Cancer 2016;59:128-33.
40. Nishimura J, Nakajima K, Omori T, et al. Surgical strategy for gastric gastrointestinal stromal tumors: laparoscopic vs. open resection. Surg Endosc 2007;21:875-8.
41. Bischof DA, Kim Y, Dodson R, et al. Open versus minimally invasive resection of gastric GIST: a multi-institutional analysis of short- and long-term outcomes. Ann Surg Oncol 2014;21:2941-8.
42. Chen K, Zhou YC, Mou YP, et al. Systematic review and meta-analysis of safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors of the stomach. Surg Endosc 2015;29:355-67.
43. MacArthur KM, Baumann BC, Nicholl MB. Laparoscopic versus open resection for gastrointestinal stromal tumors (GISTs). J Gastrointest Cancer 2017;48:20-24.
44. Hølmebakk T, Bjerkehagen B, Boye K, et al. Definition and clinical significance of tumour rupture in gastrointestinal stromal tumours of the small intestine. Br J Surg 2016;103:684-691.
45. McCarter MD, Antonescu CR, Ballman KV, et al.; American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant Gist Study Team. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. J Am Coll Surg 2012;215:53-9.
46. Takahashi T, Nakajima K, Nishitani A, et al. An enhanced risk-group stratification system for more practical prognostication of clinically malignant gastrointestinal stromal tumors. Int J Clin Oncol 2007;12:369-374.
47. Joensuu H, Martin-Broto J, Nishida T, et al. Follow-up strategies for patients with gastrointestinal stromal tumor treated with or without adjuvant imatinib after surgery. Eur J Cancer 2015; 51:1611-7.
48. Joensuu H, Reichardt P, Eriksson M, et al. Gastrointestinal stromal tumor: a method for optimizing the timing of CT scans in the follow-up of cancer patients. Radiology 2014;271:96-103.
49. Kurokawa Y, Yang HK, Cho H, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. Br J Cancer 2017;117:25-32.
50. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. Ann Surg Oncol 2010;17:407-15.
51. DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg 2007;245:347-52.
52. Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. Ann Surg 2007;245:341-6.
53. Du CY, Zhou Y, Song C, et al. Is there a role of surgery

in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomized trial in China. Eur J Cancer 2014;50:1772-8.
54. Hasegawa J, Kanda T, Hirota S, et al. Surgical interventions for focal progression of advanced gastrointestinal stromal tumors during imatinib therapy. Int J Clin Oncol 2007;12:212-7.
55. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
56. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38.
57. Demetri GD, Reichardt P, Kang YK, et al.; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
58. Shirao K, Nishida T, Doi T, et al. Phase I/II study of sunitinib malate in Japanese patients with gastrointestinal stromal tumor after failure of prior treatment with imatinib mesylate. Invest New Drugs 2010;28:866-75.
59. Komatsu Y, Ohki E, Ueno N, et al. Safety, efficacy and prognostic analyses of sunitinib in the post-marketing surveillance study of Japanese patients with gastrointestinal stromal tumor. Jpn J Clin Oncol 2015;45:1016-22.
60. Komatsu Y, Doi T, Sawaki A, et al. Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial. Int J Clin Oncol 2015;20:905-12.
61. Kang YK, Ryu MH, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175-82.

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Molecular characterization and pathogenesis of gastrointestinal stromal tumor

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Abstract: Most gastrointestinal stromal tumors (GISTs) harbor activating mutations in the receptor tyrosine kinase gene *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*), and the resultant activation of downstream signals plays a pivotal role in the development of GISTs. The sites of the tyrosine kinase gene mutations are associated with the biological behavior of GISTs, including risk category, clinical outcome and drug response. Mutations in RAS signaling pathway genes, including KRAS and BRAF, have also been reported in *KIT/PDGFRA* wild-type GISTs, though they are rare. Neurofibromin 1 (*NF1*) is a tumor suppressor gene mutated in neurofibromatosis type 1. Patients with *NF1* mutations are at high risk of developing GISTs. Recent findings suggest that altered expression or mutation of members of succinate dehydrogenase (SDH) heterotetramer are causally associated with GIST development through induction of aberrant DNA methylation. At present, GISTs with no alterations in *KIT*, *PDGFRA*, RAS signaling genes or SDH family genes are referred to as true wild-type GISTs. *KIT* and *PDGFRA* mutations are thought as the earliest events in GIST development, and subsequent accumulation of chromosomal aberrations and other molecular alterations are required for malignant progression. In addition, recent studies have shown that epigenetic alterations and noncoding RNAs also play key roles in the pathogenesis of GISTs.

Keywords: *KIT*; platelet-derived growth factor receptor alpha (*PDGFRA*); succinate dehydrogenase (SDH); RAS; neurofibromin 1 (*NF1*); DNA methylation; noncoding RNA

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Outline of the molecular pathogenesis of gastrointestinal stromal tumor (GIST)

GISTs are the most common mesenchymal tumors affecting the gastrointestinal tract (1). GISTs were formerly regarded as smooth muscle or neural neoplasms referred to as leiomyomas, leiomyosarcomas or schwannomas. However, identification of *KIT* mutations and high CD34 and c-KIT (CD117) positivity rates in these tumors led to the establishment of a new category of stromal tumors (2). The cellular origins of GISTs are thought to be interstitial cells of Cajal (ICCs), which are located in the myenteric plexus of the gastrointestinal tract, where they act as pacemaker cells for gastrointestinal motility. Subsequent studies showed that DOG1 (discovery on GIST1), also known as TMEM16A or ANO1, is a novel diagnostic marker of GISTs (3,4). Both DOG1 and KIT can serve as positive controls for immunohistochemical analysis in ICCs, though DOG1 is not expressed in KIT-positive mast cells (5). Protein kinase C θ (PKCθ) is specifically upregulated in GISTs as compared to other soft tissue tumors and, thus, it is also a useful diagnostic marker of GISTs (6).

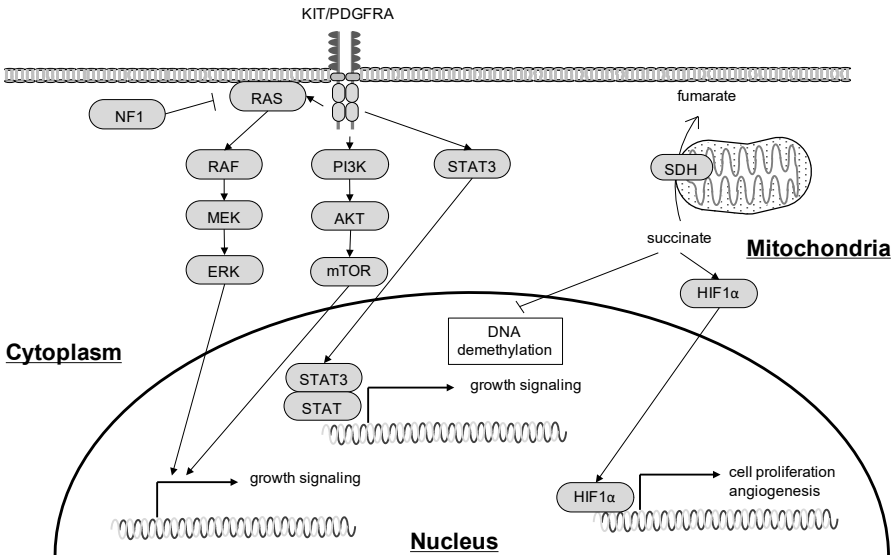

Figure 1 Key signaling pathways in GIST. The majority of GISTs harbor *KIT* or *PDGFRA* gain-of-function mutations, which lead to activation of downstream signaling, including via the MAPK, PI3K and STAT3 pathways. Minor populations of GISTs exhibit mutation of *NF1*, *RAS* or *RAF*, which leads to the activation of MAPK signaling. SDH deficiency also contributes to GIST development through activation of HIF1α and inhibition of DNA demethylation. GIST, gastrointestinal stromal tumor; *NF1*, neurofibromin 1; *PDGFRA*, platelet-derived growth factor receptor alpha.

Activating mutations in the receptor tyrosine kinase gene *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) play essential roles in the pathogenesis of GISTs through upregulation of downstream signaling pathways, including RAS/RAF/MAPK and PI3K/AKT/mTOR (*Figure 1*) (7). Mutations in RAS family genes and *BRAF* play a similar role, but are less frequently observed in GISTs (8). Succinate dehydrogenase (SDH)-deficient GISTs are characterized by wild-type *KIT*/*PDGFRA* and dysfunctional mutation or downregulation of members of the SDH heterotetramer (SDHA, SDHB, SDHC and SDHD). SDH deficiency and the resultant accumulation of succinate promote GIST development through different mechanisms than do oncogenic mutations, including upregulation of HIF1α and inhibition of DNA demethylation (*Figure 1*). Neurofibromin 1 (*NF1*) also acts as a tumor suppressor gene in GISTs, and patients with neurofibromatosis type I are known to be at high risk of developing multiple GISTs (9).

GISTs with no mutations in *KIT*, *PDGFRA* or RAS pathway genes or SDH-deficiency are referred as wild-type GISTs. They are characterized by overexpression of CALCRL/COL22A1, the tyrosine kinase NTRK2, the cyclin dependent kinase CDK6, and ERG, a member of the ETS-transcription factor family (10). A subset of wild-type GISTs exhibit mutations in *TP53*, *MEN1* or *MAX*, and are characterized by a neural-committed phenotype and upregulation of the master endocrine regulator ASCL1 (11).

Chromosomal instability plays an important role in the development of many tumor types, and GISTs are characterized by various chromosomal abnormalities. For instance, losses of 14q and 22q frequently occur during the early stages of GIST development, and some of the chromosomal aberrations are associated with the clinical characteristics of GISTs (12). Epigenetic alterations, including aberrant DNA methylation and histone modification, have also been implicated in the development of GISTs (13,14). Recent studies have begun to shed light on the physiological and pathological importance of noncoding RNAs, and several noncoding RNAs are reportedly associated with the clinicopathological features of GISTs (15).

GISTs are rare tumors with an annual incidence of 10 to 20 per 1 million cases, but recent studies have shown that small GISTs may be occurring more frequently than previously documented. For instance, Agaimy *et al.* reported that microGISTs (less than 10 mm) are found in 22.5% autopsies performed in individuals older than 50 years (16). These lesions were located in the cardia, fundus, or proximal body of the stomach, but not in the antrum, duodenum, or remainder of the bowel. All tumors

showed a histologically spindle cell morphology, and 57% of the tumors showed hyalinization and calcification. MicroGISTs were immunohistochemically positive for CD117, CD34, and vimentin, while *KIT* and *PDGFRA* mutations were found in 46% (11 of 24) and 4% (1 of 24) of these tumors, respectively (16). Kawanowa *et al.* investigated stomach specimens resected from 100 gastric cancer patients, and found a total of 50 microGISTs in 35 patients (17). All tumors were immunopositive for KIT or CD34 and negative for desmin. A large majority (45 of 50) of these tumors were located in the upper stomach, while only 8% (2 of 25) exhibited *KIT* mutation. In contrast to microGISTs, another study reported that *KIT* or *PDGFRA* mutations were detected in nearly all (12 of 13) small GISTs (less than 20 mm) (18). These results highlight the fact that although *KIT*/*PDGFRA* mutations are early events during GIST development, they are not sufficient for the progression of GISTs.

KIT mutations in GIST

KIT encodes the 145 kDa receptor tyrosine kinase c-KIT, which was identified as a normal cellular homolog of the feline sarcoma viral oncogene v-kit (19). KIT belongs to the type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, macrophage colony stimulating factor receptor (CSF1R) and FL cytokine receptor (FLT3) (20). KIT is composed of an extracellular domain, juxtamembrane domain, tyrosine kinase domain I and tyrosine kinase domain II. KIT is maintained in an inactive form through auto-inhibition of the kinase domain (21).

Stem cell factor (SCF) is a KIT ligand, the binding of which promotes dimerization of the enzyme, ATP binding to the tyrosine kinase domain and auto phosphorylation of the tyrosine residue in the juxtamembrane domain (22). The SCF-KIT signal activates downstream pathways, including the MAP kinase cascade and PI3K/AKT pathway. The former leads to upregulation of such transcriptional factors as MYC, ELK, CREB and FOS, while the latter results in downregulation of cell cycle inhibitors and promotion of anti-apoptotic effects.

Approximately 70% to 80% of GISTs exhibit *KIT* mutations (23,24). The critical role of *KIT* mutation in GIST development has been well studied. For instance, the mutant forms of KIT protein harbor autonomous activity in the absence of ligand SCF binding (2), and a mutant *Kit* knock-in mouse model resembles familial GIST syndrome patients and shows diffuse ICC hyperplasia or GIST-like tumors (25,26). The mutant KIT activates multiple downstream signals, including MAPK, AKT, S6k, STAT1 and STAT3, in a SCF independent manner (27). The $Kit^{v558\Delta/+}$ mouse model shows that the PI3K/mTOR pathway is also upregulated in GISTs, and treatment with the mTOR inhibitor everolimus suppresses tumor proliferation (27). An ETS family member, ETV1, is regulated by active KIT, and cooperates with KIT to promote GIST growth. ETV1 is highly expressed in GISTs and acts as a transcriptional master regulator by binding to enhancer regions (28). ETV1 and KIT form a positive feedback loop to regulate target genes through stabilization of ETV1, and combination treatment with the KIT inhibitor imatinib and the MEK inhibitor MEK162 suppresses GIST growth *in vivo* and *in vitro* (29).

PDGFRA is another member of the receptor tyrosine kinase family and contributes to cell viability through ERK-dependent stabilization of ETV1 in *KIT*-mutant GISTs (30). Heat shock protein 90 (HSP90) is involved in the degradation of wild-type and mutant KIT (31), and a preclinical study showed that a HSP90 inhibitor promoted KIT degradation and suppressed GIST growth *in vitro* and *in vivo* (32). In a clinical trial, however, the response rate to IPI504, an ansamycin analogue HSP90 inhibitor, was low with a high toxicity rate (33). CDC37, a HSP90 cofactor, regulates KIT activation and expression and also interacts with oncogenic KIT (33).

Within GISTs, *KIT* mutations are found in several gene regions, including exons 8, 9, 11, 13, 14, 15, and 17. Exons 8 and 9 encode the extracellular domain, exon 11 encodes the juxtamembrane domain, and exons 13 and 17 encode the tyrosine kinase domain. Approximately 70% of GISTs exhibit mutations in exon 11, and 5% to 10% of GISTs show mutations in exon 9. Mutations in exon 11 disrupt auto-inhibition and lead to constitutive activation of KIT (34). Codons 557-558 in exon 11 are mutation hot spots, and deletions of W557 and/or K558 are associated with a metastatic phenotype (35) and poor post-operative recurrence-free survival (36). Another study showed that deletion-including codon 557/558 mutations are more strongly associated with larger tumor size, high mitotic count, high risk grade, and poor disease-free survival than other mutations in exon 11 (37). A small number of GISTs (6/427, 1.4%) show deletions in the boundary between intron 10 and exon 11, which could lead to loss of the normal splice acceptor site and p.K550_K558del mutation (23). GISTs with single nucleotide substitutions in exon 11 show indolent phenotype, lower mitotic activity,

smaller tumor size, and favorable disease free survival (23,38). Within exon 11, tandem internal duplications occur mainly at the 3' end of the exon, and codons 576-579 are preferentially involved (23,39). Mutations in exon 9 are characterized by tandem duplication of six nucleotides at codons 502-503 (p.A502_Y503dup), and are associated with small bowel location, larger tumor size, older age (>60 years), female gender and spindle cell morphology (39).

Approximately 1% to 2% of *KIT* mutations are found in exons 13 and 17 (24,37,40). Most exon 13 mutations (e.g., c.1945A>G and c.1948G>A) result in p.K642E, which suppresses auto-inhibition of the juxtamembrane domain (41). About 70% of exon 17 mutations are c.2487T>A (p.N822K), while other infrequent mutations (p.N822Y, pN822K, p.N822H, p.D816F, p.D816Y, p.D820Y, p.D820V and p.Y823D) have also been identified (23,40). Exon 17 encodes the activation loop of the tyrosine kinase domain, and mutations in exon 17 are thought to be involved in maintenance of the constitutively active conformation (40). GISTs with mutations in exons 13 and 17 are associated with spindle cell morphology, and exon 13 mutations in particular correlate with the malignant potential of GISTs (40).

Mutations in exon 8 are rarely observed in GISTs, and in two cases with p.D419del mutation, one developed multiple peritoneal metastasis (42). Another study reported that, among three GISTs with exon 8 mutations (one case with p.D419del and two cases with heterozygous mutations of p.TYD417-419Y), all tumors were located at extragastric sites, and two cases showed distant metastasis (43). These reports suggest that mutations in exon 8 are potentially associated with the malignant phenotype of GISTs. Mutations in exon 14 are found as secondary mutations occurring after treatment with tyrosine kinase inhibitors (44,45). Mutations in exon 15 are rarely found in GISTs, and only c.2153C>G substitutions have been identified (46).

PDGFRA mutations in GIST

Approximately 10% to 15% of GISTs exhibit *PDFRA* mutations (47). These mutations are found in exon 12 (juxtamembrane domain), exon 14 (ATP biding domain), and exon 18 (activation loop), and cause constitutive PDGFRA activation in the absence of ligand binding, leading to downstream activation of signaling pathways. Like *KIT* mutations, *PDGFRA* mutations can activate a series of signal transduction molecules, including MAPK, AKT, STAT1 and STAT3 (47). HSP90 and a co-chaperone, CDC37, stabilize PDGFRA, and treatment with a HSP90 inhibitor represses AKT signaling (48). *KIT* and *PDGFRA* are close homologues, and their mutation occurs in a mutually exclusive manner. GISTs with *PDGFRA* mutations are characterized by gastric location, epithelioid morphology, and an indolent clinical course (49,50).

The most common *PDGFRA* mutation is p.D842V, which accounts for 60% to 65% of *PDGFRA* mutations in GISTs (approximately 5% of all GISTs) (23,37). This mutation is located in exon 18, a region encoding the second kinase domain, and is associated with extremely favorable disease-free survival as compared to other mutation types (37). Mutations in exon 14 are reportedly found in about 1% of all GISTs (51). The majority of exon 14 mutations are c.2125C>A or c.2125C>G missense mutations, which result in p.N659K, and c.2123A>T (p. N659Y) has also been reported (51). Mutations in exon 14 are associated with a gastric location, favorable clinical outcome and epithelioid morphology (51). Mutations in exon 12 are rarely observed (less than 1% of all GISTs) and include substitutions, small deletions and insertions (52). Locations and frequencies of *KIT* and *PDGFRA* mutations are summarized in *Figure 2A*.

Familial GIST

Familial GIST syndrome is characterized by germline mutation of *KIT* or *PDGFRA*, multiple GISTs, hyperpigmentation, mast cell tumors and ICC hyperplasia-associated dysphagia (53,54). *KIT* mutations observed in individuals with familial GIST include p.V559A, c.1756_1758delGAT and p.W557R in exon 11 (juxtamembrane domain) (55-57), deletion of one of two consecutive valine residues located between the transmembrane and tyrosine kinase domains (58), deletion of codon 419 in exon 8 (extracellular domain) (59), and D820Y substitution in exon 17 (53). A missense mutation (D846Y) in the exon 18 of *PDGFRA* has been also identified in familial GIST individuals (54). *PDGFRA* D846 is homologous to *KIT* D820, which is located within the tyrosine kinase domain. Most of the affected individuals develop multiple GISTs by middle age, and the tumors show histological features similar to sporadic GISTs, except for expansion of the myenteric plexus Cajal cell population (53). The ICC hyperplasia in familial GIST individuals represents non-neoplastic polyclonal proliferation, whereas GISTs in the same patients exhibit monoclonal proliferation (60). Mutations in familial GIST are summarized in *Figure 2B*.

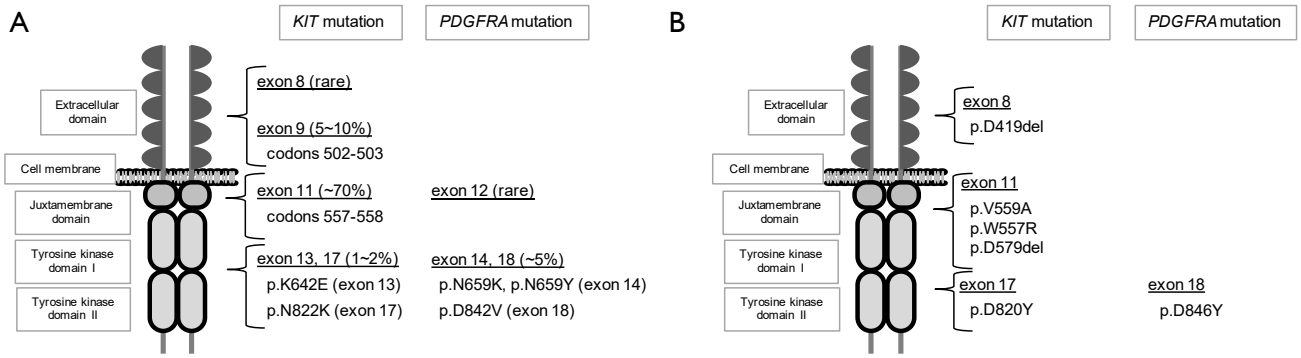

Figure 2 *KIT* and *PDGFRA* mutations in GIST. (A) Locations and frequencies of *KIT* and *PDGFRA* mutations in sporadic GISTs; (B) locations of *KIT* and *PDGFRA* mutation in familial GISTs. GIST, gastrointestinal stromal tumor; *PDGFRA*, platelet-derived growth factor receptor alpha.

SDH-deficient GIST

The most frequent molecular alteration in GISTs with wild-type *KIT/PDGFRA* is SDH deficiency. SDH consists of four subunits (SDHA, SDHB, SDHC, and SDHD), and is a component of the citric acid cycle and respiratory electron transfer chain (*Figure 3*) (61). SDH deficiency underlies Leigh syndrome, a neurodegenerative disorder caused by mitochondrial dysfunction, or several types of tumors, including paraganglioma, GIST, renal cell carcinoma and pituitary adenoma (62). SDH-deficient GISTs are immunohistochemically negative for SDHB due to its decreased expression or mutations in other SDH subunits that destabilize the SDH heterotetramer (63). Approximately 30% of SDHB-negative/SDH-deficient GISTs are also immunohistochemically negative for SDHA, the loss of which correlates generally with SDHA mutation (64). Patients with SDHA-positive GISTs are characterized by older age, female predominance, and a higher rate of liver metastasis than among those with SDHA-negative GISTs, although the mitosis rate, tumor size and clinical course are similar between SDHA-positive and -negative cases (64,65).

SDH deficiency results in the accumulation of succinate, which is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases, including the TET family of 5-methylcytosine hydroxylases (66). Members of the TET family are active DNA demethylases that convert 5-methylcytosine to 5-hydroxymethylcytosine, and inhibition of TET activities can lead to aberrant DNA methylation in GISTs. In fact, a genome-wide DNA methylation analysis of SDH-deficient GISTs revealed greater DNA hypermethylation than in GISTs with *KIT* mutation (67).

Accumulation of succinate is also involved in the stabilization of HIF1-α, which controls oncogene transcription (68). Insulin-like growth factor 1 receptor (IGF1R) is overexpressed in *KIT/PDGFR* wild-type GISTs, and the expression is particularly elevated in SDH-deficient GISTs (69-71). The IGF family consists of two ligands (IGF1 and IGF2), two receptors (IGFR1 and IGFR1) and 6 IGF binding proteins (IGFBPs), and binding of IGF and IGFR activates downstream signals, including the MAPK and PI3K/AKT pathways (72). Inhibition of IGF1R induces apoptosis and represses AKT and MAPK signaling in GIST cells, which implicates the IGF signal in the development of SDH-deficient GISTs (73).

The Carney triad, Carney Stratakis syndrome, and several sporadic GISTs are included among the SDH-deficient GISTs (*Figure 3*) (1). Carney triad is characterized by gastric stromal sarcoma, paraganglioma, and pulmonary chondroma. It predominantly affects young females but has no heritability (74-76). Carney Stratakis syndrome is characterized by gastric GISTs and paragangliomas that exhibit mutation of the SDH subunits (77). This syndrome is inherited in an autosomal dominant manner, and some patients carry germline mutations in SDH family genes (64,65).

RAS signaling gene mutations in GIST

Mutations in RAS family genes and *BRAF* are found in a subset of GISTs. RAS proteins act as molecular switches that change between active GTP-bound and inactive GDP bound states. This switching mechanism is highly conserved among species, and conversion from the inactive GDP-bound form

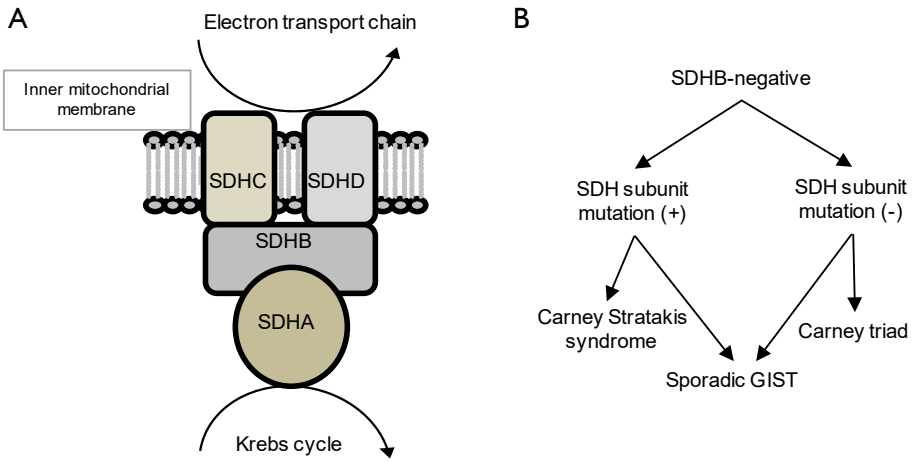

Figure 3 SDH-deficient GISTs caused by dysfunction of SDH complex. (A) SDH complex is a component of the citric acid cycle and respiratory electron transfer chain; (B) Carney Stratakis syndrome, Carney triad, and a subset of sporadic GISTs are included in SDH-deficient GISTs. SDH, succinate dehydrogenase; GIST, gastrointestinal stromal tumor.

to the active GTP-bound form is mediated by guanine nucleotide exchange-factors (GEFs), while conversion back to the inactive form is mediated by GTPase-activating proteins (GAPs) (78). *KRAS* is frequently mutated in pancreatic, colorectal, and lung cancers, and most mutations occur at codon 12 or 13. The replacement of glycine at codon12 or 13 is thought to prevent inactivation by GAPs, which results in RAS activation in the absence of upstream stimulation (79). The *BRAF* V600E mutation is detected in malignant melanoma and thyroid and colorectal cancers (80-82). The mutant BRAF cooperates with Rac1b, AKT3 and other signal molecules to promote tumor cell viability and proliferation (83).

Miranda *et al.* detected *KRAS* mutations in 3 of 60 GISTs (5%) (8). In all three cases, the *KRAS* mutation was at codon 12 and/or 13 (G12D, G13D and G12A/G13D). The tumors carrying the G12D and G12A/G13D mutations showed deletions at exon 11 of *KIT* (Δ570-576 and Δ579), while the tumor with the G13D mutation exhibited *PDGFRA* mutation at exon 18 (D842V).

Multiple studies also identified the *BRAF* V600E mutation in GISTs with wild-type *KIT/PDGFRA* (84-86). Huss *et.al*. analyzed a cohort of 444 GISTs (272 *KIT/PDGFRA*-mutant and 172 wild type GISTs) and detected *BRAF* mutations in seven tumors (1.6% of all GISTs and 3.9% of wild-type GISTs) (87). Because *BRAF* mutation is found in small GISTs with diameters of 4 mm, it is considered to be one of the earliest events in the GIST development (88).

Other gene mutations in GIST

In addition to the mutations in well-known key driver genes, including *KIT* and *PDGFRA*, recent studies have revealed genetic alterations of other tumor-related genes in GISTs. For instance, *EGFR* mutations are found in 0.93% (3/323) of primary GISTs, and do not overlap with mutations in *KIT*, *PDGFRA*, *KRAS* or *BRAF* (89). *EGFR* mutations are associated with a stomach location, female gender and low recurrence rate. *PIK3CA* mutation (p.H1047L) has also been reported in a GIST case with *KIT* exon 11 deletion (84).

Analysis of 24 wild-type GISTs (without mutations in *KIT/PDGFRA*/RAS signal genes or SDH deficiency) identified 7 commonly mutated genes, *ARID1B*, *ATR*, *FGFR1*, *LTK*, *SUFU*, *PARK2* and *ZNF217* (90). Two of these tumors harbored *FGFR1* gene fusions (FGFR1-HOOK3 and FGFR1-TACC1) and one exhibited *ETV6-NTRK3* fusion. The *ETV6-NTRK3* fusion transcript encodes the helix-loop-helix dimerization domain of ETV6 fused to the protein tyrosine kinase domain of NTRK3 (91), and the same fusion gene has been identified in breast carcinoma (92).

Alteration in protein phosphatase 2 regulatory subunit A alpha (*PPP2R1A*) causes dysfunction of protein phosphatase 2A (PP2A). Toda-Ishii *et al.* found *PPP2R1A* mutations in 17 of 94 (18%) GISTs, while a majority of the *PPP2R1A* mutant GISTs (16 of 17) harbored mutations in *KIT*, *PDGFRA* or RAS family genes and a remaining case showed SDH deficiency (93). *BRCA1* and *BRCA2* are well known

tumor suppressor genes in breast and ovarian cancer, and a potential association between *BRCA2* and GIST has been reported. An individual with a *BRCA2* 8642del3insC germline mutation developed prostate cancer, breast cancer and GIST (94).

Tumor suppressor genes in GIST

Neurofibromatosis type1 is an inheritable disease caused by bi-allelic loss of the *NF1* gene (95). Neurofibromin contains a GAP-related domain (GRD) that is responsible for converting active Ras-GTP to inactive Ras-GDP, and negatively regulates RAS signaling. Individuals with *NF1* mutations are at high risk of developing GISTs. *NF1*-associated GISTs are characterized by younger age at onset, location in the duodenum and small intestine, small size, tumor multiplicity and an indolent clinical course (9,96). Most *NF1*-associated GISTs are CD117-positive, have a spindle cell morphology, and generally show low mitotic rates. Hyperplastic foci (diffuse and focal) of CD117-positive ICCs are thought to be likely precursor lesions for GISTs, and precursors of *NF1*-associated GIST are often found around nerve plexuses. *NF1*-associated GISTs do not harbor *KIT/PDGFRA* mutations; instead, loss of NF1 leads to MAPK signal activation, while PI3K-AKT and JAK-STAT signals are less active than in common GISTs (97).

One recent study revealed that intragenic deletion of dystrophin (DMD) is a frequent event in metastatic GISTs (98). Dystrophin is expressed in sorted ICCs and inhibits GIST cell invasion, migration, anchorage independence and invadopodia formation, suggesting it plays a tumor suppressor and anti-metastatic role in GIST.

TP53 is the most frequently mutated gene in human malignancies. p53 acts as a tumor suppressor by mediating DNA repair, cell cycle arrest and apoptosis. Wild-type p53 is present at only low levels in normal cells due to its short half-life. *TP53* mutant tumor cells are immunohistochemically positive for p53 because changes in its structure inhibit its ubiquitination and proteasomal degradation (99). Within GISTs, the rate of p53 positivity increases along with elevations in the mitotic index and tumor size (100). The p53 positivity is lower in gastric than intestinal GISTs, and is associated with epithelioid cell morphology, mucosal invasion, risk category and worse clinical outcomes (101). Murine double-minute 2 (MDM2) is an E3 ubiquitin ligase that negatively regulates p53 by mediating its ubiquitination and degradation (102). Induction of p53 through MDM2 inhibition exerts a moderate growth suppressive effect in *TP53* wild-type GIST cells, suggesting p53 modulation may be an effective therapeutic strategy (103).

Chromosomal alterations in GIST

Chromosomal aberrations are prevalent among GISTs, with approximately 60% to 70% of all GISTs exhibiting alterations in chromosome 14, including loss of 14q and monosomy 14 (104,105). Loss of 14q is associated with gastric location, predominantly stable karyotypes, and favorable clinical outcomes (12). In addition, nearly half of GISTs show loss of 22q, while losses of 1p, 9p, 10q, 11p, 13q, 15q and 17p are also reported with lesser frequencies (12,106). Loss of 1p is associated with intestinal location, increased capacity for cytogenetic complexity and worse clinical outcomes, while loss of 22q is associated with increased capacity for cytogenetic complexity and poor disease-free survival (12). Losses of 9p, 11p and17p are also significantly associated with the GIST malignancy (104-107).

A number of functionally important genes are located in the regions frequently deleted in GISTs, including *PARP2*, *APEX1*, and *NDRG2* at 14q11.2; *SIVA* at 14q32.33; *MAX* at 14q23.3; and *NF2* at 22q12.2 (108). *PARP2* suppresses genomic instability by regulating DNA repair and apoptosis (109). *APEX1* also encodes a DNA repair enzyme implicated in the base excision pathway (110). *NDRG2* is downregulated in various tumor types (111,112) and acts as a tumor suppressor by inhibiting tumor proliferation and promoting apoptosis (112,113). *SIVA* encodes a pro-apoptotic protein that binds to the tumor necrosis factor receptor CD27 (114). *MAX* encodes a basic helix-loop-helix leucine zipper transcription factor that interacts with MYC (115). Hemizygous or homozygous inactivating mutations of MAX are reported in 21% of all GISTs (17% of sporadic GISTs and 50% of sporadic and NF-1-associated GISTs) (115). Inactivation of MAX is also reported in microGISTs, suggesting its early onset during the development of GISTs (115). NF2 encodes the tumor suppressor protein merlin, which suppresses tumor cell growth by inhibiting the activities of RAS and RAC (108,116).

Gains and high level amplifications at 8q (including *MYC*) and 17q (including *ERBB2*) are significantly associated with metastatic GISTs, while those at 20q (including *AIB1*, *AIB3*, *PTPN1* and *MYBL2*) are found in malignant primary and metastatic GISTs (105). *AIB1*, also referred to as nuclear receptor coactivator 3 (*NCOA3*), was first identified in a frequently amplified region in breast

cancer (117). *PTPN1* (also known as *PTP1B*) is involved in the regulation of cell growth, while *MYBL2* is associated with cell cycle progression (118,119).

Epigenetic abnormalities in GIST

DNA methylation is an important mechanism for regulating gene expression, and hypermethylation of CpG islands is a major mechanism by which tumor suppressor genes are inactivated within tumor cells. Saito *et al.* analyzed a series of representative CpG islands and found methylation of *MLH1*, *p73*, *p15*, *p16*, *CDH1* (E-cadherin), *MGMT*, *MINT1* and *MINT2* in GISTs, although the methylation status was not associated with *KIT* or *PDGFRA* mutations (120). They also concluded that 57% of GISTs exhibit hypermethylation of multiple CpG islands, which is referred as the CpG island methylator phenotype (120). Another study found that six genes (*MGMT*, *p16*, *RASSF1A*, *CDH1*, *MLH1* and *APC*) are commonly methylated in GISTs and that methylation of *CDH1* correlates with early recurrence and a poor prognosis in gastric GIST patients (13). *p16* encodes a cyclin-dependent kinase inhibitor that negatively regulates G1/S-phase transition, while methylation and reduced *p16* expression correlate with larger tumor size and poorer outcomes in GIST patients (121). A genome-wide DNA methylation analysis revealed that methylation of *RASSF1A*, *REC8*, and *PAX3* are associated with the malignancy of GISTs (122).

Seventy to 80% of GISTs are immunohistochemically positive for the hematopoietic marker CD34 (123), and expression of CD34 is regulated through DNA methylation in gastric *PDGFRA*-mutant GISTs (124). Hypermethylation of *PTEN* is observed in GIST cells after long-term exposure to the tyrosine kinase inhibitor sunitinib, which suggests epigenetic silencing of *PTEN* may lead to drug-resistance in GISTs treated with tyrosine kinase inhibitors (125). Recent studies showed that microRNA (miRNA) genes are targets of aberrant DNA methylation in cancer, and we reported methylation-associated silencing of *miR-34a* and *miR-335* in GIST cells (126).

DNA hypomethylation is associated with oncogene activation and chromosomal instability in various tumor types. ENDOGLIN/CD105 (ENG) is a transmembrane glycoprotein and auxiliary unit of the transforming growth factor-β (TGF-β) receptor encoded by *ENG*, which is overexpressed in KIT-positive GISTs (127). The elevated *ENG* expression is strongly associated with malignant and high-risk GISTs, and its overexpression is reportedly the result of DNA hypomethylation (127). About 45% of the human genome is composed of repetitive sequences, and methylation of long interspersed nuclear element-1 (LINE-1) is often used as a surrogate to evaluate global DNA hypomethylation in cancer. We reported that LINE-1 hypomethylation is strongly associated with clinical aggressiveness and DNA copy number aberrations in GISTs (128).

SETD2 is a histone methyltransferase that catalyzes methylation of histone H3 lysine 36 (H3K36), and trimethylation of H3K36 (H3K36me3) is a mark of active transcription (129). SETD2 mutations were recently identified in high-risk and metastatic GISTs (14). Loss of SETD2 is associated with reduced H3K36me3, DNA hypomethylated heterochromatin, and significantly worse outcomes in GIST patients, which suggests SETD2 is a novel GIST tumor suppressor (14).

Noncoding RNAs in GIST

Noncoding RNAs, including miRNAs and long noncoding RNAs (lncRNAs), play important roles in the development of various tumor types. miRNAs are small RNA molecules approximately 22 nt in length. Mature miRNAs are incorporated into RISC complexes and act to cleave complementary messenger RNA, or they repress translation by binding to the short complementary 3'-UTR region (130). Among their various functions, miRNAs are involved in cell proliferation, differentiation and apoptosis, and a number of miRNAs reportedly act as tumor suppressors or oncogenes (oncomir).

In GISTs, miRNA expression patterns are associated with tumor locations, risk classification and *KIT/PDGRFRA* mutation status (131,132). Because a large miRNA cluster is located in 14q32.31, loss of 14q is strongly associated with decreased expression of those miRNAs (131,132). Moreover, analysis using next generation sequencing identified a series of miRNAs differentially expressed in GISTs. These include *miR-509-3p* and *miR-215-5p*, expression of which is associated with cell type and risk grade (133). Another study showed that *miR-133b* is downregulated and its putative target gene, *fascin-1*, is overexpressed in high-risk GISTs (134). We showed that elevated expression of *miR-196a* is associated with high grade tumors and poor prognosis (15), while decreased expression of *miR-186* correlates with post-operative recurrence (135). miRNAs also impact the drug sensitivities of GISTs, and overexpression of *miR-125a-5p*

and *miR-107* is associated with imatinib resistance (136). By contrast, *miR-218* increases the sensitivity of GIST cells to imatinib by inhibiting the PI3K/AKT pathway (137).

Several studies have shown functional interactions between miRNAs and *KIT* in GISTs. For instance, expression of *miR-221* and *miR-222* correlates inversely with *KIT* expression in GISTs, suggesting these miRNAs may negatively regulate *KIT* expression (138). Other studies showed that members of the *miR-17-92 and miR-221/222* clusters target *KIT* and *ETV1* (139), and that *miR-494* targets KIT (140). These results are indicative of the therapeutic potential of miRNAs for treatment of GISTs.

LncRNAs are generally defined as transcribed RNAs that do not have protein coding potential and are greater than 200 nt in length (141). LncRNAs exert their molecular effects by interacting with other cellular molecules, including DNA, protein and RNA, and through those interactions regulate various cancer-related pathways (142). Playing important roles in metastatic tumors, *HOTAIR* (HOX transcript antisense intergenic RNA) is one of the most extensively studied oncogenic lncRNAs (143,144). *HOTAIR* interacts with polycomb repressive complex 2 (PRC2) through its 5' terminal binding domain, and promotes H3K27me3-mediated gene silencing (145). We showed that overexpression of *HOTAIR* is associated with aggressiveness, and that *HOTAIR* knockdown suppressed the invasiveness of GIST cells (15). A more recent study showed that *HOTAIR* induces SUZ12-dependent hypermethylation of the protocadherin 10 (*PCDH10*) gene promoter in GIST cells, which further confirms the role of *HOTAIR* in GIST malignancy (146).

Conclusions

Molecular biological studies have greatly improved our understanding of the pathogenesis of GISTs, which has led to the successful use of receptor tyrosine kinase inhibitors for their treatment. In addition, recent advances in genomic and epigenomic analyses have enabled us to identify novel alterations that could be causally associated with GIST development. However, drug resistance due to additional mutations acquired during treatment remains a serious issue to overcome. Moreover, no specific treatments for wild-type GIST have yet been developed. It is anticipated that further molecular characterization of GISTs will contribute to the discovery of novel therapeutic targets and improved management of GISTs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumor. J Surg Oncol 2011;104:865-73.
2. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors. Science 1998;279:577-80.
3. West RB, Corless CL, Chen X, et al. The Novel Marker, DOG1, Is Expressed Ubiquitously in Gastrointestinal Stromal Tumors Irrespective of KIT or PDGFRA Mutation Status. Am J Pathol 2004;165:107-13.
4. Espinosa I, Lee CH, Kim MK, et al. A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. Am J Surg Pathol 2008;32:210-8.
5. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009;33:1401-8.
6. Duensing A, Joseph NE, Medeiros F, et al. Protein Kinase C θ (PKCθ) Expression and Constitutive Activation in Gastrointestinal Stromal Tumors (GISTs). Cancer Res 2004;64:5127-31.
7. Duensing A, Medeiros F, McConarty B, et al. Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). Oncogene 2004;23:3999-4006.
8. Miranda C, Nucifora M, Molinari F, et al. KRAS and BRAF mutations predict primary resistance to imatinib in gastrointestinal stromal tumors. Clin Cancer Res 2012;18:1769-76.
9. Andersson J, Sihto H, Meis-Kindblom JM, et al. NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics. Am J Surg Pathol 2005;29:1170-6.
10. Nannini M, Astolfi A, Urbini M, et al. Integrated genomic study of quadruple-WT GIST (KIT/PDGFRA/SDH/RAS pathway wild-type GIST). BMC Cancer 2014;14:685.
11. Pantaleo MA, Urbini M, Indio V, et al. Genome-Wide

Analysis Identifies MEN1 and MAX Mutations and a Neuroendocrine-Like Molecular Heterogeneity in Quadruple WT GIST. Mol Cancer Res 2017;15:553-62.
12. Gunawan B, Heydebreck Av, Sander B, et al. An oncogenetic tree model in gastrointestinal stromal tumours (GISTs) identifies different pathways of cytogenetic evolution with prognostic implications. J Pathol 2007;211:463-70.
13. House M. Tumor suppressor gene hypermethylation as a predictor of gastric stromal tumor behavior. J Gastrointest Surg 2003;7:1004-14.
14. Huang KK, McPherson JR, Tay ST, et al. SETD2 histone modifier loss in aggressive GI stromal tumours. Gut 2016;65:1960-72.
15. Niinuma T, Suzuki H, Nojima M, et al. Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors. Cancer Res 2012;72:1126-36.
16. Agaimy A, Wunsch PH, Hofstaedter F, et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol 2007;31:113-20.
17. Kawanowa K, Sakuma Y, Sakurai S, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006;37:1527-35.
18. Anderson W, O'Sullivan B, Hughes F, et al. Microscopic gastrointestinal stromal tumours: a clinical and molecular study of 13 cases. Histopathology 2017;70:211-6.
19. Besmer P, Murphy JE, George PC, et al. A new acute transforming feline retrovirus and relationship of its oncogene v-kit with the protein kinase gene family. Nature 1986;320:415-21.
20. Hanks SK, Quinn AM, Hunter T. The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. Science 1988;241:42.
21. Mol CD, Dougan DR, Schneider TR, et al. Structural Basis for the Autoinhibition and STI-571 Inhibition of c-Kit Tyrosine Kinase. J Biol Chem 2004;279:31655-63.
22. Lev S, Yarden Y, Givol D. Dimerization and activation of the kit receptor by monovalent and bivalent binding of the stem cell factor. J Biol Chem 1992;267:15970-7.
23. Wozniak A, Rutkowski P, Piskorz A, et al. Prognostic value of KIT/PDGFRA mutations in gastrointestinal stromal tumours (GIST): Polish Clinical GIST Registry experience. Ann Oncol 2012;23:353-60.
24. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093-103.
25. Rubin BP, Antonescu CR, Scott-Browne JP, et al. A Knock-In Mouse Model of Gastrointestinal Stromal Tumor Harboring Kit K641E. Cancer Res 2005;65:6631.
26. Sommer G, Agosti V, Ehlers I, et al. Gastrointestinal stromal tumors in a mouse model by targeted mutation of the Kit receptor tyrosine kinase. Proc Natl Acad Sci U S A 2003;100:6706-11.
27. Rossi F, Ehlers I, Agosti V, et al. Oncogenic Kit signaling and therapeutic intervention in a mouse model of gastrointestinal stromal tumor. Proc Natl Acad Sci U S A 2006;103:12843-8.
28. Chi P, Chen Y, Zhang L, et al. ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. Nature 2010;467:849-53.
29. Ran L, Sirota I, Cao Z, et al. Combined inhibition of MAP kinase and KIT signaling synergistically destabilizes ETV1 and suppresses GIST tumor growth. Cancer Discov 2015;5:304-15.
30. Hayashi Y, Bardsley MR, Toyomasu Y, et al. Platelet-Derived Growth Factor Receptor-alpha Regulates Proliferation of Gastrointestinal Stromal Tumor Cells With Mutations in KIT by Stabilizing ETV1. Gastroenterology 2015;149:420-32.e16.
31. Fumo G, Akin C, Metcalfe DD, et al. 17-Allylamino-17-demethoxygeldanamycin (17-AAG) is effective in down-regulating mutated, constitutively activated KIT protein in human mast cells. Blood 2004;103:1078-84.
32. Bauer S, Yu LK, Demetri GD, et al. Heat shock protein 90 inhibition in imatinib-resistant gastrointestinal stromal tumor. Cancer Res 2006;66:9153-61.
33. Marino-Enriquez A, Ou WB, Cowley G, et al. Genome-wide functional screening identifies CDC37 as a crucial HSP90-cofactor for KIT oncogenic expression in gastrointestinal stromal tumors. Oncogene 2014;33:1872-6.
34. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci U S A 2009;106:1542-7.
35. Wardelmann E, Losen I, Hans V, et al. Deletion of Trp-557 and Lys-558 in the juxtamembrane domain of the c-kit protooncogene is associated with metastatic behavior of gastrointestinal stromal tumors. Int J Cancer 2003;106:887-95.
36. Martin-Broto J, Gutierrez A, Garcia-del-Muro X, et al. Prognostic time dependence of deletions affecting codons 557 and/or 558 of KIT gene for relapse-free survival (RFS) in localized GIST: a Spanish Group for Sarcoma Research (GEIS) Study. Ann Oncol 2010;21:1552-7.

37. Wozniak A, Rutkowski P, Schoffski P, et al. Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a european multicenter analysis based on ConticaGIST. Clin Cancer Res 2014;20:6105-16.
38. Steigen SE, Eide TJ, Wasag B, et al. Mutations in gastrointestinal stromal tumors – a population-based study from Northern Norway. APMIS 2007;115:289-98.
39. Antonescu CR, Sommer G, Sarran L, et al. Association of Exon 9 Mutations with Nongastric Primary Site and Aggressive Behavior. Clin Cancer Res 2003;9:3329.
40. Lasota J, Corless CL, Heinrich MC, et al. Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases. Mod Pathol 2008;21:476-84.
41. Lux ML, Rubin BP, Biase TL, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. Am J Pathol 2000;156:791-5.
42. Huss S, Kunstlinger H, Wardelmann E, et al. A subset of gastrointestinal stromal tumors previously regarded as wild-type tumors carries somatic activating mutations in KIT exon 8 (p.D419del). Mod Pathol 2013;26:1004-12.
43. Ito T, Yamamura M, Hirai T, et al. Gastrointestinal stromal tumors with exon 8 c-kit gene mutation might occur at extragastric sites and have metastasis-prone nature. Int J Clin Exp Pathol 2014;7:8024-31.
44. Nishida T, Kanda T, Nishitani A, et al. Secondary mutations in the kinase domain of the KIT gene are predominant in imatinib-resistant gastrointestinal stromal tumor. Cancer Sci 2008;99:799-804.
45. Gao J, Tian Y, Li J, et al. Secondary mutations of c-KIT contribute to acquired resistance to imatinib and decrease efficacy of sunitinib in Chinese patients with gastrointestinal stromal tumors. Med Oncol 2013;30:522.
46. Xu Z, Huo X, Tang C, et al. Frequent KIT mutations in human gastrointestinal stromal tumors. Sci Rep 2014;4:5907.
47. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA Activating Mutations in Gastrointestinal Stromal Tumors. Science 2003;299:708.
48. Matei D, Satpathy M, Cao L, et al. The platelet-derived growth factor receptor alpha is destabilized by geldanamycins in cancer cells. J Biol Chem 2007;282:445-53.
49. Lasota J, Dansonka-Mieszkowska A, Sobin LH, et al. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. Lab Invest 2004;84:874-83.
50. Sakurai S, Hasegawa T, Sakuma Y, et al. Myxoid epithelioid gastrointestinal stromal tumor (GIST) with mast cell infiltrations: A subtype of GIST with mutations of platelet-derived growth factor receptor alpha gene. Hum Pathol 2004;35:1223-30.
51. Lasota J, Stachura J, Miettinen M. GISTs with PDGFRA exon 14 mutations represent subset of clinically favorable gastric tumors with epithelioid morphology. Lab Invest 2006;86:94-100.
52. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357-64.
53. Hirota S, Nishida T, Isozaki K, et al. Familial gastrointestinal stromal tumors associated with dysphagia and novel type germline mutation of KIT gene. Gastroenterology 2002;122:1493-9.
54. Chompret A, Kannengiesser C, Barrois M, et al. PDGFRA germline mutation in a family with multiple cases of gastrointestinal stromal tumor. Gastroenterology 2004;126:318-21.
55. Beghini A, Tibiletti MG, Roversi G, et al. Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and urticaria pigmentosa. Cancer 2001;92:657-62.
56. Lasota J, Miettinen M. A new familial GIST identified. Am J Surg Pathol 2006;30:1342.
57. Robson ME, Glogowski E, Sommer G, et al. Pleomorphic characteristics of a germ-line KIT mutation in a large kindred with gastrointestinal stromal tumors, hyperpigmentation, and dysphagia. Clin Cancer Res 2004;10:1250-4.
58. Nishida T, Hirota S, Taniguchi M, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet 1998;19:323-4.
59. Hartmann K, Wardelmann E, Ma Y, et al. Novel germline mutation of KIT associated with familial gastrointestinal stromal tumors and mastocytosis. Gastroenterology 2005;129:1042-6.
60. Chen H, Hirota S, Isozaki K, et al. Polyclonal nature of diffuse proliferation of interstitial cells of Cajal in patients with familial and multiple gastrointestinal stromal tumours. Gut 2002;51:793-6.
61. Rutter J, Winge DR, Schiffman JD. Succinate dehydrogenase - Assembly, regulation and role in human disease. Mitochondrion 2010;10:393-401.
62. Gill AJ, Lipton L, Taylor J, et al. Germline SDHC mutation presenting as recurrent SDH deficient GIST and

renal carcinoma. Pathology 2013;45:689-91.
63. Gaal J, Stratakis CA, Carney JA, et al. SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. Mod Pathol 2011;24:147-51.
64. Dwight T, Benn DE, Clarkson A, et al. Loss of SDHA expression identifies SDHA mutations in succinate dehydrogenase-deficient gastrointestinal stromal tumors. Am J Surg Pathol 2013;37:226-33.
65. Miettinen M, Killian JK, Wang ZF, et al. Immunohistochemical loss of succinate dehydrogenase subunit A (SDHA) in gastrointestinal stromal tumors (GISTs) signals SDHA germline mutation. Am J Surg Pathol 2013;37:234-40.
66. Mason EF, Hornick JL. Succinate dehydrogenase deficiency is associated with decreased 5-hydroxymethylcytosine production in gastrointestinal stromal tumors: implications for mechanisms of tumorigenesis. Mod Pathol 2013;26:1492-7.
67. Killian JK, Kim SY, Miettinen M, et al. Succinate dehydrogenase mutation underlies global epigenomic divergence in gastrointestinal stromal tumor. Cancer Discov 2013;3:648-57.
68. Gill AJ. Succinate dehydrogenase (SDH) and mitochondrial driven neoplasia. Pathology 2012;44:285-92.
69. Chou A, Chen J, Clarkson A, et al. Succinate dehydrogenase-deficient GISTs are characterized by IGF1R overexpression. Mod Pathol 2012;25:1307-13.
70. Belinsky MG, Rink L, Flieder DB, et al. Overexpression of insulin-like growth factor 1 receptor and frequent mutational inactivation of SDHA in wild-type SDHB-negative gastrointestinal stromal tumors. Genes Chromosomes Cancer 2013;52:214-24.
71. Lasota J, Wang Z, Kim SY, et al. Expression of the receptor for type i insulin-like growth factor (IGF1R) in gastrointestinal stromal tumors: an immunohistochemical study of 1078 cases with diagnostic and therapeutic implications. Am J Surg Pathol 2013;37:114-9.
72. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst 2000;92:1472-89.
73. Tarn C, Rink L, Merkel E, et al. Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors. Proc Natl Acad Sci U S A 2008;105:8387-92.
74. Carney JA. Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney Triad): natural history, adrenocortical component, and possible familial occurrence. Mayo Clin Proc 1999;74:543-52.
75. Zhang L, Smyrk TC, Young WF Jr, et al. Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. Am J Surg Pathol 2010;34:53-64.
76. Carney JA, Sheps SG, Go VL, et al. The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med 1977;296:1517-8.
77. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002;108:132-9.
78. Simanshu DK, Nissley DV, McCormick F. RAS Proteins and Their Regulators in Human Disease. Cell 2017;170:17-33.
79. Scheffzek K, Ahmadian MR, Kabsch W, et al. The Ras-RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants. Science 1997;277:333-8.
80. Cheung M, Sharma A, Madhunapantula SV, et al. Akt3 and Mutant V600 B-Raf Cooperate to Promote Early Melanoma Development. Cancer Res 2008;68:3429.
81. Oliveira C, Velho S, Moutinho C, et al. KRAS and BRAF oncogenic mutations in MSS colorectal carcinoma progression. Oncogene 2007;26:158-63.
82. Mitsutake N, Knauf JA, Mitsutake S, et al. Conditional BRAF V600E Expression Induces DNA Synthesis, Apoptosis, Dedifferentiation, and Chromosomal Instability in Thyroid PCCL3 Cells. Cancer Res 2005;65:2465.
83. Matos P, Oliveira C, Velho S, et al. B-Raf(V600E) cooperates with alternative spliced Rac1b to sustain colorectal cancer cell survival. Gastroenterology 2008;135:899-906.
84. Daniels M, Lurkin I, Pauli R, et al. Spectrum of KIT/PDGFRA/BRAF mutations and Phosphatidylinositol-3-Kinase pathway gene alterations in gastrointestinal stromal tumors (GIST). Cancer Lett 2011;312:43-54.
85. Hostein I, Faur N, Primois C, et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol 2010;133:141-8.
86. Rossi S, Gasparotto D, Miceli R, et al. KIT, PDGFRA, and BRAF Mutational Spectrum Impacts on the Natural History of Imatinib-naive Localized GIST A Population-based Study. Am J Surg Pathol 2015;39:922-30.
87. Huss S, Pasternack H, Ihle MA, et al. Clinicopathological and molecular features of a large cohort of gastrointestinal stromal tumors (GISTs) and review of the literature: BRAF mutations in KIT/PDGFRA wild-type GISTs are rare

events. Hum Pathol 2017;62:206-14.
88. Agaimy A, Terracciano LM, Dirnhofer S, et al. V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRA wild-type gastrointestinal stromal tumours. J Clin Pathol 2009;62:613-6.
89. Shi SS, Wu N, He Y, et al. EGFR gene mutation in gastrointestinal stromal tumours. Histopathology 2017;71:553-61.
90. Shi E, Chmielecki J, Tang CM, et al. FGFR1 and NTRK3 actionable alterations in "Wild-Type" gastrointestinal stromal tumors. J Transl Med 2016;14:339.
91. Wai DH, Knezevich SR, Lucas T, et al. The ETV6-NTRK3 gene fusion encodes a chimeric protein tyrosine kinase that transforms NIH3T3 cells. Oncogene 2000;19:906-15.
92. Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell 2002;2:367-76.
93. Toda-Ishii M, Akaike K, Suehara Y, et al. Clinicopathological effects of protein phosphatase 2, regulatory subunit A, alpha mutations in gastrointestinal stromal tumors. Mod Pathol 2016;29:1424-32.
94. Waisbren J, Uthe R, Siziopikou K, et al. BRCA 1/2 gene mutation and gastrointestinal stromal tumours: a potential association. BMJ Case Rep 2015;2015. pii: bcr2014208830.
95. Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type 1 (NF1). J Med Genet 1996;33:2-17.
96. Miettinen M, Fetsch JF, Sobin LH, et al. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol 2006;30:90-6.
97. Maertens O, Prenen H, Debiec-Rychter M, et al. Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. Hum Mol Genet 2006;15:1015-23.
98. Wang Y, Marino-Enriquez A, Bennett RR, et al. Dystrophin is a tumor suppressor in human cancers with myogenic programs. Nat Genet 2014;46:601-6.
99. Baas IO, Mulder JW, Offerhaus GJ, et al. An evaluation of six antibodies for immunohistochemistry of mutant p53 gene product in archival colorectal neoplasms. J Pathol 1994;172:5-12.
100. Al-Bozom IA. p53 expression in gastrointestinal stromal tumors. Pathol Int 2001;51:519-23.
101. Feakins RM. The expression of p53 and bcl-2 in gastrointestinal stromal tumours is associated with anatomical site, and p53 expression is associated with grade and clinical outcome. Histopathology 2005;46:270-9.
102. Moll UM, Petrenko O. The MDM2-p53 Interaction. Mol Cancer Res 2003;1:1001-8.
103. Henze J, Muhlenberg T, Simon S, et al. p53 modulation as a therapeutic strategy in gastrointestinal stromal tumors. PLoS One 2012;7:e37776.
104. Kim NG, Kim JJ, Ahn JY, et al. Putative chromosomal deletions on 9p, 9q and 22q occur preferentially in malignant gastrointestinal stromal tumors. Int J Cancer 2000;85:633-8.
105. El-Rifai We, Sarlomo-Rikala M, Andersson LC, et al. DNA Sequence Copy Number Changes in Gastrointestinal Stromal Tumors: Tumor Progression and Prognostic Significance. Cancer Res 2000;60:3899.
106. Wozniak A, Sciot R, Guillou L, et al. Array CGH analysis in primary gastrointestinal stromal tumors: cytogenetic profile correlates with anatomic site and tumor aggressiveness, irrespective of mutational status. Genes Chromosomes Cancer 2007;46:261-76.
107. Gunawan B, Bergmann F, Höer J, et al. Biological and clinical significance of cytogenetic abnormalities in low-risk and high-risk gastrointestinal stromal tumors. Hum Pathol 2002;33:316-21.
108. Assamaki R, Sarlomo-Rikala M, Lopez-Guerrero JA, et al. Array comparative genomic hybridization analysis of chromosomal imbalances and their target genes in gastrointestinal stromal tumors. Genes Chromosomes Cancer 2007;46:564-76.
109. Fouquin A, Guirouilh-Barbat J, Lopez B, et al. PARP2 controls double-strand break repair pathway choice by limiting 53BP1 accumulation at DNA damage sites and promoting end-resection. Nucleic Acids Res 2017;45:12325-39.
110. Madhusudan S, Smart F, Shrimpton P, et al. Isolation of a small molecule inhibitor of DNA base excision repair. Nucleic Acids Res 2005;33:4711-24.
111. Kim YJ, Yoon SY, Kim JT, et al. NDRG2 expression decreases with tumor stages and regulates TCF/beta-catenin signaling in human colon carcinoma. Carcinogenesis 2009;30:598-605.
112. Lorentzen A, Lewinsky RH, Bornholdt J, et al. Expression profile of the N-myc Downstream Regulated Gene 2 (NDRG2) in human cancers with focus on breast cancer. BMC Cancer 2011;11:14.
113. Liu N, Wang L, Liu X, et al. Promoter methylation, mutation, and genomic deletion are involved in the decreased NDRG2 expression levels in several cancer cell lines. Biochem Biophys Res Commun 2007;358:164-9.

114. Prasad KV, Ao Z, Yoon Y, et al. CD27, a member of the tumor necrosis factor receptor family, induces apoptosis and binds to Siva, a proapoptotic protein. Proc Natl Acad Sci U S A 1997;94:6346-51.
115. Schaefer IM, Wang Y, Liang CW, et al. MAX inactivation is an early event in GIST development that regulates p16 and cell proliferation. Nat Commun 2017;8:14674.
116. Morrison H, Sperka T, Manent J, et al. Merlin/Neurofibromatosis Type 2 Suppresses Growth by Inhibiting the Activation of Ras and Rac. Cancer Res 2007;67:520.
117. Guan XY, Xu J, Anzick SL, et al. Hybrid selection of transcribed sequences from microdissected DNA: isolation of genes within amplified region at 20q11-q13.2 in breast cancer. Cancer Res 1996;56:3446-50.
118. Tonks NK, Muthuswamy SK. A brake becomes an accelerator: PTP1B--a new therapeutic target for breast cancer. Cancer Cell 2007;11:214-6.
119. Thorner AR, Hoadley KA, Parker JS, et al. In vitro and in vivo analysis of B-Myb in basal-like breast cancer. Oncogene 2009;28:742-51.
120. Saito K, Sakurai S, Sano T, et al. Aberrant methylation status of known methylation-sensitive CpG islands in gastrointestinal stromal tumors without any correlation to the state of c-kit and PDGFRA gene mutations and their malignancy. Cancer Sci 2008;99:253-9.
121. Mitomi H, Fukui N, Kishimoto I, et al. Role for p16(INK4a) in progression of gastrointestinal stromal tumors of the stomach: alteration of p16(INK4a) network members. Hum Pathol 2011;42:1505-13.
122. Okamoto Y, Sawaki A, Ito S, et al. Aberrant DNA methylation associated with aggressiveness of gastrointestinal stromal tumour. Gut 2012;61:392-401.
123. Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical Spectrum of GISTs at Different Sites and Their Differential Diagnosis with a Reference to CD117 (KIT). Mod Pathol 2000;13:1134-42.
124. Bure I, Braun A, Kayser C, et al. The expression of hematopoietic progenitor cell antigen CD34 is regulated by DNA methylation in a site-dependent manner in gastrointestinal stromal tumours. Int J Cancer 2017;141:2296-304.
125. Yang J, Ikezoe T, Nishioka C, et al. Long-term exposure of gastrointestinal stromal tumor cells to sunitinib induces epigenetic silencing of the PTEN gene. Int J Cancer 2012;130:959-66.
126. Isosaka M, Niinuma T, Nojima M, et al. A Screen for Epigenetically Silenced microRNA Genes in Gastrointestinal Stromal Tumors. PLoS One 2015;10:e0133754.
127. Gromova P, Rubin BP, Thys A, et al. ENDOGLIN/CD105 is expressed in KIT positive cells in the gut and in gastrointestinal stromal tumours. J Cell Mol Med 2012;16:306-17.
128. Igarashi S, Suzuki H, Niinuma T, et al. A novel correlation between LINE-1 hypomethylation and the malignancy of gastrointestinal stromal tumors. Clin Cancer Res 2010;16:5114-23.
129. Edmunds JW, Mahadevan LC, Clayton AL. Dynamic histone H3 methylation during gene induction: HYPB/Setd2 mediates all H3K36 trimethylation. EMBO J 2008;27:406-20.
130. Bartel DP. MicroRNAs: Genomics, Biogenesis, Mechanism, and Function. Cell 2004;116:281-97.
131. Choi HJ, Lee H, Kim H, et al. MicroRNA expression profile of gastrointestinal stromal tumors is distinguished by 14q loss and anatomic site. Int J Cancer 2010;126:1640-50.
132. Haller F, von Heydebreck A, Zhang JD, et al. Localization- and mutation-dependent microRNA (miRNA) expression signatures in gastrointestinal stromal tumours (GISTs), with a cluster of co-expressed miRNAs located at 14q32.31. J Pathol 2010;220:71-86.
133. Gyvyte U, Juzenas S, Salteniene V, et al. MiRNA profiling of gastrointestinal stromal tumors by next-generation sequencing. Oncotarget 2017;8:37225-38.
134. Yamamoto H, Kohashi K, Fujita A, et al. Fascin-1 overexpression and miR-133b downregulation in the progression of gastrointestinal stromal tumor. Mod Pathol 2013;26:563-71.
135. Niinuma T, Kai M, Kitajima H, et al. Downregulation of miR-186 is associated with metastatic recurrence of gastrointestinal stromal tumors. Oncol Lett 2017;14:5703-10.
136. Akcakaya P, Caramuta S, Ahlen J, et al. microRNA expression signatures of gastrointestinal stromal tumours: associations with imatinib resistance and patient outcome. Br J Cancer 2014;111:2091-102.
137. Fan R, Zhong J, Zheng S, et al. microRNA-218 increase the sensitivity of gastrointestinal stromal tumor to imatinib through PI3K/AKT pathway. Clin Exp Med 2015;15:137-44.
138. Koelz M, Lense J, Wrba F, et al. Down-regulation of miR-221 and miR-222 correlates with pronounced Kit expression in gastrointestinal stromal tumors. Int J Oncol 2011;38:503-11.
139. Gits CM, van Kuijk PF, Jonkers MB, et al. MiR-17-92 and miR-221/222 cluster members target KIT and ETV1 in human gastrointestinal stromal tumours. Br J Cancer

2013;109:1625-35.
140. Kim WK, Park M, Kim YK, et al. MicroRNA-494 downregulates KIT and inhibits gastrointestinal stromal tumor cell proliferation. Clin Cancer Res 2011;17:7584-94.
141. Iyer MK, Niknafs YS, Malik R, et al. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 2015;47:199-208.
142. Schmitt AM, Chang HY. Long Noncoding RNAs in Cancer Pathways. Cancer Cell 2016;29:452-63.
143. Liu XH, Liu ZL, Sun M, et al. The long non-coding RNA HOTAIR indicates a poor prognosis and promotes metastasis in non-small cell lung cancer. BMC Cancer 2013;13:464.
144. Sorensen KP, Thomassen M, Tan Q, et al. Long non-coding RNA HOTAIR is an independent prognostic marker of metastasis in estrogen receptor-positive primary breast cancer. Breast Cancer Res Treat 2013;142:529-36.
145. Bhan A, Mandal SS. LncRNA HOTAIR: A master regulator of chromatin dynamics and cancer. Biochim Biophys Acta 2015;1856:151-64.
146. Lee NK, Lee JH, Kim WK, et al. Promoter methylation of PCDH10 by HOTAIR regulates the progression of gastrointestinal stromal tumors. Oncotarget 2016;7:75307-18.

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Contrast enhanced ultrasound guided biopsy shows higher positive sampling rate than conventional ultrasound guided biopsy for gastrointestinal stromal tumors diagnosis

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Background: With the development of tyrosine kinase receptor inhibitor target therapy for gastrointestinal stromal tumors (GISTs), pre-treatment histopathological and immunocytochemical diagnosis of GISTs becomes important for clinical management. The purpose of this study was to compare the diagnostic accuracy of conventional ultrasound (US) guided *vs*. contrast-enhanced ultrasound (CEUS)-guided core needle biopsy for GISTs.

Materials and methods: Between September 2011 and July 2015, 53 GIST patients underwent 61 conventional US guided or CEUS guided core needle biopsy at the Cancer Hospital & Institute, Peking Union Medical College & Chinese Academy of Medical Sciences. The outcomes of the biopsies were analyzed.

Results: The diagnostic yield of CEUS guided biopsy group (96.2%, 27/28) was higher than conventional US guided biopsy group (78.8%, 26/33; P=0.042). The risk of undeterminable biopsy specimens in CEUS group (7.2%, 2/28) was lower than conventional US group (27.3%, 9/33; P=0.042). In both groups none patients had significant complications such as bleeding, pain, perforation or peritonitis after the biopsy.

Conclusions: CEUS guided core needle biopsy for the diagnosis of GIST improved the diagnostic yield and therefore the pre-treatment risk assessment for GIST. The inclusion of CEUS guided biopsy in the diagnostic work-up of advanced or metastatic GIST is recommended.

Keywords: Contrast enhanced ultrasound (CEUS); conventional ultrasound; gastrointestinal stromal tumors (GISTs); biopsy

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common subepithelial mesenchymal neoplasms in the gastrointestinal tract (1). GISTs can occur anywhere throughout the gastrointestinal tract from the esophagus to the anus; however, they are most common in the stomach (50% to 60%) and jejunum/ilium (25% to 30%). Duodenum (5%), colorectum (5% to 10%), and esophagus (1%) are

less common sites (2). These masses are frequently found incidentally on imaging for other reasons; however, patients might also present with abdominal pain, bleeding, or symptoms of a mass effect (3,4). The differential diagnosis is quite broad, including leiomyoma, leiomyosarcoma, undifferentiated sarcomas, lipoma, carcinoid tumor, granular cell tumor, gastrointestinal schwannoma, and neurofibroma. The specific diagnosis of GIST is based on immunocytochemistry. The results of immunohistochemistry tests for GISTs have been reported to be positive for KIT (CD117; 95%), CD34 antigen (70%), smooth muscle actin (30–40%), desmin (<5%), and S-100 protein (<5%) (5).

Virtually all GISTs have the potential for malignant behavior, even those two cm or less in size with bland histological features (6). The main treatment for localized GISTs is surgical resection. For advanced unresectable tumors, GISTs respond poorly to conventional cytotoxic chemotherapy agents and radiation therapy. A target therapy agent, imatinib mesylate (Glivec; Novartis Pharma), is the recommended first-line treatment for recurrence or metastatic GISTs (7). Neoadjuvant imatinib therapy should be considered for unresectable GISTs to avoid significant morbidity or loss of organ function. Many reports have been published on this approach to convert an unresectable mass to one that is surgically approachable or to reduce the morbidity of a procedure (8).

GISTs are grossly soft and fragile tumors with a theoretic risk of tumor hemorrhage and dissemination during biopsy. According to the current consensus of management of GIST, preoperative biopsy is not generally recommended for a resectable lesion in which there is a high suspicion for GIST. However, in the presence of suspected metastatic disease or large locally advanced lesions, a biopsy is indicated to confirm the diagnosis before initiation of imatinib therapy. Image-guided percutaneous biopsies carry the theoretical risk of rupture of the tumor capsule with peritoneal spread of disease. A laparoscopic surgical biopsy also carries the risk of port site metastasis and is not recommended for the diagnosis of GISTs. Endoscopic biopsy is preferred over a percutaneous biopsy; however, conventional endoscopic biopsy using biopsy forceps may not be is effective in obtaining sufficient tissue from the submucosal tumor to confirm the diagnosis. An endoscopic snare biopsy might result in perforation and should be avoided for submucosal tumors (9,10).

However, the actual risk of peritoneal seeding, needle tract seeding, or tumor bleeding of percutaneous biopsies had never been fully evaluated. Yeh *et al.* reported no needle tract seeding or procedure-related tumor bleeding was seen after percutaneous biopsies (11). Furthermore, the failure rate of endoscopic biopsy was higher than that of the percutaneous biopsy group (11). Endoscopic biopsy is more suitable for GISTs with direct mucosal invasion or for those closely contiguous with gastrointestinal mucosa (12). Compared with a conventional endoscopic biopsy, ultrasound (US) guided percutaneous biopsy is a simple and straightforward procedure requiring only local anesthesia. Imaging-guided percutaneous biopsy is particularly indicated for exophytic tumors, GISTs in the jejunum and ileum, and metastatic tumors anywhere in the chest wall, abdomen, and pelvis (11).

In any case, biopsy can obtain non-representative samples and lead to false-negative diagnosis. This is caused by tissue inhomogeneity. For GIST, guidance by conventional US might not be able to identify non-liquefied necrotic tissue in large tumors, leading to unsuccessful biopsies (13). Contrast enhanced ultrasound (CEUS) with micro-bubble based contrast agents (SonoVue®, Bracco, Italy) allows visualization of the macro- and micro-vascularization of various parenchyma and tumors (14-17). CEUS has enabled delimitation of the necrotic areas from the vascularized regions of the tumors. The guarantee of tissue viability is more likely when targeting is performed using this technique. Previous studies have shown the value of CEUS guided biopsy in liver tumors. However, till now no study has investigated the value of CEUS guidance for GIST biopsies. The purpose of this study was to compare the diagnostic accuracy of conventional ultrasound (US) guided *vs.* contrast-enhanced ultrasound (CEUS)-guided core needle biopsy for GISTs. In our series, all patients were scheduled for Imatinib treatment as palliative therapy or neoadjuvant therapy before surgery.

Methods

Patients

The study subjects included consecutive 53 patients with a clinical diagnosis of GIST and scheduled for Imatinib treatment and who underwent core needle biopsies guided by US or CEUS between September 2011 and July 2015. The patients included 29 men and 24 women, aged 27–78 years old (mean: 56 years). Twenty patients had incidental discovery of GIST without symptoms during a health checkup, and the others had symptoms such as dyspepsia (n=8), abdominal distention and pain (n=17), or obstruction of the intestinal or urinary tract (n=8). Nine patients (17.0%) had metastatic recurrence after surgical resection of the primary tumors.

All the patients had no contra-indications to percutaneous biopsy include bleeding tendency and no safe puncture path. Informed consent was obtained from all patients. The study was approved by the ethics committee of Cancer Hospital & Institute, Peking Union Medical College & Chinese Academy of Medical Sciences. The ID of the approval is NCC2013S-006. All patients gave written informed consent before taking part in the study.

Ultrasound-guided needle biopsy

Percutaneous biopsies or transrectal biopsies were guided by transabdominal US or endorectal US, depending on the site of the tumors. Patients were fasted for 8–12 hours before the procedure. All examinations were performed using a Philips iU22 unit (Philips; Bothell, WA, USA). A convex array probe (C5-2) or an end-fire type endorectal probe (C5-9 sec) was utilized. B-mode and color Doppler US exams were preliminarily performed for all patients to choose the maximum solid area of the lesion or the rim parts of the large tumors as the optimal puncture site and to evaluate the safe needle pathway that could avoid vascular structures. The maximal length, echo pattern, and internal vascularity of the tumor were recorded. Patients underwent a cleansing enema before the transrectal ultrasonography and biopsy. The skin was sterilized, and local anesthetic was applied using 1% lidocaine before the percutaneous biopsies. Aiming at the previously determined optimal puncture site, an automatic biopsy gun (Bard Biopsy Systems; Tempe, AZ, USA) combined with an 18-gauge biopsy needle was used to obtain adequate tissue. The whole process was conducted under aseptic conditions. The specimens obtained were fixed and sent for histology and immuno-histochemistry. Patients were monitored for 3–4 hours after the procedure.

Contrast-enhanced ultrasound-guided needle biopsy

Percutaneous biopsies or and transrectal biopsies were guided by transabdominal or endorectal CEUS. Preparations were similar to those for the US-guided biopsies. The tumors were first evaluated using gray scale and Doppler US exams with a Philips iU22 unit (Philips; Bothell, WA, USA). A convex array probe (C5-2) or an end-fire type endorectal probe (C5-9 sec) were utilized. The mechanical index was 0.08–0.11. The focus point was just under the deep margin of the lesion. Thereafter, a 2.4-mL bolus of SonoVue® (Bracco, Italy) was intravenously injected in an antecubital vein, followed by a 5-mL flush with normal saline. The perfusion of the target lesion was continuously observed for at least 3 minutes. The area with the most pronounced contrast enhancement in the arterial phase without necrosis was determined as the target area. Then, a second 1.2 mL dose of SonoVue® was injected for real time guidance following a standardized procedure. An 18-gauge biopsy needle coupled on a BARD automatic biopsy gun was inserted in the targeted area. The specimens obtained were fixed and sent for histology and immuno-histochemistry. The patients were monitored for 3–4 hours after the procedure.

In both groups no patients had significant bleeding, pain, perforation or peritonitis developed after the biopsy.

Immunohistochemical staining using antibodies against CD34, CD117, S100, DOG1 and smooth muscle actin was performed in the specimens. When both CD117 and DOG1 were negative, GIST diagnosis was made when C-kit and/or platelet-derived growth factor receptor (PDGFR) were positive. Immunohistochemical diagnosis was based on recent guidelines (5-8,18-22).

Statistical analysis

Statistical analysis was performed using SPSS 19.9 (IBM Corp., Armonk, NY, USA). Categorical data are expressed as percentages, and continuous data are expressed as mean ± standard deviation. The difference in tumor size between the two protocols was analyzed using Mann-Whitney U test. Chi-squared test was performed to analyze qualitative parameters. Two-sided P values <0.05 were considered statistically significant.

Results

Tumor characteristics

There were 14 lesions located in the stomach, the mean lesion size was 11.7 cm (range, 8.1–19.5 cm); 6 in the rectum, the mean lesion size was 6.7 cm (range, 2.0–10.0 cm); 4 in the duodenum, the mean lesion size was 13.8 cm (range, 8.5–19.0 cm); 3 in the liver, the mean lesion size was 4.2 cm (range, 2.2–5.4 cm), and 26 of uncertain origin, the mean lesion size was 10.1 cm (range, 6.2–19.9 cm). For all patients with uncertain origin surgery was not performed because the tumor was too large. Lesion size was not significantly different between the US and CEUS groups (*Figure 1*, 9.9±4.3 cm, n=30 *vs.* 10.2±4.6 cm, n=28; P=0.774).

There were three lesions with homogenous enhancement and 25 lesions with heterogeneous enhancement in the

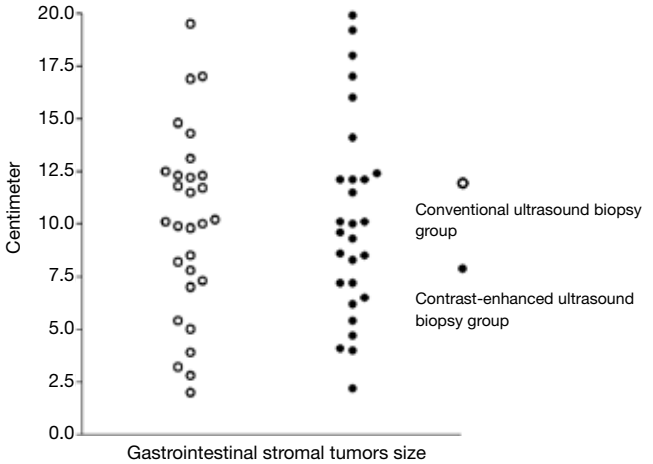

Figure 1 Size distribution of GIST tumors in conventional ultrasound guided and contrast-enhanced ultrasound guided biopsy. GIST, gastrointestinal stromal tumor.

CEUS group. Among the 25 lesions, 18 lesions show non-liquefied necrotic areas which appear hypoechoic or isoechoic on B-mode US, and a larger non-enhanced necrotic area than that detected as anechoic area by B-mode US was observed in 7 lesions (*Figure 2*). One case of rectal GIST had multiple small lesions (diameter 1.2–2.0 cm) located in distal rectum, presenting symptoms of perineal pain. Only one lesion in deeper muscular layer showed enhancement, while other lesions were not enhanced. In this case CEUS-guided biopsy for the target lesion acquired satisfactory specimen.

Diagnostic yield of ultrasound- and contrast-enhanced ultrasound-guided core needle biopsy

The biopsy working flow is shown in *Figure 3*. In the US group, there were 26 biopsy specimens with an accurate

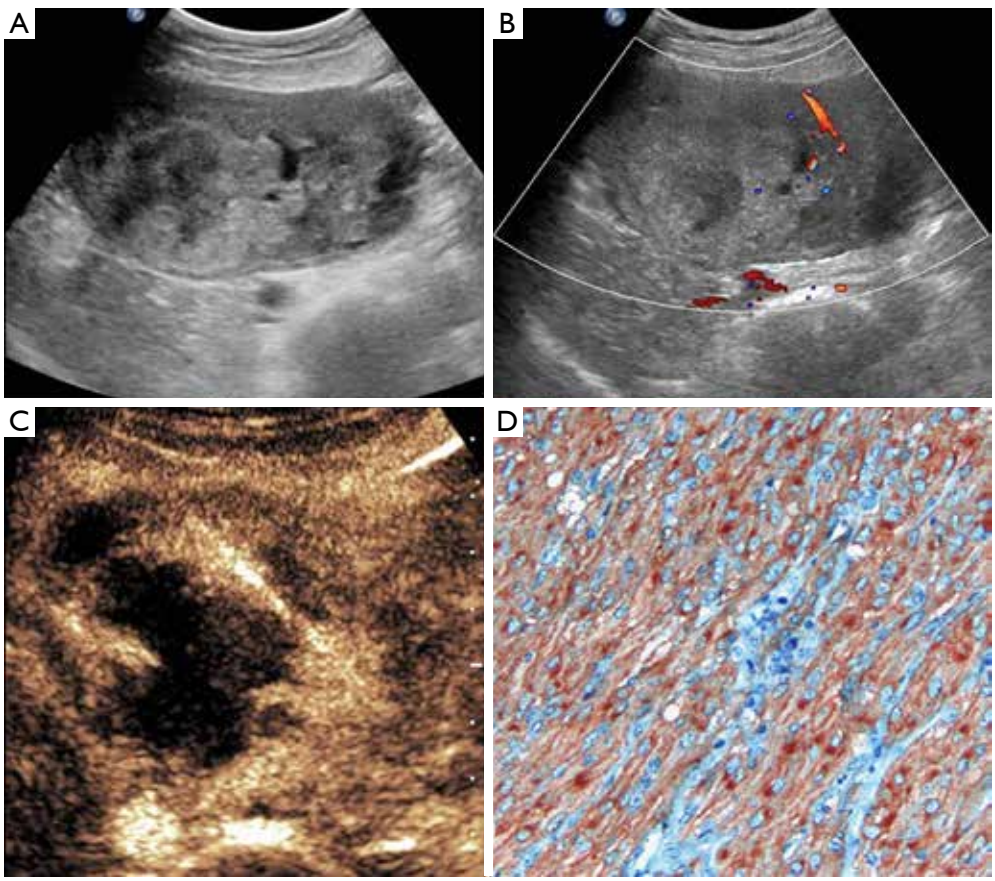

Figure 2 A 53-year-old man with lesion in stomach in CEUS group. Biopsy procedure was performed with 18-gauge automatic needle guided by contrast enhanced sonography. Pathologic diagnosis of biopsy sample was GIST. (A) Grayscale ultrasound image shows a large, well defined, heterogeneous hypo-echoic mass with necrosis located in stomach; (B) power Doppler flow image shows few vessels in the peripheral region of the mass; (C) CEUS-guided core needle biopsy is focused on the most enhanced area, avoiding the avascular region; (D) the spindle cells are diffusely positive for CD 117 (×200). CEUS, contrast enhanced ultrasound; GIST, gastrointestinal stromal tumor.

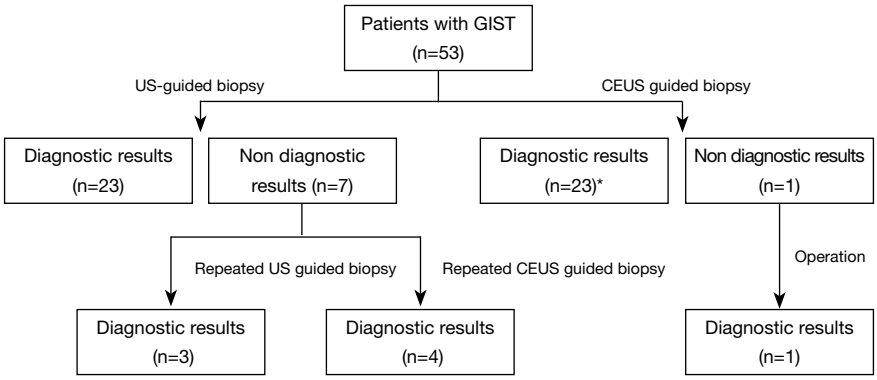

Figure 3 The flow diagram of the diagnostic biopsy workup for 53 patients with GIST. *, 1 patient took two sets of CEUS guided biopsies in different lesions of stomach and liver. GIST, gastrointestinal stromal tumor; CEUS, contrast enhanced ultrasound.

Table 1 Diagnostic yield comparison of conventional ultrasound *vs.* contrast-enhanced ultrasousnd guided core needle biopsy*

Group	Diagnostic specimens	Non diagnostic specimens	Total
US group	26	7	33
CEUS group	27	1	28
Total	53	8	61

*, P=0.042 (Chi-square test). US, ultrasound; CEUS, contrast enhanced ultrasound.

Table 2 Risk assessment for undeterminable specimen comparison of ultrasound (US)- or contrast-enhanced ultrasound (CEUS)-guided core needle biopsy*

Group	Determinable specimens	Undeterminable specimens	Total
US group	24	9	33
CEUS group	26	2	28
Total	50	11	61

*, P=0.042 (Chi-square test).

diagnosis of GIST. Three specimens showed only necrotic tissue, one specimen showed few atypical cells in large necrotic areas, one specimen revealed few spindle cells without cellular pleomorphism, and two specimens were suggestive of only a generic classification of mesenchymal tumors. The diagnostic yield of US guided biopsy for GIST was 83.3% (26/33). In the CEUS group, there were 27 biopsy specimens with accurate diagnosis of GIST. Only one specimen showed fibrous tissue and striated muscle without tumor cells. The diagnostic yield of CEUS guided biopsy for GIST was 96.2% (27/28). The difference in the diagnostic yield between the two groups was statistically significant (*Table 1*, P=0.042).

A final diagnosis of gastrointestinal stromal tumors was made according to one of the following reference methods: (I) histological and immunohistochemical biopsy findings with definite proof of gastrointestinal stromal tumors in patients with unresectable tumours according to CT/MRI scan findings and compatible clinical follow-up (n=43). Thirty-six patients were diagnosed as GISTs at the first set of biopsy; 7 patients were diagnosed as GISTs with repeated biopsies; (II) ten patients accepted Imatinib as neoadjuvant therapy and underwent surgery eventually. All of the ten patients had definite histological diagnosis of gastrointestinal stromal tumors based on surgical resection specimens. CD 117(c-KIT) was positive in 49 patients, and 36 patients were positive for CD34. Fourteen patients had a molecular diagnosis based on an active mutation in c-KIT or/and active mutation of PDGFR.

The risk for undeterminable specimens was 27.3% (9/24 lesions) in the conventional US biopsy group, and 7.2% (2/26 lesions) in the CE US biopsy group (*Table 2*, P=0.042). In both groups none patients had significant complications such as bleeding, pain, perforation or peritonitis after the biopsy.

Discussion

It is well recognized that all GISTs have some degree of malignant potential. According to the tumor size, mitotic rate, and anatomic site, the risk is classified as very low-, low-, intermediate-, or high risk (23). Accurate

preoperative diagnosis and risk stratification of GISTs is critical (24,25). For patients of GIST with metastatic disease or large locally advanced lesions, a biopsy is indicated to confirm the diagnosis before the initiation of tyrosine kinase inhibitor therapy. However, biopsy does not always provide sufficient material for an accurate histological diagnosis. Akahoshi *et al*. reported that tumor size is correlated with diagnostic yield and sensitivity (26). The diagnostic rate for the tumor less than 2, 2 to 4, and 4 cm or more were 71%, 86%, and 100%, respectively. In 29 surgically resected cases, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of endoscopic ultrasound guided final needle aspiration using immunohistochemical analysis of GIST were 100%, 80%, 96%, 100%, and 97%, respectively. Sepe *et al*. (27) reported the diagnostic yield and sensitivity of endoscopic ultrasound guided fine need aspiration cytology for the diagnosis of GIST was 78.4%. The sensitivity was 84.4% for GISTs located in the stomach, but poor for lesions located in the duodenum because none of these tumors yielded diagnostic cytology. The yield might actually decrease if the lesion is >10 cm, because larger tumors are more prone to necrosis (27). Another two studies showed an overall diagnostic accuracy for GIST of 84–92% with ultrasound fine needle aspiration (28,29). In cases with lesions for which endoscopic ultrasound fine needle aspiration is limited, percutaneous biopsy can be an effective alternative approach. Studies focusing on the diagnostic yield of percutaneous biopsies for GIST diagnosis are relatively lacking. Yeh *et al*. (11) compared 23 transluminal biopsies, 20 ultrasonography-guided biopsies, and 15 CT-guided biopsies; they reported failure rate was higher in the group of transluminal biopsies (17%).

In the present study, the diagnostic yield was 78.8% in the US group, which is similar to the results reported in the literature. The size of GISTs varied greatly, from a few millimeters to >30 cm, with a median size between 5 and 8 cm (mean: 10.1 cm). Gong *et al*. described majority of GIST are exophytic growth, necrosis is often seen in GIST and results in heterogeneous enhancement (30). Large GISTs might present with significant necrosis and cystic degeneration, with only a residual rim of viable tissue. The biopsy technique must be able to provide adequate and representative material to allow for a histopathological diagnosis. Sampling errors often happen if relying only on tissue texture during B-mode US. With contrast enhanced guided biopsy, hypervascular areas can be identified, and avascular and hypovascular areas such as necrosis, fibrosis, or desmoplastic tissue can be avoided. On the other hand, the non-liquefied necrotic area and hypovascular areas are difficult to identify on conventional grey scale US (31-35).

Our results confirmed CEUS guided biopsy improves the diagnostic yield and enables adequate sampling of GIST. In the present study, the proportions of biopsies with undeterminable samples were significantly different between the US group and CEUS group (9/33, 27.3% *vs*. 2/28, 7.2%, respectively), which can be attributed to more sufficient, representative, and viable tissue obtained with CEUS guided biopsy. GISTs rarely metastasize to the lymph node, while the liver is the most common metastatic site. In the present study, three biopsies of hepatic metastatic lesions were also obtained with diagnostic specimens.

Several studies have demonstrated US guided percutaneous core biopsy of gastrointestinal lesions is associated with a low rate of complications (11,36,37). In our series, we observed no immediate or delayed complications after the biopsy procedure during the follow-up. The results of this study suggest that, compared with conventional US guided core needle biopsy, CEUS guided core needle biopsy increases the diagnostic yield and may improves the risk assessment for the pre-treatment diagnosis of GIST. We recommend the inclusion of CEUS guided biopsy in the diagnostic work-up of advanced or metastatic GIST.

Acknowledgements

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the ethics committee of Cancer Hospital & Institute, Peking Union Medical College & Chinese Academy of Medical Sciences.

The ID of the approval is NCC2013S-006. All patients gave written informed consent before taking part in the study. Informed consent was obtained from all patients.

References

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438:1-12.
2. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100:162-8.
3. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29:52-68.
4. Wu JS, Goldsmith JD, Horwich PJ, et al. Bone and soft-tissue lesions: what factors affect diagnostic yield of image-guided core-needle biopsy? Radiology 2008;248:962-70.
5. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459-65.
6. Rubin BP, Fletcher JA, Fletcher CD. Molecular Insights into the Histogenesis and Pathogenesis of Gastrointestinal Stromal Tumors. Int J Surg Pathol 2000;8:5-10.
7. Blackstein ME, Blay JY, Corless C, et al. Gastrointestinal stromal tumours: consensus statement on diagnosis and treatment. Can J Gastroenterol 2006;20:157-63.
8. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. Lancet 2007;369:1731-41.
9. Tio TL, Tytgat GN, den Hartog Jager FC. Endoscopic ultrasonography for the evaluation of smooth muscle tumors in the upper gastrointestinal tract: an experience with 42 cases. Gastrointest Endosc 1990;36:342-50.
10. Fernández-Esparrach G, Sendino O, Solé M, et al. Endoscopic ultrasound-guided fine-needle aspiration and trucut biopsy in the diagnosis of gastric stromal tumors: a randomized crossover study. Endoscopy 2010;42:292-9.
11. Yeh CH, Pan KT, Chu SY, et al. Safety and efficacy of image-guided percutaneous biopsies in the diagnosis of gastrointestinal stromal tumors. Clin Imaging 2012;36:19-23.
12. Nesje LB, Laerum OD, Svanes K, et al. Subepithelial masses of the gastrointestinal tract evaluated by endoscopic ultrasonography. Eur J Ultrasound 2002;15:45-54.
13. Spier BJ, Johnson EA, Gopal DV, et al. Predictors of malignancy and recommended follow-up in patients with negative endoscopic ultrasound-guided fine-needle aspiration of suspected pancreatic lesions. Can J Gastroenterol 2009;23:279-86.
14. Xu X, Luo L, Chen J, et al. Acoustic radiation force impulse elastography for efficacy evaluation after hepatocellular carcinoma radiofrequency ablation: a comparative study with contrast-enhanced ultrasound. Biomed Res Int 2014;2014:901642.
15. Kaneko OF, Willmann JK. Ultrasound for molecular imaging and therapy in cancer. Quant Imaging Med Surg 2012;2:87-97.
16. Wáng YX, Choi Y, Chen Z, et al. Molecular imaging: from bench to clinic. Biomed Res Int 2014;2014:357258.
17. Cui NY, Wang Y, Zhang R, et al. Contrast enhanced ultrasound demonstration of a proliferative mass in rectum wall in a patient after rectal cancer surgery. Quant Imaging Med Surg 2012;2:130-2.
18. Singer S, Rubin BP, Lux ML, et al. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. J Clin Oncol 2002;20:3898-905.
19. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41; quiz S42-4.
20. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
21. Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. Am J Surg Pathol 2004;28:889-94.
22. West RB, Corless CL, Chen X, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol 2004;165:107-13.
23. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.
24. Gheorghe M, Predescu D, Iosif C, et al. Clinical and therapeutic considerations of GIST. J Med Life 2014;7:139-49.
25. Wang M, Xu J, Zhang Y, et al. Gastrointestinal stromal tumor: 15-years' experience in a single center. BMC Surg 2014;14:93.
26. Akahoshi K, Sumida Y, Matsui N, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. World J Gastroenterol 2007;13:2077-82.

27. Sepe PS, Moparty B, Pitman MB, et al. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc 2009;70:254-61.
28. Vander Noot MR 3rd, Eloubeidi MA, Chen VK, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer 2004;102:157-63.
29. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc 2009;69:1218-23.
30. Gong J, Kang W, Zhu J, et al. CT and MR imaging of gastrointestinal stromal tumor of stomach: a pictorial review. Quant Imaging Med Surg 2012;2:274-9.
31. Stock K, Hann von Weyhern C, Slotta-Huspenina J, et al. Microcirculation of subepithelial gastric tumors using contrast-enhanced ultrasound. Clin Hemorheol Microcirc 2010;45:225-32.
32. Kitano M, Sakamoto H, Kudo M. Contrast-enhanced endoscopic ultrasound. Dig Endosc 2014;26 Suppl 1:79-85.
33. Yamashita Y, Kato J, Ueda K, et al. Contrast-enhanced endoscopic ultrasonography can predict a higher malignant potential of gastrointestinal stromal tumors by visualizing large newly formed vessels. J Clin Ultrasound 2015;43:89-97.
34. Gong JS, Kang WY, Liu T, et al. CT findings of a gastrointestinal stromal tumor arising from small bowel. Quant Imaging Med Surg 2012;2:57-8.
35. Sakamoto H, Kitano M, Matsui S, et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). Gastrointest Endosc 2011;73:227-37.
36. Marco-Doménech SF, Gil-Sánchez S, Fernández-García P, et al. Sonographically guided percutaneous biopsy of gastrointestinal tract lesions. AJR Am J Roentgenol 2001;176:147-51.
37. de Sio I, Funaro A, Vitale LM, et al. Ultrasound-guided percutaneous biopsy for diagnosis of gastrointestinal lesions. Dig Liver Dis 2013;45:816-9.

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Diagnosis

CT and MR imaging of gastrointestinal stromal tumor of stomach: a pictorial review

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Abstract: This pictorial review illustrates CT and MR imaging appearance of gastrointestinal stromal tumor (GIST) of the stomach and other lesions with similar imaging appearance. GIST of the stomach appears as well-defined enhanced masses with characteristics of subeppthial neoplasms. Majority are exophytic growth, but can also be of intra-luminal growth. GIST can growth into a large mass without gastrointestinal tract obstruction. Necrosis is often seen in GIST and results in heterogeneous enhancement and communication with gastrointestinal tract. CT and MRI features of several other neoplasms mimicking GISTs in the stomach are also described in this review.

KeyWords: CT; MR; gastrointestinal stromal tumor (GIST)

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Gastrointestinal stromal tumor (GIST) is the most common subepithelial neoplasm that can be found throughout the gastrointestinal tract, but most of them occur in the stomach. GIST consists of spinde cells or epithelioid cells, therefore they were misdiagnose as leiomyoma or leiomyosarcoma before their immunohistochemical properties were discovered (1). The uniqueness of CD117 positive can distinguish GIST from other neoplasm with similar optical microscopical appearance (2). There are several subepithelial neoplasms of the stomach which can exhibit similar CT and MRI features as GIST. This review seeks to illustrate CT and MR manifestations of GIST of the stomach.

GIST of stomach

60-70% of GIST occurs in the stomach. They arise from interstitial cells of Cajal, which are pacemaker cells for gut movement (3). Therefore, GIST usually arises from the muscularis propria and exhibit characteristics of subepithelial neoplasms (*Figure 1*). The tumors can be extraluminal, intraluminal or mixed (dumbbell-shaped) pattern, while 79% of them are exophytic growth (4). GIST typically grows into a well-defined exophytic mass (*Figures 1*,*2*), but intraluminal masses can also be seen (*Figure 3*). Small tumors are often of homogeneous density or signal and large tumors tend to show irregular lobulated margins, mucosal ulceration, central necrosis, hemorrhage, cavitation, and heterogeneous enhancement (3) (*Figures 4*,*5*). Extensive necrosis can result in fistula formation with air-fluid level or oral contrast materials in the cavity (*Figure 6*). Mucosal ulceration can lead to gastrointestinal bleeding. Gastric GIST often has a better survival than small intestinal GIST (5). Large size, hepatic metastasis and presence of wall invasion often suggest a high-grade GIST and predict poor outcome (6) (*Figure 7*). Malignant GIST commonly metastasizes to the liver or peritoneum, whereas metastases to the lymph nodes and extra-abdominal metastases are rare.

Leiomyoma

Leiomyoma originates from either the muscularis mucosae or muscularis propria. They are composed of well-differentiated smooth muscle cells and are rare in the

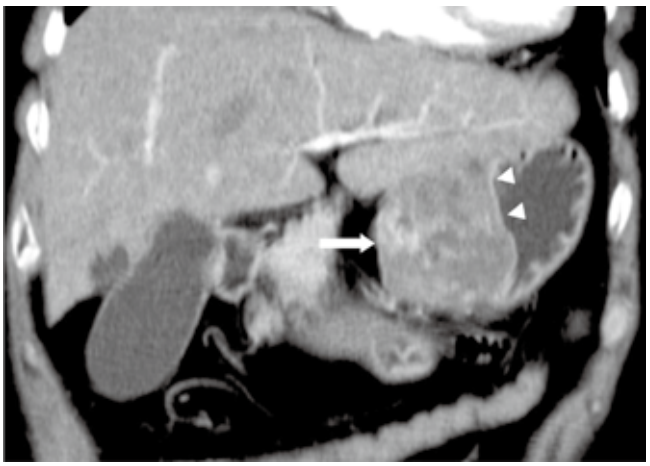

Figure 1 A 64-year-old male with a benign gastric GIST. Coronal multiple planar reformation of contrast enhanced CT shows a well-defined exophtic-growth mass (arrow) with heterogeneous enhancement arising from the small curve of the stomach. Mucosa (arrowheads) covering the tumor remains intact, which implies the mass is submucosa origination

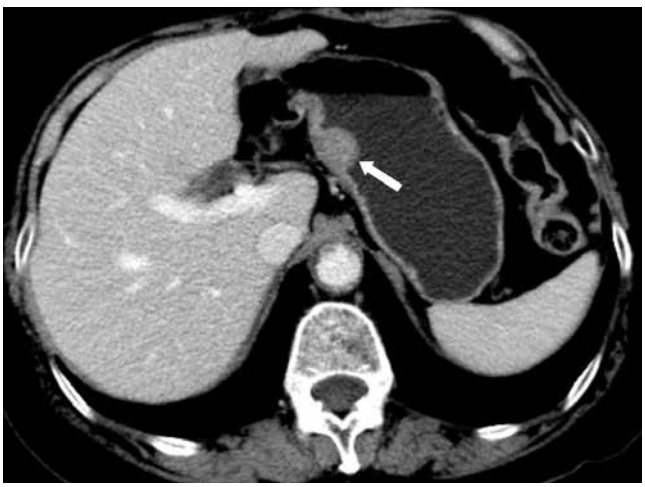

Figure 3 A 72-year-old male with benign gastric GIST. Axial enhanced CT image shows an introphytic homogeneously enhancing nodule (*arrow*) of the stomach

stomach. Although they show similar optical microscopy appearances with GIST, positive staining for a-smooth muscle actin and desmin and negative staining for CD117, CD34, and s100 proteins can distinguish them from GIST at immunohistochemical examination. Leiomyoma appears as subepithelial masses with enhancement at CT and MRI (*Figure 8*). Because their imaging findings overlap with

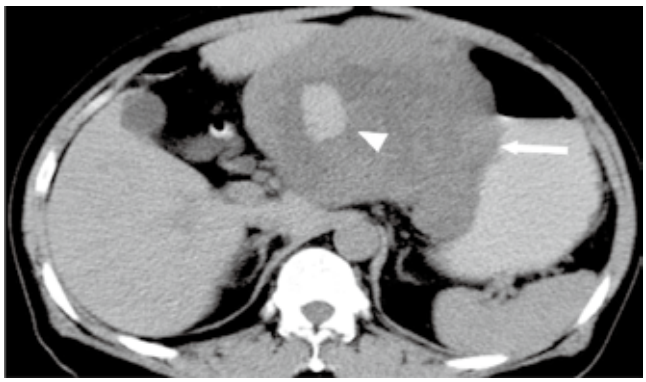

Figure 2 A 57-year-old male with malignant gastric GIST. Axial unenhanced CT image shows a well-defined exophtic-growth homogeneous mass (arrow) with hemorrhage (arrowhead) of the stomach

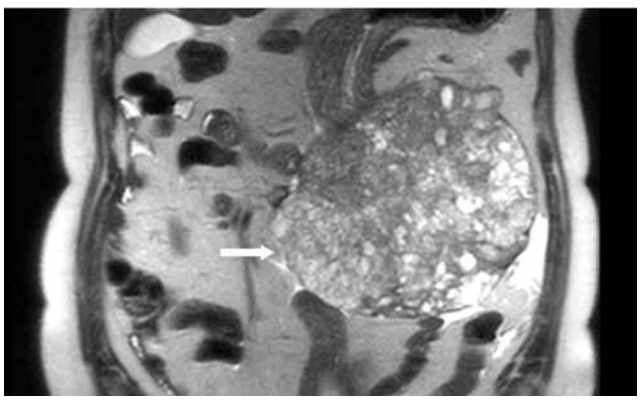

Figure 4 A 68-year-old male with malignant gastric GIST. Coronal true FISP image shows a large extraluminal heterogeneous signal mass from the large curve of stomach (arrow)

GIST, it is impossible to distinguish the two entities. The final diagnosis is established by immunohistochemical examination.

Nerve sheath tumors

Gastric schwannoma arises from the Schwann cells of the neural plexus within the stomach wall. They manifest as subepithelial masses with minimal enhancement during the arterial phase and delayed enhancement during the equilibrium phase (*Figure 9*). Malignant nerve sheath tumors may show necrosis and heterogeneous enhancement (*Figure 10*).

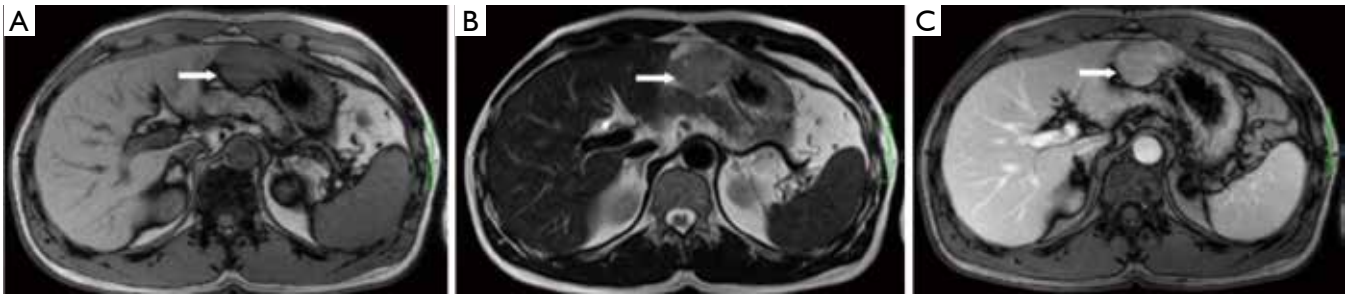

Figure 5 A 43-year-old female with benign gastric GIST. A. Axial T1-weighted image shows a homogeneous iso-intensity mass from the fundus of stomach; B. Axial T2-weighted image shows the mass is of homogeneous medium signal intensity; C. Axial enhanced T1-weighted image shows homogeneous moderate enhancement

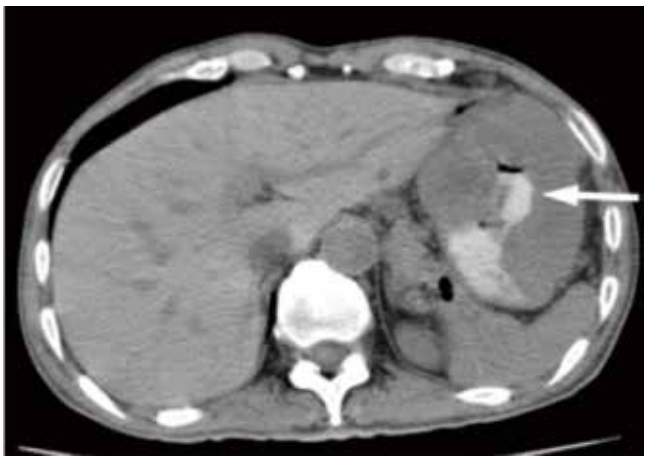

Figure 6 A 52-year-old female with malignant gastric GIST. Axial unenhanced CT image shows an extraluminal mass with necrosis cavity and communication with gastric luminal. Oral contrast materials is seen in the necrosis cavity (arrow)

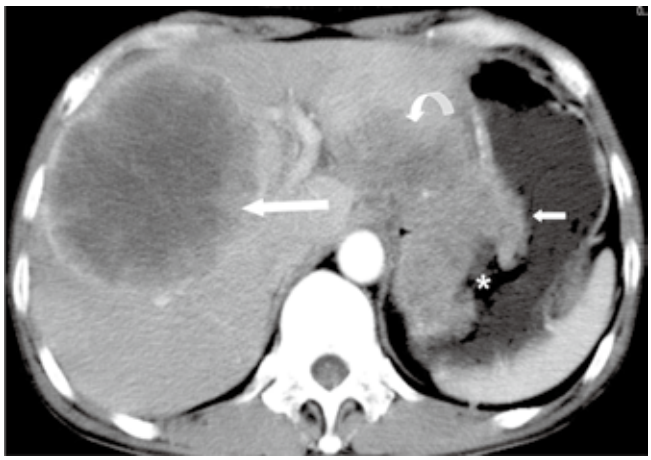

Figure 7 A 50-year-old male with malignant gastric GIST. Axial enhanced CT image shows an extraluminal mass with heterogeneous enhancement (short arrow), mural ulcer (star) and directly invading the left lobe of liver (curve arrow). A heterogeneous enhanced metastasis (long arrow) is demonstrated in the right lobe of liver

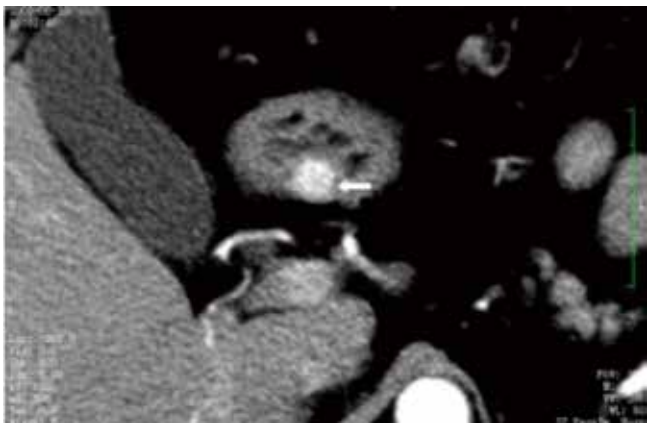

Figure 8 A 42-year-old male with gastric leiomyomas. Enhanced CT shows a subepithelial node in the gastric antrum with avid enhancement

Neuroendocrine tumors

Most neuroendocrine tumors occur in the appendix, followed by small bowel, but more gastric neuroendocrine tumors are founded recently due to endoscopic examinations. These entities manifest as subepithelial masses with avid enhancement after iv contrast materials (*Figure 11*).

Lymphoma

Gastric lymphomas account for 1-5% malignant tumors involving the stomach (7). Due to the characteristic of submucosal spread, gastric lymphomas often appears as abnormally thickened gastric walls with perigastric lymph

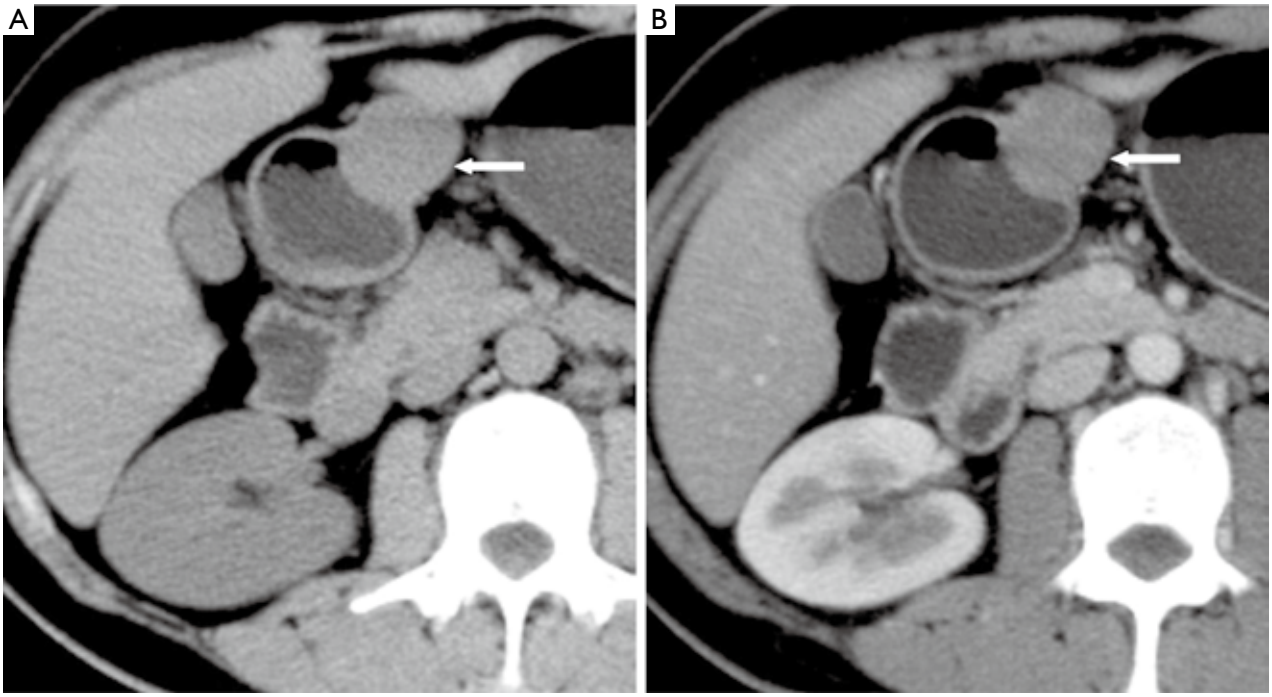

Figure 9 A 41-year-old female with a Schwannoma of the stomach. A. Unenhanced CT shows a well-defined extraluminal soft tissue mass with homogeneous density; B. Enhanced CT shows the neoplasm is of homogeneous enhancement

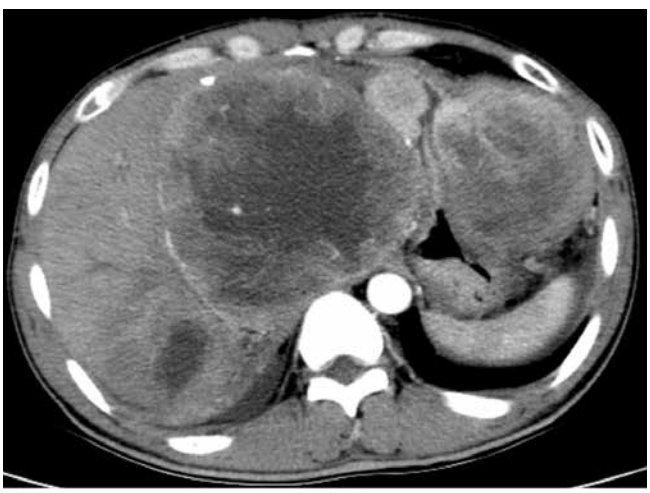

Figure 10 A 63-year-old male with malignant nerve sheath tumor. Enhance CT shows an extrophy growth mass in the large curve of the stomach with heterogeneous enhancement. Multiple metastases are noted in the liver

adenopathy (8). Sometimes, gastric lymphoma can form a focal mass which mimics a subepithelial tumor (*Figure 12*).

Miscellaneous masses

Castleman disease, solitary fibrous tumor (SFT), inflammatory myofibroblastic tumor, and schwannomas from peritoneal or retroperitoneal, as well as GIST arising from the mesentery and omentum can be adjacent to the stomach and can mimic extraluminal gastric GIST. Tumors from liver or spleen can invade or compress the stomach, which can also mimic gastric GIST (*Figures 13,14*)

Conclusions

When a mass of the stomach without characteristics of epithial tumors is encountered at CT or MRI, GIST should be considered first in the differential diagnosis. Majority of gastric GIST manifests as an extramural growth soft tissue mass. Moderate to intense enhancement can be found after iv contrast materials. Small masses often appear as homogeneous textures or enhancement, while large masses tend to show heterogeneous texture or enhancement. Extensive necrosis, even fistula between gastric lumen and necrosis cavity, can be seen. Unlike the epithial tumors, GIST seldom causes GI tract obstruction,

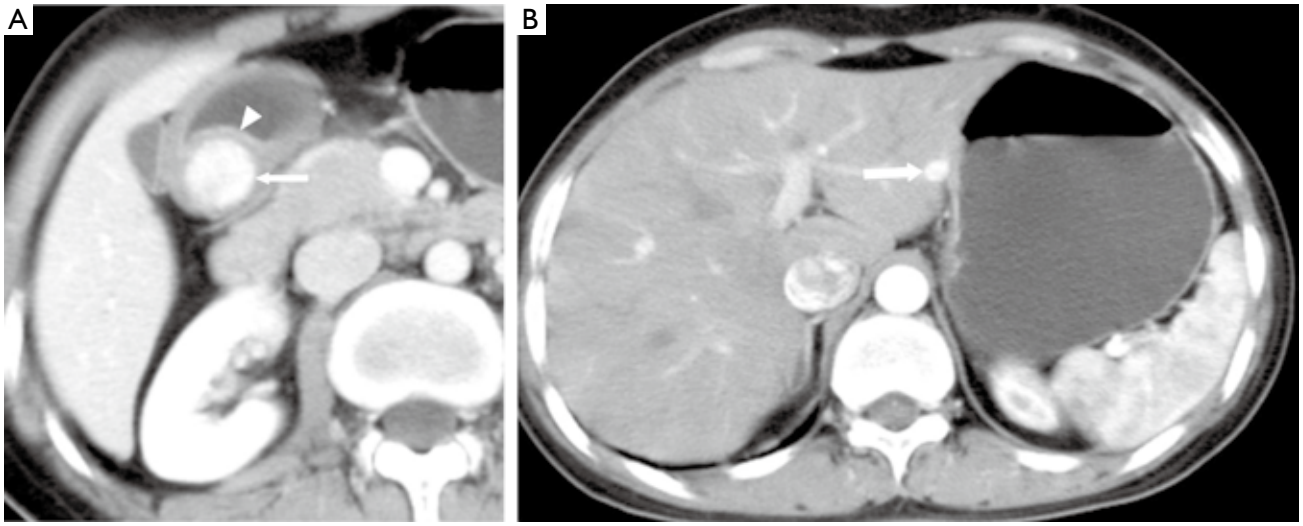

Figure 11 A 36-year-old female with malignant gastrinoma. A. Enhanced CT shows a well-defined subepithelial node with avid enhancement (arrow). The enhanced mucosa (arrow head) is intact, which is the typical characteristics of subepithelial neoplasms; B. A marked enhanced metastasis (arrow) in the liver is revealed

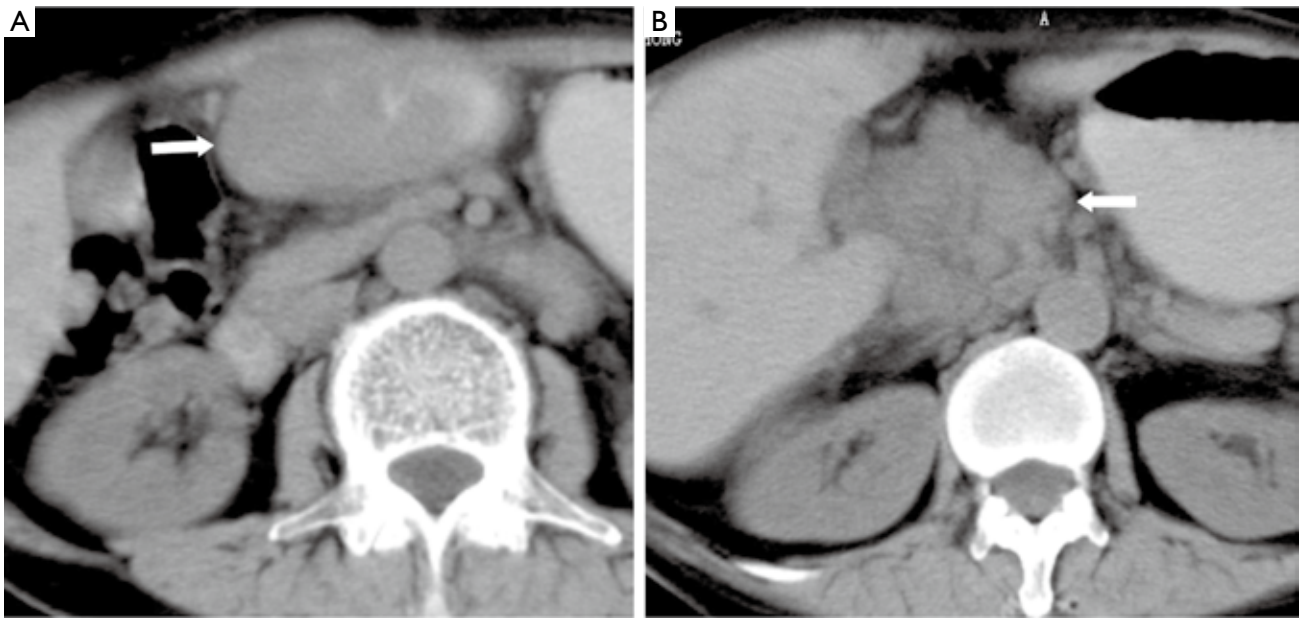

Figure 12 A 62-year-old female with primary gastric lymphoma. CT images show an irregular subepithelial mass in the gastric antrum (arrow in A) and lymph adenopathy (arrow in B)

ascites and metastasis to lymph nodes. Malignant GIST often metastasizes to the liver and mesentery. Several gastric subepithelial tumors may mimic GIST and their imaging manifestations overlap. Due to their benign biological characteristics, GIST tends to grow into a large mass when the mass products symptom and the patient seeks medical services. Therefore, when a large subepithal mass of the stomach is found at CT or MRI, it more like to be a GIST, especially when it poses extensive necrosis, fistula formation and hepatic or/and mesentery metastasis without ascites,

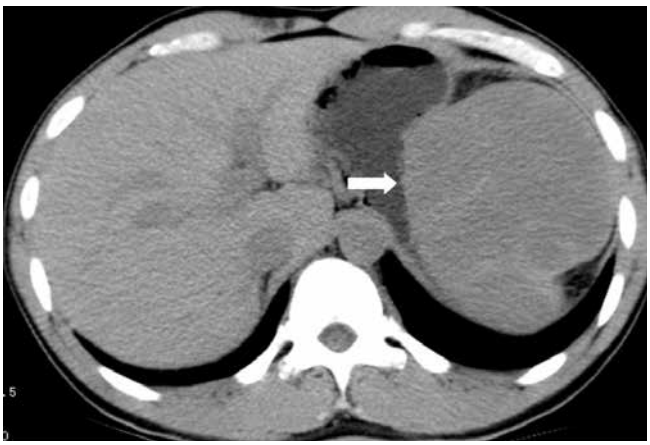

Figure 13 A 28-year-old male with spleen NHL. Unenhanced CT shows a mass compressing the greater curvature of the gastric body, which mimics a subepithelial tumor of the stomach

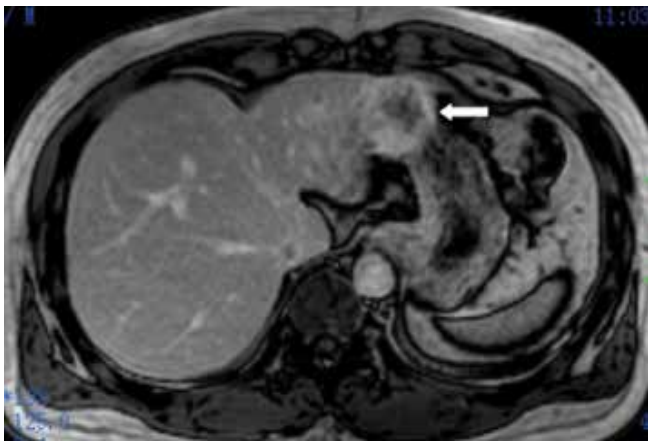

Figure 14 A 46-year-old male with hepatocellular carcinoma of the left lobe of liver. Contrast enhanced MR image shows a periphery enhanced mass invading the stomach and mimicking a gastric subepithelial mass (arrow)

lymph node enlargement and GI tract obstruct sign.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 1983;7:507-19.
2. Sarlomo-Rikala M, Kovatich AJ, Barusevicius A, et al. CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 1998;11:728-34.
3. Lee NK, Kim S, Kim GH, et al. Hypervascular subepithelial gastrointestinal masses: CT-pathologic correlation. Radiographics 2010;30:1915-34.
4. Sandrasegaran K, Rajesh A, Rushing DA, et al. Gastrointestinal stromal tumors: CT and MRI findings. Eur Radiol 2005;15:1407-14.
5. Humphris JL, Jones DB. Subepithelial mass lesions in the upper gastrointestinal tract. J Gastroenterol Hepatol 2008;23:556-66.
6. Tateishi U, Hasegawa T, Satake M, et al. Gastrointestinal stromal tumor. Correlation of computed tomography findings with tumor grade and mortality. J Comput Assist Tomogr 2003;27:792-8.
7. Brady LW, Asbell SO. Malignant lymphoma of the gastrointestinal tract. Erskine Memorial Lecture, 1979. Radiology 1980;137:291-8.
8. Buy JN, Moss AA. Computed tomography of gastric lymphoma. AJR Am J Roentgenol 1982;138:859-65.

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Technical success and short-term results of surgical treatment of gastrointestinal stromal tumors: an experience of three centers

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Background: Gastrointestinal stromal tumors (GIST) comprise about 80% of gastrointestinal sarcomas. In patients with localized disease, surgery is considered as "Gold Standard" treatment. Organ-sparing radical en-block resection is widely accepted practice. Since lymph node dissection is not routinely indicated, minimally invasive approach is of particular interest. The aim of this study is to investigate the short-term outcomes of different surgical treatment of GISTs.

Methods: We analyzed data of 116 patients who received surgical treatment for localized forms of GIST. Tumors were located in the stomach in 87 (75%) cases, in the small intestine in 26 (22.4%) cases, and extragastrointestinal GISTs were found in 3 (2.6%) patients. Four different approaches were used—open surgery (OpS, n=48), laparoscopic surgery (LS, n=40), endoscopic procedures (EP, n=22) and hybrid rendezvous (HR, n=6). Patient demographics, clinical presentation of tumors, characteristics of operation procedures (duration, intraoperative blood loss, frequency of R0-resection and fragmentation of tumor), postoperative complications and length of hospital stay were examined in all these groups.

Results: Radical treatment (R0-resection) was performed in all patients. There were no cases of tumor ruptures during surgical procedure. Mean size of GIST in OpS was 9.1±2.0 [2–35] cm; in LS: 4.9±0.8 (1.5–15) cm; in HR: 3.5±0.8 (2–4.5) cm and in EP: 2.3±0.3 (0.4–3.5) cm. Intraoperative blood loss in OpS was 369.7±209.5 [0–4,000] mL; LS: 63.9±16.0 [0–150] mL; in HR: 96.7±44.3 [50–200] mL; in EP: 33.3±11.0 [0–150] mL. Duration of operation in OpS was 160±20.4 [50–310] min; in LS: 104.7±12.7 [50–185]; in HR: 176.7±44.0 [110–260] min and in EP: 89.8±15.5 [25–190] min. Complication rate in OpS was 5 (10.4%); in LS: 3 (7.5%); in HR: 0% and in EP: 3 (13.6%). Length of hospital stay in OpS was 13.8±2.2 [7–52] days; in LS: 11, 4±2.2 [4–21] days; in HR: 11±3.2 [7–15] days and in EP: 11, 9±2.1 [5–22] days. There were no postoperative deaths.

Conclusions: There is a diversity of surgical approaches for GISTs treatment. From our point of view, the main selection criteria for certain procedure are size, localization, growth type of the tumor and status of overlying mucosa. Nevertheless, due to relative rarity and heterogeneity of this pathology, individualization is necessary in each specific case. Laparoscopic and endoscopic surgery is proved to be safe and feasible for resection of the gastric GISTs, with a reasonable operation time, low blood loss, and an acceptable complication rate. Immediate results indicate that all interventions were performed radically without mortality or serious morbidity.

Keywords: Gastrointestinal stromal tumors (GIST); endoscopic submucosal dissection (ESD); submucosal tunnel endoscopic resections (STER); endoscopic full thickness resections (EFTR); laparoscopic wedge resections

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Introduction

Since the discovery of the KIT and PDGFRA genetic mutations (1), as well as administration of tyrosine kinase inhibitors (2), our concept of molecular and clinical characteristics of gastrointestinal stromal tumors (GIST) has been considerably widened, which led to rapid and substantial changes in the approaches to the diagnostics and treatment of these tumors (3,4).

However, GISTs still represent a complex problem for surgical oncology. Although the methods of abdominal cancer treatment are presently well known and validated (5), there are no clear surgical algorithms for GISTs yet. International guidelines such as ESMO or NCCN provide a wide variety of possible treatment modalities; however, it lacks definite selection criteria (3,4). Currently, there is no unified concept of surgical interventions for GISTs located in different regions of gastrointestinal tract.

Due to characteristics of biological behavior of these tumors, which include a low rate of lymphatic metastasis and infiltrating growth, currently adopted practice such as economic resection of organs allows to perform procedure without lymph nodes dissection (6). As a result, it prompted surgeons to actively implement minimally invasive interventions in treatment of these tumors, which contributes to better functional outcomes of surgery without affecting overall and disease-free survival (OS/DFS). Currently, endoscopic submucosal dissection (ESD), submucosal tunnel endoscopic resections (STER), endoscopic full thickness resections (EFTR) and laparoscopic wedge resections are the most commonly used procedures. In addition, hybrid technologies such as rendezvous are used when endo- and laparoscopic visualizations are performed simultaneously (7,8).

Some eminent representatives of the Eastern surgical school are convinced that the practice of minimally invasive procedures should be expanded to large GISTs (9). At the same time, the European society of medical oncologists restricts laparoscopic surgery (LS) interventions only to small GISTs by arguing that this approach substantially increases the risks of damaging the fragile pseudocapsule that significantly worsens the prognosis (4). It should be also noted, that very few specialists currently use endoscopic resections due to their technical complexity. However, there is general increase in the interest for minimally invasive methods, i.e., endoscopic and laparoscopic techniques, as they allow a safe and reliable tumor resection and have a number of considerable advantages over traditional approach such as less severe postoperative pain, early realimentation, lesser risk of wound infection, reduced bleeding, and shorter hospital stay (10).

Objective

The main goal was to assess short-term outcomes of different surgical approaches for GIST and to describe certain technical parameters influencing the choice of a specific intervention.

Methods

We have performed a retrospective analysis from a prospectively documented database of 116 patients with localized forms of GIST who underwent surgical treatment between 2010 and 2016 at Federal State-Funded Budgetary Public Health Facility L.G. Sokolov' Hospital N 122 of the Federal Medical and Biological Agency, Federal State-Funded Budgetary Facility N.N.Petrov' Research Institute of Oncology Ministry of Health of the Russian Federation, and Federal State-Funded Budgetary Facility Saint-Petersburg Multifield Center Ministry of Health of the Russian Federation. The diagnosis was verified by immunohistochemistry in all patients. Written informed consent and Institutional Review Board approval were obtained before review of any patient material.

Eighty eight (75.8%) patients were admitted to hospitals according to scheduled hospitalization. The analysis of clinical presentation in these cases reveals that tumor was occasionally found in 67 patients (57.7%) during routine endoscopic examination. Twenty one patients (18.1%)

sought medical attention due to abdominal bloating, epigastric discomfort, symptoms of disruption of abdominal food transit, a palpable lump in the abdomen, fatigue, weight loss, pain and others. All routinely admitted patients were fully examined including endoscopic ultrasonography and three-phase contrast-enhanced computer tomography of the chest and abdominal cavities. If it was necessary, medical diagnosis was done collectively in form of multidisciplinary team by surgeon, endoscopist, radiologist, oncologist, and pathologist. None of patients received neoadjuvant imatinib therapy.

The rest 28 (24.2%) patients were admitted due to life-threatening evidence of GISTs (gastrointestinal bleeding in 14.7%, perforation in 5.3%, and bowel obstruction in 4.1% cases). These patients underwent an emergency surgical intervention. Therefore, this group was not examined at all and only surgeons that were on duty made the decision.

The following was obtained without comparative analysis due to significant difference between each group of patients: baseline and clinicopathological data including patient demographics, clinical presentation of tumors, tumor size and location, characteristics of operation procedures (duration, intraoperative blood loss, frequency of R0-resection and fragmentation of tumor), postoperative complications and length of hospital stay. GIST pathology was defined according to the GIST Risk Calculator tool based on research from Dr. Heikki Joensuu (4).

Statistical analyses were performed using SPSS for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA). Univariate analyses were performed using Student's *t*-tests and Mann-Whitney U tests. A P value <0.05 was considered significant.

Results

There were 71 (61.2%) females and 45 (38.8%) males in the study. The average age of patients was 61.2±2.13 y.o. (under 50 y.o.: 17.0%; 50 to 70 y.o.: 58,5%; over 70 y.o.: 24.5%). There were no statistically significant differences in groups of different types of surgery with respect to demographics. The tumors were located in the stomach in 87 patients (75%), in the small intestine in 26 patients (22.4%), and extragastrointestinal GISTs were in 3 patients (2.6%). Notably, this is consistent with reference literature data (11,12).

The average size of resected specimen was 5.7±0.85 cm. According to approved TNM classification of GIST with T criterion based on tumor size (13), 22 (19.0%) patients were diagnosed with T1, 51 (44.0%) with T2, 27 (23.2%) with T3, and 16 (13.8%) with T4 tumors. There were no cases of regional lymph nodes involvement. In accordance with tumor morphology and intraoperative data the risk of recurrence was very low in 12 (10.3%), low in 25 (21.6%), intermediate in 46 (39.7%), and high in 33 (28.4%) cases.

Forty (34.5%) patients underwent laparoscopic tumor resection. A traditional surgical intervention was performed in 48 (41.4%) patients; endoscopic procedures (EP) were performed in 22 (19.0%) patients, and a hybrid technique was used in 6 (5.1%) cases. *Table 1* describes these surgical approaches. The most frequent procedures in open surgery (OpS) group were partial gastrectomy [13 (27%) patients] and small bowel resections [15 (31.3%) patients]. Moreover, in certain cases more extensive interventions were performed due to large size of the tumor or invasive growth with spread to nearby organs: 6 (12.5%) patients underwent multi-visceral excision of stomach, spleen and pancreas, 4 (8.3%) patients underwent subtotal gastrectomy, 2 (4.2%) patients underwent total gastrectomy, 1 (2.1%) patient underwent pancreatoduodenal resection, and 3 (6.3%) patients underwent excision of retroperitoneal lesion. Simultaneous interventions (tumor resection + cholecystectomy or sigmoid resection due to the presence of concomitant pathology) were performed in 4 (8.3%) patients. Of the 91 patients who underwent laparoscopic resections, 28 (70%) had wedge resection, 4 (10%) underwent subtotal gastrectomy, 3 (7.5%) underwent sleeve-resection, 2 (5%) underwent transgastric wedge-resection (in the cases of posterior gastric wall localization), 3 (7.5%) underwent small bowel resection. EPs included submucosal dissection in 6 (27.2%) patients, tunnel resections in 8 (36.4%) patients, and full-thickness resections in 8 (36.4%) patients.

All tumors were extracted without rupture. In 3 (7.5%) cases laparoscopic procedure was converted to laparotomy. In two patients it was due to the invasion of the tumor into the spleen and pancreas found during intraoperative revision. In another incident, tumor was located on posterior wall of the subcardial section of the stomach. In this case it was rather challenging to perform wedge resection because of high risk of postoperative stenosis of cardioesophageal junction.

All tumors were excised with negative microscopic margins (R0), and there was no postoperative mortality. Blood loss and surgical intervention duration were significantly higher in OpS compared to minimally invasive surgery group. At the same time, this may be explained due to the fact of traditional approach prevalence in patients

Table 1 Comparative characteristics of surgical approaches

Characteristics	Laparoscopy group (n=40)	OpS group (n=48)	Endoscopy group (n=22)	Hybrid group (n=6)
Tumor localization				
Stomach	36 (90%)	27 (56.3%)	21 (95.5%)	6 (100%)
Intestines	4 (10%)	22 (37.5%)	1 (4.5%)	0%
Extragastrointestinal	0%	3 (6.2%)	0%	0%
Size of removed specimen, mean ± SD (range), cm	4.9±0.8 [1.5–15]	9.1±2.0 [2–35]	2.3±0.3 [0.4–3.5]	3.5±0.8 [2–4.5]
R-0 resection	100%	100%	100%	100%
Postoperative mortality	0%	0%	0%	0%
Hospital stay, mean ± SD [range], day	11.4±2.2 [4–21]	13.8±2.2 [7–52]	11.9±2.1 [5–22]	11±3.2 [7–15]
Operative time, mean ± SD [range], min	104.7±12.7 [50–185]	160±20.4 [50–310]	89.8±15.5 [25–190]	176.7±44.0 [110–260]
Blood loss, mean ± SD [range], mL	63.9±16.0 [0–150]	369.7±209.5 [0–4,000]	33.3±11.0 [0–150]	96.7±44.3 [50–200]

OpS, open surgery.

Table 2 Complications that required surgical or endoscopic intervention

Grade	Complications	Laparoscopy group	OpS group	Endoscopy group
IIIa	Staple line bleeding	1 (2.5%)		
	Resistant pylorospasm	1 (2.5%)		
IIIb	Staple line bleeding		2 (4.2%)	
	Two-stage spleen rupture		1 (2.1%)	
	Sigmorecto anastomotic leakage		1 (2.1%)	
	Decompensated stenosis of the stomach output		1 (2.1%)	
	Early adhesive obstruction	1 (2.5%)		
	Delayed perforations			2 (9.1%)
	Pharyngeal wall tear			1 (4.5%)

OpS, open surgery.

with larger tumors (9.1 *vs.* 4.9 cm, P<0.05). In addition, patients who underwent OpS displayed a slight tendency to longer inpatient period; although, the difference is not statistically significant (13.1 *vs.* 11.5 days, P>0.05).

Overall complication rate and particular complications that required surgical or endoscopic intervention [grade IIIa and IIIb according to Clavien-Dindo classification (14)] were demonstrated in *Table 2*. It is clearly represented that early complications occurred slightly more frequently in endoscopic group than in OpS and laparoscopy (13.6% *vs.* 10.4% and 7.5%). There were no postoperative complications after hybrid "rendezvous" procedures.

Discussion

GISTs that originate from the intestinal cells of Cajal are rare but represent the largest subset of mesenchymal-derived tumor of the gastrointestinal tract (3-5). Every GIST is considered to have a potential to be malignant, and surgical removal is the only curative therapy for localized GISTs. Complete excision, avoiding tumor rupture is potentially curative and the mainstay of treatment for primary, resectable GIST (8,15,16).

Traditionally, GISTs resection was done with OpS, but more recently, less invasive methods has gained

widespread acceptance. It is connected with several recent case series and systematic reviews which have reported that laparoscopic and endoscopic resections were superior to open resection in terms of short-term postoperative outcomes such as decreased blood loss, lower morbidity rate and shorter hospital stay without compromising the oncologic outcomes (7,12).

It is worth noting that it is technically possible to remove any tumor through laparoscopic or endoscopic approach, but it is imperative to remember that safe oncologic resection is the primary concern when considering minimally invasive techniques for GIST tumor rupture incomplete resections in these cases must always be avoided. Thus, each surgeon must proceed from his technical capabilities and maintain a delicate balance between the use of minimally invasive interventions and compliance with oncological requirements of surgery.

Despite the simplified surgical approach in stromal tumors in comparison with adenocarcinomas, the results of this study demonstrate a post-operative complications rate, 9.5% in overall study population. Since surgeons started practicing endoscopic and laparoscopic techniques in GIST surgery relatively recently, many surgeons still have to gain more experience. In addition, it could be relevant to the lack of interdisciplinary interaction between surgeons and endoscopists, wide application of staple technologies, absence of clear guidelines on surgery techniques, forced surgery in emergency hospital due to life-threatening signs of tumor. In order to solve this problem, it is essential to work out an optimal solution to pinpoint the most relevant surgical approach in regards of tumor localization, size, and growth pattern.

OpS is considered to be a method of choice for small intestine and extragastrointestinal tumors (2). Small bowel remains a difficult location for endoscopy and laparoscopy due to its lesser wall thickness in comparison to the stomach; and therefore, more complex manipulations are required. Nevertheless, there is a tendency to use laparoscopic approach, even in cases of tumors over 5 cm. Thus, in our study one patient with a tumor of 8 cm in diameter underwent a laparoscopic intestinal resection. Handport technique was used for a stromal tumor of approximately 15 cm in diameter in another case. Retroperitoneal tumors are seldom diagnosed at early stages and often reach considerable dimensions. Besides, the lack of clear anatomical marks creates further difficulty in application of laparoscopic technologies in these patients.

Thus, it is necessary to recognize that the stomach is the only field for the application of various minimally invasive technologies. Endoscopic approach is considered to be safe and feasible if tumor size that does not exceed 3 cm (17-19). This is determined by the high risk of complications during peroral extraction of larger tumor. We observed such incident in our study when posterior pharyngeal wall tear was registered after an attempt to remove 3.5 cm GIST. In addition, during an assessment stage by using endoscopic ultrasound, it is important to determine from which echo layer the lesion originates. If localization is in the muscularis mucosae, an ESD procedure is feasible because the perforation or bleeding risk is minimal (17,20). If the tumor originates from the muscularis propria, STER is preferable because this method prevents perforation due to maintaining of muscular layer continuity by forming a valve from mucosal and submucosal layers (18). If there is ulceration of overlying mucosa, fibrosis of submucosal layer resulting from previous biopsies or there is an intramural GIST attached by wide base, EFTR is the only possible endoscopic option. Thus, Zhou *et al.* (21) successfully removed tumors by EFTR in 26 patients with gastric GIST stemming from the muscularis propria. R0 resection was obtained in 100% of cases; the average tumor size was 2.8 cm (range 1.2 to 4.5 cm). Application of clip-assisted system OTSC together with twin grasper allowed effortlessly closing the wall defect of 3 cm or more (22,23). In our study, we observed two delayed perforations after applying this technique. Thereby, we came to conclusion that in some cases it is safer to perform laparoscopic closure of artificial perforations after EFTR.

It is evident that laparoscopic approach is safe and effective in GISTs under 5 cm (9,12,16). In our study, we demonstrated that laparoscopic approach could be applied in larger-sized tumors as well. Thus, 15 patients who had GISTs over 5 cm in size were successfully removed: 4 patients presented with 8 cm tumor, 4 with 7 cm and 7 with 6 cm in diameter. The low rate (7.5%) of conversion to OpS also highlights the feasibility of the laparoscopic approach. It is important to note, that conversion to OpS did not result in increased morbidity or mortality. Italian investigators revealed similar short-term results in retrospective case-control study of open versus laparoscopic resection of large GIST (24). Nevertheless, in the course of our study, patients underwent selection for a specific intervention, so there was bias in decision-making. Difficult-to-access GISTs with invasive growth were resected via OpS.

Surgery techniques can vary greatly depending on tumor localization and its relation to nearby structures. There is

no need to perform gastric mobilization in extraluminal and transmural tumor growth on the anterior body wall and greater gastric curvature. The tumor is clearly visualized, patency and leakage are highly visible, and a stapled resection within healthy tissues can be monitored by a gauging probe with later endoscopic control of suture-line hemostasis. If the tumor is localized on the lesser gastric curvature, it is necessary to perform dissection on lesser gastric curvature with its partial mobilization before resecting the tumor in order to preserve the branches of vagus nerve leading to the antrum and gall bladder, which are needed to prevent post-operative complications. If the tumor is located close to cardioesophageal junction or pylorus, it is more advisable to perform gastric resection with unipolar coagulation or ultrasound scalpel prior to staple resection in order to remove as less surrounding healthy tissue as possible. This approach will have smaller risk of deformation and stenosis in the post-operative period (5). The most difficult localization for laparoscopic approach is a posterior wall of the stomach. Among our patients, this type of tumor location was found in three people. It is difficult to provide recommendations based on limited experience. However, it is worth mentioning that performing a gastrotomy with the following dislocation of tumor onto the anterior wall facilitates the operative procedure and does not require extensive mobilization of the stomach.

If a GIST under 5 cm in diameter with intraluminal or transmural growth type is located near cardioesophageal junction and pylorus and on the posterior wall of lesser curvature, it seems reasonable to perform hybrid interventions with simultaneous application of laparoscopic and endoscopic visualization in order to establish the exact borders of tumor and perform a precise resection and a reliable restoration of continuity of the gastric wall (25). Currently, we have gained experience of applying rendezvous technology in only 6 patients, but we hope to gain more experience in the future.

Finally, it should be mentioned that endoscopic and laparoscopic techniques are currently actively implemented in clinical practice for treatment of patients with GISTs (8). Minimally invasive procedures, as well as OpS, allow performing radical tumor resection. However, we are still experiencing a high rate of post-operative complications, which means that the problem of GIST surgical treatment still exists. Application of heterogeneous and non-standardized approaches represents a potential risk. The development of optimal solution based on tumor localization and topographic anatomy will allow us to improve safety and reliability of the treatment. Further analysis and more active implementation of modern approaches such as hybrid rendezvous (HR) techniques are required in order to increase effectiveness of localized GIST surgical treatments.

Our study is limited exclusively to a review of surgical tactics and early outcomes without analyzing of long-term results such as estimation of recurrence and survival rates as well as adjuvant imatinib administration. Also, there was relatively small sample size and the retrospective design. To further improve the management of GISTs, randomized double-blinded controlled trials have to be performed in order to compare the OpS versus laparoscopy and endoscopy for the treatment of these tumors.

Conclusions

There is a diversity of surgical modalities for GISTs treatment. From our point of view the main selection criteria for certain procedure are size, localization, growth type of the tumor and status of overlying mucosa. Nevertheless, due to relative rarity and heterogeneity of this pathology, individualization is necessary in each specific case. Laparoscopic and endoscopic surgery proved to be safe and feasible for resection of the gastric GISTs, with a reasonable operation time, low bleeding, and an acceptable complication rate. Moreover, immediate results indicate that all interventions were performed radically without mortality or serious morbidity.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Written informed consent and Institutional Review Board approval were obtained before review of any patient material.

References

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
2. Dagher R, Cohen M, Williams G, et al. Approval

summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 2002;8:3034-8.
3. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41; quiz S42-4.
4. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii21-6.
5. Chissov VI, Davydov MI. Oncology. National guideline. Moscow: GEOTAR-Media; 2014. Available online: http://www.rosmedlib.ru/book/ISBN9785970431535.html
6. Sorour MA, Kassem MI, Ghazal Ael-H, et al. Gastrointestinal stromal tumors (GIST) related emergencies. Int J Surg 2014;12:269-80.
7. Karachun AM, Kashchenko VA, Pelipas IV, et al. The current view on the features of surgical treatment of gastrointestinal stromal tumors. Clinical hospital 2016;16:48-57.
8. Ko WJ, Cho JY. Current Techniques for Treating Gastrointestinal Stromal Tumors in the Upper Gastrointestinal Tract. Clin Endosc 2016;49:226-8.
9. Lin J, Huang C, Zheng C, et al. Laparoscopic versus open gastric resection for larger than 5 cm primary gastric gastrointestinal stromal tumors (GIST): a size-matched comparison. Surg Endosc 2014;28:2577-83.
10. De Vogelaere K, Hoorens A, Haentjens P, et al. Laparoscopic versus open resection of gastrointestinal stromal tumors of the stomach. Surg Endosc 2013;27:1546-54.
11. Miettinen M, Lasota J. Gastrointestinal stromal tumors. Gastroenterol Clin North Am 2013;42:399-415.
12. Valsangkar N, Sehdev A, Misra S, et al. Current management of gastrointestinal stromal tumors: Surgery, current biomarkers, mutations, and therapy. Surgery 2015;158:1149-64.
13. Edge SB, Byrd DR, Compton CC, et al. Gastrointestinal stromal tumor. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2010.
14. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-96.
15. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
16. Nishida T, Hirota S, Yanagisawa A, et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. Int J Clin Oncol 2008;13:416-30.
17. Białek A, Wiechowska-Kozłowska A, Pertkiewicz J, et al. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). Gastrointest Endosc 2012;75:276-86.
18. Gong W, Xiong Y, Zhi F, et al. Preliminary experience of endoscopic submucosal tunnel dissection for upper gastrointestinal submucosal tumors. Endoscopy 2012;44:231-5.
19. Lee IL, Lin PY, Tung SY, et al. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. Endoscopy 2006;38:1024-8.
20. Hwang JC, Kim JH, Kim JH, et al. Endoscopic resection for the treatment of gastric subepithelial tumors originated from the muscularis propria layer. Hepatogastroenterology 2009;56:1281-6.
21. Zhou PH, Yao LQ, Qin XY, et al. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. Surg Endosc 2011;25:2926-31.
22. Sarker S, Gutierrez JP, Council L, et al. Over-the-scope clip-assisted method for resection of full-thickness submucosal lesions of the gastrointestinal tract. Endoscopy 2014;46:758-61.
23. Schmidt A, Bauerfeind P, Gubler C, et al. Endoscopic full-thickness resection in the colorectum with a novel over-the-scope device: first experience. Endoscopy 2015;47:719-25.
24. Milone M, Elmore U, Musella M, et al. Safety and efficacy of laparoscopic wedge gastrectomy for large gastrointestinal stromal tumors. Eur J Surg Oncol 2017;43:796-800.
25. Tsujimoto H, Yaguchi Y, Kumano I, et al. Successful gastric submucosal tumor resection using laparoscopic and endoscopic cooperative surgery. World J Surg 2012;36:327-30.

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Surgery for metastatic gastrointestinal stromal tumor: to whom and how to?

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Abstract: Although imatinib is a standard treatment for metastatic or recurrent gastrointestinal stromal tumors (GISTs), acquired *c-kit* mutations reportedly cause secondary resistance to imatinib. Sunitinib is a tyrosine kinase inhibitor (TKI) that can be used as second-line therapy in imatinib-resistant or -intolerant GISTs. For sunitinib-resistant or -intolerant GISTs, regorafenib is a standard third-line treatment. Although TKI therapies have revolutionized the treatment of recurrent or metastatic GISTs, they cannot cure GISTs. Therefore, in the era of TKIs, role of cytoreductive surgery for recurrent or metastatic GISTs has been discussed. Retrospective studies of treatment strategies with front-line surgery prior to imatinib have shown that initial cytoreduction confers no benefit in cases of advanced or recurrent GIST, and administering imatinib is the principle treatment. Most retrospective studies report cytoreductive surgery to be feasible in patients with metastatic GIST whose disease is stable or responsive to imatinib. Cytoreductive surgery may be indicated in limited disease progression refractory to imatinib when complete resection is possible, but case selection is critical. Cytoreductive surgery for metastatic GIST treated with sunitinib seems less feasible because of high rates of incomplete resections and complications. The role of cytoreductive surgery for metastatic GISTs would be difficult to establish in a prospective study; individualized treatments need to be carefully designed based on *c-kit* and platelet-derived growth factor receptor alpha (*PDGFRA*) mutations and other factors.

Keywords: Metastatic gastrointestinal stromal tumor (metastatic GIST); cytoreductive surgery; imatinib; sunitinib; multidisciplinary treatment

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Introduction

Gastrointestinal stromal tumors (GISTs), which originate from the interstitial cells of Cajal (ICC) or their progenitor cells, are the most common mesenchymal neoplasm in the human digestive tract (1,2). Most GISTs have a gain-of-function mutation of the *c-kit* or platelet-derived growth factor receptor alpha (*PDGFRA*) genes in ICC, which results in ligand-independent activation of the receptors and consequential tumor progression (3-5). Although surgery is the most effective treatment for resectable primary GISTs without metastasis, post-operative recurrence or metastasis occurs in nearly 30% of patients within 3 years after complete resection in the absence of adjuvant therapy, and those metastatic GISTs are difficult to cure with surgery alone (6-8).

An orally bioactive tyrosine kinase inhibitor (TKI), imatinib mesylate (Glivec®, Gleevec®; Novartis, Basel,

Switzerland), has been shown to inhibit KIT and PDGFR *in vitro* (9), and the safety and efficacy of imatinib treatment in patients with metastatic GIST has been confirmed by the results of phase I/II trials (10,11). Although imatinib is thought to be the most effective agent for treating GISTs, about half of patients with unresectable or metastatic GIST develop secondary resistance within 2 years of beginning imatinib therapy (12). A small-molecule TKI, sunitinib malate (Sutent®; Pfizer, New York, NY, USA), has been shown to selectively inhibit KIT, PDGFRA, PDGFRB, vascular endothelial growth factor receptor 1-3 (VEGFR1-3), FMS-like tyrosine kinase 3 (FLT3), and the receptor encoded by the proto-oncogene *RET* (13,14); the clinical benefits of sunitinib were shown in a phase III trial of patients with advanced GIST after failure of imatinib (15). However, median time to tumor progression was 6.8 months (95% CI: 4.0–8.0 month) in patients treated with sunitinib and most patients developed resistance or intolerance to sunitinib (15). An orally active TKI regorafenib (Stivarga®; Bayer, Leverkusen, Germany) was shown to inhibit KIT, PDGFRB, VEGFR1-3, TIE-2, fibroblast growth factor receptor 1 (FGFR1), RET, RAF-1, and BRAF (16); its clinical benefit was shown in a phase III trial for advanced GISTs after failure of imatinib and sunitinib (17). Although median progression-free survival (PFS) was significantly improved with regorafenib vs placebo control [4.8 *vs.* 0.9 month, hazard ratio (HR): 0·27, 95% CI: 0·19–0·39 months; P<0·0001], the anti-tumor effect was limited in these advanced GIST patients who had been repeatedly treated with TKIs; most patients developed resistance or intolerance to regorafenib within a year (17).

Since the safety and efficacy of imatinib treatment has been confirmed in clinical trials, treatment strategies for recurrent or metastatic GISTs have dramatically changed. Although other TKIs, including sunitinib and regorafenib, have also improved recurrent or metastatic GISTs treatment, GISTs cannot be cured with TKIs alone. Therefore, in the era of TKIs, a multidisciplinary approach that includes cytoreductive surgery for recurrent or metastatic GISTs has been discussed. In this review, we summarize the current status of surgery for recurrent or metastatic GISTs.

Front-line surgery prior to imatinib therapy

Baseline tumor size when starting imatinib is an important predictive factor for prognosis of advanced GIST patients treated with imatinib, as it reportedly correlates with imatinib resistance in some retrospective analyses (18,19). As this relationship implied that cytoreductive surgery before imatinib therapy would decrease the rate of imatinib resistance and improve the prognosis of advanced GIST patients, some studies have retrospectively evaluated the usefulness of front-line surgery prior to imatinib. An *et al.* retrospectively reviewed 249 advanced GIST patients, and compared outcomes of patients whose initial cytoreductive surgery removed ≥75% of their tumor bulk (n=35) with outcomes of the other 214 patients, but found that, although these patients had significantly smaller baseline tumors when starting imatinib, their outcomes were not significantly better (20). Chang *et al.* conducted a prospective collecting retrospective review of advanced GIST patients (metastatic, unresectable, and recurrent GIST) (21). In this study, 76 patients who underwent cytoreductive surgery were divided into two groups; 54 patients who underwent cytoreductive surgery before treatment with imatinib (early group) and 22 patients who received surgery after imatinib therapy (late group). Although PFS and overall survival (OS) were comparable between the early and late groups, the late group had a higher R0 resection rate (21). Sato *et al.* retrospectively analyzed 14 cases of synchronous metastatic GIST from the Kinki GIST registry in Japan, and investigated outcomes of combined primary surgery and TKI treatments (22). Patients who underwent R0/R1 and those who underwent R2 resection did not significantly differ in 5-year OS, whereas survival time from diagnosis was correlated with duration of imatinib therapy, which suggests that primary surgery alone may not be beneficial, and continuous TKI therapy may be more appropriate as frontline treatment (22). Kanda *et al.* conducted a multicenter prospective study to clarify the efficacy and safety of surgery and imatinib for liver oligometastasis of GIST (23). Because the trials were prematurely terminated due to amendment of guidelines for adjuvant imatinib therapy and low patient accrual, this study did not yield any evidence supporting the preference for surgical resection in patients with resectable metastatic liver GIST. Notably, all the six patients enrolled in the surgery trial showed hepatic recurrence with median recurrence-free survival of 145 days (range, 62–1,366 days), suggesting that metastatic liver GIST may not be controllable by surgery alone and require concomitant imatinib therapy (23). Taken together, these retrospective and prospective studies suggest that initial cytoreduction does not have a beneficial effect for recurrent or metastatic GISTs. Therefore, imatinib should be the first treatment of choice in this population (*Figure 1*).

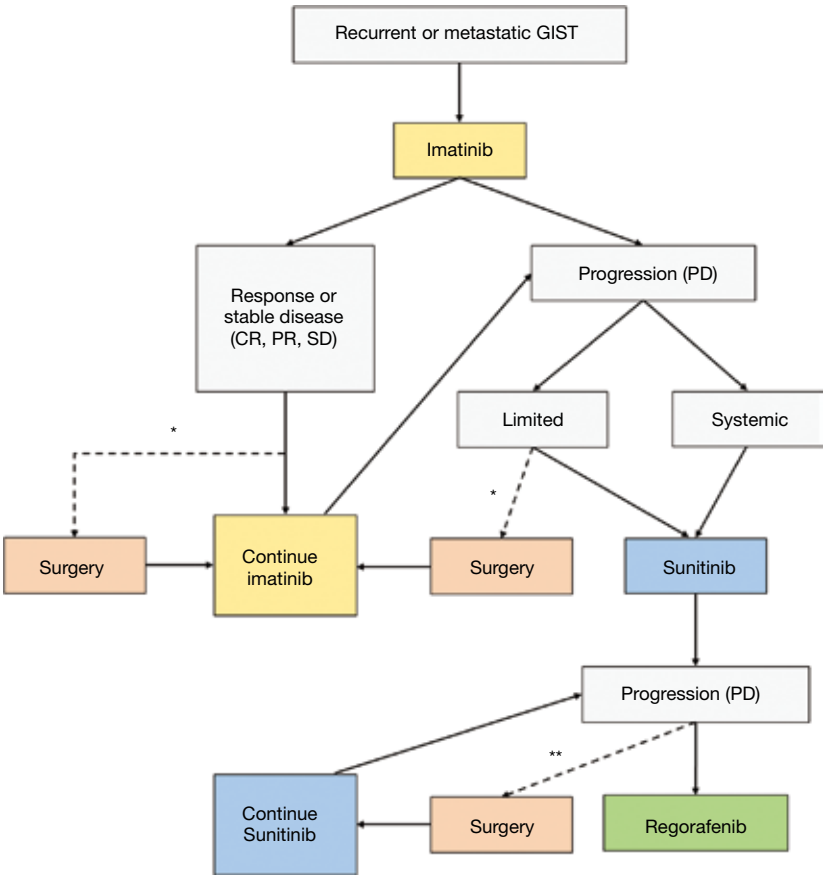

Figure 1 Proposed algorithm for clinical management of patients with recurrent or metastatic GIST. *, consider surgery if R0 resection can be obtained and imatinib can be restarted early after operation; **, surgery may be indicated for management of symptomatic bleeding or obstruction. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; GIST, gastrointestinal stromal tumor.

Cytoreductive surgery for metastatic GISTs responding to imatinib

Many retrospective studies of the feasibility of cytoreductive surgery during therapy with TKIs in patients with recurrent or metastatic GIST were conducted in American, European, and Asian institutions (24-36). *Table 1* summarizes the results of 11 principal retrospective studies on cytoreductive surgery for recurrent or metastatic GISTs treated with TKIs. Of those, 6 studies only analyzed cytoreductive surgery during imatinib therapy and 3 studies included GIST patients treated with imatinib and sunitinib. Although differences in patients' backgrounds and enrollment periods might have affected outcomes, due to higher availability of sunitinib and regorafenib in later cases, these retrospective studies consistently showed higher complete resection rates and longer PFS and OS for patients who underwent cytoreductive surgery for recurrent or metastatic GISTs that were responding to imatinib compared with those undergoing surgery for imatinib -resistant GISTs. However, the prognosis of patients with recurrent or metastatic GISTs who were treated with imatinib but not cytoreductive surgery also reportedly correlates with response to imatinib (37). Furthermore, these retrospective studies on cytoreductive surgery appear to have selection biases for patients with relatively good status. Therefore, whether cytoreductive surgery has a survival benefit for patients with metastatic GISTs that respond to imatinib is impossible to conclude based only on retrospective studies.

Only few randomized clinical trials (RCTs) on cytoreductive surgery for recurrent or metastatic GIST on imatinib treatment have been performed, with small numbers of patients. Xia *et al.* randomly assigned 41 patients with GIST and liver metastases to an operation group (neoadjuvant therapy + resection + adjuvant therapy with

Table 1 Retrospective studies of cytoreductive surgery in patients with recurrent or metastatic GIST on TKI therapy

Study	Month/year of surgery	N	TKI at surgery imatinib/ sunitinib	Median [range] preoperative TKI duration (months)	Complete resection % by disease status at time of surgery				Median follow-up from time of surgery (months)	Median PFS by disease status at time of surgery (months)				2-year PFS by disease status at time of surgery (%)				Median OS by disease status at time of surgery (months)				2-year OS by disease status at time of surgery (%)			
					O	R/S	LR	SR		O	R/S	LR	SR	O	R/S	LR	SR	O	R/S	LR	SR	O	R/S	LR	SR
Raut, 2006 (24)	Mar 2002–Nov 2004	69	45/21	–	–	78	25	7	14.6 [0.5–36]	–	NR	7.7	2.9	–	58	18	0	–	NR	29.8	5.6	–	90	72	0
DeMatteo, 2007 (25)	Jan 2001–Jul 2005	40	37/3	15 [1–48]	62.5	85	46.2	28.6	15 [6–46]	15	NR	12	3	39	61	24	0	39	NR	19	11	62	100	36	0
Gronchi, 2007 (26)	Jan 2001–Jun 2005	38	38/0	>12	81.5	88.9	50	100	29 [6–36]	–	NR	3	–	–	69	0	0	–	NR	NR	–	–	100	60	0
Sym, 2008 (27)	Jun 2001–Jan 2006	26	26/0	18.1 [2.2–53]	62	79	33	14	25.7 [4.3–59]	–	21.8	5.1	3.3	–	65	0	0	–	NR	22.5	23.5	–	96	68	38
Yeh, 2010 (28)	Jan 2001–May 2009	35	35/0	>14	18.4	42.9	4.8	0	37 [7.7–75]	–	NR	8.3	2	–	59.4	35.9	0	–	NR	NR	–	–	69.6	48.4	–
Mussi, 2010 (29)	Jul 2002–Oct 2007	80	80/0	>15	–	88	45	–	>13 [0–76]	–	NR	8	–	–	64.4	9.7	–	–	NR	NR	–	–	82.9	67.6	–
Park, 2014 (30)	Jan 2001–Jun 2010	42	42/0	19.1 [7.2–87]	62	62	–	–	58.9 [15–129]	87.7	87.7	–	–	–	–	–	–	NR	NR	–	–	–	–	–	–
Rubió-Casadevall, 2015 (31)	Jan 2001–Dec 2008	27	27/0	49	–	70.4	25	–	56.6	73.4	73.4	–	–	–	–	–	–	87.6	87.6	–	–	–	–	–	–
Fairweather, 2017 (32)	Jan 2001–Dec 2014	400	234/93	20 [8–39]	34	–	–	–	33.6 [9.5–45]	11	31/19	10	5	–	–	–	–	81	NR/110	54	26	–	–	–	–
		234	234/0	16 [7–36]	–	–	–	–	–	16	36/30	11	6	–	–	–	–	105	NR/110	59	24	–	–	–	–
		93	0/93	25 [12–39]	–	–	–	–	–	7	–	–	–	–	–	–	–	48	–	–	–	–	–	–	–
Raut, 2010 (33)	Feb 2003–Feb 2008	50	0/50	6.7 [1.9–48]	50	40	64	39	15.2 [1.0–54]	5.8	11	6.1	4.1	–	–	–	–	16.4	NR	18.5	8.9	–	–	–	–
Yeh, 2017 (34)	Aug 2001–Dec 2014	26	0/26	6.2 [1–41]	–	–	–	–	15.2 [1.0–54]	5.2	–	5.2	–	–	–	–	–	20	–	20	–	–	–	–	–

TKI, tyrosine kinase inhibitor; GIST, gastrointestinal stromal tumor; O, overall; R/S, response/stable; LR, limited resistance; SR, systemic resistance.

imatinib) or a nonoperation group (imatinib alone), and analyzed their survival, monitored for up to 36 months (38). OS was significantly better in the operation group compared with the nonoperation group (1- and 3-year OS; 100% and 89% versus 85% and 60%, respectively, P=0.03) (38). Du *et al.* conducted a multicenter RCT in China to assess whether cytoreductive surgery for patients with recurrent or metastatic GISTs responding to imatinib improves PFS compared with imatinib treatment alone (39). This RCT was closed early due to poor accrual and only 41 patients were enrolled. After a median follow-up of 23 months (range, 15–34 months), PFS did not significantly differ between the surgery arm (n=19) and imatinib alone arm (n=22; 2-year PFS: 88.4% *vs.* 57.7%, P=0.089) (39).

Because of the lack of RCTs, the impact of cytoreductive surgery on PFS and OS of patients with recurrent or metastatic GIST remains unclear. Although we cannot base evidence on the retrospective studies or results in prospective studies without statistical significance, cytoreductive surgery appears to be feasible and may be beneficial to some patients with recurrent or metastatic GISTs responding to imatinib (*Figure 1*). However, case selection is critical in ensuring cytoreductive surgery for those tumors. In a retrospective study of 239 patients with metastatic GIST who underwent metastasectomy and received imatinib therapy, long-term survival was observed in patients in whom complete macroscopic resection (R0 + R1) of metastatic disease can be achieved, and incomplete resection (R2) does not seem to prolong survival (36). Although this study enrolled GIST patients who were treated with imatinib either before or after metastasectomy, the results suggest that cytoreductive surgery may be indicated for metastatic GISTs responding to imatinib when complete resection can be obtained. In addition, it is important to restart imatinib as soon as the patient is able to tolerate oral medication after surgery (*Figure 1*). Further studies are needed to establish more detailed criteria to select patients to whom cytoreduction is beneficial, and cytoreductive surgery on imatinib treatment is being subjected to detailed investigation at special hospitals and institutions.

Cytoreductive surgery for imatinib-resistant GISTs

As described above, retrospective studies have indicated better outcomes after cytoreductive surgery for imatinib-responsive recurrent or metastatic GISTs than for imatinib-resistant GISTs. However, because effects of sunitinib and regorafenib beyond second-line treatment are considerably less than the huge survival benefit of imatinib in first-line treatment, cytoreductive surgery for imatinib-resistant GISTs warrants discussion. Retrospective studies of cytoreductive surgery during imatinib therapy indicate that PFS and OS were longer after surgery for patients with limited resistance to imatinib than for patients with systemic resistance (*Table 1*). In 2006 and 2007, two independent papers on surgical management of advanced GIST after TKI treatments were published from Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston and Memorial Sloan-Kettering Cancer Center in New York, USA (24,25). These studies evaluated outcomes in their institution series of 69 and 40 consecutive patients, respectively, who were treated with TKIs and then underwent surgery for advanced or metastatic GISTs. These papers both concluded that patients with advanced or metastatic GISTs that respond, or show only focal resistance, to TKIs may benefit from elective resection, whereas surgery for patients with metastatic GIST who have multifocal resistance is generally not indicated. However, these studies included not only GIST patients treated with imatinib but also those treated with sunitinib, although 82 (75%) were treated with imatinib alone before surgery (24,25). In 2017, these two American institutes collected their data, analyzed clinicopathological data of 400 surgeries on 323 patients with TKI-treated metastatic GIST, and reported that surgery for metastatic imatinib-treated GIST in the absence of multifocal progressive disease was associated with outcomes at least comparable with second-line sunitinib, and may be considered in select patients (32). Kanda *et al.* retrospectively analyzed 48 patients with unresectable and metastatic GISTs who were diagnosed with imatinib secondary resistance (ISR) and/or underwent treatment for ISR (40). Of 24 patients who underwent surgical resection of progressive diseases (PD), 20 did so as second-line treatment after imatinib therapy. Long PFS in first-line imatinib therapy, small diameter of PD and surgical resection of PD were identified as favorable independent prognostic factors (40).

Although some retrospective studies of cytoreductive surgery for partially imatinib-resistant GIST have been conducted, their results may reflect patient-selection bias, and safety and efficiency of such therapy remain controversial. In addition, the survival benefit of cytoreductive surgery for imatinib-resistant GIST appears to be affected by postoperative course including

the continuous administration of imatinib after complete resection of imatinib-resistant GIST and the administration of sunitinib and regorafenib after developing 2nd recurrence. Although there are only retrospective data and careful patient selection is needed, cytoreductive surgery may be indicated in limited disease progression refractory to imatinib if complete resection can be achieved (*Figure 1*). However, further studies are needed to establish criteria to select patients to whom cytoreduction is beneficial, and cytoreductive surgery for imatinib-resistant GIST warrants detailed investigations at hospitals and institution with significant experience of multidisciplinary treatment for advanced GISTs where all treatment options, including nonsurgical protocol therapies, can be discussed and performed.

Cytoreduction after second-line therapy

Surgical management following second-line treatment with sunitinib was the focus of wider discussion before regorafenib was introduced as a third-line therapy (33,41,42). In 2009, Ruka *et al.* reported four patients with inoperable and/or metastatic, imatinib-resistant GIST who had responded to sunitinib therapy and underwent surgical removal of residual disease (41). Macroscopically complete resection of residual disease was achieved in three of four cases; viable GIST cells were detected histologically in the resection specimens. In all cases, sunitinib treatment was resumed post-surgery, and none of the patients experienced any postoperative complications during 13–16 months of follow-up (41). In contrast, Raut *et al.* retrospectively reviewed 50 patients on sunitinib treatment who underwent surgery, and reported in 2010 that macroscopically complete resections were achieved only in 25 patients (50%) and completeness of resection did not correlate with response to sunitinib at time of surgery (33). Of importance, complication rate was high 54% and reoperations were required in 16% of cases. They concluded that rates of incomplete resections and complications are high, and benefits of surgery should be weighed against symptoms and alternative treatments (33). In a recent prospective cohort study, Yeh *et al.* investigated 26 patients who experienced local progression on sunitinib treatment and underwent surgeries, and reported that the complication rate was 15.3% and no additional operation was required (34). In this study, sunitinib-treated GIST patients with local progression who underwent cytoreductive surgery (n=26) gained significant PFS and OS benefits (P=0.003 and 0.02, respectively) compared with those not undergoing surgery (n=43), and the authors conclude that surgery is feasible for highly selected patients with metastatic GIST who are receiving sunitinib and experiencing local progression (34). The indication of cytoreductive surgery for GIST patients on sunitinib treatment is controversial. Notably, most of these retrospective studies of cytoreductive surgery for GIST patients treated with sunitinib occurred before regorafenib became clinically available. Furthermore, GIST treated with sunitinib at this relatively late phase tended to be biologically complex due to heterogeneity of genetic and epigenetic background in addition to baseline mutations in the *c-kit* gene that were acquired during first-line imatinib and second-line sunitinib treatment. We treated a patient who quickly relapsed after resection of a sunitinib-resistant GIST that harbored a secondary mutation at exon 13 of the *c-kit* gene. In this case, high proliferative activity of the recurrent foci was associated with sunitinib resistance and the perioperative withdrawal of sunitinib appeared to cause incomplete resection due to uncertain tumor burden at time of surgery and rapid postoperative growth of residual tumors (43). Taken together, although controversial, cytoreductive surgery for patients with metastatic GIST on sunitinib seem infeasible because of high rates of incomplete resections and complications, and more biologically complex and advanced disease, and may be indicated only for management of symptomatic bleeding or obstruction (*Figure 1*).

Individualization of multidisciplinary treatments based on c-kit and PDGFRA mutations

Although most patients with recurrent or metastatic GISTs treated with front-line imatinib achieve clinical benefit, approximately 10% progress within 6 months of initiating therapy (12). Response to imatinib depends on mutation of the *c-kit* or *PDGFRA* genes that occur in primary GIST (44). GISTs harboring primary mutations at exon 11 of the *c-kit* gene are likely to respond well to imatinib, whereas GISTs with mutations at exon 18 of the PDGFRA gene and those without mutations on *c-kit* or *PDGFRA* (wild-type GISTs) generally show primary resistance to imatinib. *In vitro* studies also revealed that GIST-associated KIT mutant isoforms including exon 9 and 11 were inhibited by imatinib with sensitivity similar to that of ligand-activated wild-type KIT, whereas the *PDGFRA* D842V mutant isoform was not inhibited by imatinib (44). In recurrent or metastatic GISTs harboring *PDGFRA* D842V mutation or wild-type

GISTs that show primary resistance to imatinib, frontline surgery may be a treatment option. However, those tumors are reported to have more indolent disease courses (45,46). Surgery for such slowly growing metastases of wild-type GIST or those with *PDGFRA* mutations must be very carefully weighed against the risks.

Heinrich *et al.* have demonstrated that clinical activity of sunitinib is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases of imatinib-resistant GIST (47). *In vitro* studies have revealed that KIT double mutants, in which the second mutation occurred in the activation loop (V560D + D816H, V560D + D820G, V560D + N822K, and V560D + Y823D), were resistant to inhibition by sunitinib (47). Furthermore, primary and secondary *c-kit* or *PDGFRA* mutations were determined using biopsied specimens from patients with imatinib-refractory GIST who received sunitinib as part of a phase I/II trial. PFS and OS were longer and the clinical benefits were better in patients with imatinib-resistant GIST harboring secondary mutation at exon 13 or 14 (i.e., ATP-binding-pocket) than those with secondary mutation at exon 17 or 18 (i.e., activation loop) of the *c-kit* gene. Recurrent or metastatic GISTs on second-line therapy with sunitinib appear to have a more biologically complex and advanced nature than those on the first-line treatment with imatinib. Therefore, patient cohorts with such tumors are very heterogeneous, with different primary and secondary mutations that affect response to sunitinib. In addition, individual patients with different secondary mutations may show heterogeneity within multiple metastatic foci. The mutational status of primary and metastatic tumors is a critical consideration with regard to cytoreductive surgery for recurrent or metastatic GIST on sunitinib.

The principle treatment strategy of recurrent or metastatic GIST is sequential administration of imatinib, sunitinib and regorafenib, according to the results of RCTs. When considering cytoreductive surgery for recurrent or metastatic GISTs on imatinib therapy, postoperative courses are important determinants of PFS and OS. Imatinib should be reintroduced as immediately as possible after cytoreductive surgery. When postoperative recurrence appears, sunitinib should be introduced followed by regorafenib for sunitinib-resistant tumors (*Figure 1*). In such a treatment course after cytoreductive surgery, surgical complications often interfere with or delay TKI administration. Therefore, we need to carefully consider surgical procedures and indication, based on the patient's comorbidities, general conditions and tumor status.

Taken together, individualization of multidisciplinary treatments needs to be planned based on *c-kit* and *PDGFRA* mutations in addition to the patient's status so that cytoreductive surgery can be safely and appropriately performed.

Conclusions

Initial cytoreduction apparently offers no benefit in cases of recurrent or metastatic GISTs; the principle treatment strategy is imatinib administration. Although case selection is critical, cytoreductive surgery seems feasible in patients with recurrent or metastatic GISTs responding to imatinib or those with limited focal progression if complete resection can be achieved. Cytoreductive surgery for patients with metastatic GIST on sunitinib seems infeasible. Individualization of multidisciplinary treatments needs to be designed based on *c-kit* and *PDGFRA* mutations in addition to the patient's status.

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Footnote

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References

1. Kindblom LG, Remotti HE, Aldenborg F, et al. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998;152:1259-69.
2. O'Leary T, Berman JJ. Gastrointestinal stromal tumors: answers and questions. Hum Pathol 2002;33:456-8.
3. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
4. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660-7.
5. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors.

Science 2003;299:708-10.
6. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-74.
7. Casali PG, Le Cesne A, Poveda Velasco A, et al. Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. J Clin Oncol 2015;33:4276-83.
8. DeMatteo RP, Shah A, Fong Y, et al. Results of hepatic resection for sarcoma metastatic to liver. Ann Surg 2001;234:540-7; discussion 547-8.
9. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 2000;295:139-45.
10. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001;344:1052-6.
11. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 2001;358:1421-3.
12. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620-5.
13. O'Farrell AM, Abrams TJ, Yuen HA, et al. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood 2003;101:3597-605.
14. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003;9:327-37.
15. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38.
16. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 2011;129:245-55.
17. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
18. Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. J Clin Oncol 2005;23:5795-804.
19. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 2010;28:1247-53.
20. An HJ, Ryu MH, Ryoo BY, et al. The effects of surgical cytoreduction prior to imatinib therapy on the prognosis of patients with advanced GIST. Ann Surg Oncol 2013;20:4212-8.
21. Chang SC, Liao CH, Wang SY, et al. Feasibility and Timing of Cytoreduction Surgery in Advanced (Metastatic or Recurrent) Gastrointestinal Stromal Tumors During the Era of Imatinib. Medicine (Baltimore) 2015;94:e1014.
22. Sato S, Tsujinaka T, Yamamoto K, et al. Primary surgery as a frontline treatment for synchronous metastatic gastrointestinal stromal tumors: an analysis of the Kinki GIST registry. Surg Today 2016;46:1068-75.
23. Kanda T, Masuzawa T, Hirai T, et al. Surgery and imatinib therapy for liver oligometastasis of GIST: a study of Japanese Study Group on GIST. Jpn J Clin Oncol 2017;47:369-72.
24. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006;24:2325-31.
25. DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg 2007;245:347-52.
26. Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. Ann Surg

2007;245:341-6.
27. Sym SJ, Ryu MH, Lee JL, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). J Surg Oncol 2008;98:27-33.
28. Yeh CN, Chen TW, Tseng JH, et al. Surgical management in metastatic gastrointestinal stromal tumor (GIST) patients after imatinib mesylate treatment. J Surg Oncol 2010;102:599-603.
29. Mussi C, Ronellenfitsch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol 2010;21:403-8.
30. Park SJ, Ryu MH, Ryoo BY, et al. The role of surgical resection following imatinib treatment in patients with recurrent or metastatic gastrointestinal stromal tumors: results of propensity score analyses. Ann Surg Oncol 2014;21:4211-7.
31. Rubió-Casadevall J, Martinez-Trufero J, Garcia-Albeniz X, et al. Role of surgery in patients with recurrent, metastatic, or unresectable locally advanced gastrointestinal stromal tumors sensitive to imatinib: a retrospective analysis of the Spanish Group for Research on Sarcoma (GEIS). Ann Surg Oncol 2015;22:2948-57.
32. Fairweather M, Balachandran VP, Li GZ, et al. Cytoreductive Surgery for Metastatic Gastrointestinal Stromal Tumors Treated With Tyrosine Kinase Inhibitors: A 2-institutional Analysis. Ann Surg 2017. [Epub ahead of print].
33. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. Ann Surg Oncol 2010;17:407-15.
34. Yeh CN, Wang SY, Tsai CY, et al. Surgical management of patients with progressing metastatic gastrointestinal stromal tumors receiving sunitinib treatment: A prospective cohort study. Int J Surg 2017;39:30-6.
35. Al-Batran SE, Hartmann JT, Heidel F, et al. Focal progression in patients with gastrointestinal stromal tumors after initial response to imatinib mesylate: a three-center-based study of 38 patients. Gastric Cancer 2007;10:145-52.
36. Bauer S, Rutkowski P, Hohenberger P, et al. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib -- analysis of prognostic factors (EORTC-STBSG collaborative study). Eur J Surg Oncol 2014;40:412-9.
37. Le Cesne A, Van Glabbeke M, Verweij J, et al. Absence of progression as assessed by response evaluation criteria in solid tumors predicts survival in advanced GI stromal tumors treated with imatinib mesylate: the intergroup EORTC-ISG-AGITG phase III trial. J Clin Oncol 2009;27:3969-74.
38. Xia L, Zhang MM, Ji L, et al. Resection combined with imatinib therapy for liver metastases of gastrointestinal stromal tumors. Surg Today 2010;40:936-42.
39. Du CY, Zhou Y, Song C, et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China. Eur J Cancer 2014;50:1772-8.
40. Kanda T, Ishikawa T, Kosugi SI, et al. Prognostic factors after imatinib secondary resistance: survival analysis in patients with unresectable and metastatic gastrointestinal stromal tumors. Int J Clin Oncol 2016;21:295-301.
41. Ruka W, Rutkowski P, Szawlowski A, et al. Surgical resection of residual disease in initially inoperable imatinib-resistant/intolerant gastrointestinal stromal tumor treated with sunitinib. Eur J Surg Oncol 2009;35:87-91.
42. Pantaleo MA, Di Battista M, Catena F, et al. Surgical debulking of gastrointestinal stromal tumors: is it a reasonable option after second-line treatment with sunitinib? J Cancer Res Clin Oncol 2008;134:625-30.
43. Kikuchi H, Miyazaki S, Setoguchi T, et al. Rapid relapse after resection of a sunitinib-resistant gastrointestinal stromal tumor harboring a secondary mutation in exon 13 of the c-KIT gene. Anticancer Res 2012;32:4105-9.
44. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
45. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
46. Lasota J, Miettinen M. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). Semin Diagn Pathol 2006;23:91-102.
47. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352-9.

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Treatment

Minimally invasive surgery for gastric gastrointestinal stromal tumors

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Abstract: Minimally invasive surgery has been increasingly performed for gastric gastrointestinal stromal tumors (GIST). In this review we discuss and summarize the current evidence on minimally invasive surgery for gastric GISTs. Laparoscopic resection for gastric GIST has been consistently shown to be associated with superior perioperative outcomes with no compromise in oncological outcomes when compared to open resection in numerous retrospective case-control studies. It has also been shown to be safe and feasible for large tumors or tumors located in unfavorable sites. However, to date, there remains a lack of level 1 evidence from prospective randomized control trials in support of laparoscopic resection.

Keywords: Laparoscopic; robotic; minimally invasive surgery; gastric; gastrointestinal stromal tumor (GIST)

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Introduction

Over the past 2 decades, minimally invasive surgery has emerged as the standard of care for surgical procedures of the appendix, gallbladder, spleen, and colon. Laparoscopic procedures confer perioperative benefits of shortened hospitalization, faster recovery, earlier oral intake as compared to the traditional open procedures (1-6). Similarly, these benefits have been observed when laparoscopic resection is performed for gastric gastrointestinal stromal tumors (GIST). Numerous retrospective case control studies have confirmed the benefits of faster recovery, lower perioperative morbidity and overall superior short-term outcomes of laparoscopic versus open resection for gastric GISTs (7,8). However, studies reporting on long term oncological outcomes of minimally invasive surgery for gastric GIST remains limited (7) and no randomized trials have been reported to date. Nonetheless, level 1 evidence from randomized trials have reported equivalent oncological outcomes of laparoscopic surgery for gastric and colorectal cancers (9,10). Laparoscopic lymphadenectomy and adequate resection margins have also been shown to be technically reproducible and feasible (4-6,9,10). These promising results can be extrapolated to laparoscopic resection of gastric GISTs because of a similar, if not lower, level of complexity of oncological resection. More recently, propensity matched analysis and matched case control studies have been reported similarly supporting the oncological safety for laparoscopic resection for gastric GISTs (11).

The surgical approach for gastric GISTs is usually straightforward in expert hands because local resection is adequate and formal gastrectomy with regional lymphadenectomy is not usually required (12,13). Even though ideally tumor-free resection margins should be obtained, wide resection margins are not mandatory unlike gastric adenocarcinomas as submucosal lymphatic spread does not occur. Furthermore, it has been observed

that microscopically involved margins have no apparent detrimental effect on overall survival after complete surgical resection for GIST (14). The favorable disease biology of GIST, allows laparoscopic organ sparing surgery in the majority of cases with excellent long term functional outcomes. In a prospective single institution study, the average Gastrointestinal Quality of Life Index (GIQLI) of the patients who underwent laparoscopic gastric wedge resection was similar to otherwise healthy participants. With the exception of a minority of the patients (~10%) having worse regurgitation symptoms, the majority had a GIQLI within normal range, correlating with an excellent quality of life (15).

Resection for tumors in difficult locations

As shown in many studies, organ sparing surgery in the form of wedge resections can be carried out expeditiously for most gastric GISTs in favorable locations such as the anterior wall and greater curve of the stomach (6-8). However, this approach is sometimes challenging in difficult anatomic locations, such as the gastric cardia or distal antrum. A recent study presented the feasibility of laparoscopic wedge resections for GIST at these difficult locations under the guidance of intraoperative endoscopy. In that study, over 40% of the cases presented were located in the lesser curve, antrum or cardiac. Wedge resection guided by intraoperative endoscopy resulted in a 100% R0 resection with similarly favorable perioperative and long term oncological outcomes, where over 95% 5-year overall survival was achieved (16). More complex approaches such as the intragastric or "endoluminal" surgery through the use of intra-gastric working ports have also been described for challenging locations such as posterior wall gastric GISTs (17,18). Tumors in the abovementioned locations require more advanced laparoscopic skills such as suture manipulation of the tumour, intra-gastric dissection and intra-corporeal suturing to achieve safe resection and reconstruction.

When treating gastric GISTs, the surgeon should be aware of the rare and challenging situation of an extra-intestinal GISTs. These lesions when located posterior to the stomach, have a tendency to invade the surrounding structures such as the pancreas and spleen necessitating a more complex and extensive surgical procedure which might be challenging if attempted laparoscopically (19). The open approach remains the preferred surgical approach for GISTs that require complex multivisceral resection or large lesions that require delicate tissue handling (to prevent tumor rupture) or necessitating a large incision for specimen retrieval (20).

Resection for large GISTs

Despite the advances and increasingly widespread adoption of minimally invasive surgery for gastric GISTs, intraoperative rupture of GISTs remains a significant challenge especially for large cystic GISTs. Should tumor rupture and spillage occur, the prognosis of the patient will be significantly compromised and this should be weighed against the perioperative benefits of the laparoscopic approach (11,21). However, with favorable case selection and expertise in minimally invasive surgery, several authors have reported that selected cases of large gastric GISTs can safely undergo laparoscopic resection (22-24) with minimal risk of rupture. In two recent studies which compared the outcomes of laparoscopic versus open resection of gastric GISTs larger than 5 cm, the laparoscopic approach continued to yield superior perioperative outcomes with no significant differences in complication rates (overall morbidity ~10%, major morbidity <5%, perioperative mortality 1% or less), 5-year disease free survival rates at around 92% or overall survival rates over 93% (24,25). Similarly, results from expert centers have also demonstrated that laparoscopic resection is safe and feasible even for tumors located in unfavorable locations (26).

Comparison between laparoscopic versus open resection for GISTs

To date, several large case-control studies have reported on the outcomes of laparoscopic resection of gastric GIST in comparison with conventional open resection. *Tables 1-3* summarizes the results from several of these large (n>50) case-control studies demonstrating that laparoscopic resection can be performed with a low conversion rate and was associated with superior perioperative outcomes such as shorter hospital stay, earlier oral intake, lower morbidity with similar oncological outcomes compared to the open approach (27-32). Similarly, several systematic reviews and meta-analyses have demonstrated that laparoscopic resection was superior in perioperative outcomes compared to open surgery (33-35). In the latest systematic review of 24 studies involving 2,140 patients demonstrated that laparoscopy was associated with superior outcomes including decreased operative time [weighted mean

Table 1 Summary of studies of laparoscopic resection of gastric GISTs (n>50) showing conversion rates

Author	Country	Year	Study period	LAP	Open	Conversion (%)	LAP, follow up duration (months)	Open, follow up duration (months)
Lee *et al.* (27)	Republic of Korea	2011	2001–2008	50	50	2	21.1 [0–64]	22.3 [0–93]
Wan *et al.* (28)	China	2012	2004–2011	68	88	NR	29 [4–89]	36 [4–90]
Kim *et al.* (29)	Republic of Korea	2014	1998–2012	156	250	NR	42.9 [2–166]	NR
Cai *et al.* (30)	China	2015	2006–2013	90	66	NR	21 [1–90]	44.5 [1–96]
Goh *et al.* (8)	Singapore	2015	1988–2013	50	50	10	27 [1–140]	60 [6–170]
Chen *et al.* (31)	China	2016	2006–2012	71	71	0	36 [1–111]	NR
Hu *et al.* (32)	China	2016	2009–2014	91	85	0	32±16.3	34.2±14.5

NR, not reported; GIST, gastric gastrointestinal stromal tumor; LAP, laparoscopic.

Table 2 Summary of studies of laparoscopic resection of gastric GISTs (n>50) showing oral intake and hospital stay

Author	Country	Year	Study period	LAP, mean time to oral intake (days)	Open, mean time to oral intake (days)	LAP, mean hospital stay (days)	Open, mean hospital stay (days)
Lee *et al.* (27)	Republic of Korea	2011	2001–2008	2.3	3.5	5.7	7.8
Wan *et al.* (28)	China	2012	2004–2011	NR	NR	NR	NR
Kim *et al.* (29)	Republic of Korea	2014	1998–2012	NR	NR	NR	NR
Cai *et al.* (30)	China	2015	2006–2013	3.2	4.1	6	8
Goh *et al.* (8)	Singapore	2015	1988–2013	3	5	4	6
Chen *et al.* (31)	China	2016	2006–2012	3.9	5.1	8.8	13.3
Hu *et al.* (32)	China	2016	2009–2014	7.6	8.2	8.8	15.3

NR, not reported; GIST, gastric gastrointestinal stromal tumor; LAP, laparoscopic.

Table 3 Summary of studies of laparoscopic resection of gastric GISTs (n>50) showing complications and recurrence rates

Author	Country	Year	Study period	LAP recurrence	Open recurrence	LAP complications	Open complications
Lee *et al.* (27)	Republic of Korea	2011	2001–2008	NR	NR	2/50 (4%)	1/50 (2%)
Wan *et al.* (28)	China	2012	2004–2011	3/68 (4.4%)	4/88 (4.5%)	4/68 (5.9%)	20/88 (2.3%)
Kim *et al.* (29)	Republic of Korea	2014	1998–2012	0/156 (0%)	11/250 (4.4%)	NR	NR
Cai *et al.* (30)	China	2015	2006–2013	2/90 (2.2%)	2/66 (3%)	4/90 (4.4%)	8/66 (12.1%)
Goh *et al.* (8)	Singapore	2015	1988–2013	0/50 (0%)	4/50 (8%)	3/50 (6%)	5/50 (10%)
Chen *et al.* (31)	China	2016	2006–2012	6/71 (8.5%)	5/71 (7%)	4/71 (5.6%)	16/71 (22.5%)
Hu *et al.* (32)	China	2016	2009–2014	12/91 (13.2%)	17/85 (2%)	9/91 (9.9%)	16/85 (18.8%)

NR, not reported; GIST, gastric gastrointestinal stromal tumor; LAP, laparoscopic.

difference (WMD), –30.71 min; 95% CI, –58.48 to –2.95]; decreased intraoperative blood loss (WMD, –60.90 mL; 95% CI, –91.53 to –30.28); decreased time to flatus (WMD, –1.10 days; 95% CI, –1.41 to –0.79); decreased time to oral intake (WMD, –1.25 days; 95% CI, –1.64 to –0.86); decreased length of hospital stay (WMD, –3.42 days; 95% CI, –4.37 to –2.46); decreased morbidity (OR, 0.38; 95% CI, 0.27–0.54); and lower recurrence (OR, 0.45; 95% CI, 0.30–0.66) (35). Nonetheless, it is important to emphasize that current evidence in support of the minimally invasive approach is presently limited to retrospective case control studies with an inherent potential for selection bias. However, although ideal, the rarity of GIST and the lack of obvious therapeutic equipoise makes prospect of conducting a prospective randomized control trial difficult today.

Robotic resection for GISTs

Robotic surgery was first introduced to overcome the limitations of conventional laparoscopy especially with the high definition 3D monitor and the increased dexterity of the robotic arms. With regards to resection for gastric GISTs, the robotic approach potentially expands the indications of minimally invasive surgery by enabling minimally invasive procedures for tumors located in places that are more difficult to access via conventional laparoscopic surgery such as in the cardioesophageal and duodenogastric junctions. It also simplifies complex tasks such as intracorporeal suturing in difficult locations (36). Presently, experience with robotic resection for gastric GISTs remains limited. However, several small case series have demonstrated the oncological safety, low complication and low conversion rates associated with robotic assisted excision of large GISTs (>5 cm) in difficult locations (37-41). However, robotic assistance has been reported to be associated with an increase in operating time and its cost-effectiveness remain a major obstacle to the widespread adoption of this technology.

Conclusions

In summary, minimally surgery for gastric GISTs has been widely adopted today and is an excellent procedure especially for tumors in favorable locations within the stomach allowing patients to enjoy superior perioperative outcomes over the open approach without compromising oncological outcomes. In expert hands, the surgical indications can potentially be safely expanded to large tumors or tumors in difficult locations.

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Footnote

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References

1. Keus F, de Jong JA, Gooszen HG, et al. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev 2006;(4):CD006231.
2. Barbaros U, Dinççağ A, Sümer A, et al. Prospective randomized comparison of clinical results between hand-assisted laparoscopic and open splenectomies. Surg Endosc 2010;24:25-32.
3. Mehrabi A, Hafezi M, Arvin J, et al. A systematic review and meta-analysis of laparoscopic versus open distal pancreatectomy for benign and malignant lesions of the pancreas: it's time to randomize. Surgery 2015;157:45-55.
4. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-8.
5. Kim W, Kim HH, Han SU, et al. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-term Outcomes From a Multicenter Randomized Controlled Trial (KLASS-01). Ann Surg 2016;263:28-35.
6 Koh YX, Chok AY, Zheng HL, et al. A systematic review and meta-analysis comparing laparoscopic versus open gastric resections for gastrointestinal stromal tumors of the stomach. Ann Surg Oncol 2013;20:3549-60.
7 Bischof DA, Kim Y, Dodson R, et al. Open versus minimally invasive resection of gastric GIST: a multi-institutional analysis of short- and long-term outcomes. Ann Surg Oncol 2014;21:2941-8.
8 Goh BK, Goh YC, Eng AK, et al. Outcome after laparoscopic versus open wedge resection for suspected gastric gastrointestinal stromal tumors: A matched-pair case-control study. Eur J Surg Oncol 2015;41:905-10
9 Boutros M, Hippalgaonkar N, Silva E, et al. Laparoscopic resection of rectal cancer results in higher lymph node

yield and better short-term outcomes than open surgery: a large single-center comparative study. Dis Colon Rectum 2013;56:679-88.
10 Lu W, Gao J, Yang J, et al. Long-term clinical outcomes of laparoscopy-assisted distal gastrectomy versus open distal gastrectomy for early gastric cancer: A comprehensive systematic review and meta-analysis of randomized control trials. Medicine (Baltimore) 2016;95:e3986.
11 Xu C, Chen T, Hu Y, et al. Retrospective study of laparoscopic versus open gastric resection for gastric gastrointestinal stromal tumors based on the propensity score matching method. Surg Endosc 2017;31:374-81
12 DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51-8.
13 Chok AY, Koh YX, Ow MY, et al. A systematic review and meta-analysis comparing pancreaticoduodenectomy versus limited resection for duodenal gastrointestinal stromal tumors. Ann Surg Oncol 2014;21:3429-38.
14 McCarter MD, Antonescu CR, Ballman KV, et al. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. J Am Coll Surg 2012;215:53-9
15 Dressler JA, Palazzo F, Berger AC, et al. Long-term functional outcomes of laparoscopic resection for gastric gastrointestinal stromal tumors. Surg Endosc 2016;30:1592-8.
16 Mueller CL, Braun J, Leimanis ML, et al. Application of an individualized operative strategy for wedge resection of gastric gastrointestinal stromal tumors: Effectiveness for tumors in difficult locations. Surgery 2016;160:1038-48.
17 Novitsky YW, Kercher KW, Sing RF, et al. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. Ann Surg 2006;243:738-45; discussion 745-7.
18 Maker AV. A technique for laparoendoscopic resection of posterior fundic gastric GISTs without need for a gastrotomy. Ann Surg Oncol 2013;20:4238.
19 Goh BK, Chow PK, Kesavan SM, et al. A single-institution experience with eight CD117-positive primary extragastrointestinal stromal tumors: critical appraisal and a comparison with their gastrointestinal counterparts. J Gastrointest Surg 2009;13:1094-8.
20 Casali PG, Jost L, Reichardt P, et al. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:64-7.
21 Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41
22 Masoni L, Gentili I, Maglio R, et al. Laparoscopic resection of large gastric GISTs: feasibility and long-term results. Surg Endosc 2014;28:2905-10.
23 Lin J, Huang C, Zheng C, et al. Laparoscopic versus open gastric resection for larger than 5 cm primary gastric gastrointestinal stromal tumors (GIST): a size-matched comparison. Surg Endosc 2014;28:2577-83.
24 Khoo CY, Goh BKP, Eng AK, et al. Laparoscopic wedge resection for suspected large (≥5 cm) gastric gastrointestinal stromal tumors. Surg Endosc 2017;31:2271-9.
25 Piessen G, Lefèvre JH, Cabau M, et al. Laparoscopic Versus Open Surgery for Gastric Gastrointestinal Stromal Tumors: What Is the Impact on Postoperative Outcome and Oncologic Results? Ann Surg 2015;262:831-9
26 Huang CM, Chen QF, Lin JX, et al. Can laparoscopic surgery be applied in gastric gastrointestinal stromal tumors located in unfavorable sites?: A study based on the NCCN guidelines. Medicine (Baltimore) 2017;96:e6535
27 Lee HH, Hur H, Jung H, et al. Laparoscopic wedge resection for gastric submucosal tumors: a size-location matched case-control study. J Am Coll Surg 2011;212:195-9.
28 Wan P, Yan C, Li C, et al. Choices of surgical approaches for gastrointestinal stromal tumors of the stomach: laparoscopic versus open resection. Dig Surg 2012;29:243-50.
29 Kim IH, Kim IH, Kwak SG, et al. Gastrointestinal stromal tumors (GISTs) of the stomach: a multicenter, retrospective study of curatively resected gastric GISTs. Ann Surg Treat Res 2014;87:298-303.
30 Cai JQ, Chen K, Mou YP, et al. Laparoscopic versus open wedge resection for gastrointestinal stromal tumors of the stomach: a single-center 8-year retrospective cohort study of 156 patients with long-term follow-up. BMC Surg 2015;15:58.
31 Chen QF, Huang CM, Lin M, et al. Short- and long-term outcomes of laparoscopic versus open resection for gastric gastrointestinal stromal tumors: a propensity score-matching analysis. Medicine 2016;95:e3135.
32 Hu J, Or BH, Hu K, et al. Comparison of the post-operative outcomes and survival of laparoscopic versus open resections for gastric gastrointestinal stromal tumors: a multi-center prospective cohort study. Int J Surg 2016;33 Pt A:65-71.
33 Liang JW, Zheng ZC, Zhang JJ, et al. Laparoscopic versus

open gastric resections for gastric gastrointestinal stromal tumors: a meta-analysis. Surg Laparosc Endosc Percutan Tech 2013;23:378-87.
34 Zheng L, Ding W, Zhou D, et al. Laparoscopic versus open resection for gastric gastrointestinal stromal tumors: a meta-analysis. Am Surg 2014;80:48-56.
35 Xiong H, Wang J, Jia Y, et al. Laparoscopic surgery versus open resection in patients with gastrointestinal stromal tumors: An updated systematic review and meta-analysis. Am J Surg 2017 Sep;214:538-46
36 Buchs NC, Bucher P, Pugin F, et al. Robot-assisted oncologic resection for large gastric gastrointestinal stromal tumor: a preliminary case series. J Laparoendosc Adv Surg Tech A 2010;20:411-5
37 Noshiro H, Nomura A, Akashi M, et al. Pure Robotic Surgery for Intraluminally Growing Gastrointestinal Stromal Tumors around the Esophagogastric junction or Pyloric Ring. Hepatogastroenterology 2015;62:629-34.
38 de'Angelis N, Genova P, Amiot A, et al. Robotic Versus Laparoscopic Gastric Resection for Primary Gastrointestinal Stromal Tumors >5 cm: A Size-Matched and Location-Matched Comparison. Surg Laparosc Endosc Percutan Tech 2017;27:65-71
39 Desiderio J, Trastulli S, Cirocchi R, et al. Robotic gastric resection of large gastrointestinal stromal tumors. Int J Surg 2013;11:191-6.
40 Moriyama H, Ishikawa N, Kawaguchi M, et al. Robot-assisted laparoscopic resection for gastric gastrointestinal stromal tumor. Surg Laparosc Endosc Percutan Tech 2012;22:e155-6
41 Vicente E, Quijano Y, Ielpo B, et al. Robot-assisted resection of gastrointestinal stromal tumors (GIST): a single center case series and literature review. Int J Med Robot 2016;12:718-23

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Endoscopic resection of gastric gastrointestinal stromal tumors

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract, and about 60% of them are found in the stomach. With the widespread application of endoscopy and endoscopic ultrasonography (EUS), more and more gastric GISTs are being found in an early stage (with a relative small diameter and no metastasis), giving the chance of complete resection. Endoscopic resection such as endoscopic band ligation (EBL), endoscopic submucosal dissection (ESD), endoscopic submucosal excavation (ESE), endoscopic full-thickness resection (EFTR) and submucosal tunneling endoscopic resection (STER), is a minimally invasive method compared with the conventional surgical approaches (open or laparoscopic), and has been demonstrated to be safe and effective for treating gastric GISTs. This review summarizes the recent advances on endoscopic resection of gastric GISTs, aiming to provide a rational management strategy for gastric GISTs.

Keywords: Endoscopic surgical procedures; gastric neoplasm; gastrointestinal stromal tumor (GIST)

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract, and the estimated clinical incidence is 1 in 100,000 populations per year (1). GISTs can occur anywhere in the gastrointestinal tract, and in rare cases, in intra-abdominal sites (such as omentum, mesentery, and retroperitoneum), among which the stomach is the most common site (about 60%) (1). With the widespread use of endoscopy and endoscopic ultrasonography (EUS), more and more gastric GISTs are being found in an early stage, providing the chance of complete resection. Laparoscopic surgery (LAP) has been regarded as the standard methods for treatment of gastric GISTs <5 cm (2-4). Endoscopic resection takes advantages over LAP in reducing intraoperative blood loss, operating time and hospital stay without any compromise in success rate or increase in complications, and has been widely accepted as an alternative method for gastric GISTs originating from the MP layer (5-7). Available endoscopic methods include endoscopic band ligation (EBL), endoscopic submucosal dissection (ESD), endoscopic submucosal excavation (ESE), endoscopic full-thickness resection (EFTR), submucosal tunneling endoscopic resection (STER), and laparoscopic and endoscopic cooperative surgery (LECS) (8). This review summarizes recent advances on endoscopic resection of gastric GISTs, aiming to provide a rational management strategy for gastric GISTs.

Indications of endoscopic resection of gastric GISTs

Gastric submucosal tumors (SMTs) are found in 0.36% of middle-aged adults by health examination, and most of them are asymptomatic or have nonspecific symptoms (9). Once a gastric SMT is found, EUS is usually recommended

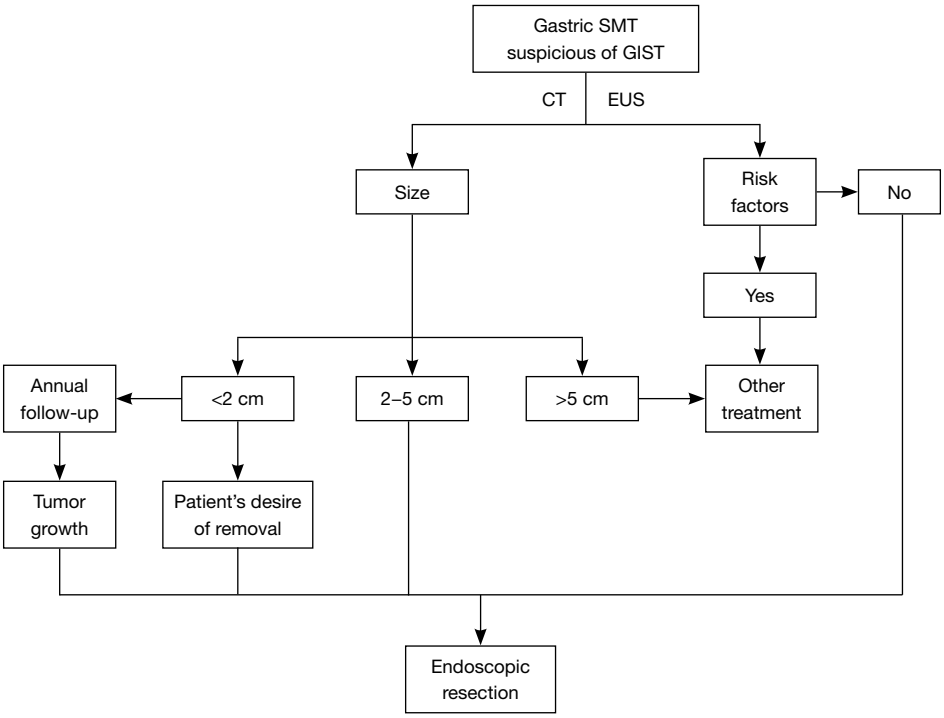

Figure 1 The patient selection diagram of endoscopic resection for gastric GISTs in our hospital. Risk factors: ulceration or erosion at the site of tumor location; EUS shows irregular border, internal heterogeneity include anechoic area (i.e., necrosis) and echogenic loci (i.e., bleeding), heterogeneous enhancement, regional lymph node swelling; CT show metastasis or invasion out of the gastrointestinal tract; a Zubrod-ECOG performance status ≥2; have severe cardiopulmonary disease or blood coagulation disorders. GIST, gastrointestinal stromal tumor; EUS, endoscopic ultrasonography; CT, computed tomography; SMT, submucosal tumor.

to further determine the characteristics of the SMT, such as the originating layer, echo, lymph node, which is helpful to differentiating GISTs from other mesenchymal tumors. Specific findings of GIST on EUS include: low echo, inhomogeneous, anechoic or high echo (when tumors are malignant), and it is usually located in the third or fourth layer, rarely the second layer (10). If an SMT is highly suggestive of a GIST and is considered resectable, preoperative biopsy is not necessary (11). Periodical surveillance is recommended for small (<2 cm) asymptomatic gastric GISTs. However, it involves issues related to the patient's compliance and stress, cost-effectiveness, and the risk associated with repeated endoscopic procedures and delayed diagnosis of malignancy (12,13). Moreover, it is believed that small gastric GISTs also have malignant potential and that the size of small gastric GISTs could increase significantly during follow-up (13,14). Therefore, some researchers suggested that once a gastric GIST was suspected, it should be resected by surgical or endoscopic approaches (13,15), although the NCCN guideline did not recommend immediate resection for GISTs <2 cm (2). *Figure 1* shows the patient selection diagram of endoscopic resection for gastric GISTs in our hospital.

Endoscopic methods for gastric GIST

EBL

EBL was first reported for treating esophageal varices (16), and was then applied to the treatment of gastrointestinal superficial lesions (17). Sun *et al.* (18) firstly reported the feasibility and safety of EBL in the treatment of gastric GISTs, and complete resection was achieved in 96.6% (28/29) of the cases, with a low complication rate (3.4%, 1/29) and recurrence rate (3.4%, 1/29). The standard procedure of EBL is as follows: aspirating the tumor into a transparent cap, releasing the band, cutting the overlying mucosal and submucosal layer and then dissecting the

Table 1 Studies about endoscopic resection for gastric GISTs

Ref.	N	Method	Mean tumor diameter [range] (mm)	Mean operation time (min)	Complete resection rate (%)	Complication (%)	Recurrence (%)
Sun *et al.* (18)	29	EBL	9.2 [7–12]	–	96.6	1 bleeding	3.4
Nan *et al.* (19)	24	EBL	8 [7–12]	–	100	0	0
Huang *et al.* (21)	38	EBL	<12	–	100	3 perforation	–
Nan *et al.* (20)	177	EBL	8 [5–12]	–	100	2 perforation	–
An *et al.* (22)	168	ESD	15 [5–60]	46.5 [33–181]	100	2 bleeding, 71 gastric wall defect	0
He *et al.* (23)	25/31[†]	ESD	27 [20–50]	70.16 [40–105]	100	3 bleeding, 6 perforation	0
Zhang *et al.* (24)	69	ESE	18.7 [7–30]	41.07±10.79	100	6 bleeding, 23 perforation, 5 surgery-related complication	0
Huang *et al.* (21)	18	ESE	>15	–	100	0	–
Wang *et al.* (25)	86	ESE	–	–	100	5 bleeding, 9 perforation	5.8
Shi *et al.* (26)	43/60[‡]	ESE	1.4 [5–50]	38	100	–	–
Wang *et al.* (27)	30	ESE	22 [10–35]	50±5 [20–120]	100	6 perforation	0
Shi *et al.* (28)	68	EFTR	26	41	100	1 Mallory-Weiss syndrome, 1 delayed bleeding	0
Mori *et al.* (29)	16	EFTR	28.3	271	100	0	0
Huang *et al.* (21)	13	EFTR	>20	–	100	0	–
Lu *et al.* (30)	36/47[§]	STER	14 [5–50]	79.3 [45–150]	100	3 peumoperitoneum	0
Li *et al.* (31)	11/32[§]	STER	23 [10–50]	51.8 [25–125]	100	Intraoperative: 1 bleeding, 6 peumoperitoneum; postoperative: 3 pneumothorax, 3 pleural effusion, 1 subphrenic infection	0
Mao *et al.* (32)	10/56[§]	STER	18 [10–32]	41.5 [20–65]	100	9 gas-related complications with or without pleural effusion	0
Kikuchi *et al.* (33)	10	LECS	24.1±7.6	253±45	100	1 intra-abdominal abscess	0
Qiu *et al.* (34)	69	LECS	28±16	86.1	–	1 leakage, 1 bleeding	0
Hiki *et al.* (35)	10	LECS	46±3	169±17	100	0	–

[†], 25 of the 31 GISTs were located in the stomach; [‡], 43 of the 60 GISTs were located in the stomach; [§], n/m, these 3 studies are about STER for gastric submucosal tumors, n of the m submucosal tumors are gastric GISTs. GISTs, gastrointestinal stromal tumors; EBL, endoscopic band ligation; ESD, endoscopic submucosal dissection; ESE, endoscopic submucosal excavation; EFTR, endoscopic full-thickness resection; STER, submucosal tunneling endoscopic resection; LECS, laparoscopic and endoscopic cooperative surgery.

tumor. EUS is usually used to confirm whether the mass is completely confined within the band, and hemoclips are placed around the band to reduce the tension and potential perforation. Several clinical studies have demonstrated the safety and efficacy of EBL for gastric GISTs, with favorable complete rate, low complication and recurrence rate (19,20) (*Table 1*). The most common complications reported are perforation and bleeding (18-20,36). In addition, Meng *et al.* (5) demonstrated that EBL could reduce operation time, estimated blood loss, complications, hospital stay and cost, compared with ESD and LAP. The major disadvantage of EBL is the restriction of maximal resectable size (≤12 mm) due to the size of the transparent cap. And EBL is feasible only for GISTs originating from superficial muscularis propria layer. EBL is now less used and mostly be replaced by other endoscopic methods.

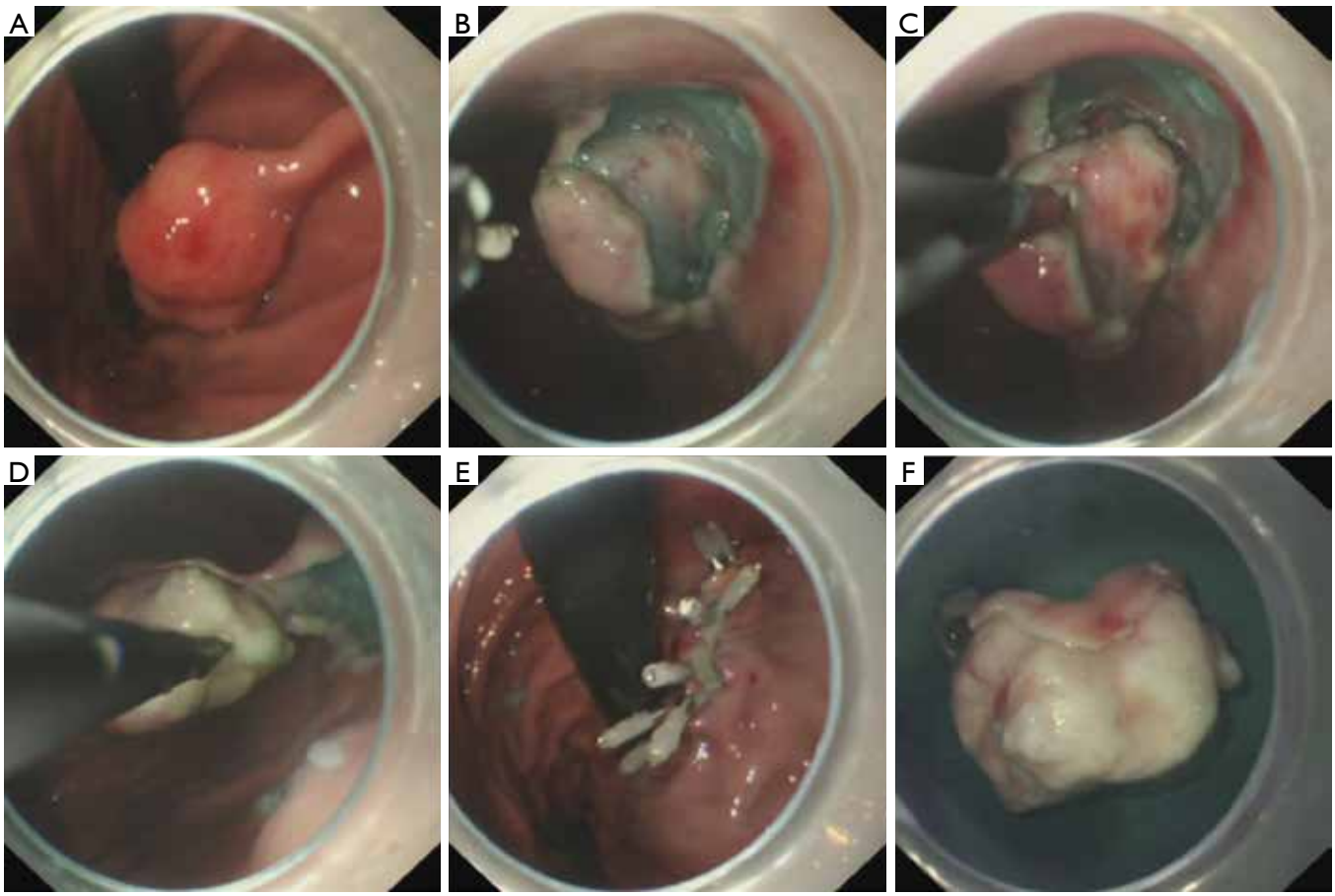

Figure 2 Case illustration of endoscopic submucosal dissection. (A) We could see a submucosal tumor in the gastric fundus; (B) after making dots and submucosal injection, we precut the mucosal and submucosal layer using a dual knife, and the submucosal tumor is shown; (C,D) dissect the tumor with a dual knife; (E) close the wound with several clips; (F) the resected tumor.

ESD

ESD was firstly used to treat early stage gastric cancer (37), and was then applied to the treatment of gastric SMTs, including gastric GISTs (38,39). The standard procedure of ESD is as follows: making marking dots around the lesion, submucosal injection, precutting the mucosal and submucosal layer and then dissecting the tumor (*Figure 2*). Compared with EBL, ESD enables a larger resectable size and provides a higher *en bloc* resection rate. Although many clinical studies concerning the treatment of ESD for gastric SMTs (GISTs included) have been reported [see in detail in review (40)], only two studies have been published regarding ESD as a treatment for pure gastric GISTs (*Table 1*), and both of their results were exciting. Moreover, Meng *et al.* (41) demonstrated that the efficacy of ESD and LAP for treating small gastric GISTs was comparable, but ESD could reduce the operation time, estimated blood loss and hospital stay. Perforation and bleeding are the major complications associated with gastric ESD, whose incidence have been reported to range from 0% to 8.2% and 0% to 15.6%, and most of them can be successfully managed by appropriate endoscopic interventions [see in detail in review (42,43)]. Other rare but serious complications include aspiration pneumonia, stenosis, venous thromboembolism, and air embolism (44-47). Endoscopists should be aware of these complications and their associated risk factors (44-47), so as to prevent their occurrence and reduce the harm. And to achieve an *en bloc* resection, ESD is only recommended for SMTs originating from the superficial MP layer.

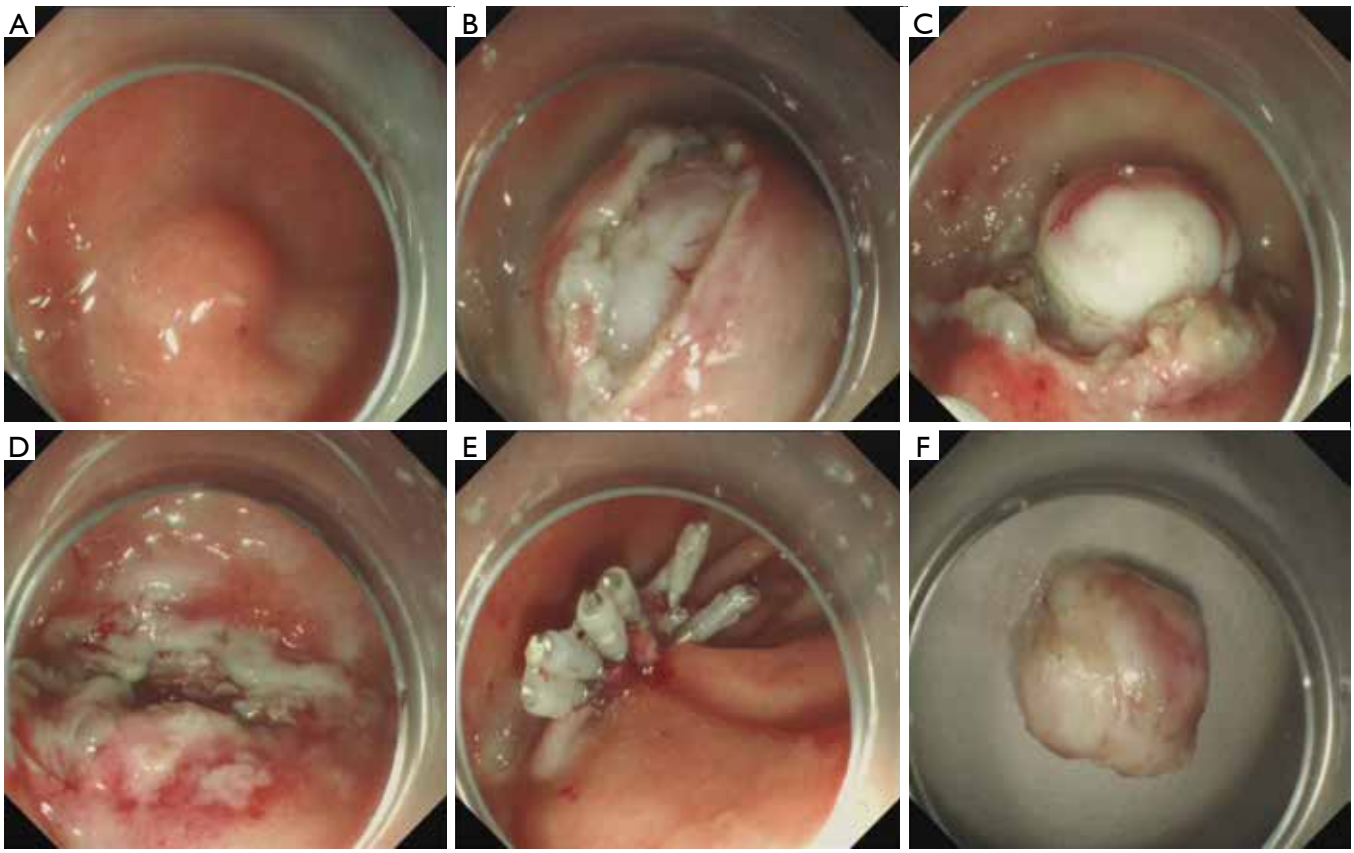

Figure 3 Case illustration of endoscopic submucosal excavation. (A) We could see a submucosal tumor in the gastric corpus; (B) after making dots and submucosal injection, we precut the mucosal and submucosal layer covering the submucosal tumor to expose the tumor; (C) excavate the tumor from the muscularis propria layer; (D) the wound surface after tumor removal; (E) close the wound with several clips; (F) the resected tumor.

ESE

Although ESD is effective for treating gastric GISTs, the en bloc resection rate sometimes is not that satisfactory, especially for those originating from deep MP layer. ESE, allowing deep excavation, is a better choice. ESE was first reported by Jeong *et al.* (48) for treating gastric SMTs (GISTs included) originating form the MP layer, with a high complete resection rate and acceptable complication rate. The standard procedure of ESE is as follows: making marking dots around the lesion, submucosal injection, precutting the mucosal and submucosal layer and excavating the tumor (*Figure 3*). The major difference between ESD and ESE procedure is the depth of endoscopic resection. As deep excavation was necessary during ESE, an insulated-tip knife is usually recommended during excavation to avoid or reduce unintentional injury, while in the ESD procedure, the dissection could achieved by other endoscopic knives such as dual knife, hook knife, etc. Several studies have demonstrated the safety and efficacy of ESE for gastric GISTs, with favorable complete rate and low recurrence rate (24,26,27) (*Table 1*). The most common complication reported is perforation, whose incidence was up to 33.3%. However, most of them could be successfully managed by endoscopy, only few needed surgical intervention. Other reported complications include bleeding, surgery-related complications, bacteremia (21,24,26,27,48,49). CO_2 is recommended during the procedure, as it can reduce the pain score and increase the visual analog scale score, compared with air insufflation (26).

EFTR

EFTR was firstly reported by Suzuki and Ikeda for treating

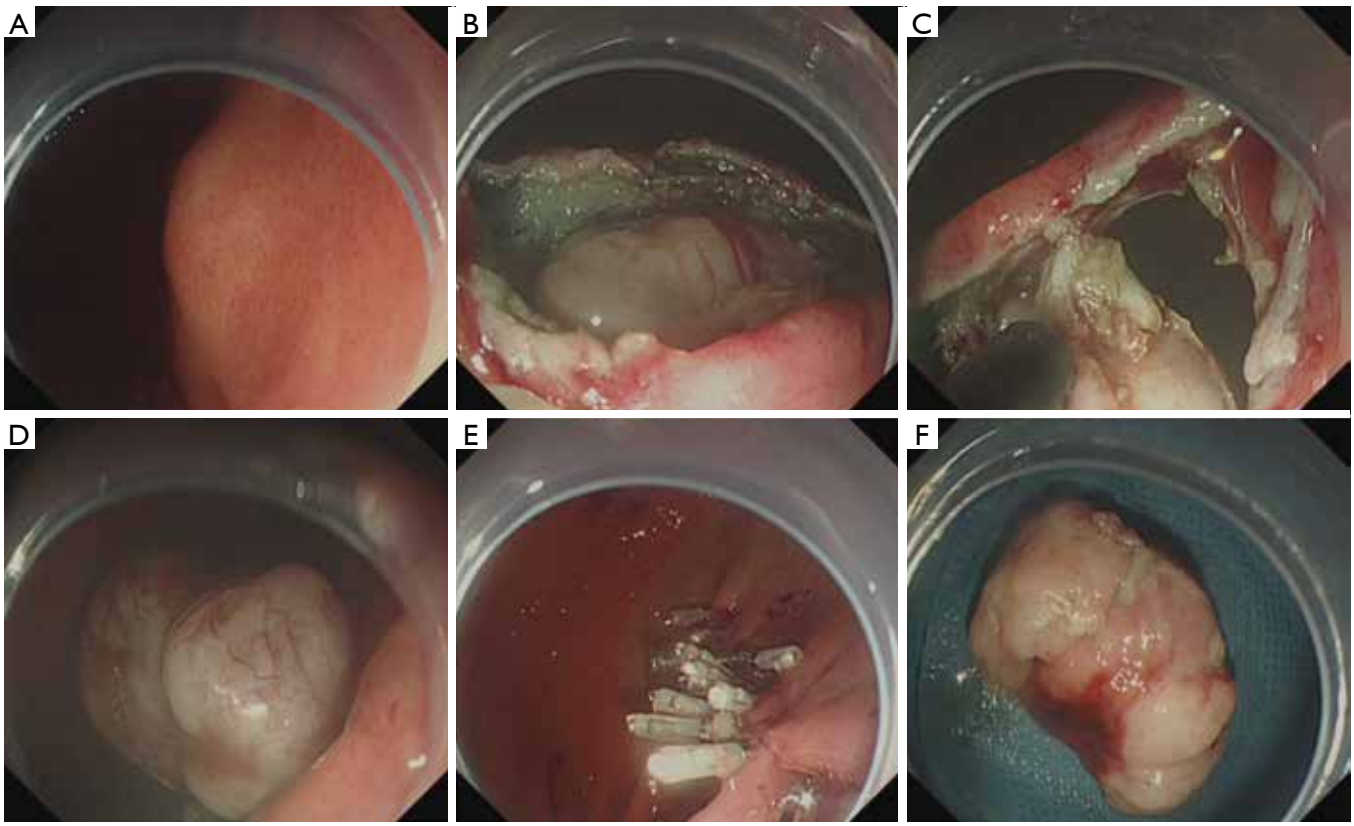

Figure 4 Case illustration of endoscopic full-thickness resection. (A) We could see a submucosal tumor in the gastric corpus; (B) after submucosal injection, we precut and remove the mucosal and submucosal layer to expose the tumor; (C,D) endoscopic full-thickness resection of the tumor, we could see the abdominal cavity through the "active perforation"; (E) close the wound with several clips; (F) the resected tumor.

two rectal carcinoids and one duodenal carcinoid using the snaring technique (50), and then Ikeda *et al.* reported EFTR using the ESD technique on a porcine stomach (51). Wang *et al.* (52) firstly introduced EFTR into clinical practice for treating gastric GISTs. The standard procedure of EFTR is as follows: submucosal injection, precutting the mucosal and submucosal layer around the lesion, circumferential incision as deep as the MP layer around the lesion, incision into the serosal layer around the lesion, full-thickness resection of the tumor including the serosal layer and closing the gastric-wall defect (*Figure 4*). Although many clinical studies concerning EFTR for gastric SMTs have been published, only three studies are available about EFTR for pure gastric GISTs (21,28,29), and the clinical outcomes were promising (*Table 1*). In EFTR, perforation is not considered as a complication. Reported complications include bleeding, localized peritonitis, abdominal distention, etc., and the overall complication rates were very low [in detail in review (53,54)]. Furthermore, Wang *et al.* (55) found that the safety and efficacy of EFTR and LAP for small gastric GIST is comparable, however, EFTR could reduce the procedure time, intraoperative bleeding volume and hospital stay. Besides, 12 of the 33 cases needed intraoperative endoscopy to precise identify the GISTs in the LAP group.

STER

STER was initially used as a therapeutic technique for treating esophageal and cardia SMTs (56-59). The standard procedure is as follows: submucosal injection, creating tunnel entry, submucosal tunnel creation, finding and dissecting the SMT, and then closing the tunnel entry (*Figure 5*). Compared with other endoscopic methods, STER possesses multiple advantages including the maintenance of mucosal integrity, the facilitation of an increased healing rate and a decreased risk of pleural/

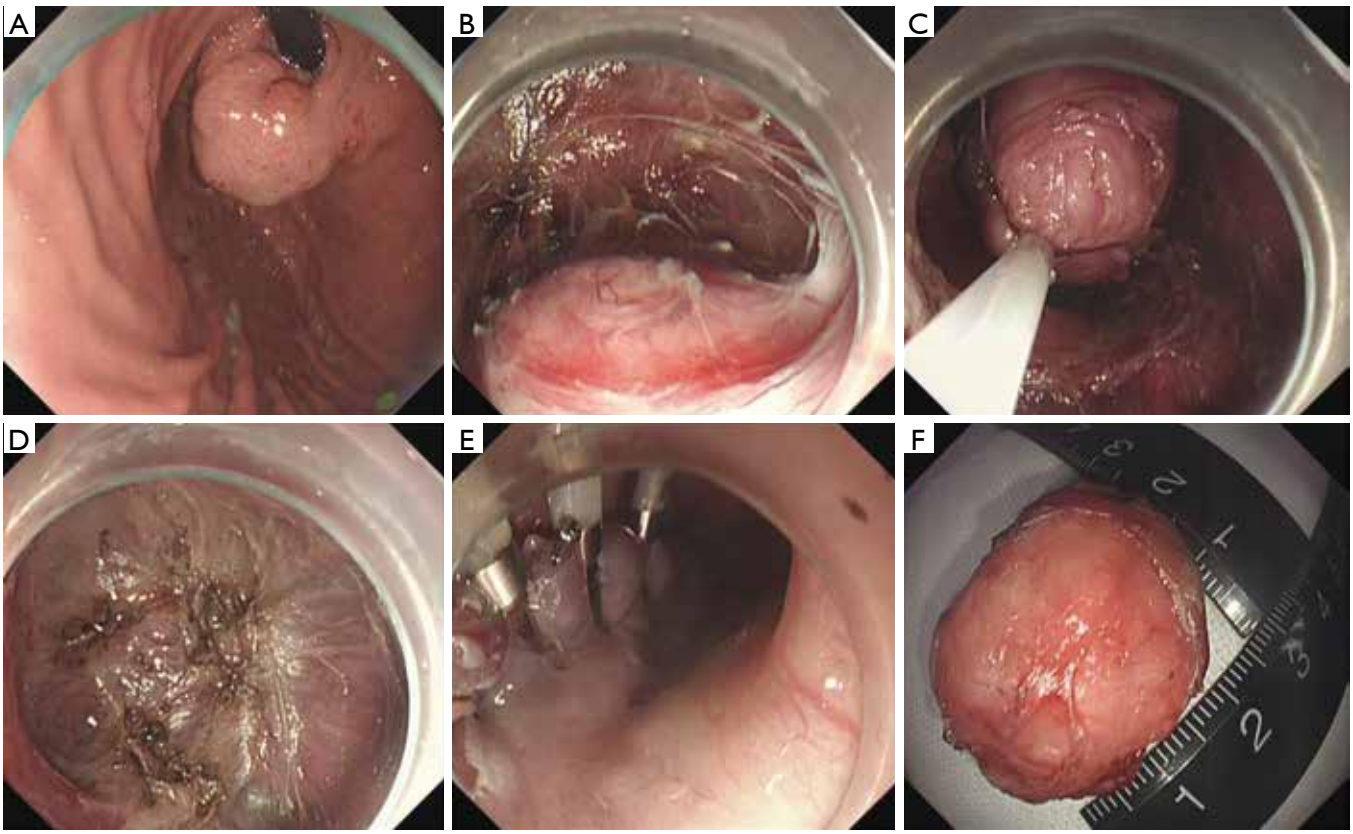

Figure 5 Case illustration of submucosal tunneling endoscopic resection. (A) We could see a submucosal tumor in the gastric fundus; (B) after submucosal injection, a longitudinal mucosal incision was made 3 cm above the tumor, and a submucosal tunnel was created between the submucosal and muscularis propria layer, and then the submucosal tumor was visible; (C) carefully dissected the tumor from the muscularis propria layer and remove the tumor; (D) the wound surface after tumor removal; (E) close the tunnel entry with several clips; (F) the resected tumor.

abdominal infection (60-62). Several studies have demonstrated the safety and efficacy of STER for treating gastric SMTs, half of whom were gastric GISTs (30-32). Zhang *et al.* (63) found that compared with endoscopic nontunneling methods (ESD and EFR), STER has no distinct advantages in treating relatively small gastric SMTs, but Tan *et al.* (64) found that the safety and efficacy between STER and EFTR were comparable, but patients who received EFTR needed more clips to close the gastric wall defect. Common complications of STER include gas-related complications, bleeding, pleural effusion, mucosal injury, etc. Although the overall incidence of complications is relatively high, only a small part of them need therapeutic intervention (59,65), suggesting STER is a safe and effective method.

LECS

All the above endoscopic methods have limitations in terms of rumor size and location, thus the concept of LECS was devised, consisting of endoscopic surgery in the form of endoscopic mucosal incision and LAP (35). In this advanced technique, incision lines are confirmed endoscopically and accurately determined by application of an endoscopic mucosal/submucosal incision technique, while the seromuscular layer is incised laparoscopically and the incision line is closed using a laparoscopic stapling device, resulting in minimal dissection of the normal gastric wall with minimal gastric transformation. Currently, LECS has been recommended by NCCN as a treatment for gastric GIST less than 50 mm in diameter regardless of the tumor

Table 2 Comparison of different endoscopic methods for gastric GISTs

Ref.	Method	N	Mean tumor diameter (mm)	Mean operation time (min)	*En bloc* resection rate (%)	Complication (%)	Follow-up time (months)	Recurrence (%)
Meng *et al.* (5)	EBL *vs.* ESD	72 *vs.* 27	10.68 *vs.* 11.78	17.11 *vs.* 65.26	–	1.39 *vs.* 18.52	6 *vs.* 7	15 *vs.* 9.1
Tan *et al.* (64)	STER *vs.* EFTR	20 *vs.* 32	17.8 *vs.* 15.4	74.9 *vs.* 69.1	95 *vs.* 96.9	5 *vs.* 15.6	10.9 *vs.* 23.8	0 *vs.* 0
Zhang *et al.* (63)	Nontunneling *vs.* STER	78 *vs.* 19	15 *vs.* 20	50 *vs.* 75	95.9 *vs.* 94.1	26.9 *vs.* 36.8	–	0 *vs.* 0
Balde *et al.* (66)	LECS *vs.* ESD	30 *vs.* 30	15 *vs.* 15	96.5 *vs.* 41.5	100 *vs.* 100	3.3 *vs.* 26.7	–	0 *vs.* 14.3
Ojima *et al.* (67)	LECS *vs.* EIGS	21 *vs.* 26	25 *vs.* 23	139 *vs.* 108	100 *vs.* 100	4.8 *vs.* 40	21 *vs.* 61	4.8 *vs.* 4

GISTs, gastrointestinal stromal tumors; EBL, endoscopic band ligation; ESD, endoscopic submucosal dissection; EFTR, endoscopic full-thickness resection; STER, submucosal tunneling endoscopic resection; LECS, laparoscopic and endoscopic cooperative surgery; EIGS, endoscopic intragastric surgery.

location (2). Since it's first reported by Hiki *et al.* (35), two other studies have explored the efficacy of LECS for gastric GISTs and have shown exciting results (33,34). In addition, Balde *et al.* (66) found that although ESD had a shorter operation time, the rate of intraoperative complications was lower in the LECS group. Ojima *et al.* (67) found that compared with LECS, endoscopic intragastric surgery (EIGS) had a higher perioperative complications rate and a longer time to resumption of first oral intake.

Postoperative management

All the patients are kept nil per os (NPO) for at least 72 h, a liquid diet for 5 days, and returned gradually to a normal diet within 2 weeks. And intravenous proton pump inhibitor (PPI) and antibiotics were recommended for at least 3 days. For patients with GISTs located in the gastric fundus, they are asked to keep a semireclining position for 3 days. A contrast roentgenography is performed on postoperative day 3 to check for any occurrence of leakage. Ultrasound was applied to check the presence of any abdominal or pelvic dropsy.

The resected specimens are fixed, embedded with paraffin and then sectioned. Hematoxylin and eosin and immunohistochemical staining (CD117, CD34, Dog-1, Ki67, SMA, etc.) are carried out to determine whether the SMT is a GIST or not. If the SMT is highly suspected of a GIST but all the markers above are negative, KIT and/or PDGFRA mutation should be detected (68). A risk category should obtained based on the tumor size, mitotic index and primary tumor site using the modified NIH classification system (69), classifying them as very low risk, low risk, intermediate risk and high risk, which is helpful to predict recurrence. For those patients classified as intermediate or high risk, additional surgery and/or adjuvant treatment (imatinib, etc.) are recommended.

Postoperative follow-up is necessary for GISTs patients who received endoscopic resection, and the surveillance interval varies according to the risk classification. For patients with high or intermediate risk, abdominal and pelvic CT or EUS every 3–4 months is recommended in the first 3 years after endoscopic treatment, and then every 6 months until 5 years after treatment and then annually thereafter. For those with very low or low risk, CT and/or EUS are recommended every 6 months in the first 5 years (68,70). Surveillance endoscopy is recommended to be performed at 3 months, and 12 months after treatment to observe healing of the wound and to check for any residual tumor.

Conclusions and perspectives

Unpredictable malignant potential and rare lymph node metastasis provide the theoretical basis of minimally invasive treatment of gastric GISTs. Currently, many studies concerning endoscopic resection for gastric GISTs have been published, and the primary results were exciting (*Table 1*). However, the follow-up of these studies were relative short (usually <2 years), thus warranting a long-term follow-up. What's more, few studies that focused on the comparison among different endoscopic methods or between endoscopic and surgical methods have been published (*Tables 2,3*). Thus more evidence is required to recommend endoscopic resection as the first-line treatment

Table 3 Comparison between endoscopic and surgical methods for gastric GISTs

Ref.	Method	N	Mean tumor diameter (mm)	Mean operation time (min)	Complete resection rate (%)	Complication (%)	Follow-up time (months)	Recurrence (%)
Meng *et al.* (5)	EBL *vs.* LAP	72 *vs.* 48	10.68 *vs.* 12.02	17.11 *vs.* 90.81	–	1.39 *vs.* 4.17	6 *vs.* 6	15.00 *vs.* 11.76
Meng *et al.* (41)	ESD *vs.* LAP	75 *vs.* 51	14.4 *vs.* 14.6	63.59 *vs.* 79.12	–	2.67 *vs.* 1.96	40.1 *vs.* 40.9	2.67 *vs.* 1.96
Wang *et al.* (55)	EFTR *vs.* LAP	35 *vs.* 33	13 *vs.* 16	91 *vs.* 155	100 *vs.* 100	11.4 *vs.* 13.3	–	0 *vs.* 0
Wu *et al.* (71)	EFTR *vs.* LAP	50 *vs.* 42	–	85 *vs.* 88	100.0 *vs.* 92.9	0 *vs.* 4.8	–	0 *vs.* 0
Huang *et al.* (72)	EFTR *vs.* LAP	32 *vs.* 30	–	78.5 *vs.* 80.9	100.0 *vs.* 93.3	0 *vs.* 3.3	–	0 *vs.* 0
Wang *et al.* (52)	EFTR *vs.* LAP	66 *vs.* 43	15 *vs.* 11	53.6 *vs.* 139	98.4 *vs.* 100.0	24.2 *vs.* 14.0	–	0 *vs.* 0
Dong *et al.* (73)	EFTR *vs.* MLIGS	10 *vs.* 8	16.5 *vs.* 27.5	120 *vs.* 85	100 *vs.* 100	10 *vs.* 0	–	0 *vs.* 0

GISTs, gastrointestinal stromal tumors; EBL, endoscopic band ligation; ESD, endoscopic submucosal dissection; EFTR, endoscopic full-thickness resection; LAP, laparoscopic surgery; MLIGS, modified laparoscopic intragastric surgery.

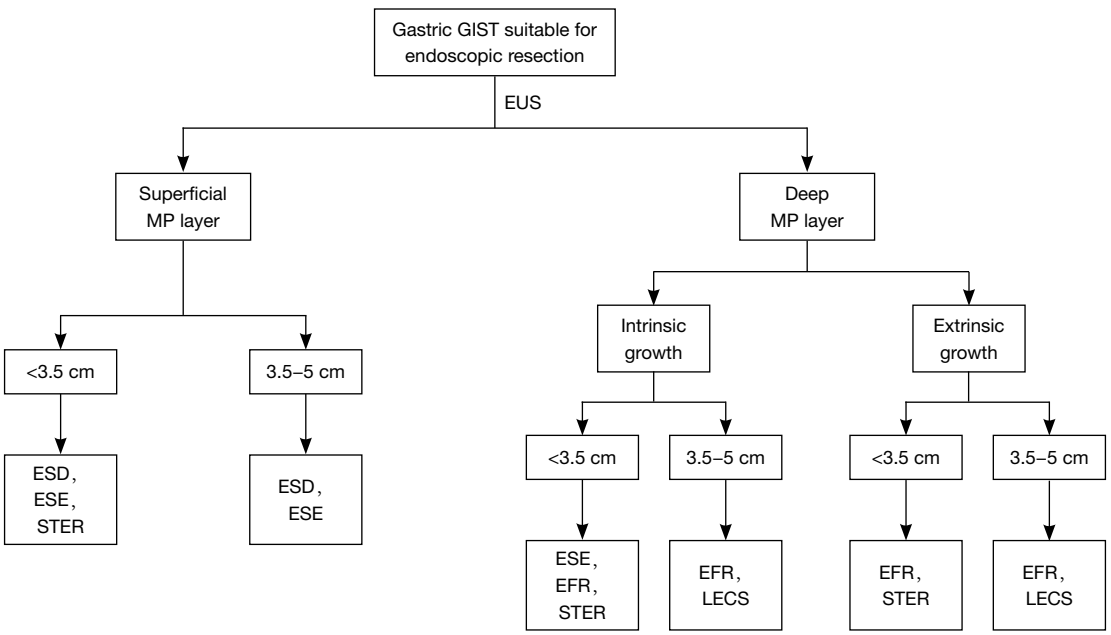

Figure 6 Algorithm on endoscopic management of gastric GISTs in our hospital. GIST, gastrointestinal stromal tumor; EUS, endoscopic ultrasonography; MP, muscularis propria; ESD, endoscopic submucosal dissection; ESE, endoscopic submucosal excavation; STER, submucosal tunneling endoscopic resection; EFR, endoscopic full-thickness resection; LECS, laparoscopic and endoscopic cooperative surgery.

of gastric GISTs. In our hospital, we use an algorithm as proposed in *Figure 6*.

Furthermore, to expand the role of endoscopy on the treatment of gastric GISTs, several technical problems need to be resolved. Firstly, we need to find ways to reduce complications of endoscopic resection, especially perforation. Although several devices such as over-the-scope clip have been proposed [see in review (74,75)], most of them are not suitable for large GISTs, thus warranting the development of new devices. Secondly, there is a

possibility of pseudocapsule injury during endoscopic resection of a gastric GIST, providing the risk of peritoneal seeding. Thus a more secure endoscopic method is needed, and it should be performed by a well-trained endoscopist. Recently, novel hybrid techniques, such as combination of laparoscopic and endoscopic approaches to neoplasia with non exposure technique (CLEANNET) (76) and non-exposed endoscopic wall-inversion surgery (NEWS) (77,78), could avoid exposing malignant SETs to the peritoneal cavity. In conclusion, technical modifications and improvements are required to define the role of endoscopy for treating gastric GISTs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumour. Lancet 2013;382:973-83.
2. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41; quiz S42-44.
3. Chen QL, Pan Y, Cai JQ, et al. Laparoscopic versus open resection for gastric gastrointestinal stromal tumors: an updated systematic review and meta-analysis. World J Surg Oncol 2014;12:206.
4. Honda M, Hiki N, Nunobe S, et al. Long-term and surgical outcomes of laparoscopic surgery for gastric gastrointestinal stromal tumors. Surg Endosc 2014;28:2317-22.
5. Meng Y, Cao C, Song S, et al. Endoscopic band ligation versus endoscopic submucosal dissection and laparoscopic resection for small gastric stromal tumors. Surg Endosc 2016;30:2873-8.
6. Joo MK, Park JJ, Kim H, et al. Endoscopic versus surgical resection of GI stromal tumors in the upper GI tract. Gastrointest Endosc 2016;83:318-26.
7. Zhou PH, Yao LQ, Qin XY, et al. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. Surg Endosc 2011;25:2926-31.
8. Kim HH. Endoscopic treatment for gastrointestinal stromal tumor: Advantages and hurdles. World J Gastrointest Endosc 2015;7:192-205.
9. Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. Surg Endosc 1991;5:20-3.
10. Nishida T, Kawai N, Yamaguchi S, et al. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. Dig Endosc 2013;25:479-89.
11. Dumonceau JM, Deprez PH, Jenssen C, et al. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated January 2017. Endoscopy 2017;49:695-714.
12. Casali PG, Jost L, Reichardt P, et al. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:64-7.
13. Koga T, Hirayama Y, Yoshiya S, et al. Necessity for resection of gastric gastrointestinal stromal tumors </= 20 mm. Anticancer Res 2015;35:2341-4.
14. Fang YJ, Cheng TY, Sun MS, et al. Suggested cutoff tumor size for management of small EUS-suspected gastric gastrointestinal stromal tumors. J Formos Med Assoc 2012;111:88-93.
15. Yegin EG, Duman DG. Small EUS-suspected gastrointestinal stromal tumors of the stomach: An overview for the current state of management. Endosc Ultrasound 2016;5:69-77.
16. El-Newihi HM, Achord JL. Emerging role of endoscopic variceal band ligation in the treatment of esophageal varices. Dig Dis 1996;14:201-8.
17. Nwakakwa V, Fleischer D. Endoscopic mucosal resection of the esophagus: band ligation technique. Gastrointest Endosc Clin N Am 2001;11:479-88, vi.
18. Sun S, Ge N, Wang C, et al. Endoscopic band ligation of small gastric stromal tumors and follow-up by endoscopic ultrasonography. Surg Endosc 2007;21:574-8.
19. Nan G, Siyu S, Shiwei S, et al. Hemoclip-reinforced and EUS-assisted band ligation as an effective and safe technique to treat small GISTs in the gastric fundus. Am J Gastroenterol 2011;106:1560-1.
20. Nan G, Siyu S, Sheng W, et al. The role of hemoclips

reinforcement in the ligation-assisted endoscopic enucleation for small GISTs in gastric fundus. Biomed Res Int 2014;2014:247602.
21. Huang LY, Cui J, Liu YX, et al. Endoscopic therapy for gastric stromal tumors originating from the muscularis propria. World J Gastroenterol 2012;18:3465-71.
22. An W, Sun PB, Gao J, et al. Endoscopic submucosal dissection for gastric gastrointestinal stromal tumors: a retrospective cohort study. Surg Endosc 2017;31:4522-31.
23. He Z, Sun C, Zheng Z, et al. Endoscopic submucosal dissection of large gastrointestinal stromal tumors in the esophagus and stomach. J Gastroenterol Hepatol 2013;28:262-7.
24. Zhang JS, Ye LP, Wang CY, et al. Endoscopic submucosal enucleation of small gastric gastrointestinal stromal tumors with cross-shaped incision: report of sixty-nine cases. Hepatogastroenterology 2012;59:440-3.
25. Wang Y, Li Y, Luo H, et al. Efficacy analysis of endoscopic submucosal excavation for gastric gastrointestinal stromal tumors. Zhonghua Wei Chang Wai Ke Za Zhi 2014;17:352-5.
26. Shi WB, Wang ZH, Qu CY, et al. Comparison between air and carbon dioxide insufflation in the endoscopic submucosal excavation of gastrointestinal stromal tumors. World J Gastroenterol 2012;18:7296-301.
27. Wang S, Shen L. Efficacy of Endoscopic Submucosal Excavation for Gastrointestinal Stromal Tumors in the Cardia. Surg Laparosc Endosc Percutan Tech 2016;26:493-6.
28. Shi D, Li R, Chen W, et al. Application of novel endoloops to close the defects resulted from endoscopic full-thickness resection with single-channel gastroscope: a multicenter study. Surg Endosc 2017;31:837-42.
29. Mori H, Kobara H, Fujihara S, et al. Establishment of the hybrid endoscopic full-thickness resection of gastric gastrointestinal stromal tumors. Mol Clin Oncol 2015;3:18-22.
30. Lu J, Jiao T, Li Y, et al. Heading toward the right direction--solution package for endoscopic submucosal tunneling resection in the stomach. PLoS One 2015;10:e0119870.
31. Li QL, Chen WF, Zhang C, et al. Clinical impact of submucosal tunneling endoscopic resection for the treatment of gastric submucosal tumors originating from the muscularis propria layer (with video). Surg Endosc 2015;29:3640-6.
32. Mao XL, Ye LP, Zheng HH, et al. Submucosal tunneling endoscopic resection using methylene-blue guidance for cardial subepithelial tumors originating from the muscularis propria layer. Dis Esophagus 2017;30:1-7.
33. Kikuchi S, Nishizaki M, Kuroda S, et al. Nonexposure laparoscopic and endoscopic cooperative surgery (closed laparoscopic and endoscopic cooperative surgery) for gastric submucosal tumor. Gastric Cancer 2017;20:553-7.
34. Qiu WQ, Zhuang J, Wang M, et al. Minimally invasive treatment of laparoscopic and endoscopic cooperative surgery for patients with gastric gastrointestinal stromal tumors. J Dig Dis 2013;14:469-73.
35. Hiki N, Yamamoto Y, Fukunaga T, et al. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. Surg Endosc 2008;22:1729-35.
36. Xing XB, Wang JH, Chen MH, et al. Perforation posterior to endoscopic band ligation of a gastric submucosal tumor. Endoscopy 2012;44 Suppl 2 UCTN:E296-7.
37. Yamamoto H, Yube T, Isoda N, et al. A novel method of endoscopic mucosal resection using sodium hyaluronate. Gastrointest Endosc 1999;50:251-6.
38. Fujishiro M, Yahagi N, Nakamura M, et al. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. Gastrointest Endosc 2006;63:243-9.
39. Lee IL, Lin PY, Tung SY, et al. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. Endoscopy 2006;38:1024-8.
40. Kim SY, Kim KO. Management of gastric subepithelial tumors: The role of endoscopy. World J Gastrointest Endosc 2016;8:418-24.
41. Meng Y, Li W, Han L, et al. Long-term outcomes of endoscopic submucosal dissection versus laparoscopic resection for gastric stromal tumors less than 2 cm. J Gastroenterol Hepatol 2017;32:1693-7.
42. Oda I, Suzuki H, Nonaka S, et al. Complications of gastric endoscopic submucosal dissection. Dig Endosc 2013;25 Suppl 1:71-8.
43. Saito I, Tsuji Y, Sakaguchi Y, et al. Complications related to gastric endoscopic submucosal dissection and their managements. Clin Endosc 2014;47:398-403.
44. Miyahara K, Iwakiri R, Shimoda R, et al. Perforation and postoperative bleeding of endoscopic submucosal dissection in gastric tumors: analysis of 1190 lesions in low- and high-volume centers in Saga, Japan. Digestion 2012;86:273-80.
45. Suzuki H, Oda I, Sekiguchi M, et al. Management and associated factors of delayed perforation after gastric

endoscopic submucosal dissection. World J Gastroenterol 2015;21:12635-43.
46. Park CH, Lee SK. Preventing and controlling bleeding in gastric endoscopic submucosal dissection. Clin Endosc 2013;46:456-62.
47. Libânio D, Costa MN, Pimentel-Nunes P, et al. Risk factors for bleeding after gastric endoscopic submucosal dissection: a systematic review and meta-analysis. Gastrointest Endosc 2016;84:572-86.
48. Jeong ID, Jung SW, Bang SJ, et al. Endoscopic enucleation for gastric subepithelial tumors originating in the muscularis propria layer. Surg Endosc 2011;25:468-74.
49. Li G, Zeng S, Chen Y, et al. Bacteremia after Endoscopic Submucosal Excavation for Treating the Gastric Muscular Layer Tumors. Gastroenterol Res Pract 2015;2015:306938.
50. Suzuki H, Ikeda K. Endoscopic mucosal resection and full thickness resection with complete defect closure for early gastrointestinal malignancies. Endoscopy 2001;33:437-9.
51. Ikeda K, Fritscher-Ravens A, Mosse CA, et al. Endoscopic full-thickness resection with sutured closure in a porcine model. Gastrointest Endosc 2005;62:122-9.
52. Wang L, Ren W, Fan CQ, et al. Full-thickness endoscopic resection of nonintracavitary gastric stromal tumors: a novel approach. Surg Endosc 2011;25:641-7.
53. Mori H, Kobara H, Nishiyama N, et al. Review of Pure Endoscopic Full-Thickness Resection of the Upper Gastrointestinal Tract. Gut Liver 2015;9:590-600.
54. Schmidt A, Meier B, Caca K. Endoscopic full-thickness resection: Current status. World J Gastroenterol 2015;21:9273-85.
55. Wang H, Feng X, Ye S, et al. A comparison of the efficacy and safety of endoscopic full-thickness resection and laparoscopic-assisted surgery for small gastrointestinal stromal tumors. Surg Endosc 2016;30:3357-61.
56. Xu MD, Cai MY, Zhou PH, et al. Submucosal tunneling endoscopic resection: a new technique for treating upper GI submucosal tumors originating from the muscularis propria layer (with videos). Gastrointest Endosc 2012;75:195-9.
57. Inoue H, Ikeda H, Hosoya T, et al. Submucosal endoscopic tumor resection for subepithelial tumors in the esophagus and cardia. Endoscopy 2012; 44:225-30.
58. Wang H, Tan Y, Zhou Y, et al. Submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors originating from the muscularis propria layer. Eur J Gastroenterol Hepatol 2015;27:776-80.
59. Tan Y, Huo J, Liu D. Current status of submucosal tunneling endoscopic resection for gastrointestinal submucosal tumors originating from the muscularis propria layer (Review). Oncol Lett 2017;14:5085-90.
60. Lu J, Lu X, Jiao T, et al. Endoscopic management of upper gastrointestinal submucosal tumors arising from muscularis propria. J Clin Gastroenterol 2014;48:667-73.
61. Wang L, Ren W, Zhang Z, et al. Retrospective study of endoscopic submucosal tunnel dissection (ESTD) for surgical resection of esophageal leiomyoma. Surg Endosc 2013;27:4259-66.
62. Tan Y, Lv L, Duan T, et al. Comparison between submucosal tunneling endoscopic resection and video-assisted thoracoscopic surgery for large esophageal leiomyoma originating from the muscularis propria layer. Surg Endosc 2016;30:3121-7.
63. Zhang Q, Wang F, Wei G, et al. Endoscopic resection of gastric submucosal tumors: A comparison of endoscopic nontunneling with tunneling resection and a systematic review. Saudi J Gastroenterol 2017;23:52-9.
64. Tan Y, Tang X, Guo T, et al. Comparison between submucosal tunneling endoscopic resection and endoscopic full-thickness resection for gastric stromal tumors originating from the muscularis propria layer. Surg Endosc 2017;31:3376-82.
65. Chen T, Zhang C, Yao LQ, et al. Management of the complications of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors. Endoscopy 2016;48:149-55.
66. Balde AI, Chen T, Hu Y, et al. Safety analysis of laparoscopic endoscopic cooperative surgery versus endoscopic submucosal dissection for selected gastric gastrointestinal stromal tumors: a propensity score-matched study. Surg Endosc 2017;31:843-51.
67. Ojima T, Nakamura M, Nakamori M, et al. Laparoscopic and endoscopic cooperative surgery is a feasible treatment procedure for intraluminal gastric gastrointestinal stromal tumors compared to endoscopic intragastric surgery. Surg Endosc 2017. [Epub ahead of print].
68. Koo DH, Ryu MH, Kim KM, et al. Asian Consensus Guidelines for the Diagnosis and Management of Gastrointestinal Stromal Tumor. Cancer Res Treat 2016;48:1155-66.
69. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.
70. Blay JY, Bonvalot S, Casali P, et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol

2005;16:566-78.
71. Wu CR, Huang LY, Guo J, et al. Clinical Control Study of Endoscopic Full-thickness Resection and Laparoscopic Surgery in the Treatment of Gastric Tumors Arising from the Muscularis Propria. Chin Med J (Engl) 2015;128:1455-9.
72. Huang LY, Cui J, Wu CR, et al. Endoscopic full-thickness resection and laparoscopic surgery for treatment of gastric stromal tumors. World J Gastroenterol 2014;20:8253-9.
73. Dong HY, Wang YL, Jia XY, et al. Modified laparoscopic intragastric surgery and endoscopic full-thickness resection for gastric stromal tumor originating from the muscularis propria. Surg Endosc 2014;28:1447-53.
74. Yılmaz B, Unlu O, Roach EC, et al. Endoscopic clips for the closure of acute iatrogenic perforations: Where do we stand? Dig Endosc 2015;27:641-8.
75. Akimoto T, Goto O, Nishizawa T, et al. Endoscopic closure after intraluminal surgery. Dig Endosc 2017;29:547-58.
76. Nabeshima K, Tomioku M, Nakamura K, et al. Combination of Laparoscopic and Endoscopic Approaches to Neoplasia with Non-exposure Technique (CLEAN-NET) for GIST with Ulceration. Tokai J Exp Clin Med 2015;40:115-9.
77. Mitsui T, Niimi K, Yamashita H, et al. Non-exposed endoscopic wall-inversion surgery as a novel partial gastrectomy technique. Gastric Cancer 2014;17:594-9.
78. Kim DW, Kim JS, Kim BW, et al. Non-Exposed Endoscopic Wall-Inversion Surgery for Gastrointestinal Stromal Tumor of the Stomach: First Case Report in Korea. Clin Endosc 2016;49:475-8.

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Non-exposed endoscopic wall-inversion surgery for gastrointestinal stromal tumor

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Abstract: Laparoscopic and endoscopic cooperative surgery (LECS) is an accepted method of laparoscopic wedge resection, which is minimally invasive, for gastrointestinal stromal tumors (GISTs). We established a type of LECS achieving a full-thickness resection, non-exposed endoscopic wall-inversion surgery (NEWS), in an effort to prevent exposure of the peritoneal cavity to gastric intraluminal contents. We employed this surgical technique in 28 gastric GIST patients. We failed to complete NEWS in the initial two patients and in one patient with a large tumor (40 mm × 35 mm), but otherwise carried out the procedure successfully. Although a learning effect is speculated to occur, based on a decreasing trend in the operation time, the median operation time was 184 minutes showing that NEWS is still a time-consuming method. No significant differences were recognized in tumor size or location, except near the esophagogastric junction (EGJ), nor in the cross-sectional circumference. NEWS is feasible and appears to be a good option, especially for small GISTs with mucosal ulceration rendering full-thickness enucleation by opening of the gastric wall unfeasible.

Keywords: Gastrointestinal stromal tumor (GIST); laparoscopic and endoscopic cooperative surgery (LECS); non-exposed technique

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the alimentary tract, and the stomach is the most frequently affected site, accounting for roughly of 60% of all patients with a GIST (1,2). Since gastric GIST rarely metastasizes to perigastric lymph nodes, gastric local resection without lymphadenectomy is accepted as a standard treatment. Laparoscopic local resection was thus introduced as a minimally-invasive approach and has achieved an acceptable outcome.

Tumor rupture is associated with a very high risk of recurrence (2), mainly within the peritoneal cavity (3). Therefore, preservation of the pseudocapsule and avoidance of tumor spillage resulting from rupture are the basic principles adhered to when resecting a GIST. Accordingly, laparotomy is basically employed for large GISTs to prevent unexpected tumor rupture during surgery, and a minimally-invasive approach is recommended only for smaller tumors (4). Furthermore, tumor ulceration is also considered to potentially be associated with tumor cell spillage. Local resection with intentional gastric perforation should be avoided in this situation because it results in a communication between the peritoneal cavity and the gastric intraluminal space.

With the aim of preventing exposure of the peritoneal cavity to gastric intraluminal contents, we established and reported a novel technique achieving full-thickness resection without the risk of gastric perforation; non-exposed endoscopic wall-inversion surgery (NEWS) (5-7). This is a form of laparoscopic and endoscopic cooperative

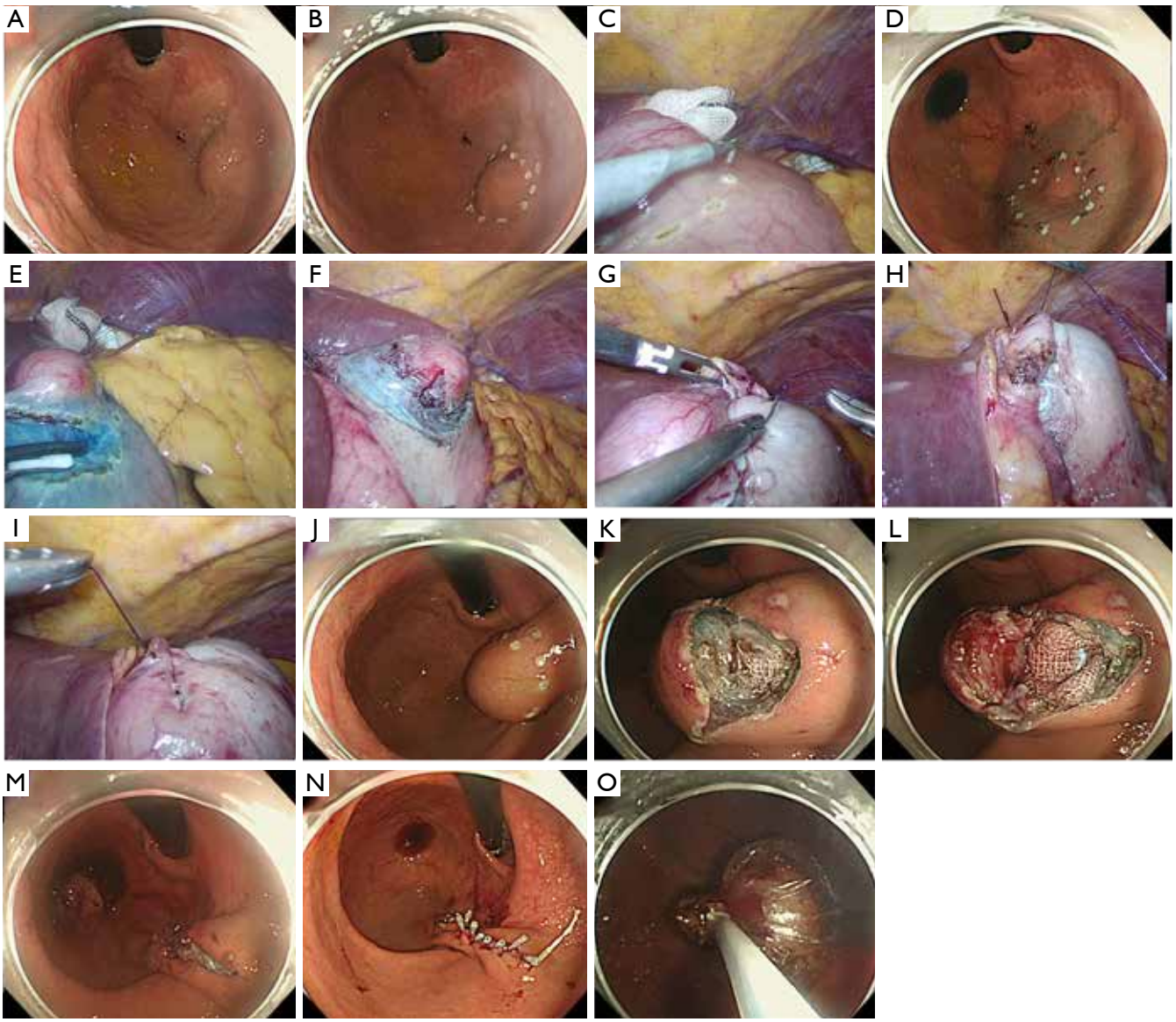

Figure 1 Technical detail of non-exposed endoscopic wall-inversion surgery for gastric gastrointestinal stromal tumor. (A) Identification of the tumor location; (B) markings on the mucosa around the lesion; (C) markings on the serosa; (D) injection into the submucosal layer; (E,F) circumferential seromuscular layer cutting; (G-I) seromuscular suturing with inversion of the lesion with a gauze spacer; (J) extensive protrusion of the gastric mucosa due to the inverted tissue; (K-M) incision of the muco-submucosal layer; (N) endoscopic clips placement to close an artificial linear ulcer; (O) oral extraction using an endoscopic retrieval device.

surgery (LECS). The concept of this technique was initially described based on results obtained with *ex vivo* experimentation (5), and the first application to clinical practice was reported in 2014 (7). We herein describe the technical details and also the short-term results obtained with this procedure.

Procedure of NEWS

Technical procedures are detailed in the images presented as *Figure 1* and illustrated in *Figure 2*. A 12-mm camera port is inserted via the umbilicus and pneumoperitoneum is then established. Three 5-mm trocars are placed in the left upper, left lower, and right upper quadrants, and one 12-

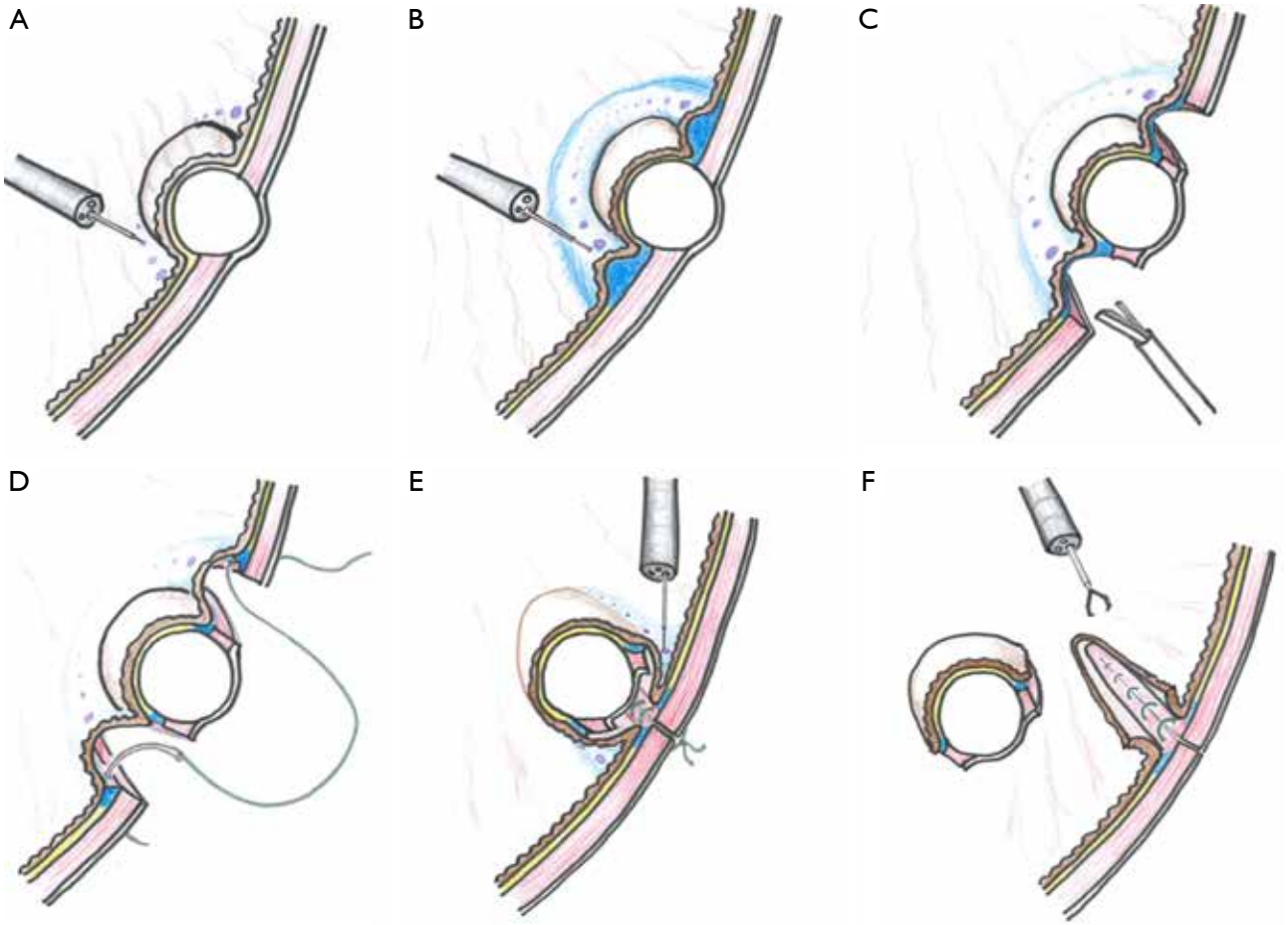

Figure 2 Illustrations to explain the procedures. (A) Markings on the mucosa around the lesion; (B) injection into the submucosal layer; (C) circumferential seromuscular layer cutting; (D) seromuscular suturing; (E) incision of the muco-submucosal layer after inversion of the lesion; (F) loss of continuity between the lesion and gastric wall.

mm trocar in the right lower quadrant. The tumor location is confirmed employing an endoscope with a carbon dioxide supplier (*Figure 1A*). Markings are made by electrocautery on the mucosa around the lesion under endoscopic vision (*Figures 1B* and *2A*) as well as laparoscopically on the serosa just opposite the mucosal markings, guided by pressing the gastric wall using the endoscopic device, or the fiber-optic probe of a diode laser system (*Figure 1C*). A 0.4% sodium hyaluronate solution with a small amount of indigo carmine dye is endoscopically injected into the submucosal layer circumferentially around the mucosal markings with a standard injection needle, of the type used during endoscopic submucosal dissection (*Figure 1D* and *2B*). The seromuscular layer is then incised circumferentially around the serosal markings (*Figures 1E,F* and *2C*). The seromuscular layer is linearly sutured using 3-0 absorbable thread (*Figures 1G* and *2D*). The lesion is naturally inverted into the stomach (*Figure 2E*), and a gauze spacer is inserted between the seromuscular suture plane and the seromuscular surface of the inverted tissue which facilitates the subsequent muco-submucosal incision (*Figure 1H,I*). Endoscopy shows extensive protrusion of the gastric mucosa due to the inverted tissue (*Figure 1J*). The muco-submucosal layer is circumferentially incised outside the mucosal markings, using an endoscopic submucosal dissection technique, until the gauze spacer is found (*Figure 1K,L*). After removal of the gauze spacer, the muco-submucosal incision is completed (*Figures 1M* and *2F*). The resulting artificial linear ulcer is closed using endoscopic clips to promote mucosal healing (*Figure 1N*). The specimen is extracted orally using an endoscopic retrieval device (*Figure 1O*).

Results

We employed NEWS in 28 patients with a GIST between January 2012 and August 2017. The clinicopathological characteristics and operative data of our series are presented in *Table 1*. In the first case, the procedure had to be converted to classical LECS because the tumor was of the totally intraluminal growth type and the tumor margin was poorly recognized on the laparoscopic view. Mucosal injury with a small perforation occurred during the laparoscopic seromuscular cutting phase in case 2. We therefore made two modifications to our technique; employment of the optical fiber system to identify the tumor border clearly from the serosal side and doubling the amount of hyaluronate solution to be injected into the submucosal layer before the laparoscopic seromuscular cutting phase. After these modifications, the full NEWS process was successfully carried out in 25 patients. In case 25, the resected tissue could not be retrieved through the esophagus due to the short axis diameter of the resected GIST being 35 mm, and it was extracted via the gastric window and a small laparotomy incision.

Excluding this patient, case 25, the tumor diameter ranges were 10–45 mm for the long axis and 9–26 mm for the short axis. The only postoperative complication was a fever of unknown origin in one case (Clavien-Dindo grade II), with postoperative courses otherwise being uneventful. Neither conversion of the retrieval route nor unexpected gastric perforation during the procedure was associated with negative postoperative outcomes.

The median operation time was 184 minutes. The operation time gradually decreased during the study period and was within 3 hours for most patients managed during the later part of this study, the exception being one patient with a tumor near the esophagogastric junction (EGJ) (327 min). No significant differences were recognized in tumor size or location, except near the EGJ, nor in the cross-sectional circumference.

Discussion

LECS has now become accepted as a minimally invasive surgical technique for gastric GIST, having gained widespread acceptance since the first report of classical LECS in 2008 (8). Extra-gastric growth type GISTs can easily be identified solely based on a laparoscopic view and laparoscopic wedge resection can be achieved even without support from an endoscopist. However, endoscopy does indeed facilitate identifying the exact tumor location, especially for intraluminal growth type GIST with no significant serosal distortion. Furthermore, it allows the boundary of the GIST to be recognized by endoscopy, while also offering the essential negative margin and minimizing the resected gastric tissues thereafter. However, classical LECS has an innate flaw due to the deliberate gastric perforation that is potentially associated with the risks of bacterial infection and/or tumor cell implantation to the peritoneal surface when gastric juice contains tumor cells dispersed from the primary GIST. Therefore, we hesitate to employ the original LECS procedure with intentional gastric perforation for GISTs with either ulceration or delle formation, or even an artificial ulcer after an extensive biopsy procedure, due to possible tumor cell spillage into the peritoneal cavity.

Employing a non-exposed technique for the digestive tract theoretically reduces the surgical site infection rate and, thereby, postoperative inflammatory responses as well. Although this overcomes the flaw of classical LECS and appears to be an ideal method, NEWS has a major limitation in terms of tumor size due to the tumor retrieval route. The esophageal orifice and EGJ are both among the most inherently narrow areas in the human body. In our series, the maximum tumor size which could be extracted orally was 45 mm in the longest axis and 26 mm in the shortest axis. One tumor, 40 mm × 35 mm in size, could not be retrieved orally and had to be extracted via the abdominal wall. NEWS can be employed basically for small GIST. Based on our experience, the short axis diameter of the tumor is the determinant of NEWS feasibility. With a short axis diameter of less than 30 mm, NEWS is feasible. Therefore, meticulous evaluation of tumor size prior to performing NEWS appears to be essential. Endoscopic ultrasound sonography and computed tomography are recommended for evaluating the exact tumor size.

The procedure is still time-consuming though a learning effect, as indicated by the decreasing trend in operation time, is speculated to be present. Insertion of a gauze spacer accompanied by wall inversion after seromuscular cutting has been employed in recent cases. This maneuver reduces the operation time by facilitating the muco-submucosal incision phase owing to the creation of a wider space between the closed seromuscular plane and the tissue to be resected. Given that seromuscular layer suturing alone is acceptable for alimentary tract anastomosis, endoscopic clipping of the artificial linear ulcer might be optional. Further time reduction might thus be achieved by omitting

Table 1 Characteristics of 28 consecutive patients with gastric GIST

Case No.	Age (years)	Sex	Location	Cross-sectional circumference	Maximum diameter of resected specimen, mm	Tumor size (long axis), mm	Tumor size (short axis), mm	Mucosal ulceration	Mitotic index (Mitoses/hpf)	Malignant risk	Retrieval route	Operation time, min	Perforation	Complication (Clavien-Dindo classification)
1	59	M	U	Post	45	19	16	No	>10/50 hpf	High	Transabdominal	292	Yes	None
2	61	M	U	Post	33	26	26	No	≤5/50 hpf	Low	Transoral	357	Yes	None
3	71	F	U	Ant	38	25	23	No	≤5/50 hpf	Low	Transoral	265	No	None
4	79	F	U	Ant	35	25	20	No	≤5/50 hpf	Low	Transoral	190	No	None
5	49	M	U	Ant	28	17	17	No	≤5/50 hpf	Very low	Transoral	140	No	None
6	58	F	M	Post	48	30	23	No	≤5/50 hpf	Low	Transoral	191	No	None
7	61	M	M	Ant	30	25	20	No	≤5/50 hpf	Low	Transoral	162	No	None
8	71	M	U	Ant	50	45	25	Yes	≤5/50 hpf	Low	Transoral	263	No	None
9	64	F	M	Post	36	18	18	No	≤5/50 hpf	Very low	Transoral	183	No	None
10	76	M	M	Post	24	24	20	No	≤5/50 hpf	Low	Transoral	175	No	None
11	65	M	L	Post	30	10	9	No	≤5/50 hpf	Very low	Transoral	217	No	None
12	76	F	U	Post	25	18	18	Yes	≤5/50 hpf	Very low	Transoral	214	No	None
13	77	M	M	Post	40	40	20	No	≤5/50 hpf	Low	Transoral	194	No	None
14	70	F	U	Post	20	17	14	No	6-10/50 hpf	Low	Transoral	191	No	None
15	52	M	U	Post	30	22	17	No	≤5/50 hpf	Low	Transoral	159	No	None
16	67	M	U	Post	20	20	18	No	≤5/50 hpf	Very low	Transoral	148	No	None
17	68	F	U	Less	38	30	20	No	≤5/50 hpf	Low	Transoral	156	No	Grade II
18	67	M	U	Less	28	22	19	No	6–10/50 hpf	Intermediate	Transoral	200	No	None
19	50	F	EGJ	Gre	37	34	23	No	6–10/50 hpf	Intermediate	Transoral	327	No	None
20	65	M	M	Less	22	12	9	No	≤5/50 hpf	Very low	Transoral	98	No	None
21	85	M	U	Ant	45	30	26	No	≤5/50 hpf	Low	Transoral	185	No	None
22	54	M	U	Post	27	25	20	Yes	≤5/50 hpf	Low	Transoral	189	No	None
23	55	M	U	Ant	35	24	22	No	≤5/50 hpf	Low	Transoral	176	No	None
24	76	M	U	Ant	38	15	14	No	≤5/50 hpf	Very low	Transoral	132	No	None
25	82	M	M	Ant	40	40	35	No	≤5/50 hpf	Low	Transabdominal	161	Yes	None
26	72	M	U	Ant	30	17	14	No	≤5/50 hpf	Very low	Transoral	146	No	None
27	53	F	U	Post	18	15	12	No	≤5/50 hpf	Very low	Transoral	122	No	None
28	76	M	U	Ant	37	30	22	No	≤5/50 hpf	Low	Transoral	174	No	None

GIST, gastrointestinal stromal tumor; M, male; F, female; U, upper third; M, middle third; L, lower third; EGJ, esophagogastric junction; Post, posterior wall; Ant, anterior wall; hpf, high power fields.

endoscopic clipping.

Local resection with complete preservation of the vagal nerve system, minimal resected volume of the unaffected stomach wall and the least possible deformation of the stomach is ideal for preserving inherent gastric function to the maximum extent possible. Given that gastric GISTs 5 cm or smaller can potentially be removed through laparoscopic wedge resection (9), a non-exposed LECS technique appears to be the best current option for small GISTs with mucosal ulceration rendering full-thickness enucleation by opening of the gastric wall unfeasible. It is not clear that the same concept can be employed for GISTs in other organs such as the esophagus, duodenum, and colon. We hope the unique concept of this technique might promote a discussion about establishing and offering a new treatment modality for alimentary neoplasms, especially given the risk of peritoneal seeding when techniques with exposure are applied.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130:1466-78.
2. Joensuu H, Vehtari A, Riihimäki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-74.
3. Hohenberger P, Ronellenfitsch U, Oladeji O, et al. Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. Br J Surg 2010;97:1854-9.
4. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii21-6.
5. Goto O, Mitsui T, Fujishiro M, et al. New method of endoscopic full-thickness resection: a pilot study of non-exposed endoscopic wall-inversion surgery in an ex vivo porcine model. Gastric Cancer 2011;14:183-7.
6. Mitsui T, Goto O, Shimizu N, et al. Novel technique for full-thickness resection of gastric malignancy: feasibility of nonexposed endoscopic wall-inversion surgery (news) in porcine models. Surg Laparosc Endosc Percutan Tech 2013;23:e217-21.
7. Mitsui T, Niimi K, Yamashita H, et al. Non-exposed endoscopic wall-inversion surgery as a novel partial gastrectomy technique. Gastric Cancer 2014;17:594-9.
8. Hiki N, Yamamoto Y, Fukunaga T, et al. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. Surg Endosc 2008;22:1729-35.
9. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41; quiz S42-4.

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Endogastric resection of gastrointestinal stromal tumor

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Abstract: Gastric gastrointestinal stromal tumors (GIST) have a distinct surgical therapy compared to gastric adenocarcinoma. Large oncologic margins and lymphadenectomy are not necessary rendering local resections suitable to treat the disease and spare the stomach. That may be accomplished through a minimally invasive approach. We present a case of a 67-year-old woman with an endophytic 3.5 cm gastric GIST located in the posterior wall of the gastric body that underwent an endogastric resection. Operation was uneventful. The patient was discharged in the following day. Pathologic examination showed free margins and a low grade GIST. Endogastric resection is a feasible option in endophytic GISTs located in the posterior wall of the stomach.

Keywords: Gastrointestinal stromal tumor; stomach; laparoscopy; endogastrosurgery; minimally invasive

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Introduction

Gastric gastrointestinal stromal tumors (GIST) have a distinct surgical therapy compared to gastric adenocarcinoma. Large oncologic margins and lymphadenectomy are not necessary rendering local resections suitable to treat the disease and spare the stomach. That may be accomplished through a minimally invasive approach.

Most authors adopt a tailored approach to gastric GISTs (1-4). Exophytic tumors are generally resected via laparoscopy while endophytic tumors or those located in the posterior gastric wall, cardia or pylorus may be resected through an endogastro (transgastric) approach.

We present a video of a 67-year-old woman with an endophytic 3.5 cm gastric GIST located in the posterior wall of the gastric body. An uneventful endogastric resection was carried out. The patient was discharged in the following day. Pathologic examination showed free margins and a low grade GIST.

Patient selection and workup

Preoperative biopsy is not necessary, due to low accuracy (2). Endoscopy (*Figure 1*), CT scan (*Figure 2*) and endoscopic ultrasound (*Figure 3*) are necessary to diagnose, locate and measure the tumor.

Loss of integrity and spillage of tumor cells increase the risk for recurrence, thus some guidelines limit the size for minimally invasive resection (5). Experienced groups; however, are able to resect large tumors intact.

Pre-operative preparation

Preoperative endoscopic tattooing of the tumor is usually not necessary, unless the size of the mass is very small.

Equipment preference card

Balloon-tipped trocars may be used to facilitate the transgastric stage of the procedure (4) but they are not essential as shown in the presented video. In this case, hooked needles (endoclose®) to fish the retention stiches are useful. Staplers make the procedure much easier, especially with an articulated head. A standard gastrointestinal load is sufficient.

Procedures

Surgeon may be located either in the right-hand side of

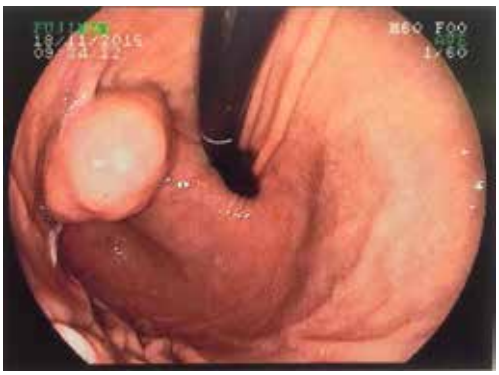

Figure 1 Upper endoscopy disclosing an endophytic 3.5 cm gastric gastrointestinal stromal tumors (GIST) located in the posterior wall of the gastric body.

Figure 4 This video discloses an endogastric resection of an endophytic 3.5 cm gastric gastrointestinal stromal tumors (GIST) located in the posterior wall of the gastric body (6).
Available online: http://www.asvide.com/articles/1143

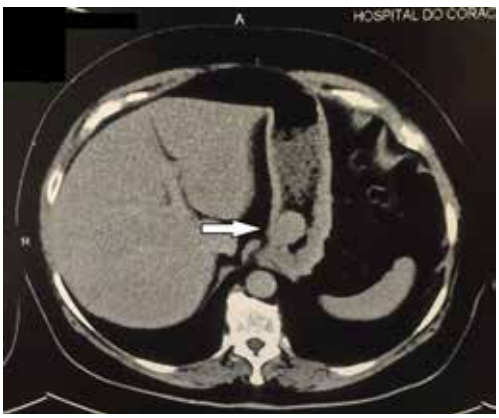

Figure 2 Computerized tomography showing an intraluminal gastric mass originated in the gastric wall (arrow).

Figure 3 Endoscopic ultrasound depicting the regular margins of the tumor originated in the gastric wall.

the patient or between the legs depending on his/her experience with gastrectomy/gastroplasty or antireflux operations. Ports placement also may follow previous experience; however, liver retraction is not necessary unless a hepatomegaly is present.

Abdominal cavity is searched for the main tumor and eventual metastasis. If the transgastric approach is decided, 3 trocars are inserted in the stomach to allow the camera and the hands of the surgeon to operate inside the stomach. The ports may be secured with a balloon-tipped trocar or retention stitches as shown in the video (*Figure 4*). Tumor is located and stapled. The specimen is removed protected in a bag. Stomach incisions are closed.

Role of team members

Usually a single assistant is needed to handle the camera. Intraoperative endoscopy may be necessary in rare cases to locate small tumors or retrieve per mouth a larger specimen.

Post-operative management

Recovery is usually fast. Diet may be resumed in the same day and the patient may be discharged in the day following the procedure.

Tips, tricks and pitfalls

There is no need to pull the stomach to the abdominal wall. A nasogastric tube helps inflate or deflate the stomach as necessary. Tumor must be handled very carefully to prevent

spillage. Normal mucosa around the tumor must be grasped not the tumor itself. Stitches may help presentation of the tumor too. Since extended margins are not necessary, there is no need to include too much gastric wall in the stapler to avoid unintentional inclusion of external vessels or structures.

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Footnote

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Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

References

1. Kawamura H, Shibasaki S, Yoshida T, et al. Strategy of Laparoscopic Partial Resection for Gastric Gastrointestinal Stromal Tumors According to the Growth Pattern. Surg Laparosc Endosc Percutan Tech 2015;25:e175-9.
2. Valle M, Federici O, Carboni F, et al. Gastrointestinal stromal tumors of the stomach: the role of laparoscopic resection. Single-centre experience of 38 cases. Surg Endosc 2014;28:1040-7.
3. Ma JJ, Hu WG, Zang L, et al. Laparoscopic gastric resection approaches for gastrointestinal stromal tumors of stomach. Surg Laparosc Endosc Percutan Tech 2011;21:101-5.
4. Sasaki A, Koeda K, Obuchi T, et al. Tailored laparoscopic resection for suspected gastric gastrointestinal stromal tumors. Surgery 2010;147:516-20.
5. Blay JY, Bonvalot S, Casali P, et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol 2005;16:566-78.
6. Herbella FA, Tamasauskas I, Moura EG. This video discloses an endogastric resection of an endophytic 3.5 cm gastric gastrointestinal stromal tumors (GIST) located in the posterior wall of the gastric body. Asvide 2016;3:374. Available online: http://www.asvide.com/articles/1143

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Molecular target therapy for gastrointestinal stromal tumors

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Abstract: Gastrointestinal stromal tumors (GIST), the most common gastric mesenchymal tumor is unique due to the presence of a driver mutation called c-kit and the usage of imatinib as the targeted therapy. For resectable tumors, surgery is the preferred option and patients with high-risk GIST are considered for adjuvant imatinib for 3 years. The role of neoadjuvant imatinib is evolving. For the management of metastatic GIST, the FDA has approved imatinib, sunitinib and regorafenib as first, second and third line targeted therapy respectively. The increased prevalence of imatinib resistance has paved the way to the development of multiple other secondary and tertiary targeted agents. We present a brief review on the pathophysiology and resistance pathways and a comprehensive review of the various targeted agents which have been developed for the treatment of GIST.

Keywords: Gastrointestinal stromal tumors (GIST); imatinib; regorafenib; sunitinib; targeted therapy

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Introduction

Gastrointestinal stromal tumors (GIST) initially named by Mazur and Clark in 1983 (1) are the most common mesenchymal tumors of the GI tract with a specific mutation and a suitable targeted treatment. They occur most commonly in the stomach (60-70%) and small intestine (25-35%) and rarely in the colorectal region (5%), esophagus (<2%), appendix, omentum, mesentery or retroperitoneum (2) occurring most commonly in the 5th to 6th decade of life. Various risk stratification schemes have been identified for prognostication of GIST. As an addition to these factors, tumor genotyping is being studied extensively and in future may also be incorporated into the risk stratification schemes. Tumor genotyping involves the identification of the causative genetic alteration and tailored therapy catering to that particular genetic abnormality (3). Here we present a comprehensive review of targeted therapy used in the management of GIST.

Pathology

On histo-pathology, GISTs are made of fascicles of spindle cells with eosinophilic cytoplasm, nuclear palisading, inconspicuous nucleoli and extracellular collagen. They can be of three types: spindle (70%), epitheloid or mixture of both (2). On immunohistochemistry (IHC), along with diffuse CD117 positivity (about 95%), other markers which are useful diagnostically are BCL-2 (80%) and CD34 positivity (70%), variable expression of smooth muscle actins (20-30%) and S100 protein (10%) and desmin negativity (2-4% positive). DOG-1 (discovered on GIST) is a novel marker, which is a calcium dependent protein and is positive in GIST irrespective of the mutation status (4). Most of the tumors have low rate of mitoses. These tumor cells are admixed with lymphocytes and apoptotic debris giving a false impression of high mitotic index. Calculation of mitoses is one of the major tasks in calculation of the recurrence risk and the loophole is the difficulty in calculating mitotic count, as most pathologists tend to over count it due to the miscount of lymphocytes and apoptotic and karyorrhectic bodies as part of active mitotic figures (5). The dilemma lies in where exactly the mitotic count has to be assessed and how large the 50 high power fields (HPF) must be. While the area of each HPF has varied from

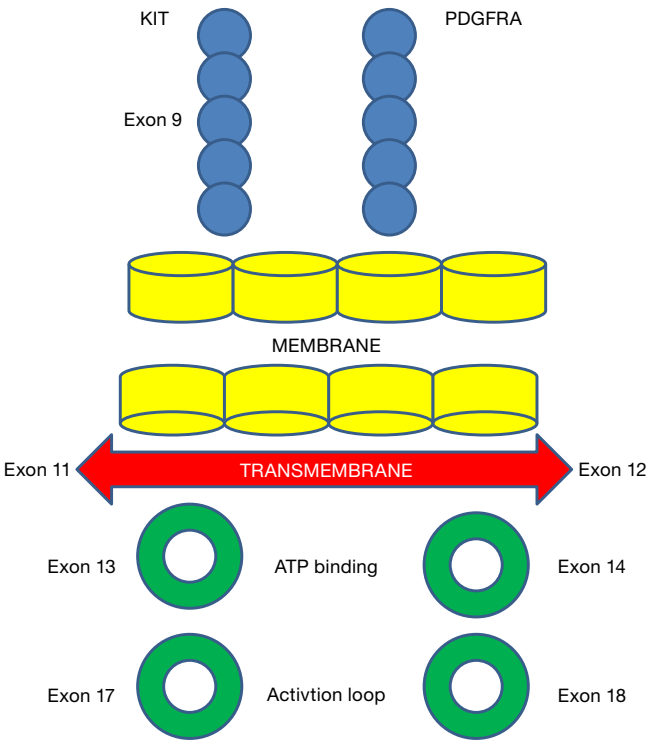

Figure 1 KIT and PDGFRA receptor complex with mutations. PDGFRA, platelet derived growth factor receptor alpha.

5 to 12 mm^2, the ESMO recommendation is an area of 10 mm^2. Moreover, whether the areas should be consecutive or randomly selected in highly cellular parts has not been standardized.

Molecular basis and mutations driving therapy

CD117 (*KIT*) mutation is the most common mutation seen in GIST (80-85%) (6). It was discovered by Hirota *et al.* in 1998 (7). It is encoded by the *KIT* proto-oncogene which is present on chromosome 4 (8). In physiologic conditions, the ligand for *KIT* receptor called the stem cell factor (SCF) (steel factor) binds at the receptor and then after homodimerisation results in a cascade of events causing cell survival and proliferation. Under malignant conditions, this cascade gets activated due to activating mutations and the same cycle is continued irrespective of ligand binding and results in tumorigenesis (9). The pathways activated are the Ras/Raf/MAPK pathway, JAK-STAT pathway, IGF pathway, PI3K/AKT and mTOR pathways (10,11). CD117 is expressed on the interstitial cells of Cajal which are responsible for GI peristalsis, thus hypothesized to be the cell of origin for GIST (7). Exon 11 *KIT* mutations are the most common (65-70%), which happens usually in the juxtamembrane domain (*Figure 1*). These could be point mutations, deletions or duplications and are more common in gastric GIST and show good response to imatinib, whereas exon 9 mutations (5-10%) usually are 2-codon 502-503 duplications in the extracellular domain (made up of five immunoglobulin like molecules) and these occur predominantly in intestinal versus gastric GISTs and are less responsive to imatinib. Other mutations could occur in the ATP binding domain of exon 13 and 14 or exon 17 at the activation loop of the kinase domain (12). In patients with *KIT* negative tumors (15%), 30-40% will be positive for platelet derived growth factor receptor alpha (*PDGFRA*), the gene for which is also situated on chromosome 4 and these tumors are usually of epitheloid variant and gastric in location (8,13). *PDGFRA* mutations could be in exon 18 (most common) (activation loop domain), 12 (juxtamembrane domain) or 14 (ATP binding domain) (11,13). A minority of the cases especially in pediatric age group will be wild type GISTs. *KIT* negative tumors have a better prognosis than *KIT* positive tumors (14). Patients with *KIT* mutation have a poor prognosis especially those with deletions affecting codons 557-558 (15,16). Presently studies are undergoing to study the genetic expression of GIST. Stomach and small bowel GISTs have varying genetic expression. High gene expression of vascular endothelial growth factor (VEGF), Macrophage colony stimulating factor, and *BCL2* was noticed in the wild-type group, and Mesothelin in exon 9 mutation group (17). AKT3 and Ezrin was expressed more in *KIT* exon 11 and 9 mutations and less in *PDGFRA* mutated GISTs whereas MEK and T Cell receptor signaling genes were found to be high in *PDGFRA* mutated tumors (18). In addition to the above mutations, loss of tumor suppressor genes present on chromosome 14 and 22q have also been seen (19). Other GISTs could be familial (mutation in exon 8, 11, 13 or 17) or associated with neurofibromatosis 1, Carney's triad or Carney-Stratakis syndrome (20).

Management of non-metastatic GIST

Neoadjuvant therapy and surgery

The success of imatinib in metastatic GIST led its entry into neo-adjuvant and adjuvant setting. Surgical resection with clear margins should be the main goal while treating GISTs with curative intent. While the median survival post complete resection is approximately 66 months, it gets reduced to 22 months if the disease is unresectable (9). Tumors more than 2 cm should be resected and lymph node dissection

Table 1 NIH, AFIP and Joensuu risk stratification system

Risk stratification (31-33)	Tumor size (cm)	Mitotic count (per HPF)	Tumor site	Tumor rupture
NIH-Fletcher				
Very low risk	<2	<5		
Low risk	2-5	<5		
Intermediate risk	<5	6-10		
	5-10	<5		
High risk	>5	>5		
	>10	Any		
	Any	>10		
AFIP				
Group 1	≤2	≤5		
Group 2	>2 to ≤5	≤5		
Group 3a	>5 to ≤10	≤5		
Group 3b	>10	≤5		
Group 4	≤2	>5		
Group 5	>2 to ≤5	>5		
Group 6a	>5 to ≤10	>5		
Group 6b	>10	>5		
Joensuu				
Very low	<2	≤5	Any site	
Low	2.1-5	≤5	Any site	
Intermediate	2.1-5	>5	Gastric	
	<5	6-10	Any	
	5.1-10	≤5	Gastric	
High	Any	Any	Any	Yes
	>10	Any	Any	
	Any	>10	Any	
	>5	>5	Any	
	≤5	>5	Non gastric	
	5.1-10	≤5	Non gastric	

NIH, National Institutes of Health consensus; AFIP, Armed Forces Institute of Pathology criteria; HPF, high power field.

is not recommended as metastases to nodes are rare (21). Imatinib when used in borderline resectable locally advanced cases can reduce the tumor bulk and make the tumor amenable for surgery with clear margins especially in critical sites like rectum (22,23). In a study of 46 patients, they found that all eleven patients with locally advanced disease could undergo complete surgical resection after a median of 11.9 months of neoadjuvant imatinib (24). The duration of neoadjuvant imatinib is not clearly defined. In a study they found that post neoadjuvant imatinib the 2-year recurrence-free survival (RFS) was 85% and 44% and overall survival (OS) was 97% and 73% for primary and recurrent/metastatic disease, respectively. Moreover on univariate analysis, the duration of neoadjuvant therapy of more than 365 days (P=0.02) was associated with a higher risk of recurrence (25). In a pooled database of ten EORTC STBSG sarcoma centers, patients with locally advanced GIST who received neo-adjuvant imatinib were studied. After a median 40 weeks of imatinib, the rate of R0 resection was 83% and the 5-year disease free survival (DFS) was 65% with median OS of 104 months (26). In a study done at Tata Memorial hospital in India, after a median duration of 8.5 months of neo-adjuvant imatinib, the response rate was 79% with a manageable post-operative complication rate of 14% and a 3-year OS of 100% (27).

Risk stratification and adjuvant therapy

In the absence of adjuvant therapy, 50% patients recurred, especially in the first 5 years (28). Patients with high risk of recurrence are recommended to take adjuvant imatinib after complete gross resection (28-30). There are a number of risk stratification systems to predict the recurrence of GIST after complete surgical resection. The important ones being (*Table 1*):

(I) The National Institutes of Health (NIH) consensus criteria (Fletcher's criteria);
(II) The Armed Forces Institute of Pathology (AFIP) criteria (Miettinen's criteria);
(III) Joensuu's modified NIH classification (J-NIHC) (the two modifications were):
  (i) Tumor rupture was added;
  (ii) Non-gastric tumors in the intermediate risk were converted to high risk;
(IV) The American Joint Committee on Cancer staging system (AJCCS);
(V) The Japanese modified NIH criteria.

The NIH, AFIP and Joensuu's criteria are the most commonly used. Bases on good to poor prognosis the site predilection is as follows: gastric, small intestine, colorectal, extra GI GISTs. Based on size, the 10-year recurrence rate for <1 cm (micro GIST), 5-10 cm and 10-15 cm tumors is 0%, 50% and 70% respectively. Based on mitosis, the 10-year recurrence rate for <5 and >5 mitoses/HPF is 25% and 70% respectively (34). According to the modified NIH criteria, the 10-year RFS for very low, low, intermediate and high risk is 95%, 90%, 85% and 35% respectively (34). Of 127 patients were analyzed at the MSKCC with localized primary GIST

who underwent complete gross surgical resection of disease. After a median follow-up of 4.7 years, RFS was 83%, 75%, and 63% at 1, 2, and 5 years, respectively. Factors predictive of increased recurrence were ≥5 mitoses/50 HPF, tumor size 10 cm, and patients with small intestine tumors did worse. While *KIT* exon 11 point mutations and insertions had a good prognosis, *KIT* exon 9 mutations or exon 11 deletions involving amino acid W557 and/or K558 had a bad prognosis and wild type GISTs had intermediate outcome (35). A nomogram to predict RFS based on tumor size, location and mitotic index (<5 or ≥5/HPF) after surgery in the absence of adjuvant imatinib was proposed by Gold *et al*. The concordance probability was 0.78 (standard error ±0.02). Moreover this nomogram was better than the NIH staging system and equivalent to the AFIP staging system for recurrence prediction (36). Yanagimoto *et al*. analyzed 712 GIST patients after surgery and compared the above systems. They found that the factors significant on multivariate analysis were size >5 cm, mitotic count >5/50 HPF, non-gastric location, and the presence of rupture and/or macroscopic invasion. They also found out that the J-NIHC and AJCCS were respectively the most sensitive and accurate tools to predict recurrence (37). Zhao *et al*. further classified the high risk group into very high risk group which included tumors having mitoses count >10/50 HPF and serosal invasion. Specifically in tumors with serosal invasion, despite adjuvant imatinib the recurrence rates were high, thus stressing the importance of neoadjuvant imatinib so that serosal invasion is reduced (38). In another study by the same authors, they found that Ki67 index >8% also was a poor prognostic factor (39).

In the ACOSOG Z9000 phase II trial, 107 high risk recurrence (tumor size >10 cm, tumor rupture, or <5 peritoneal metastases) patients received 1 year of imatinib 400 mg as adjuvant therapy and was compared with placebo. The 1- , 3- and 5-year RFS was 96%, 60% and 40% and OS was 99%, 97% and 83% respectively. While the median RFS was 4 years, the median OS had not been reached (40). In the subsequent phase III trial (ACOSOG Z9001) patients with tumor >3 cm were randomized to adjuvant imatinib versus placebo for 1 year. The RFS was 98% in the imatinib arm and 83% in the placebo arm [hazard ratio (HR), 0.35; 95% confidence interval (CI), 0.22-0.53; P<0.0001], especially better in patients with high (size ≥10 cm) and intermediate (≥6 to <10 cm) risk. However there was no difference in OS which could be as a result of crossover to imatinib arm on progression (41). In this study, 28% patients discontinued imatinib due to toxicity. Based on these results, adjuvant imatinib was granted accelerated FDA approval in the year 2008 which in 2012 was converted to full approval. In a recent publication, in the same study they showed that large tumor size, small bowel location and high mitotic rate had lower RFS irrespective of the tumor genotype. Moreover, adjuvant imatinib improved RFS in *KIT* exon 11 deletions but not in KIT exon 11 insertions or point mutations, *KIT* exon 9 mutations, *PDGFRA* mutation or wild type GIST (41).

In the subsequent phase III Scandinavian Sarcoma Group/Arbeitsgemeinschaft Internistische Onkologie trial XVIII (SSG XVIII/AIO) trial, patients at high risk for recurrence (with at least one of the following: longest tumor diameter >10 cm, mitotic count >10/50 HPF, tumor diameter >5 cm, and mitotic count >5 or tumor rupture) after surgical removal, were randomly assigned to either 1 or 3 years of adjuvant imatinib. The 5-year RFS and OS were 66% versus 48% (HR, 0.46; 95% CI, 0.32-0.65; P<0.0001) and 92% versus 82% (HR, 0.45; 95% CI, 0.22-0.89; P=0.02), respectively in the 3- and 1-year group (29). 13.6% of patients in the 3-year arm discontinued imatinib due to adverse events than 7.5% in the 1-year arm. In another study 900 patients with intermediate- or high-risk resected GIST were randomized to 2 years of adjuvant imatinib versus no adjuvant therapy. The 3- and 5-year RFS was 84% versus 66% (P<0.001) and 69% versus 65% (P<0.001) in the imatinib versus no adjuvant therapy arms, respectively (42). In the phase II PERSIST-5 trial (Post resection Evaluation of Recurrence-free Survival for gastrointestinal Stromal Tumors) the benefit of 5 years of adjuvant imatinib will be studied. The current recommendation is to give 3 years of adjuvant imatinib for tumors with high risk of recurrence after complete gross resection (30,43).

Management of metastatic GIST

Surgery in metastatic GIST

The role of surgery after imatinib pre-treatment in metastatic patients is controversial. Cheng *et al*. studied the significance of pathological complete response (pCR) post imatinib in metastatic GIST and found out that patients with pCR had better PFS and OS than those without pCR [2-year PFS and OS: 82.5% and 100% versus 35.6% and 49.4%, (P=0.014 and P=0.004) respectively]. They also found that patients with pCR had lesser secondary mutations (44). In another study, patients with recurrent or metastatic GIST who had stable disease after 6 months of imatinib were randomized to surgery followed by imatinib continuation versus surgery alone and found that the surgery group had better PFS (HR, 2.326;

95% CI, 1.034-5.236; P=0.0412) and OS (HR, 5.464; 95% CI, 1.460-20.408; P=0.0117) (45). In a study done in China, the 2-year PFS was 88.4% in the surgery arm and 57.7% in the imatinib alone arm (P=0.089) while the median OS was not reached in the surgery arm and was 49 months in patients with Imatinib-alone arm (P=0.024) (46). In spite of all these data, surgery in metastatic patients is not recommended as a guideline and may be decided on an individual patient's basis based on patient symptoms. The indications for surgery recommended by the NCCN in recurrent or metastatic GIST are (21):

(I) Disease that is stable or shrinking on TKI therapy when complete gross resection is possible;
(II) Isolated clones progressing on TKI therapy after initial response while other sites of disease remain stable;
(III) Emergencies like hemorrhage, perforation, obstruction or abscess.

First line TKI therapy for metastatic GIST

With the use of imatinib, the survival of advanced GIST can extend up to 5 years (47). Imatinib produces response rate of 67% in exon 11 *KIT* mutation and 40% in exon 9 mutation (48). Before the advent of imatinib, the OS of GIST patients varied from 10 to 20 months. The initial studies of imatinib in metastatic GIST were phase II trials which showed response rate of 82% with time to treatment progression (TTP) of 24 months and OS of 57 months (49,50). These benefits were later reconfirmed with phase III randomized trials (51,52). In the The EORTC Soft Tissue and Bone Sarcoma Group phase III randomised trial, 946 patients were randomised to receive 400 or 800 mg once daily imatinib. On progression on 400 mg, patients were allowed to crossover to the 800 mg arm. After a median follow-up of 2 years, the response rate in both groups was around 50% and OS at 1 and 2 years was 85% and 70% in the 400 mg and 800 mg groups respectively with many patients in the 800 mg arm requiring dose reductions (52). Even in the North American Sarcoma Intergroup study (S0033) 746 patients were randomised in a similar manner as the EORTC study. Even in this study the objective response rate (ORR), PFS and OS was similar in both the groups (53). Meta-analysis of these trials showed that the median OS was 4 years and both the doses were equivalent, however patients with exon 9 required 800 mg imatinib (54).

In metastatic patients, imatinib has to be continued until disease progression. In the French Sarcoma Group trial, 58 patients were randomised to imatinib continuation versus interruption after 1 year of treatment. Most of the patients in the interrupted group progressed, however majority of them responded to reintroduction of imatinib and no difference was seen in OS, resistance patterns or quality of life (55). The phase III Intergroup trial proved that *KIT* exon 11-mutant GIST had a better ORR of 71% and OS of 60 months, versus 45% (P=0.01) for both exon 9-mutant and *KIT*/*PDGFRA* wild-type tumors with OS of 39 and 49 months (P=0.049) (56).

Masitinib mesylate is another TKI with greater selectivity than imatinib especially in exon 11 mutation which has shown promising results in phase II trials when used as 1st line in metastatic GIST with a PFS of approximately 41 months and is currently being studied in phase III trials (57,58).

Response assessment to imatinib in GIST

RECIST which is used for response assessment in most solid tumors is not a very good criterion for assessing response to TKI in GIST, as due to necrosis and cystic degeneration, only calculation of tumor size may not be accurate. Choi *et al*. proposed different criteria (*Table 2*) in which along with size, tumor density is also taken into account (59). While routine CT scan is sufficient for assessing response, ^{18}FDG-PET can be used for (59):

(I) Staging and detecting metastases that may otherwise not be apparent;
(II) Detecting an otherwise unknown primary site;
(III) Monitoring response to TKI therapy especially if quick responses need to be assessed for planning early surgery (PET response post imatinib appears as early as 24 hours);
(IV) Detecting primary and secondary resistance to TKI;
(V) When the CT findings are inconclusive or inconsistent with clinical findings.

Second line therapy for metastatic GIST

Sunitinib is recommended as the second line agent in metastatic GIST patients who have progressed on imatinib or are intolerant to imatinib (60). Sunitinib is a TKI which acts against the stem cell-factor receptor (*KIT*), PDGFR—VEGF receptor, glial cell line-derived neurotrophic factor receptor [rearranged during transfection (RET)], colony-stimulating factor-1 receptor (CSF1R), and Fms-like tyrosine kinase-3 receptor (FLT3) (61). In a phase III trial, the PFS was 24 versus 6 months for patients on sunitinib versus placebo respectively (60). In another phase

Table 2 Assessing response on tyrosine kinase inhibitor therapy

Response	Choi criteria	RECIST criteria
Complete response (CR)	(I) Disappearance of all lesions; (II) No new lesions	Same
Partial response (PR)	(I) A decrease in size of 10% or more or a decrease in tumor density (HU) of 15% or more on CT; (II) No new lesions; (III) No obvious progression of non-measurable disease	At least a 30% decrease in the sum of diameter of target lesions
Stable disease (SD)	(I) Does not meet criteria for CR, PR, or progression; (II) No symptomatic deterioration attributed to tumor progression	Same as (I)
Progressive disease	(I) An increase in tumor size of disease 10% or more AND does not meet criteria of partial response by HU on CT; (II) New lesions; (III) New intra tumoral nodules or increase in the size of existing intra tumoral nodules	(I) At least a 20% increase in the sum of diameter of target lesions, along with an absolute increase of at least 5 mm; (II) New lesions

III trial, the PFS with sunitinib was 7, 9 and 13 months in patients who progressed after 1, 3 and 5 years of imatinib respectively (62). In a study by Demetri *et al*., once daily sunitinib 50 mg was given for 4 weeks with a 2-week break and was compared with placebo (patients on placebo arm could cross over to sunitinib arm on disease progression). Although there was no significant difference in OS due to crossover, TTP was 27 weeks in the sunitinib arm versus 6 weeks in the placebo arm. Patients in the placebo arm had a 3-fold greater risk of disease progression (HR, 0.339; 95% CI, 0.244-0.472; P≤0.001) (63). The side effects most commonly encountered with sunitinib are fatigue, anorexia, stomatitis, diarrhea, hand foot syndrome, thrombocytopenia, hypertension and hypothyroidism (64). When sunitinib is used in imatinib failure patients, it is more sensitive in patients with exon 9 mutation and wild type GISTs (65). The mechanisms proposed for sunitinib resistance are increased expression of interleukin-8, AMFR gene expression which is involved in angiogenesis and extracellular matrix metalloproteinase inducer (EMMPRIN), however most of these resistance mechanisms have been studied in renal cell carcinoma patients (66-68).

Third line therapy for metastatic GIST

Regorafenib which is structurally similar to sorafenib, is recommended once patients have progressed on imatinib and sunitinib. It is a pan-TKI which has multiple targets: *KIT*, RET, RAF1, BRAF, VEGFR1-3, TEK, PDGFR and fibroblast growth factor receptor (FGFR) (69,70). The dose recommended is 160 mg oral tablet once daily for 21 days, with cycle of 28 days each. In the initial multicentre phase II study, regorafenib as 3rd line agent showed a PFS of 10 months (71). In the subsequent phase III randomized study (GRID), 199 patients were randomized to third-line regorafenib versus placebo. Patients on progression in the placebo arm were allowed to cross over to the regorafenib arm. At 3 and 6 months, PFS was 60% versus 11% and 38% versus 0% in the regorafenib versus placebo arm respectively. The median PFS was 4.8 versus 0.9 months in the regorafenib versus placebo arms respectively (HR, 0.27, 95% CI, 0.19-0.39; P<0.0001), whereas the disease control rate was 53% versus 9% (P<0.0001). However as expected, due to crossover OS was not statistically different (72). Moreover the benefit of regorafenib was less if the patient had received less than 6 months of imatinib. Toxicity greater than grade 3 or more (HFS, mucositis, diarrhea, hypertension, fatigue) was seen in about 60%, with half the patients requiring dose reductions, however only 2% discontinued treatment due to toxicity. Based on the GRID study, the FDA in 2013 approved regorafenib as a third-line agent (progressed or intolerant to imatinib and sunitinib) in metastatic GIST.

Another option for patients in third-line setting is to rechallenge the patient with imatinib after progression on imatinib and sunitinib, however the patients should have

Table 3 Mutations and response to TKI

Gene	Exon mutation	Imatinib response	Sunitinib response	Regorafenib response
KIT	9	Yes, 800 mg preferred	Yes, marked	Yes
KIT	11	Yes, marked, Val559Ile resistant	Yes	Yes
KIT	13	Yes	Yes	Yes
KIT	17	Yes, Asn822Lys resistant	Minimal	Yes
PDGFR	12, 14	Yes	Yes	Yes
PDGFR	18 D842V	No	No	No
Wild type		Yes	Yes	Yes

TKI, tyrosine-kinase inhibitor; *PDGFR*, platelet derived growth factor receptor.

Table 4 Key phase III randomized trials with tyrosine kinase inhibitors in patients with GIST

Name of study	Setting	N	Randomized arms	PFS/RFS	OS	Response rate
ACOSOG Z9001 (41)	Adjuvant	713	1-year imatinib *vs*. placebo	1-year RFS 98% *vs*. 83% (P<0.0001)	HR =0.816; P=0.438	Not available
SSG XVIII/AIO (29)	Adjuvant	400	1- *vs*. 3-year imatinib	5-year RFS 66% *vs*. 48% (P<0.0001)	5-year OS 92% *vs*. 82% (P=0.02)	Not available
EORTC (52)	1st line metastatic	946	400 *vs*. 800 mg imatinib	2-year PFS 56% *vs*. 50% (P=0.026)	2-year OS 69% *vs*. 74%	50% *vs*. 54%
North American Sarcoma Intergroup study (S0033) (53)	1st line metastatic	746	400 *vs*. 800 mg imatinib	2-year PFS 50% *vs*. 53%	2-year OS 73% *vs*. 78%	43% *vs*. 41%
Demetri *et al*. (63)	2nd line metastatic	243	Sunitinib *vs*. placebo	Median 27.3 *vs*. 6.4 weeks (P<0.0001)	Median 72.7 *vs*. 64.9 weeks (P=0.306)	Not available
GRID (72)	3rd line metastatic	199	Regorafenib *vs*. placebo	Median 4.8 *vs*. 0.9 months P<0.0001)	Same (HR =0.77; P=0.199)	76% *vs*. 35%

GIST, gastrointestinal stromal tumors; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio.

initially shown some response to imatinib. This was studied in a randomized manner in the phase III RIGHT study, in which 81 patients were randomized to imatinib 400 mg daily or placebo as 3rd line agent. The disease control rate with imatinib was 32% and the PFS was 1.8 versus 0.9 months in the imatinib versus placebo arms respectively, however there was no OS benefit (73).

Table 3 shows the response of various TKIs based on the mutation. *Table 4* summarizes the key phase III trials.

Mechanism/drivers of resistance to molecular therapy

In metastatic patients, after a few years of imatinib, the tumors become resistant. However most of the times this resistance is partial, i.e., only few clones become resistant and grow, while few other clones are still sensitive. Imatinib resistance could be either primary or secondary. Primary imatinib resistant tumors progress within the initial few months of therapy whereas secondary resistance happens later due to the development of new secondary mutations, which prevent the binding of imatinib to the *KIT* receptor (74,75). Some of the mechanisms proposed for Imatinib resistance are (76):

(I) Development of secondary mutations in *KIT* and *PDGFRA* which are resistant to imatinib (77);
(II) Amplification and over expression of the *KIT* genome (irrespective of mutation);
(III) Activation of alternate receptor tyrosine kinases;
(IV) Functional resistance—activation of other sites in the *KIT* apparatus (other than usual juxtamembrane site).

Primary resistance is seen in mutations in the activating loop of *PDGFRA* such as D842V in which imatinib is unable to bind to the ATP-binding site of the tyrosine kinase receptor (79,80) and in 15% of *KIT* exon

9 mutations. Secondary mutations usually affect *KIT* exons 13 to 17 (11). In tumors with mutations in exons 13 and 14 which corresponds to the ATP-binding region of the kinase domain, competitive inhibition of imatinib is impaired, where as in exons 17 and 18 mutations the activation loop is affected. Hence in the former more potent TKIs like sunitinib may be beneficial whereas the latter are equally resistant to most TKIs (80).

D842V mutations are usually also resistant to 2nd and 3rd line agents like sunitinib and regorafenib (65,71,79,81) while exon 9 mutations may benefit with higher dose (800 mg) imatinib.

In an EORTC study, factors predictive of early and late resistance were studied. While the presence of lung metastases and absence of liver metastases predicted early resistance, late resistance was predicted by high baseline granulocyte count, a non-stomach primary tumor, large primary size, and low initial imatinib dose (76). Imatinib causes cell death by apoptosis, however some cells escape this due to quiescence, during which the cells are sent to resting phase and hence they escape death by imatinib. This process of quiescence is further enhanced by DREAM complex, hence in imatinib resistant cases, targeting this DREAM complex is also an active part of research in the recent times (82).

In phase II studies sunitinib as third-line therapy had a response rate of 10% with PFS of 5 months (80,83). Another TKI which has got significant benefit in chronic myeloid leukemia called nilotinib failed to demonstrate any benefit in GIST both as 1st line and 3rd line agent in phase III trial (84,85). Ponatinib in another TKI which was initially studied in CML is now being probed in GIST also (86). Heat shock protein (HSP) prevents the proteosomal degradation of *KIT*, hence the new area of interest in the management of GIST is HSP90 inhibitors (87), especially in imatinib resistant cases. Presently the HSP90 inhibitors which are under clinical trials are STA-9090, AT-13387 and AUY922 (88-90). In imatinib resistant clones the PI3K/AKT pathway plays an important role in cell survival and hence targeting this pathway with PI3K inhibitors looks promising (91,92). The MAPK pathway stabilizes ETS translocation variant 1 (ETV_1), which is a transcription factor responsible for tumorigenesis. The transcription factor ETV_1 involved in the MAPK pathway is also expressed on GIST cells, which has led to the study of MEK 162 which is a MEK inhibitor along with imatinib in GIST (93).

Studies have shown that in wild type GISTs with imatinib resistance, there is deficiency in succinate dehydrogenase (SDH) activity which is most often the result of up regulation of IGF1 receptor (10). Hence in wild type GIST the IGF1 receptor inhibitor linsitinib is being studied in phase II trials currently. Other targets which are being studied in imatinib resistance are the downstream signaling pathway molecules like m TOR inhibitors (everolimus and temsirolimus), AKT inhibitor (perifosine), CDK inhibitor (flavopiridol) (11), IGF1 and BRAF inhibitors. Crenolanib is an oral benzimidazole which is a selective and potent inhibitor of *PDGFRA* and *PDGFRB*. It is found to be 135 fold more potent than imatinib in *PDGFRA* D842V mutated GISTs (94). Recently, an anti-*KIT* monoclonal antibody called SR1 has been identified which is active in both imatinib sensitive and resistant cell lines. SR1 reduces cell surface *KIT* expression and also enhances macrophagic phagocytosis of cancer cells causing immunologic cell mediated tumor clearance (95). The development of so many molecules is the proof that imatinib resistance is an active field in current medical research and like the recent approval of regorafenib we are hopeful to have many approvals in the near future.

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Footnote

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References

1. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 1983;7:507-19.
2. Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer 2002;38:S39-51.
3. Wozniak A, Rutkowski P, Schöffski P, et al. Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a European multicenter analysis based on ConticaGIST. Clin Cancer Res 2014;20:6105-16.
4. West RB, Corless CL, Chen X, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol 2004;165:107-13.
5. Agaimy A. Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need

for a standardized GIST reporting. Int J Clin Exp Pathol 2010;3:461-71.
6. Andersson J, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors with KIT exon 11 deletions are associated with poor prognosis. Gastroenterology 2006;130:1573-81.
7. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
8. Stenman G, Eriksson A, Claesson-Welsh L. Human PDGFA receptor maps to the same region on chromosome 4 as the KIT oncogene. Genes Chromosomes Cancer 1989;1:155-8.
9. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51-8.
10. Songdej N, von Mehren M. GIST treatment options after tyrosine kinase inhibitors. Curr Treat Options Oncol 2014;15:493-506.
11. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology 2008;53:245-66.
12. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumors: origin and molecular oncology. Nat Rev Cancer 2011;11:865-78.
13. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708-10.
14. Kontogianni-Katsarou K, Lariou C, Tsompanaki E, et al. KIT-negative gastrointestinal stromal tumors with a long term follow-up: A new subgroup does exist. World J Gastroenterol 2007;13:1098-102.
15. Taniguchi M, Nishida T, Hirota S, et al. Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. Cancer Res 1999;59:4297-300.
16. Martín J, Poveda A, Llombart-Bosch A, et al. Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS). J Clin Oncol 2005;23:6190-8.
17. Antonescu CR, Viale A, Sarran L, et al. Gene expression in gastrointestinal stromal tumors is distinguished by KIT genotype and anatomic site. Clin Cancer Res 2004;10:3282-90.
18. Subramanian S, West RB, Corless CL, et al. Gastrointestinal stromal tumors (GISTs) with KIT and PDGFRA mutations have distinct gene expression profiles. Oncogene 2004;23:7780-90.
19. El-Rifai W, Sarlomo-Rikala M, Andersson LC, et al. DNA sequence copy number changes in gastrointestinal stromal tumors: tumor progression and prognostic significance. Cancer Res 2000;60:3899-903.
20. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumor. Lancet 2013;382:973-83.
21. Demetri GD, Benjamin RS, Blanke CD, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007;5 Suppl 2:S1-29; quiz S30.
22. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009;99:42-7.
23. McAuliffe JC, Hunt KK, Lazar AJ, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol 2009;16:910-9.
24. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol 2007;14:14-24.
25. Bednarski BK, Araujo DM, Yi M, et al. Analysis of prognostic factors impacting oncologic outcomes after neoadjuvant tyrosine kinase inhibitor therapy for gastrointestinal stromal tumors. Ann Surg Oncol 2014;21:2499-505.
26. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol 2013;20:2937-43.
27. Shrikhande SV, Marda SS, Suradkar K et al. Gastrointestinal stromal tumors: case series of 29 patients defining the role of imatinib prior to surgery. World J Surg 2012;36:864-71.
28. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumor: a randomised, doubleblind, placebo-controlled trial. Lancet 2009;373:1097-104.
29. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs. three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-72.
30. National Comprehensive Cancer Network (NCCN). (2013) NCCN Clinical Practice Guidelines in Oncology: soft tissue

sarcoma. Available online: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Version I. 2013.
31. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459-65.
32. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.
33. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-19.
34. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumor after surgery: An analysis of pooled population-based cohorts. Lancet Oncol 2012;13:265-74.
35. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer 2008;112:608-15.
36. Gold JS, Gonen M, DeMatteo RP. Development and Validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localized, primary gastrointestinal stromal tumor (GIST): A retrospective analysis. Lancet Oncol 2009;10:1045-52.
37. Yanagimoto Y, Takahashi T, Muguruma K, et al. Re-appraisal of risk classifications for primary gastrointestinal stromal tumors (GISTs) after complete resection: indications for adjuvant therapy. Gastric Cancer 2015;18:426-33.
38. Zhao WY, Xu J, Wang M, et al. Evaluation of high-risk clinicopathological indicators in gastrointestinal stromal tumors for prognosis and imatinib treatment outcome. BMC Gastroenterology 2014;14:105-12.
39. Zhao WY, Xu J, Wang M, et al. Prognostic value of Ki67 index in gastrointestinal stromal tumors. Int J Clin Exp Pathol 2014;7:2298-304.
40. DeMatteo RP, Ballman KV, Antonescu CR, et al. Long-term results of adjuvant imatinibmesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. Ann Surg 2013;258:422-9.
41. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 2014;32:1563-70.
42. Casali PG, Le Cesne A, Velasco AP, et al. Imatinib failure-free survival (IFS) in patients with localized gastrointestinal stromal tumors (GIST) treated with adjuvant imatinib (IM): The EORTC/AGITG/FSG/GEIS/ISG randomized controlled phase III trial. J Clin Oncol 2013;31 suppl:abstr 10500.
43. The ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 suppl 7:vii49-55.
44. Cheng CT, Tsai CY, Yeh CN, et al. Clinical significance of pathological complete response in patients with metastatic gastrointestinal stromal tumors after imatinib mesylate treatment - lessons learned. Anticancer Res 2014;34:6617-25.
45. Park SJ, Ryu MH, Ryoo BK, et al. The role of surgical resection following imatinib treatment in patients with recurrent or metastatic gastrointestinal stromal tumors: results of propensity score analyses. Ann Surg Oncol 2014;21:4211-7.
46. Du CY, Zhou Y, Song C, et al. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China. Eur J Cancer 2014;50:1772-8.
47. Blanke CD, Joensuu H, Demetri GD, et al. Outcome of advanced gastrointestinal stromal tumor (GIST) patients treated with imatinib mesylate: four-year follow-up of a phase II randomized trial. ASCO Gastrointestinal Cancers Symposium, 2006:Abstract 7.
48. Heinrich MC, Shoemaker JS, Corless CL, et al. Correlation of target kinase genotype with clinical activity of imatinib mesylate (IM) in patients with metastatic GI stromal tumors (GISTs) expressing KIT (KIT1). J Clin Oncol 2005;23:7.
49. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
50. Blanke CD, Demetri GD, Von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620-5.
51. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol2008;26:626-32.
52. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumors with high-dose imatinib: randomised trial. Lancet 2004;364:1127-34.
53. Benjamin RS, Rankin C, Fletcher C, et al. Phase III dose-

randomized study of imatinib mesylate (STI571) for GIST: Intergroup S0033 early results. [Abstract] Proceedings of the American Society of Clinical Oncology 2003;22:A-3271.
54. Gastrointestinal Stromal Tumor Meta-Analysis Group. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 2010;28:1247-53.
55. Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007;25:1107-13.
56. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360-7.
57. Le Cesne A, Blay JY, Bui BN, et al. Phase II studyof oral masitinib mesilate in imatinib-naive patients with locally advanced or metastatic gastro-intestinalstromal tumor (GIST). Eur J Cancer 2010;46,1344-51.
58. Clinical Trials identifier: NCT00812240. A Phase 3 Study to Evaluate Efficacy and Safety of Masitinib in Comparison to Imatinib in Patients With Gastro-Intestinal Stromal Tumor in First Line Medical Treatment. (Recruiting).
59. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography (CT) and positron emission tomography (PET) in patients with metastatic GIST treated at a single institution with imatinibmesylate: proposal of new CT response criteria. J Clin Oncol 2007;25:1753-9.
60. Younus J, Verma S, Franek J, et al. Sunitinib malate for gastrointestinal stromal tumor in imatinib mesylate-resistant patients: recommendations and evidence. Curr Oncol 2010;17:4-10.
61. Sweeney CJ, Chiorean EG, Verschraegen CF, et al. A phase I study of sunitinib plus capecitabine in patients with advanced solid tumors. J Clin Oncol 2010;28:4513-20.
62. Bertucci F, Ray-Coquard IL, Nguyen BB, et al. Effect of five years of imatinib on cure for patients with advanced GIST: Updated survival results from the prospective randomized phase III BFR14 trial. J Clin Oncol 2012;30:abstr 10095.
63. Demetri GD, Garrett CR, Schoffski P, et al. Complete longitudinal analyses of the randomized, placebo controlled,phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res 2012;18:3170-9.
64. Kim S, Ding W, Zhang L, et al. Clinical response to sunitinib as a multitargeted tyrosine-kinase inhibitor (TKI) in solid cancers: a review of clinical trials. Onco Targets Ther 2014;7:719-28.
65. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352-9.
66. Shojaei F, Lee JH, Simmons BH, et al. HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. Cancer Res 2010;70:10090-100.
67. Thodima VJ. Molecular classification of sunitinib response in metastatic renal cell carcinoma (mRCC) patients by gene expression profiling. 2011 ASCO Annual Meeting. Chicago, USA, 2011:abtr 4556.
68. Sato M, Nakai Y, Nakata W, et al. EMMPRIN promotes angiogenesis, proliferation, invasion and resistance to sunitinib in renal cell carcinoma, and its level predicts patient outcome. PLoS One 2013;8:e74313.
69. Serrano C, George S. Recent advances in the treatment of gastrointestinal stromal tumors. Ther Adv Med Oncol 2014;6:115-27.
70. Ferraro D, Zalcberg J. Regorafenib in gastrointestinal stromal tumors: clinical evidence and place in therapy. Ther Adv Med Oncol 2014;6:222-8.
71. George S, Wang Q, Heinrich MC, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. J Clin Oncol 2012;30:2401-7.
72. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
73. Kang YK, Ryu MH, Ryoo BY, et al. Randomized phase III trial of imatinib (IM) rechallenge versus placebo in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) after failure of at least both IM and sunitinib (SU): Right study. J Clin Oncol (Meeting Abstracts) 2013;31:LBA10502.
74. Debiec-Rychter M, Cools J, Dumez H, et al. Mechanisms of resistance to imatinibmesylate in gastrointestinal

stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology 2005;128:270-9.
75. Heinrich MC, Corless C, Blanke C, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764-74.
76. Fletcher JA, Corless CL, Dimitrijevic S, et al. Mechanisms of resistance to imatinibmesylate (IM) in advanced gastrointestinal stromal Tumor (GIST). Proc Am Soc Clin Oncol 2003;22.
77. Antonescu CR, Besmer P, Guo, T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 2005;11:4182-90.
78. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vivo sensitivity to imatinib. J Clin Oncol 2005;23:5357-64.
79. Cassier PA, Fumagalli E, Rutkowski P, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res 2012;18:4458-64.
80. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352-9.
81. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumor after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38.
82. DeCaprio JA, Duensing A. The DREAM complex in antitumor activity of imatinibmesylate in gastrointestinal stromal tumors. Curr Opin Oncol 2014;26:415-21.
83. Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377-83.
84. Reichardt P, Blay JY, Gelderblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol 2012;23:1680-7.
85. Blay JY, Shen L, Kang YK, et al. Phase III trial of nilotinib versus imatinib as first-line targeted therapy of advanced gastrointestinal stromal tumors (GIST). J Clin Oncol 2013;31:abstr 10501.
86. Lierman E, Smits S, Cools J, et al. Ponatinib is active against imatinib-resistant mutants of FIP1L1-PDGFRA and KIT, and against FGFR1-derived fusion kinases. Leukemia 2012:26:1693-5.
87. Bauer S, Yu LK, Demetri GD, et al. Heat shock protein 90 inhibition in imatinib resistant gastrointestinal stromal tumor. Cancer Res 2006;66:9153-61.
88. Clinical Trials Identifier: NCT01039519. A Study Evaluating STA-9090 in Patients With Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST). (Completed).
89. Clinical Trials identifier: NCT01294202. A Study to Investigate the Safety and Efficacy of AT13387, Alone or in Combination with Imatinib, in Patients with GIST. (Completed).
90. Clinical Trials identifier: NCT01404650. Study of Hsp90 Inhibitor AUY922 for the Treatment of Patients with Refractory Gastrointestinal Stromal Tumor. (Ongoing).
91. Bauer S, Duensing A, Demetri GD, et al. KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway. Oncogene 2007;26:7560-8.
92. Floris G, Wozniak A, Sciot R, et al. A potent combination of the novel PI3K Inhibitor, GDC-0941, with imatinib in gastrointestinal stromal tumor xenografts: long-lasting responses after treatment withdrawal. Clin Cancer Res 2013;19:620-30.
93. Chi P, Chen Y, Zhang L, et al. ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumors. Nature 2010;467:849-53.
94. Heinrich MC, Griffith D, McKinley A, et al. Crenolanib inhibits the drug-resistant PDGFRA D842V mutation associated with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res 2012;18:4375-84.
95. Edris B, Willingham SB, Weiskopf K, et al. Anti-KIT monoclonal antibody inhibits imatinib-resistant gastrointestinal stromal tumor growth. Proc Natl Acad Sci U S A 2013;110:3501-6.

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Treatment

The incidence of second primary malignancies after gastrointestinal stromal tumor before and after the introduction of imatinib mesylate

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Imatinib mesylate was FDA-approved in 2002 for the treatment of unresectable and metastatic GISTs and has become the standard of care. Its use has resulted in greatly increased survival rates for patients with GIST. The increased survival in patients with GIST raises concerns about long term effects of therapy, particularly the development of second primary malignancies (SPMs), which has been reported with imatinib treatment of chronic myeloid leukemia. In addition, the diagnosis of GIST itself may pose a risk for the development of SPMs. The purpose of this study was to examine the incidence of SPMs after GIST, particularly before (pre-imatinib era: 1992-2001) and after (imatinib era: 2002-2009), and factors related to the occurrence of SPMs. Data from the NCI's Surveillance Epidemiology and End Results (SEER) 1992-2009 program was utilized. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for these were calculated using SEER*Stat 8.0.1. Observed incidences were then compared between pre-imatinib and imatinib eras using Fisher's exact test. The relationship between the presence of SPMs and each of the variables was examined using logistic regression. There were significantly more patients in the imatinib era alive after follow-up (n=533, 63.99%) than in the pre-imatinib era (n=130, 22.41%, P<0.001). Overall, the rate of SPMs after GIST in the imatinib era was 7.07%, compared with the rate of 1.15% that occurred in the pre-imatinib era (P=0.030). This difference was mainly accounted for by a higher incidence of colon adenocarcinoma in the imatinib era (P=0.023). Renal cell carcinoma also accounted for this difference. In contrast, the rate of melanoma of the skin was significantly lower in the imatinib era compared with the pre-imatinib era (P=0.030). In the pre-imatinib era for melanoma, the SIR was 17.64 (95% CI: 3.64-51.57). Patients with SPMs were significantly older at diagnosis (mean =64.18, SD =12.95) than patients without SPMs (mean =60.63, SD =15.27, P=0.024). Marital status was significantly related to the presence of SPMs (78.26% *vs*. 65.62%, P=0.0154) with those patients with SPMs more likely to be married compared to those without SPMs. This relationship is most likely due to increased survival. Of note, patients with SPMs had greater number of months of survival (mean =70.83, SD =51.54) than those without SPMs (mean =39.33, SD =37.30, P<0.0001). The findings in our study demonstrate that patients after GIST are at increased risk of developing SPMs and that this risk is increased following the introduction of imatinib in 2002. The increased incidence of SPMs in the era of imatinib could be explained by the increased survival of patients with metastatic GIST and therefore more time to develop SPMs, however, further studies are needed to investigate this mechanism.

Keywords: Gastrointestinal stromal tumor (GIST); imatinib mesylate; second primary malignancies

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract with an annual frequency of 10 to 14.5 per one million of the population (1). GISTs express the cell-surface transmembrane receptor c-kit, a protein coded by the KIT proto-oncogene possessing tyrosine kinase activity. The numerous mutations of KIT seen in GIST result in constitutive activation of tyrosine kinase signaling, leading to uncontrolled cell proliferation and resistance to apoptosis (2-4). Tumors that lack KIT mutations have been found to express activating mutations in the related tyrosine kinase platelet derived growth factor receptor alpha (PDGFR) (5,6). Diagnosis of GIST has greatly increased following pathologic reclassification and the widespread adoption of c-kit immunoshistochemical staining (7,8). Prior to 2000, many GISTs were misdiagnosed as other smooth muscle tumors including sarcoma and leiomyosarcoma (3,7).

Imatinib mesylate, a tyrosine kinase inhibitor, competitively inhibits KIT, BCR-ABL, ARG, PDGFR, and PDGFR tyrosine kinases (9-12). Imatinib was FDA approved in 2002 for the treatment of unresectable and metastatic GISTs, and has since become the standard of care. Its use has resulted in greatly improved survival rates (13,14). Historically, treatment of GISTs had consisted of surgical resection of localized disease with an overall 5 year survival rate of approximately 50% (15-17). Patients with more advanced disease that could not be resected had a median survival less than 21 months. Responses to conventional chemotherapy and/or radiotherapy were poor (16,18-20).

Improved longevity in patients with GIST raises questions regarding the development of second malignancies in these patients. Not only may these patients have an increased risk due to the presence of a primary malignancy, but imatinib itself has been implicated in the development of second primary malignancies following increased survival (21). Studies have demonstrated a small risk of second cancers in patients receiving therapy with tyrosine kinase inhibitors for hematologic malignancies, mostly for CML (22). Additionally, patients with GIST have also been shown to be at risk for the development of SPMs regardless of treatment (23-25). The actual risk, particularly with regard to use of imatinib, is unknown.

The purpose of this study was to examine the incidence of SPMs after GIST, particularly before (pre-imatinib era: 1992-2001) and after (imatinib era: 2002-2009), and factors related to the occurrence of SPMs using a population-based approach.

Methods

Data collection

Data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) 1992-2009 program were utilized. Registries included were those from the SEERS 13 (San Francisco-Oakland, Connecticut, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterrey, Louisiana, Alaska, rural Georgia, and Detroit), representing approximately 13.4% of the U.S. population (26). All cases examined were confirmed to be malignant microscopically, not by death certificate or autopsy. Patients included were only those with active follow-up with primary endpoint data. Cases excluded were those in which the primary site of the tumor was unknown, and those in which GIST was considered localized as these patients would not have been considered as candidates for imatinib therapy during the time period studied [imatinib was only recently approved for adjunctive therapy for localized surgical resection (27,28)].

Diagnostic codes used for data from 1992-2000 were 8936 (GIST) from any site, and 8935 (sarcoma), 8890 (leiomyosarcoma), and 9560 (neurilemmoma) in the gastrointestinal tract (middle 1/3 of esophagus until the rectum). We included these soft tissue tumors of the gastrointestinal tract as these were likely originally misclassified cases of GIST (3,29). As the diagnostic accuracy of GIST improved after the widespread use of c-kit staining, only tumors classified as GIST were examined from 2001-2009. Variables examined in our analysis were sex, race, marital status, radiation, grade, vital status, age of diagnosis, months of survival, and person-time-years (time during which a subject is at risk of the study event).

Statistical analysis

The observed incidence of SPMs after GISTs was determined over time, as well as in each of the time periods, pre-imatinib and imatinib. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated using the estimated incidence in the age-adjusted general population in each of the time periods using SEER*Stat 8.0.1. Observed incidences were then compared between pre- and post-imatinib eras using Fisher's exact test.

The relationship between the presence of SPMs and each of the variables was examined using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. Variables found to be significant or marginally significant (P<0.10) in each of the analyses were included in a logistic regression analysis that was then used to examine the odds of having an SPM or not. A similar analysis was undertaken to examine the relationship of era (pre- or post-imatinib) to each of the variables. Survival analysis was done using Kaplan-Meier method. Non-parametric measures were utilized due to the low incidence of SPMs. Statistical analysis system (SAS) was used for analysis. For all values, the significance level was set to P<0.05.

Results

Overall, the rate of SPMs after GIST in the imatinib era was 7.07%, compared with the rate of 1.15% that occurred in the pre-imatinib era (P=0.030). This difference was mainly accounted for by a higher incidence of colon adenocarcinoma in the imatinib era (P=0.023). Renal cell carcinoma also accounted for this difference. In the imatinib era, the SIR of renal cell carcinoma was 4.57, which was significantly elevated compared with the expected age- and time- adjusted incidence for the general population (95% CI: 1.68-9.96). In contrast, the rate of melanoma of the skin was significantly lower in the imatinib era compared with the pre-imatinib era (P=0.030). In the pre-imatinib era for melanoma, the SIR was 17.64 (95% CI: 3.64-51.57) (*Table 1*).

Patients with SPMs were often older at diagnosis (mean =64.18, SD =12.95) than patients without SPMs (mean =60.63, SD =15.27, P=0.024) (*Figure 1*). Marital status was significantly related to the presence of SPMs (P=0.0154). There were more married patients with SPMs (78.26%) than without SPMs (65.62%).

There was no significant difference in person-time years. Patients with SPMs were at risk for 5 years (SD =5.32), while patients without were at risk for 2.93 years (SD =2.79). Sex (P=1.00), race (P=0.3631), grade (P=0.6862), radiation treatment (P=1.00) were not associated with the presence of SPMs (*Table 2*). In the multivariable logistic regression analysis, age was the most important factor related to someone's odds of developing an SPM or not in any time period. Patients who were older had a 3.7% greater odds per year (OR =1.037, CI: 1.002-1.073) of developing an SPM. Of note, patients with SPMs were more likely to be alive (62.5%) than those without SPMs (45.68%, P=0.0010) at the end of follow-up. In addition, they had greater number of months of survival (mean =70.83, SD =51.54) than those without SPMs (mean = 39.33, SD =37.30, P<0.0001) (*Figure 2*).

For validation of the pre-imatinib and imatinib era comparisons, other factors were compared between these cases. There were no differences between the pre-imatinib and imatinib eras with regard to age (P=0.0937), sex (P=0.9129), race (P=0.2163), marital status (P=1.00), grade (P=0.1506), or person time years (P=0.1346). There were more patients in the post-imatinib era alive (n=533, 63.99%) than in the pre-imatinib era (n=130, 22.41%) by the end of follow-up (P<0.0001). There were more people in the pre-imatinib era who received radiation for their tumors (n=36, 6.23%) than in the imatinib era (n=8, 0.96%) (*Table 3*).

Discussion

Our results demonstrate a higher incidence of certain SPMs after GIST compared with the general population, particularly melanoma and renal cancers (*Table 1*). This is consistent with previous studies which demonstrate the development of SPMs following increased survival after GIST (21,23). The higher incidence may also be related to increased medical surveillance following primary diagnosis, exposure to risk factors for GIST, or genetic predispositions of individuals to cancer. A small percentage of GISTs (less than 5%) may be associated with autosomal dominant germ line Kit or PDGFR mutations (30), which may predispose patients to develop tumor syndromes such as neurofibromatosis type 1, Carney triad, and familial GIST syndrome (31). There have been several reviews and case reports that demonstrate that GIST may occur synchronously with other tumors (23-25,31-35). These may be a result of a common exposure to carcinogenic agents resulting in the concurrent presence of malignancies. A study of 783 patients with GIST showed that approximately 20% develop other primary malignancies (23). The most common malignancies reported in patients with GIST include hematologic, prostate, breast, kidney, lung, female genital tract, and carcinoid tumors. Soft tissue and bone sarcomas, malignant melanoma, and seminoma have also been reported after GIST (24). Acute myelogenous leukemia has also been thought to be associated with GIST (36). Our findings of significantly higher rates of melanoma and genitourinary cancers, particularly renal cell carcinoma, after GIST are in line with these. Renal

Table 1 The incidence of SPMs after GIST in the pre-imatinib and imatinib eras

	1992-2001 pre-imatinib era						2002-2009 imatinib era						P value
	Observed	% O/total [336]	O/E	CI lower	CI upper	Excess risk	Observed	O/total [905]	O/E	CI lower	CI upper	Excess risk	(observed/ total)
All sites	13	1.146131805	2.037618	0.34	2.05	16.96	55	7.06940874	1.27	0.96	1.66	35.47	0.0303
Head and neck (tongue)	0	0	0	0	27.39	–2.94	1	0.128534704	1.07	0.03	5.97	0.2	1
Gastrointestinal tract (colon, stomach)	0	0.286532951	0	0	2.7	–29.78	12	1.542416452	1.31	0.68	2.28	8.44	0.0227
Respiratory system (lung)	1	0	1	0.03	5.59	0.05	9	1.156812339	1.35	0.62	2.56	6.97	0.1877
Melanoma of the skin	3	0.286532951	17.64#	3.64	51.57	58.65	0	0	0	0	2.72	–4.05	0.0295
Other non-epithelial skin	0	0	0	0	158.43	–0.51	2	0.257069409	11.76#	1.42	42.47	5.47	1
Soft tissue	1	0	35.29	0.89	196.6	21.46	0	0	0	0	16.01	–0.69	0.3103
Female breast	1	0.286532951	1.37	0.03	7.61	5.84	3	0.385604113	0.6	0.12	1.74	–6.07	1
Female genital system (uterine)	0	0	0	0	13.27	–6.06	3	0.385604113	1.55	0.32	4.53	3.18	0.5567
Ovary	0	0	0	0	46.89	–1.72	2	0.257069409	3.74	0.45	13.5	4.38	1
Male genital system (prostate)	4	0	3.05	0.83	7.82	26.02	8	1.028277635	0.96	0.41	1.89	–1.08	1
Urinary system (renal cell)	0	0	0	0	7.33	–10.98	8	1.028277635	2.26	0.98	4.45	13.34	0.0641
Urinary bladder	1	0	2.91	0.07	16.22	14.5	2	0.257069409	0.94	0.11	3.39	–0.39	1
Kidney and renal pelvis	0	0	0	0	23.97	–3.36	6	0.771208226	4.57#	1.68	9.96	14.03	0.1854
Eye and orbit	1	0	126.99#	3.22	707.52	21.64	0	0	0	0	71.19	–0.16	0.3097
Brain and other nervous system	0	0	0	0	61.69	–1.3	2	0.257069409	4.83	0.58	17.44	4.74	1
Endocrine system (thyroid)	0	0	0	0	63.35	–1.27	2	0.257069409	3.29	0.4	11.88	4.16	1
All lymphatic and hematopoietic diseases	1	0	3.89	0.1	21.68	16.41	3	0.385604113	0.84	0.17	2.44	–1.76	1
Kaposi sarcoma	0	0	0	0	477.21	–0.17	1	0.128534704	28.23	0.71	157.32	2.89	1

cancers occurred at a disproportionately higher rate than that for the general population after the introduction of imatinib, while melanoma occurred at lower rates after the introduction of imatinib.

While most melanomas involve persistent activation of MAPK pathways that involve signaling through serine/threonine kinase BRAF, various growth factor receptors including c-kit are likely overactivated in this cascade (37). A small percentage of melanomas demonstrate activating mutations of KIT, for which imatinib demonstrates significant efficacy (38,39). The observed decrease in incidence of melanoma in patients with GIST after the introduction of imatinib may speak to this shared mechanism by which GIST and melanoma evolve. The relationship between imatinib and renal cancers is less clear. There is a well-demonstrated role for vascular endothelial growth factor (VEGF) receptor tyrosine kinases in the pathogenesis of renal cell carcinoma (40). Tyrokine kinase inhibitors that target VEGF such as sunitinib have been successfully used in the treatment of renal cell carcinoma (41). Sunitinib is a distinct class of tyrosine kinase inhibitor with an entirely different mechanism than imatinib. It is unlikely to have affected a decrease in the incidence of renal cancers in GIST patients, but it remains unclear as to why the incidence would have risen. This is also the case for second primary gastrointestinal cancers (mostly colon adenocarcinomas), which occurred at a higher rate in GIST patients after the introduction of imatinib in our

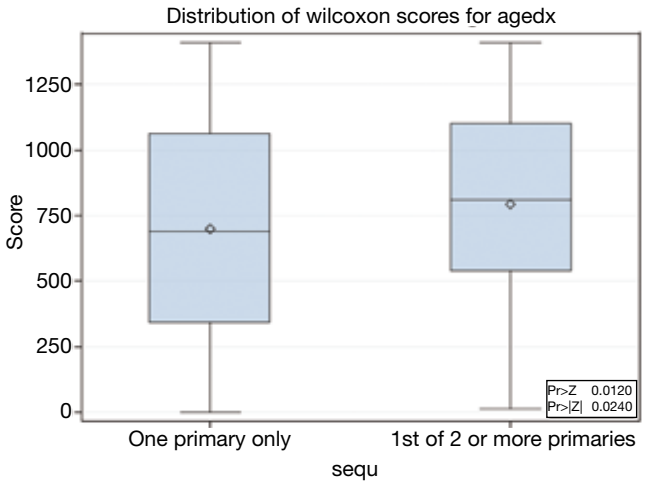

Figure 1 Patients with GIST diagnosed at an older age were significantly more likely to develop SPMs (P=0.024).

Table 2 Differences between patients with only one primary and those with second primary malignancies

Variable (n, % or mean, SD)		One primary only	At least 1 SPM	P value
Age		60.63 (15.27)	64.18 (12.95)	0.0240
Sex	Female	559 (42.70)	44 (42.31)	1.00
	Male	750 (57.30)	60 (57.69)	
Race	Black	218 (16.65)	13 (12.50)	0.3631
	White	879 (67.15)	71 (68.27)	
	Asian/Pacific Islander	207 (15.81)	19 (18.27)	
	American Indian/Alaskan	5 (0.38)	1 (0.96)	
Marital status	Married	754 (65.62)	72 (78.26)	0.0154
	Unmarried (single, widowed, divorced)	395 (34.38)	20 (21.74)	
Grade	Well-differentiated (grade I)	49 (12.73)	3 (9.68)	0.6892
	Moderately differentiated (grade II)	106 (27.53)	6 (19.35)	
	Poorly differentiated (grade III)	78 (20.26)	8 (25.81)	
	Undifferentiated/anaplastic (grade IV)	152 (39.48)	14 (45.16)	
Radiation	Yes	41 (3.14)	3 (2.88)	1.00
	No	1,266 (96.86)	101 (97.12)	
Vital status	Alive	598 (45.68)	65 (62.5)	0.0010
	Dead	711 (54.32)	39 (37.5)	
Survival (months)		39.33 (37.30)	104 (51.54)	<0.0001
Person time years at risk		2.93 (2.79)	5.11 (5.31)	0.3264

study. This, in addition to the higher rate of genitourinary cancers in patients with GIST, is consistent with findings in the literature (23,24). VEGF also plays a role in the pathogenesis of colon cancer, in addition to epidermal growth factor receptor (EGFR). Agents targeting VEGF and EGFR are utilized in colon cancer (42,43), which also have distinct targets from imatinib.

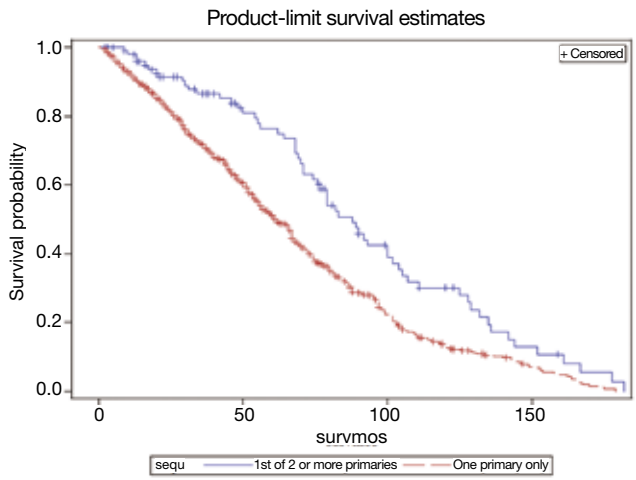

Figure 2 Patients with more than one primary were more likely to have survived longer than those patients who never developed SPMs (P<0.0001).

In our sub-analysis of the risk factors for SPMs after GIST, we found that older and married patients are more likely to develop SPMs. This is likely related to their increased survival and time available to develop SPMs. We found that patients who went on to develop SPMs had more months of survival and were more likely to be alive at the end of follow up. Several studies have shown that marriage is associated with increased survival (44-46). This finding, however, does not downplay the role of other factors such as imatinib in the increased incidence of SPMs. As our findings show, person-time-years was not significantly different between patients between the 2 eras (*Table 3*), implying that survival time was not the only risk factor for the development of SPMs.

The biggest limitation to our study is the assumption that imatinib was offered to patients who met the criteria for treatment after its FDA approval as SEER does not collect data on medication. To support this assumption, we demonstrated that there were no significant differences between the pre- and post-imatinib population with regard to age, sex, marital status, or grade (*Table 3*). There was however a significant difference with regard

Table 3 Comparison of pre-imatinib and imatinib populations

Variable (n, % or mean, SD)		Pre-imatinib	Imatinib	P value
Age		61.65 (15.52)	60.37 (14.85)	0.0935
Sex	Female	249 (42.93)	354 (42.50)	0.9129
	Male	331 (57.07)	479 (57.50)	
Race	Black	84 (14.48)	147 (17.65)	0.2163
	White	407 (70.17)	543 (65.19)	
	Asian/Pacific Islander	86 (14.83)	140 (16.81)	
	American Indian/Alaskan	3 (0.52)	3 (0.36)	
Marital status	Married	352 (66.54)	474 (66.57)	0.5191
	Unmarried (single, widowed, divorced)	177 (33.46)	238 (33.43)	
Grade	Well-differentiated (grade I)	27 (10.67)	25 (15.34)	0.1506
	Moderately differentiated (grade II)	80 (31.62)	32 (19.63)	
	Poorly differentiated (grade III)	48 (18.97)	38 (23.31)	
	Undifferentiated/anaplastic (grade IV)	98 (38.74)	68 (41.72)	
Radiation	Yes	36 (6.23)	8 (0.96)	<0.0001
	No	542 (93.77)	825 (99.04)	
Vital status	Alive	130 (22.41)	533 (63.99)	<0.0001
	Dead	450 (77.59)	300 (36.01)	
Person time years at risk		3.25 (3.62)	2.73 (2.07)	0.1346

to the administration of radiation, a treatment modality that is recorded by SEER. As radiation was shown to be ineffective, it was used significantly less frequently in the era of imatinib. This further supports the ability of SEER data to detect patterns in treatment modalities. Another limitation was that GISTs were not able to be distinguished from other gastrointestinal smooth muscle tumors prior to widespread use of c-kit staining, and were often misclassified. We corrected for this by identifying and including sarcomas, leiomyosarcomas and neurilemomas as tumors for which early GISTs were likely mistaken (3,29). As in many epidemiologic survey studies, we must also be aware of the surveillance bias, which may have affected the incidence of SPMs in patients who already carried a primary diagnosis of cancer.

In summary, the findings in our study demonstrate that patients after GIST are at increased risk of developing SPMs and that this risk is increased following the introduction of imatinib in 2002, particularly those of the gastrointestinal and genitourinary tracts. While it is unknown why there is an increased risk of these cancers, the increased incidence of SPM in the era of imatinib is likely explained by the increased survival of patients with metastatic GIST and therefore more time available to develop SPM. Nonetheless, clinicians following these patients should certainly be aware of the risk to allow for proper follow-up. Further studies are needed to investigate the mechanism.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer 2005;103:821-9.
2. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
3. Rubin BP, Fletcher JA, Fletcher CD. Molecular insights into the histogenesis and pathogenesis of gastrointestinal stromal tumors. Int J Surg Pathol 2000;8:5-10.
4. Ali S, Ali S. Role of c-kit/SCF in cause and treatment of gastrointestinal stromal tumors (GIST). Gene 2007;401:38-45.
5. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357-64.
6. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
7. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 1999;30:1213-20.
8. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 2001;61:8118-21.
9. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 2000;295:139-45.
10. Heinrich MC, Griffith DJ, Druker BJ, et al. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000;96:925-32.
11. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2:561-6.
12. Okuda K, Weisberg E, Gilliland DG, et al. ARG tyrosine kinase activity is inhibited by STI571. Blood 2001;97:2440-8.
13. Perez EA, Livingstone AS, Franceschi D, et al. Current incidence and outcomes of gastrointestinal mesenchymal tumors including gastrointestinal stromal tumors. J Am Coll Surg 2006;202:623-9.
14. Artinyan A, Kim J, Soriano P, et al. Metastatic gastrointestinal stromal tumors in the era of imatinib: improved survival and elimination of socioeconomic survival disparities. Cancer Epidemiol Biomarkers Prev 2008;17:2194-201.
15. Clary BM, DeMatteo RP, Lewis JJ, et al. Gastrointestinal stromal tumors and leiomyosarcoma of the abdomen and retroperitoneum: a clinical comparison. Ann Surg Oncol 2001;8:290-9.
16. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and

prognostic factors for survival. Ann Surg 2000;231:51-8.
17. Ng EH, Pollock RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. Cancer 1992;69:1334-41.
18. Licht JD, Weissmann LB, Antman K. Gastrointestinal sarcomas. Semin Oncol 1988;15:181-8.
19. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. J Natl Cancer Inst 1991;83:926-32.
20. Shiu MH, Farr GH, Papachristou DN, et al. Myosarcomas of the stomach: natural history, prognostic factors and management. Cancer 1982;49:177-87.
21. Roy L, Guilhot J, Martineau G, et al. Unexpected occurrence of second malignancies in patients treated with interferon followed by imatinib mesylate for chronic myelogenous leukemia. Leukemia 2005;19:1689-92.
22. Verma D, Kantarjian H, Strom SS, et al. Malignancies occurring during therapy with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML) and other hematologic malignancies. Blood 2011;118:4353-8.
23. Pandurengan RK, Dumont AG, Araujo DM, et al. Survival of patients with multiple primary malignancies: a study of 783 patients with gastrointestinal stromal tumor. Ann Oncol 2010;21:2107-11.
24. Agaimy A, Wünsch PH, Sobin LH, et al. Occurrence of other malignancies in patients with gastrointestinal stromal tumors. Semin Diagn Pathol 2006;23:120-9.
25. Wronski M, Ziarkiewicz-Wroblewska B, Gornicka B, et al. Synchronous occurrence of gastrointestinal stromal tumors and other primary gastrointestinal neoplasms. World J Gastroenterol 2006;12:5360-2.
26. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Research Data, Nov 2012 Sub (1992-2010) <Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, based on the November 2012 submission.
27. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-104.
28. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-72.
29. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130:1466-78.
30. Gupta P, Tewari M, Shukla HS. Gastrointestinal stromal tumor. Surg Oncol 2008;17:129-38.
31. Ruka W, Rutkowski P, Nowecki Z, et al. Other malignant neoplasms in patients with gastrointestinal stromal tumors (GIST). Med Sci Monit 2004;10:LE13-4.
32. Liu YJ, Yang Z, Hao LS, et al. Synchronous incidental gastrointestinal stromal and epithelial malignant tumors. World J Gastroenterol 2009;15:2027-31.
33. Liszka Ł, Zielińska-Pajak E, Pajak J, et al. Coexistence of gastrointestinal stromal tumors with other neoplasms. J Gastroenterol 2007;42:641-9.
34. Kawanowa K, Sakuma Y, Sakurai S, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006;37:1527-35.
35. Ponti G, Luppi G, Martorana D, et al. Gastrointestinal stromal tumor and other primary metachronous or synchronous neoplasms as a suspicion criterion for syndromic setting. Oncol Rep 2010;23:437-44.
36. Miettinen M, Kraszewska E, Sobin LH, et al. A nonrandom association between gastrointestinal stromal tumors and myeloid leukemia. Cancer 2008;112:645-9.
37. Monsel G, Ortonne N, Bagot M, et al. c-Kit mutants require hypoxia-inducible factor 1alpha to transform melanocytes. Oncogene 2010;29:227-36.
38. Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. JAMA 2011;305:2327-34.
39. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 2011;29:2904-9.
40. Nicol D, Hii SI, Walsh M, et al. Vascular endothelial growth factor expression is increased in renal cell carcinoma. J Urol 1997;157:1482-6.
41. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584-90.
42. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
43. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl

J Med 2007;357:2040-8.
44. Berntsen KN. Trends in total and cause-specific mortality by marital status among elderly Norwegian men and women. BMC Public Health 2011;11:537.
45. Manzoli L, Villari P, M Pirone G, et al. Marital status and mortality in the elderly: a systematic review and meta-analysis. Soc Sci Med 2007;64:77-94.
46. Johnson NJ, Backlund E, Sorlie PD, et al. Marital status and mortality: the national longitudinal mortality study. Ann Epidemiol 2000;10:224-38.

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Treatment of refractory gastrointestinal stromal tumor using pazopanib

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Comment on: Mir O, Cropet C, Toulmonde M, *et al.* Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. Lancet Oncol 2016;17:632-41.

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Gastrointestinal stromal tumor (GIST) is the most common sarcoma in the gastrointestinal tract. Its incidence rate is 1–1.5 per 100,000 per year (1), consistent to the worldwide incidence of approximately 10–20 million people per year (2). Although GIST is generally resistant to both radiation therapy and chemotherapy, over the last two decades GIST has become one of the most controllable sarcoma by molecularly targeted therapies (3). Most GIST express aberrantly activated transmembrane tyrosine kinase (TK) receptors, either KIT or PDGRFA (4). KIT mutation accounts for 80% of GISTs and is most common in exon 11 (65%) followed by exon 9 (8%) (1,2). PDGFRA mutation accounts for less than 10% of cases. GIST without identifiable KIT or PDGFRA mutations are collectively called wild-type and account for 10–15% of patients (5).

Tyrosine kinase inhibitors (TKI) have been extremely successful in the treatment of GIST having KIT mutations. In the metastatic setting, multiple lines of therapy are available including imitanib (first line), sunitinib (second line), and regorafenib (third line) (6). Adjuvant imatinib has significantly improved the recurrence-free survival of patients with GISTs (7,8). However, the development of imatinib resistance is a major challenge in GIST treatment. Patients on imatinib sometimes develop secondary KIT mutations conferring resistant to imatinib. Although sunitnib can sometimes be effective in the second line of treatment, patients will ultimately become resistant to sunitinib as well (9,10). In patients who have progressed on imatinib and sunitinib, regorafenib was shown to significantly improve progression-free survival (PFS) compared with placebo (11) leading to FDA approval for advanced GIST. A number of agents have been tested in subsequent lines of therapy including panopanib (4,12), sorafenib (13), nilotinib (14).

In the recent *Lancet* article (12), Dr. Olivier Mir and fellow colleagues published the results of a randomized, multicenter, open-label phase 2 clinical trial of pazopanib in patients with known resistance to imatinib and sunitinib. Pazopanib is a multitargeted TKI which inhibits KIT, PDGFR, and has particularly potent activity of VEGFR (4). A total of 81 patients were enrolled in the clinical trial from April 12, 2011 to December 9, 2013. Advanced GIST patients were stratified by the number of treatments (2 *vs.* ≥3), then randomly assigned to two groups—pazopanib plus the best supportive care (PBSC) (40 patients) or the best supportive care (BSC) alone (41 patients). Patients were assessed at week 4, 10, and 16 and then every 8 weeks until treatment discontinuation. The primary endpoint was PFS based on both the investigator-assessed progression and centrally assessed progression. Results demonstrated that the centrally assessed 4-month PFS rate was significantly longer in the

PBSC at 44.3% (95% confidence interval of 28.1–59.3%) compared to the survival rate of BSC at 17.6% (95% confidence interval of 7.8–30.8%). The investigator-assessed 4-month PFS showed consistent results. Median investigator-assessed PFS is 3.4 months (95% CI of 2.4–5.6) in the PBSC and 2.3 months (95% CI of 2.1–3.3) in the BSC [hazard ratio (HR) 0.59 (95% CI of 0.37–0.96)]. A trend towards improved overall survival was not statistically significant. The authors concluded that pazopanib had significant effect in controlling activity of GIST after resistant to imitanib and sunitanib. This result contrasts with the marginal activity of pazopanib for advanced GIST after resistant to imitanib and sunitanib reported by a separate study published by Ganjoo *et al.* in 2014 (4). One potentially contributory factor noted by the current study is that patients with a prior history of gastrectomy or with the PDGRFA mutation do not significantly benefit from pazopanib. Prior gastrectomy may be associated with increased gastrointestinal pH levels leading to decreased efficacy of pazopanib. Patients with PDGRFA mutation may be less responsive to pazopanib. These categorizations were not defined in the study by Ganjoo *et al.* The lower efficacy found in their study could be due to the potential higher percentage of participants in these two groups. The lower number of participants, only 25 patients, in the prior study, also likely contributed to the non-significant result.

One important note is that results in Mir *et al.*'s study patients did not receive regorafenib, which is now typically given as the third line treatment for most advanced GIST patients after imitanib and sunitanib resistance in the United States and therefore further study on the efficacy in the modern refractory population is still warranted. Patients with refractory GIST have several options including sorafenib (13) and nilotinib (14). This randomized trial, now establishes pazopanib as a particularly important option for patients with refractory GIST.

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Footnote

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References

1. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer 2005;103:821-9.
2. Stamatakos M, Douzinas E, Stefanaki C, et al. Gastrointestinal stromal tumor. World J Surg Oncol 2009;7:61.
3. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 2001;61:8118-21.
4. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236-40.
5. Bachet JB, Hostein I, Le Cesne A, et al. Prognosis and predictive value of KIT exon 11 deletion in GISTs. Br J Cancer 2009;101:7-11.
6. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer 2016;19:3-14.
7. Nilsson B, Sjölund K, Kindblom LG, et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). Br J Cancer 2007;96:1656-8.
8. Ray-Coquard IL, Bui NB, Adenis A, et al. Risk of relapse with imatinib (IM) discontinuation at 5 years in advanced GIST patients: Results of the prospective BFR14 randomized phase III study comparing interruption versus continuation of IM at 5 years of treatment: A French Sarcoma Group Study. J Clin Oncol 2010;28:10032.
9. Heinrich MC, Maki RG, Corless CL, et al. Sunitinib (SU) response in imatinib-resistant (IM-R) GIST correlates with KIT and PDGFRA mutation status. J Clin Oncol 2006;24:9502.
10. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci U S A 2009;106:1542-7.
11. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID):

an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
12. Mir O, Cropet C, Toulmonde M, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. Lancet Oncol 2016;17:632-41.
13. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. Eur J Cancer 2013;49:1027-31.
14. Montemurro M, Schöffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293-7.

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Neoadjuvant therapy for gastrointestinal stromal tumor

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Abstract: Molecular-targeting therapy using tyrosine kinase inhibitor imatinib mesylate is effective for metastasis/recurrent gastrointestinal stromal tumors (GISTs). Likewise, imatinib would be effective in the neoadjuvant therapy for high-risk GIST. Neoadjuvant therapy may have the potential to increase the complete resection rate and to avoid the surgical rupture by decreasing the tumor size. Thereby, it is expected that improvement of recurrence rate and survival rate can be obtained by neoadjuvant therapy. Neoadjuvant therapy is also expected to be favored from the viewpoint of organ/function preservation by tumor shrinkage. The existing results of clinical trials established the feasibility of neoadjuvant imatinib therapy. However, proof of the survival effectiveness of neoadjuvant imatinib therapy has not been sufficiently demonstrated. The aim of this article is to introduce previous evidence and strategies regarding neoadjuvant therapy for GIST.

Keywords: Gastrointestinal stromal tumor (GIST); imatinib mesylate; neoadjuvant therapy

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Introduction

Adjuvant therapy is one of useful options for multidisciplinary treatment of advanced gastrointestinal tumors. The objective of adjuvant therapy is to control remnant micrometastases that may be left even after radical surgery, thereby suppressing recurrence and improving survival compared with that of surgery only. Neoadjuvant therapy is strictly a preoperative treatment for the purpose of improving survival in patients with resectable tumors, unlike treatment for the patients with unresectable/metastatic tumors. Since gastrointestinal surgery may change the state of oral intake greatly and decrease postoperative treatment tolerability, the role of neoadjuvant therapy is considered to be particularly important. For example, a randomized trial comparing postoperative and preoperative chemotherapy for localized advanced esophageal carcinoma revealed that the overall survival (OS) of the neoadjuvant group was better than that of the adjuvant group (1).

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor in the digestive tract. Patients with large tumor size and large mitotic count have a high risk of recurrence after surgery (2), and researches about neoadjuvant therapy are being conducted, similar to the case in gastrointestinal carcinoma. Most GISTs express KIT, a receptor tyrosine kinase encoded by proto-oncogene *c-kit*, and gain-of-function mutations of *c-kit* are a major cause of tumorigenesis and proliferation (3). Heretofore, tyrosine kinase inhibitors have been effective, and dramatic improvements have been seen in the prognosis of metastasis/recurrent GIST especially after the molecular-targeting therapeutic agent imatinib mesylate has been introduced into therapy (4).

In the neoadjuvant setting, it is expected that improvement of recurrence rate and survival rate can be obtained by imatinib therapy, which has already been proved to have a high clinical efficacy for metastasis/recurrent GIST. GIST usually shows expansive growth and is often found after

Table 1 Multicenter trials of neoadjuvant imatinib therapy for GIST

Ref.	Design	Endpoint	No. of patients	Dose (mg)	Duration	R0 resection rate (%)	Adjuvant imatinib	Survival outcome
Eisenberg *et al.* (5) 2009; Wang *et al.* (6) 2012	Phase II	RFS	31	600	8–10 weeks	68	24 months	2-yr RFS: 83.9%; 5-yr RFS: 56.7%
Blesius *et al.* (7) 2011	Subset analysis of phase III	–	9	400	4.2 months (median)	56	13–24 months	3-yr PFS: 67%; 3-yr OS: 89%
Doyon *et al.* (8) 2012	Phase II	Response rate	12	400	6 months	100	12 months	4-yr DFS: 100%; 4-yr OS: 64%
Hohenberger *et al.* (9) 2012	Phase II	Overall tumor response	41	400	6 months	88	Not planned	3-yr RFS: 85.2%
Tielen *et al.* (10) 2013	Database analysis	PFS	57	400	8 months (median)	84	1, 2 years or lifelong	5-yr PFS: 77%; 5-yr OS: 88%
Rutkowski *et al.* (11) 2013	Database analysis	–	161	400	40 weeks (median)	83	At least 1 year	5-yr DFS: 65 %; 5-yr DSS: 95%
Kurokawa *et al.* (12) 2017	Phase II	PFS	53	400	6–9 months	91	36 months	2-yr PFS: 89%; 2-yr OS: 98%

RFS, recurrent free survival; PFS, progression free survival; OS, overall survival; DFS, disease free survival; DSS, disease specific survival.

the tumor is already quite large. For radical surgery, it may be necessary to sacrifice organ function or to require resection of other organs. Neoadjuvant therapy for large GISTs may have the potential to increase the complete resection rate by decreasing the tumor size and perhaps more importantly, to decrease the risk of surgical rupture or extended surgery. The aim of this article is to introduce previous evidence and strategies regarding neoadjuvant therapy for GIST.

Clinical trials

Although case reports on neoadjuvant imatinib therapy have been seen since 2003, the results of multicenter trials were first reported in 2009 (*Table 1*). Retrospective analyses focusing on neoadjuvant therapy were conducted from two large-scale clinical databases: the BFR14 trial (7), a phase III trial for interruption of imatinib in non-progressive patients and a database from ten centers of the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) (11). The following three trials are representative phase II trials aimed at neoadjuvant imatinib therapy.

RTOG0132 trial

RTOG (Radiation Therapy Oncology Group) 0132 was the first trial of preoperative imatinib in GIST (5,6). It was a prospective phase II study of neoadjuvant/adjuvant imatinib mesylate for operable GIST cases registered in the United States from 2002 to 2006. Short-term and long-term results have been reported. The subjects were KIT-positive GIST patients with either primary disease (>5 cm) or metastatic/recurrent disease (>2 cm). Thirty-one primary GIST patients were analyzed as the neoadjuvant group. Sixteen (52%) were patients with GIST of the stomach and 4 (13%) had GIST of the small intestine. The median tumor size was 8.7 cm. Imatinib was administered at 600 mg/day for 8 to 12 weeks before surgery, and imatinib administration also continued for 2 years after surgery. For all 52 patients in the early report, the rates of grade 3, 4, and 5 preoperative toxicities were 21%, 12%, and 2%, respectively, and the median period of preoperative imatinib was 65 days. In the evaluation by RECIST, partial response (PR) was 7%, stable disease (SD) was 83%, and 21 of 31 patients (68%) underwent R0 resection. The rates of grade 3, 4, and 5 postoperative toxicities were 34%, 20.8%, and 1.9%,

respectively. In the primary GIST group, the progression-free survival (PFS), which was the primary end point of this trial, was calculated as 83.9% for 2 years and 56.7% for 5 years. The 5-year OS was 76%. This trial demonstrated the feasibility of preoperative imatinib, but failed to demonstrate the superiority of adding neoadjuvant therapy compared with the results of adjuvant therapy alone.

APOLLON trial

The APOLLON trial was a prospective, phase II study of neoadjuvant imatinib for advanced GIST registered between 2005 and 2009 in Germany (9). The subjects were locally advanced, non-metastatic GIST cases, and there was no provision for tumor size. Forty-one patients with primary GIST were enrolled and the median tumor size was 10.8 cm. The preoperative dose of imatinib was 400 mg/day for 6 months, with an average of 200 days administered. Dose reduction or interruption due to toxicity was required in two patients. Surgical resection was performed in 34 cases, and R0 resection was undergone in 30 cases. Postoperative treatment was not planned in the study. The 3-year relapse-free survival (RFS) was 85.2%. Since this result did not depend on adjuvant therapy, the potential of neoadjuvant imatinib was expected.

Asian multinational phase II study

Between 2010 and 2014, a phase II study of neoadjuvant imatinib for large gastric GIST was conducted in Japan and Republic of Korea. Its short-term results were recently reported (12). The 53 patients registered in this study had no previous treatment and primary gastric GIST ≥10 cm. The median tumor size was 12.0 cm. Prior to surgery, imatinib treatment was set at 400 mg daily for 6–9 months, and the median duration of neoadjuvant therapy was 26 weeks. The most frequent Grade 3–4 adverse events were rashes, at 9%, followed by neutropenia, at 8%. Although dose reduction of imatinib was required in 14 patients, 46 patients (87%) received preoperative administration for more than 6 months. The response rate by RECIST was 62%. Surgical resection was performed in 50 patients, and R0 excision was performed in 48 patients (91%). Furthermore, forty-two patients achieved preservation of at least half of the stomach. Forty patients received adjuvant imatinib and 38 of these continued imatinib therapy for at least 1 year after surgery. At the median follow-up time of 32 months, 2-year PFS and OS were 89% and 98%, respectively. This study showed that neoadjuvant imatinib for 6–9 months was feasible and brought about a high R0 resection rate. Long-term results are expected to provide improved evidence of the survival benefit of neoadjuvant imatinib for high-risk GISTs.

Selection of therapeutic agents

Generally, drugs used for neoadjuvant therapy are required to have high antitumor efficacy. Molecular targeting therapy using imatinib mesylate, which is the standard treatment for unresectable or metastatic/recurrent GISTs, would also be appropriate for agent of neoadjuvant. It does not necessarily have an excellent response rate by the RECIST criteria. The B2222 trial was a randomized Phase II study comparing imatinib at 400 and 600 mg/day for unresectable or metastatic GIST (13). The overall objective response rate was 68%, and 23 patients (16%) achieved SD. The estimated 5-year OS was 55%, equal in patients who achieved either SD or PR. The efficacy of molecular target therapy for GIST patients should be determined by the disease control rate (DCR), which is the sum of complete response (CR), PR, and SD. The DCR of imatinib therapy in various clinical studies of advanced GIST has been reported as 70–90% (13-16). The efficacy of imatinib therapy for advanced GIST is high in this regard, so imatinib therapy would be recommended also for neoadjuvant therapy.

The initial dose of imatinib of 400 mg/day is considered to be reasonable as a standard dose. In the early days of neoadjuvant imatinib therapy, high doses such as 600 and 800 mg/day were also examined, but no obvious superiority was observed compared to 400 mg/day (5,6,17). Demetri *et al.* examined the plasma level of imatinib mesylate and grouped patients into quartiles according to their imatinib trough concentration (18). The time to progression was equivalent among the three groups except for the lowest-concentration group (<1,100 ng/mL). This indicates that high-dose administration is not necessary in imatinib treatment if sufficient plasma concentration is obtained. Bouchet *et al.* also reported that the effectiveness is low when the imatinib plasma level is not sufficient, and a trough concentration of 760 ng/mL is required regardless of the primary organ (19). There are individual differences in the blood concentration of the drug, and it is recommended to investigate the imatinib trough level when performing neoadjuvant therapy. On the other hand, it had been confirmed that the high-dose imatinib administration have

a PFS advantage on the therapy of unresectable/metastatic GISTs with KIT exon 9 mutations (20). It is also known that there are the imatinib-resistant GISTs such as the GISTs with wild-type KIT, platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation and so on (21). The examination of the KIT/PGDFRA mutation status is recommended if the biopsy is possible before surgery.

Multikinase inhibitors such as sunitinib malate and regorafenib are also used as molecular targeted therapeutic agents for the treatment of GIST. These can be expected to be effective against imatinib-resistant GIST, and there are a few case reports in which neoadjuvant sunitinib therapy was conducted (22). However, these multi-kinase inhibitors have been implicated in various complications in surgery, such as hypertension, thrombosis, delayed wound healing and so on. Raut *et al.* reported that surgical morbidity after sunitinib administration was as high as 54% (23). Unlike imatinib therapy, the use of multikinase inhibitors in a neoadjuvant setting needs to be weighed carefully in terms of its potential advantages and risks.

Preoperative treatment period

There is not enough evidence about the appropriate treatment period of neoadjuvant imatinib therapy for advanced GIST. Raut *et al.* examined surgical cases in the state of stable disease, limited disease progression, and generalized disease progression after imatinib treatment (24). Twelve-month progression-free survival was 80% for patients with SD, better than 33% for those with limited progression and 0% for those with generalized progression. The authors concluded that surgery has little to offer in the setting of generalized progression while surgery for patients with disease control during imatinib therapy is meaningful. Mussi *et al.* also reported the surgical outcomes of 80 patients with metastatic GIST after imatinib treatment (25). The survival outcome of surgery for patients at the time of best clinical response was better than that of focal progression (2-year PFS, 64% versus 10%; 5-year disease specific survival, 83% versus 68%). From these results, it is recommended that surgery on patients treated with imatinib mesylate should be timed to coincide with the best clinical response.

The pharmacological effect of imatinib therapy is promptly expressed, but it takes time to decrease tumor size because imatinib works as a cytostatic agent. Therefore, imatinib needs to be administered for longer periods than the usual neoadjuvant chemotherapies for carcinoma. In the B2222 trial it was reported that the median time to the response of patients who gained effects higher than PR was 2.7 months, and it took 5.3 months for 75% of patients to get a response (26). Tirumani *et al.* reported that best response to neoadjuvant imatinib was seen at 28 weeks and plateau response was seen at 34 weeks (16). From these results, it seems that the neoadjuvant treatment period of 2 to 3 months established in the RTOG 0132 trial was too short for imatinib treatment to exert a beneficial decrease in tumor size. In order to obtain sufficient cytoreductive or cytocidal effect, imatinib should be administered for at least 6 months prior to surgery.

On the other hand, too long a treatment also has risks. Surgery should also be performed before drug resistance to imatinib occurs. In the B2222 trial, half of the patients had tumor progression within 2 years after starting imatinib administration (15). The median time to progression in patients with stable disease was 12 months. Surgical intervention after disease progression should be avoided, and surgery should be considered cautiously if imatinib treatment has been carried out for more than 1 year.

Postoperative therapy

Although it must be carefully considered whether neoadjuvant therapy should be performed on GIST patients who have a high risk of recurrence, adjuvant imatinib therapy after curative surgery is standard treatment for these high-risk patients. Rutkowski *et al.* analyzed data of 161 GIST patients who received neoadjuvant imatinib therapy in EORTC-STBSG (11). One year or more of adjuvant imatinib therapy was conducted in 91 patients (57%), and the median period of adjuvant imatinib administration was 40 weeks. Among patients who received adjuvant therapy, the five-year DFS was 72%, better than that of the 70 patients who did not receive postoperative treatment, 57%. Even after neoadjuvant therapy, postoperative adjuvant imatinib therapy is considered essential.

The SSG XVIII/AIO trial, a randomized phase III study, compared the 1-year versus 3-year administration of adjuvant imatinib in the treatment of high-risk GIST patients (27). In the 3-year treatment group, the five-year RFS was 65.6%, better than the 47.9% in the 1-year treatment group. In addition, the five-year OS was also better in the 3-year treatment group (92% versus 81.7%). This study demonstrated that adjuvant imatinib therapy improves the prognosis of high risk GIST. Recently, the results of a single-arm, phase II trial of 5-year administration of adjuvant imatinib were reported (PERCIST-5 trial) (28).

The long-term survival was good: the 8-year RFS was 81% and 8-year OS was 95%, respectively. Although an appropriate period is not clear in postoperative treatment for patients after neoadjuvant imatinib, at least 3 to 5 years' administration seems to be needed as with simple adjuvant imatinib therapy.

Prevention of extended surgery

GIST develops in any part of the gastrointestinal tract from the esophagus to the rectum, but has a high incidence in the stomach (60%) and the small intestine (30%). Lymph node metastasis is rarely seen, so lymph node dissection and extensive excision of associated organs is unnecessary in contrast to the radical surgery for gastrointestinal carcinoma (29). However, GIST often shows expansive development, and is often diagnosed after experiencing an increase in size without defined subjective symptoms such as obstruction, bleeding and pain. Therefore, the range of organ resection may be enlarged or multiple organ involvement may be necessary for resection of large tumors. For this reason, preoperative treatment is also expected to be favored from the viewpoint of organ/function preservation by tumor shrinkage.

The most commonly reported treatment for organ preservation is rectal primary GIST. Although rectal GIST is uncommon, only about 5% of all GIST, it becomes a problem as to whether the anus can be preserved in order to secure a sufficient margin. Wilkinson *et al.* reported 15 patients with rectal GIST who received neoadjuvant imatinib therapy, and nine of these patients underwent surgery (30). Neoadjuvant therapy enabled sphincter-preserving surgery to be undertaken in seven patients who would have otherwise required abdominoperineal resection or pelvic exenteration. Pai *et al.* reported a retrospective analysis of rectal GIST (31). Only 3 of 9 patients were able to preserve the sphincter despite the fact that the DCR was 92% including 54% partial response. Although the efficacy for quality of life is great if neoadjuvant imatinib can preserve the anal sphincter and avoid an ostomy, it should be noted that the clinical situations such as tumor localization or other factors can make this difficult.

In the case of duodenal GIST, the pancreas is adjacent, and combined resection may be necessary. Lv *et al.* reported that neoadjuvant imatinib administration was performed on ten locally advanced duodenal GIST patients in whom nine were deemed eligible for pancreatic preservation surgery (32). To avoid postoperative pancreatitis or pancreatic fistula, neoadjuvant imatinib for patients with large duodenal GIST may be considered. In the case of gastric GIST, neoadjuvant imatinib has been reported to be helpful for avoiding total gastrectomy (12,33). There is also the merit of making laparoscopic radical surgery possible by reducing the size of the tumor (34). Although there are few reports about GIST of the esophagus or esophagogastric junction, neoadjuvant imatinib may have the potential to eliminate the need for a transthoracic approach at curative resection (35-37).

Research on neoadjuvant imatinib aiming at organ preservation is still insufficient. It should make sure the period of neoadjuvant therapy does not become unnecessarily long by seeking too great a decrease in tumor size; the timing of the best response should not be missed.

Conclusions

The importance of neoadjuvant treatment lies in its feasibility and its survival outcome. The feasibility of neoadjuvant imatinib therapy seems to be well established from the results of clinical trials. However, proof of the survival effectiveness of neoadjuvant-setting imatinib therapy has not been sufficiently demonstrated. It is expected that the long-term results of phase II study for large gastric GIST in Japan and Republic of Korea will prove the survival benefit of neoadjuvant imatinib therapy. Clinical questions still remain about the most appropriate period of pre- and post-operative imatinib administration in the neoadjuvant protocol. The benefits of neoadjuvant therapy with other tyrosine kinase inhibitors against imatinib-resistant GIST are also controversial. Since GIST is a rare disease and cases are limited, neoadjuvant therapy should be registered in nationwide or worldwide clinical trials/databases to compile meaningful bodies of evidence.

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Footnote

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References

1. Ando N, Kato H, Igaki H, et al. A randomized trial

comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012;19:68-74.
2. Rutkowski P, Debiec-Rychter M, Nowecki ZI, et al. Different factors are responsible for predicting relapses after primary tumors resection and for imatinib treatment outcomes in gastrointestinal stromal tumors. Med Sci Monit 2007;13:CR515-22.
3. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
4. Verweij J, van Oosterom A, Blay JY, et al. Imatinib mesylate (STI-571 Glivec, Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. Eur J Cancer 2003;39:2006-11.
5. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 2009;99:42-7.
6. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol 2012;19:1074-80.
7. Blesius A, Cassier PA, Bertucci F, et al. Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial. BMC Cancer 2011;11:72.
8. Doyon C, Sidéris L, Leblanc G, et al. Prolonged Therapy with Imatinib Mesylate before Surgery for Advanced Gastrointestinal Stromal Tumor Results of a Phase II Trial. Int J Surg Oncol 2012;2012:761576.
9. Hohenberger P, Langer C, Wendtner CM, et al. Neoadjuvant treatment of locally advanced GIST: results of APOLLON, a prospective, open label phase II study in KIT- or PDGFRA-positive tumors. J Clin Oncol 2012;30:abstr 10031.
10. Tielen R, Verhoef C, van Coevorden F,et al. Surgical treatment of locally advanced, non-metastatic, gastrointestinal stromal tumours after treatment with imatinib. Eur J Surg Oncol 2013;39:150-5.
11. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol 2013;20:2937-43.
12. Kurokawa Y, Yang HK, Cho H, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. Br J Cancer 2017;117:25-32.
13. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620-5.
14. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127-34.
15. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008;26:626-32.
16. Nishida T, Shirao K, Sawaki A, et al. Efficacy and safety profile of imatinib mesylate (ST1571) in Japanese patients with advanced gastrointestinal stromal tumors: a phase II study (STI571B1202). Int J Clin Oncol 2008;13:244-51.
17. McAuliffe JC, Hunt KK, Lazar AJ,et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol 2009;16:910-9.
18. Demetri GD, Wang Y, Wehrle E, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. J Clin Oncol 2009;27:3141-7.
19. Bouchet S, Poulette S, Titier K, et al. Relationship between imatinib trough concentration and outcomes in the treatment of advanced gastrointestinal stromal tumours in a real-life setting. Eur J Cancer 2016;57:31-8.
20. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 2010;28:1247-53.
21. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
22. Svetlichnaya J, Huyck TK, Wayne JD, et al. Neoadjuvant use of sunitinib in locally advanced GIST with intolerance

to imatinib. Chemotherapy 2012;58:30-3.
23. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. Ann Surg Oncol 2010;17:407-15.
24. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006;24:2325-31.
25. Mussi C, Ronellenfitsch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol 2010;21:403-8.
26. Tirumani SH, Shinagare AB, Jagannathan JP, et al. Radiologic assessment of earliest, best, and plateau response of gastrointestinal stromal tumors to neoadjuvant imatinib prior to successful surgical resection. Eur J Surg Oncol 2014;40:420-8.
27. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-72.
28. Raut CP, Espat NJ, Maki RG, et al. Extended treatment with adjuvant imatinib (IM) for patients (pts) with high-risk primary gastrointestinal stromal tumor (GIST): The PERSIST-5 study. J Clin Oncol 2017;35:abstr 11009.
29. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459-65.
30. Wilkinson MJ, Fitzgerald JE, Strauss DC, et al. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. Br J Surg 2015;102:965-71.
31. Pai VD, Demenezes JL, Patil PS, et al. Multimodality therapy of rectal gastrointestinal stromal tumors in the era of imatinib-an Indian series. J Gastrointest Oncol 2016;7:262-8.
32. Lv A, Qian H, Qiu H, et al. Organ-preserving surgery for locally advanced duodenal gastrointestinal stromal tumor after neoadjuvant treatment. Biosci Trends 2017;11:483-9.
33. Annaberdyev S, Gibbons J, Hardacre JM. Dramatic response of a gastrointestinal stromal tumor to neoadjuvant imatinib therapy. World J Surg Oncol 2009;7:30.
34. Cavaliere D, Vagliasindi A, Mura G, et al. Downstaging of a gastric GIST by neoadjuvant imatinib and endoscopic assisted laparoscopic resection. Eur J Surg Oncol 2007;33:1044-6.
35. Duffaud F, Meeus P, Bertucci F, et al. Patterns of care and clinical outcomes in primary oesophageal gastrointestinal stromal tumours (GIST): A retrospective study of the French Sarcoma Group (FSG). Eur J Surg Oncol 2017;43:1110-6.
36. Sato H, Kanda T, Hirota S, et al. Surgical resection of gastrointestinal stromal tumor of esophagus following preoperative imatinib treatment: a case report. Esophagus 2010;7:65.
37. Staiger WI, Ronellenfitsch U, Kaehler G, et al. The Merendino procedure following preoperative imatinib mesylate for locally advanced gastrointestinal stromal tumor of the esophagogastric junction. World J Surg Oncol 2008;6:37.

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Cost-effectiveness of precision medicine in gastrointestinal stromal tumor and gastric adenocarcinoma

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Abstract: Over the past 20 years, with the incorporation of genetic sequencing and improved understanding regarding the mechanisms of cancer growth/metastasis, novel targets and their associated treatments have emerged in oncology and are now regularly incorporated into the clinical care of patients in the US. Novel, more tumor-specific, non-chemotherapy agents, including agents that are commonly used in the treatment of patients with gastric adenocarcinoma (GA) and gastrointestinal stromal tumor (GIST), fall under a broader treatment strategy, termed "precision medicine". While diagnostic testing and associated treatments in metastatic GA (mGA) are costly and may produce marginal benefit, those associated with GIST, despite being costly, produce significant improvements in patient outcomes. Despite the significant difference in impact, the agents associated with these cancers have similar acquisition costs. In this paper, we will review the current literature regarding cost and cost-effectiveness associated with precision medicine diagnosis and treatment strategies for GA and GIST.

Keywords: Cost-effectiveness; gastrointestinal stromal tumor (GIST); gastric adenocarcinoma (GA); cost; targeted agents

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Introduction to precision medicine in gastric cancers

With an estimated 26,370 new diagnoses and 10,730 deaths in the US in 2016, gastric adenocarcinoma (GA) remains an uncommon, but deadly cancer within the Western world (1). Its associated high mortality is due to not only the tumor's innate aggressiveness, but also to its late stage of presentation, with more than 60% of patients diagnosed with at least locally advanced disease. Despite recent advances in diagnosis and treatment, the 5-year overall survival (OS) remains poor at 29% (2). Meanwhile, gastrointestinal stromal tumors (GIST), with an estimated 4,000–6,000 new diagnoses in the US in 2016, is an extraordinarily rare, but highly curable cancer, with a 5-year OS ranging from 60–85% (1,3). As opposed to those with GA, the OS for patients with GIST, especially those with more advanced disease, has improved markedly over the past decade.

Within the past 15–20 years, with the incorporation of high output tumor mutational analyses and improved understanding regarding the mechanisms of cancer growth/metastasis, novel targets and their associated treatments have emerged within the field of oncology and are now regularly incorporated into the clinical care of patients in the US. Novel, more tumor-specific, non-chemotherapy

agents, which include those that are commonly used in the treatment of patients with both GA and GIST, fall under a broader treatment strategy, termed "precision medicine" (4). The Precision Medicine Initiative (PMI), which called for the allocation of $215 million US dollars to the National Institutes of Health (NIH) and the National Cancer Institute (NCI), was recently unveiled by US President Barack Obama, and not only highlighted the successes and limitations of precision medicine as it pertained to past and current aspects of medical diagnosis and treatment, but also the value in its potential future utility with regard to improving cancer care in the US and decreasing cancer-specific patient mortality (5).

Gastric adenocarcinoma (GA)

Through the use of precision medicine-associated diagnostic testing, 7–22% of GA have been found to overexpress the human epidermal receptor 2 (HER2), a prerequisite for the use and beneficial effect of the HER2 targeting agent, trastuzumab (6-11). Based upon these initial studies and other early phase studies, a phase III trial was conducted to evaluate trastuzumab in HER2 positive (HER2+) metastatic GA (mGA). Patients randomized to receive trastuzumab, in conjunction with chemotherapy (cisplatin and capecitabine or 5-fluorouracil) and then as monotherapy thereafter, had a significantly improved OS compared to those who received chemotherapy alone (13.8 *vs.* 11.1 months; hazard ratio 0.74; 95% CI, 0.60–0.91; P=0.0046). The results of this study served as the impetus for the drug's ensuing Food and Drug Administration (FDA) approval (9).

Other HER2 targeting agents have shown mixed results in GA. Pertuzumab has recently been FDA approved for use in select patients with HER2 positive breast cancer and has demonstrated considerable synergistic activity with trastuzumab (12). Clinical trials determining its effectiveness are ongoing and include the phase III JACOB trial evaluating the combination of pertuzumab, trastuzumab, and chemotherapy in mGA and the phase III PETRARCA trial comparing standard combination chemotherapy with trastuzumab and pertuzumab with combination chemotherapy for neoadjuvant use in locally advanced GA (13). Meanwhile, ado-trastuzumab emtansine (T-DM1), another recently approved HER2 targeted agents used and shown to be very effective for select patients with breast cancer has also been evaluated in GA (14). The phase III GATSBY trial compared T-DM1 with taxane chemotherapy in advanced gastric cancer, but a preliminary analysis revealed that the study failed to meet their primary endpoint (15). Lapatinib, an agent that targets both epidermal growth factor receptor (EGFR) and HER2, has been shown to have clinical benefit in select HER2 positive breast cancer patients (16). However, two phase III trials have evaluated its use in the 1st (LOGIC) and 2nd line setting (TyTAN) when combined with standard chemotherapy and have found no benefit (17).

Similar to other solid tumors, the uncontrolled growth characterized by GA is highly dependent upon local blood supply and angiogenesis. With this in mind, the anti-angiogenic agent ramucirumab, which primarily targets an angiogenesis mediator vascular endothelial growth factor 2 (VEGFR2), was shown to marginally, but significantly improve OS in mGA patients (5.2 *vs.* 3.8 months; hazard ratio 0.78; 95% CI, 0.60–0.99; P=0.047). Subsequently, the FDA approved the drug for the use of patients with mGA, either as monotherapy, or in combination with paclitaxel chemotherapy (18).

Gastrointestinal stromal tumors (GISTs)

Mutational analysis, with regard to GIST, have found that mutations tend to be mutually exclusive, and that 80% have protein coding (*KIT*) gene mutations that lead to the activation of a targetable KIT receptor (19-21). While nearly 75% of these mutations affect exon 11, they can also affect exon 9, 13, or 17 (22,23). Approximately 7% of GISTs harbor mutations in the tyrosine kinase platelet derived growth factor receptor (PDGFRA), and even less commonly, have only an inactivation of the succinate dehydrogenase complex (24,25). The discovery and in-depth characterization of the mutations have not only led to the use of precision medicine for GIST, but also reemphasized an important concept of precision medicine: different targetable mutations have varying responses to different drugs, and specific mutations can dictate the minimal effective treatment dose. Imatinib, a tyrosine kinase inhibitor (TKI) that is historically known for its revolutionary impact in the treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia through the inhibition of the *BCR-ABL* gene product, has been found to also inhibit c-KIT and PDGFA. As a result of the improved relapse free survival (RFS) seen in a recent phase III trial among patients with high-risk resected GIST who received 36 versus 12 months (the previous approved treatment duration) of adjuvant therapy, the FDA updated the drug's prior approval for this indication (26). Although

imatinib was initially FDA approved in the unresectable/metastatic setting based upon improved response rates compared with systemic chemotherapy, it was subsequently shown to also improve OS when used for this indication (27). Sunitinib, another multi-targeted TKI, through its inhibition of PDGFR, was found in a phase III trial to be effective and improve outcomes among unresectable/metastatic GIST patients who were intolerant or refractory to imatinib (28). Finally, regorafenib, another multi-targeted TKI, through its inhibition of KIT and PDGFR, was shown in a phase III trial to improve outcomes among unresectable/metastatic GIST patients who were refractory to both imatinib and sunitinib (29).

Precision medicine has become a national priority and has not only been incorporated into the care of patients with GA and GIST, but in some instances, has been shown to significantly improve outcomes. Despite its successes and potential future utility, precision medicine can be costly. In fact, a recent study determined that the total yearly cost of cancer care in US was approximately $124.5 billion dollars, a number that was projected to increase to approximately $157.7 billion by 2020 (30). With the surge in innovation comes an important discussion regarding the cost, management, and sequencing of therapies, as well as the concern regarding the overall sustainability of the current health care system and the ability of public and private payers to cover increasing costs. In this paper, we will review the current literature regarding cost and cost-effectiveness associated with precision medicine in GA and GIST.

Drug prices vary between different countries

The price of oncology drugs varies considerably by country, as was shown in a recent study looking at the prices in 16 European countries, Australia, and New Zealand and found that the difference from the highest to lowest priced country varied between 28% and 388% (31). From a US perspective, the average price of cancer drugs for a year of therapy increased from $5,000 to $10,000 before 2000 to more than $100,000 by 2012 and although 85% of cancer basic research is funded through public payment, the US pays 50% to 100% more for the same drug compared to other countries (32). Given the paucity of cost effective analyses for each individual country, the study relies on international data and thus caution must be taken when attempting to extrapolate cost analyses from one country to another.

Gastric/esophagogastric adenocarcinomas (GA)

Biomarker testing

Similar to its use in breast cancer, HER2 testing typically involves initial tumor testing with immunohistochemistry (IHC), with grading scores ranging from 0–3+. If a tumor is found to have 0 or 1+ HER2 expression, they are deemed to have HER2 negative GA and no further testing is performed. Conversely, if the tumor is found to have 3+ HER2 expression, tumors are considered HER2+ and no additional testing is performed. In cases where tumors are deemed to have 2+ HER2 expression, or there is a question regarding the accuracy of a tumor with 0 or 1+ expression, fluorescent in-situ hybridization (FISH) (via chromogenic or silver in-situ hybridization) using either HER2 copy number or HER2/chromosome 17 ratio (HER2/CEP17) (33) is performed for confirmation. If the tumor is found to have an average HER2 copy number ≥6.0 signals/cell and/or a HER2/CEP17 ratio of 2 or greater, the tumor is considered HER2+. Trastuzumab has been found to improve OS most significantly among patients with IHC 3+ tumors, compared with patients with IHC 2+, FISH positive tumors where it is less effective, and IHC 0 or 1+ tumors where it has been found to be ineffective (9). Although the technique has yet to be widely adopted secondary to availability and cost, there is some evolving research in the utility of a reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) assay that not only measures relative HER2 mRNA levels, but has been shown to be highly concordant with the other, more widely used methods of detecting HER2 expression (34).

There have been several concerns related to HER2 testing in GA. HER2 protein expression in GA, as opposed to similar testing in breast cancer, tends to spare the digestive luminal membrane, and thus results in a greater false positive rate. Similar to HER2 testing done in other cancer types, GA intra-tumor HER2 heterogeneity increases the risk for false positives and false negatives, which have been reported to be as high as 17% (35).

Trastuzumab

The National Institute for Health and Care Excellence (NICE) is a British governmental agency that was established in its current state in 2005. Based upon cost-effectiveness analyses, they publish guidelines related to health technologies, clinical practice, public health, and social services within the National Health Service (NHS; new and existing) (36). These guidelines are used to

Table 1 Agents associated with precision medicine that is used for the treatment of gastric adenocarcinoma and gastrointestinal stromal tumors, their associated approvals, and acquisition costs

Drug	Indication	FDA approval date	Monthly cost (41)	NICE recommendation	Date of NICE Recommendation
Trastuzumab	Metastatic, HER2+ gastric adenocarcinoma, in combination with cisplatin and either capecitabine or fluorouracil for 6 cycles followed by monotherapy	October 20, 2010	$6,726	Recommends use for IHC 3+ HER2-positive treatment naive metastatic gastric adenocarcinoma	November 2010
Ramucirumab	Advanced or metastatic gastric adenocarcinoma: as a single agent or in combination with paclitaxel	April 21, 2014	$15,338	No recommendation at present	Anticipated publication date: January 2016
Imatinib	GIST (adjuvant)	Accelerated: 2002, regular approval: February 1, 2012	$12,147	Recommended for 3 years for patients with GIST following complete resection	October 2004
	GIST (unresectable/metastatic)	2008	$12,147	Recommended at 400 mg/day as first-line treatment in patients with KIT-positive unresectable/ metastatic GISTs	November 2014
Sunitinib	GIST	January 26, 2006	$16,156	Unresectable/metastatic GIST refractory to imatinib	September 2009
Regorafenib	Locally-advanced, unresectable, or metastatic GIST	February 25, 2013	$19,996	No recommendation due to lack of data	February 2015

FDA, Food and Drug Administration; NICE, National Institute for Health and Care Excellence; HER2, human epidermal receptor 2; IHC, immunohistochemistry; GIST, gastrointestinal stromal tumor.

ultimately decide whether or not a health technology, such as a new drug, can be used in clinical practice within the United Kingdom (UK). In response to public pressure due to the UK Prime Minister David Cameron introduced the Cancer Drugs Fund (CDF) in 2011 to fund drugs that were not approved by NICE. Although the fund initially called for a budget of $370 million/year, during 2014–2015, the NHS reported going over budget by over $100 million and would have to subsequently cut funding for more than 20 oncology drugs (37,38). Using data from the TOGA trial (9), NICE estimated the incremental cost effectiveness ratio (ICER) of trastuzumab to be between $49,011–$54,457, and subsequently appraised its use for treatment naïve mGA patients, whose tumors were deemed to be HER2+ as defined by an IHC 3+ result (39,40) (*Table 1*). This appraisal was in contrast to their previous decision for the same indication, but which also included those patients with HER2 IHC 2+/FISH positive, for which trastuzumab was determined to have an ICER between $73,006 and $108,747 (42). A Japanese study reported similar findings to NICE, and found that tumors from patients which were IHC 2+/FISH+ were associated with an ICER of $90,440/quality adjusted life years (QALY) and $65,379/life year gained (LY), whereas patients with tumors that were deemed IHC 3+ had an associated ICER of $59,930/QALY and $42,496/LY (43). A study examined the trastuzumab prescribing impact in a large teaching hospital in Ireland, and found that the total treatment related cost of trastuzumab was $26,152/patient, with a total cost per year (1 teaching hospital) of $287,668, and a total cost per year (country of Ireland) of $915,306 (44).

Health utility values, elicited through the use of well-established, preference-based measures, such as the EuroQol-5 Dimension (EQ-5D), serve a critical role in cost-effectiveness studies as they are able to quantify particular health states that are encountered among cancer patients. A recent review article found that the health

utility value of newly diagnosed mGA fell somewhere between 0.66–0.73, but found that these health states dropped precipitously (disutility: –0.20–0.50) with multiple treatments, multiple progressions, and disease/treatment related side effects affecting quality of life (QOL), most notably dysphagia and weight loss (45).

Ramucirumab

Although there is a paucity of data looking at the cost-effectiveness of ramucirumab in mGA, one recent review questioned the likelihood of its cost-effectiveness given the results of the phase III trial REGARD, which compared it to placebo and led to the drug's FDA approval (median OS: 5.2 *vs.* 3.8 months) (46,47). Although an official guideline is scheduled to be released in January of 2016, the NICE cost-effectiveness analysis concluded that the most plausible ICER for ramucirumab plus paclitaxel, compared with best supportive care (BSC) plus paclitaxel, for patients with mGA was $443,386/QALY gained, and $204,314/QALY gained for ramucirumab monotherapy when compared with BSC (48). Although the study looked at ramucirumab as it is used in metastatic colorectal cancer (mCRC), the OS improvement reported in the phase III mCRC RAISE trial (1.6 months) was similar to that seen in the mGA REGARD trial (1.4 months). The monthly drug acquisition cost of ramucirumab was calculated to be $15,338, which was significantly greater than that of bevacizumab and ziv-aflibercept, both of which were previously shown to not be cost-effective in mCRC (49,50). Despite these studies, the jury is still out on its cost-effectiveness in mGA and more data will need to be generated in order to properly evaluate ramucirumab in mGA.

Gastrointestinal stromal tumors (GISTs)

Biomarker testing

Most experts recommend a more detailed analysis regarding the KIT mutation in patients with unresectable/metastatic GIST, as it provides the patient and clinician with valuable prognostic and predictive information (51). For example, patients with exon 11 KIT mutations unresectable/metastatic GIST not only have a substantially greater imatinib treatment response, but also have an improved progression free survival (PFS) and OS, when compared to those patients with either exon 9 KIT mutations, or those without a detectable mutation in either KIT or PDGFRA (52). Dose-response trials have shown that, as opposed to tumors harboring exon 11 KIT mutation or those that are KIT wild-type, higher daily doses of imatinib were found to improve treatment response and PFS among those with exon 9 KIT mutations (52,53). As a result of these studies, the National Comprehensive Cancer Network (NCCN) recommended the use of imatinib at a starting dose of 800 mg daily for those patients with exon 9 KIT mutation GISTs (54). However, given the fact that some centers do not have access to a more detailed mutational analysis, many will employ a maneuver, in which they treat all patients starting at 400 mg daily and then upon tumor progression, will either increase the dose or switch to second-line therapy.

Studies have shown that different GIST PDGFRA mutations confer varying degrees of imatinib sensitivity (24,55). One large series of PDGFRA-mutant GISTs showed that 63% of patients had the imatinib-resistant substitution D842V (23). Comprehensive molecular analyses, which specify the type of PDGFRA GIST mutation, are currently not routinely carried out at all hospitals, but given promising recent evidence, may play a role in the future management of GIST. Currently, there are clinical trials underway that are evaluating the safety and efficacy of new TKIs that are specifically engineered for the treatment of tumors with the PDGFRA D824V mutation (56).

Mutational testing in GIST has been performed through a variety of methods, all of which have varying degrees of sensitivity and associated cost. One method, referred to denaturing high-pressure liquid chromatography (DHPLC), was found in a recent study to be less costly and labor-intensive and with comparable sensitivity, when compared with the most commonly used technique, direct polymerase chain reaction (PCR) sequencing (57). Another study investigated the utility of microfluidic deletion/insertion analysis as an initial GIST mutation screening strategy and found that although it only detected 75% of KIT mutated cases, it was associated with a significantly lower cost than both DHPLC and PCR and showed future promise as a screening tool (58). Other techniques that have been investigated as tools for GIST mutation detection have included PCR-single strand conformation polymorphism testing and length analysis of PCR products, both of which deliver very accurate and detailed results, but are associated with a considerable cost (59).

TKI therapy

Using the results of a phase III trial, a recent study evaluated

the CE of 3-year of adjuvant imatinib versus 1-year of therapy (prior standard of care). With a total lifetime per-patient cost of $302,100 (3 years), compared to a total lifetime per-patient cost of $217,800 (1 year), the ICER was found to be $62,600/QALY, well within the commonly cited willingness to pay (WTP) thresholds for cost effective cancer therapy (60). A similar study, conducted from a European perspective, also found that 3 years of adjuvant imatinib therapy was cost-effective when compared to 1 year, with an even lower ICER of $32,619/QALY (61). Another model developed by Novartis before the drug price increase in 2012 found that that the ICER of adjuvant imatinib decreased over time: $56,251–$107,981 after 2 years, $29,844–$52745 after 5 years, and from $23,372–$37,100 after 10 years (62). Subsequently, based upon these and other studies, NICE issued an appraisal for imatinib for 3 years of adjuvant therapy (63). Researchers evaluated the budgetary impact of treatment with adjuvant imatinib for 1 year following surgical resection of KIT-mutated GIST, and found the net budgetary impact to be $0.01 per member per month in the third year after introduction, with 11.7–21.9% of the budgetary cost being offset by the reduction in costs associated with GIST recurrence (64).

Imatinib, when used in unresectable/metastatic GIST, has been shown to improve OS when compared to placebo (5.8 *vs.* 2.7 years). Using data from this phase III trial, a cost-effectiveness analysis was conducted and found that the ICER was $38,723/QALY (65). Another study conducted a cost-effectiveness analysis of second-line treatment in unresectable/metastatic GIST with high dose imatinib (800 mg PO daily), sunitinib, or BSC and found that high dose imatinib had a median cost of treatment of $35,225, whereas sunitinib and palliative care were associated with median costs of $17,805 and $2,071, respectively (66). Sunitinib, by delivering the greatest survival benefit (5.64 progression free months, 1.4 LYG), was found to be cost effective and fall below a WTP threshold of $50,000 in 38% of patients. Meanwhile, imatinib and BSC were both associated with a lower OS (5.28 *vs.* 2.58 progression free months, 1.31 and 1.08 LYG) and lower likelihood of being found to be cost effective.

A similar study from China found the ICER to be $5,664/QALY when comparing sunitinib versus intermediate dose imatinib 600 mg and $19,554/QALY, when comparing treatment with sunitinib versus BSC (67). Look-Hong *et al.* created a Markov model that evaluated the costs associated with surgery in combination with imatinib or sunitinib in seven different scenarios, which varied by type of TKI, TKI dose, and disease status. They found that the most inexpensive scenario was no surgery and the most costly was surgery in patients with progressive disease plus treatment with imatinib 800 mg. Most of the costs incurred in the seven different scenarios were attributed to the TKI drug acquisition cost (68). Based upon these studies, NICE advised against the use of imatinib at a dose of 600 or 800 mg for patients with unresectable/metastatic GISTs whose disease had progressed after treatment with imatinib at a dose of 400 mg (69). Meanwhile, they approved the use of sunitinib for the same indication (70).

A study looked at the cost-effectiveness of regorafenib compared with BSC in unresectable/metastatic GIST and found the total costs of patients treated with regorafenib to be $28,283, compared with $21,136 for BSC, with an ICER of $32,760/QALY (71). A study from Turkey found that the total costs associated with regorafenib were $7,553 compared with $558 for BSC, yielding an ICER of $5,435/QALY (72). Given the lack of published high quality data, NICE has yet to issue a statement with regard to the use of regorafenib for patients with unresectable/metastatic GIST (73).

Conclusions and future directions

Future approvals

There are several emerging precision medicine-related diagnostic approaches and treatments in GA and GIST that have the possibility of coming to the forefront. Some of these treatments include the previously mentioned HER2 targeted agent pertuzumab, which when combined with trastuzumab and docetaxel in the first-line HER2 positive mBC cancer setting, was not a cost-effective strategy when compared to trastuzumab and docetaxel alone (74). However, a criticism of this analysis was that it failed to account for the sequential (as opposed to one time) drug prescribing practice that is commonly employed in patients with metastatic disease (75). Another emerging treatment option is immune checkpoint inhibitor, pembrolizumab, which acts through the inhibition of programmed death 1 (PD1) and was recently shown in a phase II trial to have an impressive overall response rate in several solid tumors. If this agent were to be FDA approved in the future, not only would drug acquisition costs be a factor, but also its associated biomarker testing (IHC staining for programmed death ligand 1) (76). A phase II trial looking at the poly-ADP ribose polymerase (PARP) inhibitor olaparib showed encouraging activity in mGA, especially among patients with low ataxia telangiectasia (ATM) protein

expression (77). Therefore, once again not only would a future approval bring the CE of the drug into question, but also the aforementioned biomarker. In regards to unresectable/metastatic GIST, other TKI's, such as sorafenib, dasatinib, nilotinib, ponatinib, and pazopanib, have been used in early phase trials and show some promise. If they are able to demonstrate favorable phase III results in the future, all of these agents have the possibility of being FDA approved, especially if they are shown to have activity in KIT wild-type GIST, where TKIs only produce modest response rates (78-80). All of these TKIs have been shown to have significant acquisition costs and treatment related costs related to rare but serious adverse effects.

Framework of cost-effectiveness studies and their impact on healthcare policy in both the US and internationally

Over the past 10–15 years, novel treatments have emerged for cancers such as GA and GIST. While diagnostic testing and associated treatments in GA are expensive and produce only marginal benefit, those associated with GIST, despite being costly, produce significant improvements in patient outcomes. Despite the significant difference in impact, the agents associated with these cancers have similar acquisition costs. Currently, the cost-effectiveness of a drug or biomarker has no impact on its FDA approval, and once approved, public and private payers typically have to reimburse manufacturers without negotiation. In fact, the Patient Protection and Affordable Care Act of 2010 prohibited Centers for Medicare & Medicaid Services (CMS) from using cost-effectiveness as a factor in making reimbursement and coverage decisions about health care services and products (81). With the refusal to acknowledge the importance of regulation and value-based health care pricing, the US now leads all major countries in health care spending [17.5% of the US gross domestic product (GDP); $618.7 billion CMS spending in 2014], which most notably includes drug acquisition, procedure, and hospitalization costs. Given the significant spending, the strained healthcare system has created an unsustainable predicament for the US economy.

Despite its healthcare spending, the US consistently ranks near the middle of the pack among developed nations in healthcare quality and efficiency (includes measures such as life expectancy and cancer-related mortality) (82). As precision medicine in GA and GIST continues to evolve, the importance of value-based medicine has become even more paramount.

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Footnote

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. SEER Stat Fact Sheets: Stomach Cancer. Available online: http://seer.cancer.gov/statfacts/html/stomach.html. Accessed January 5th, 2016.
3. Call J, Walentas CD, Eickhoff JC, et al. Survival of gastrointestinal stromal tumor patients in the imatinib era: life raft group observational registry. BMC Cancer 2012;12:90.
4. Park YS, Hwang HS, Park HJ, et al. Comprehensive analysis of HER2 expression and gene amplification in gastric cancers using immunohistochemistry and in situ hybridization: which scoring system should we use? Hum Pathol 2012;43:413-22.
5. President Obama Announces Plans for New Precision Medicine Initiative. American Association for Cancer Research. Available online: http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Pages/CPM150210-president-obama-announces-plans-for-new-precision-medicine-initiative.aspx#.Vo7DgBUrLWI
6. Barros-Silva JD, Leitão D, Afonso L, et al. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. Br J Cancer 2009;100:487-93.
7. Takehana T, Kunitomo K, Kono K, et al. Status of c-erbB-2 in gastric adenocarcinoma: a comparative study of immunohistochemistry, fluorescence in situ hybridization and enzyme-linked immuno-sorbent assay. Int J Cancer 2002;98:833-7.
8. Liang Z, Zeng X, Gao J, et al. Analysis of EGFR, HER2, and TOP2A gene status and chromosomal polysomy in gastric adenocarcinoma from Chinese patients. BMC Cancer 2008;8:363.
9. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer

(ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
10. Kim KC, Koh YW, Chang HM, et al. Evaluation of HER2 protein expression in gastric carcinomas: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. Ann Surg Oncol 2011;18:2833-40.
11. Koopman T, Smits MM, Louwen M, et al. HER2 positivity in gastric and esophageal adenocarcinoma: clinicopathological analysis and comparison. J Cancer Res Clin Oncol 2015;141:1343-51.
12. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
13. "Pertuzumab" and "Gastric". Clinicaltrials.gov. U.S. National Institutes of Health. Available online: https://clinicaltrials.gov/ct2/results?term=pertuzumab+gastric&Search=Search
14. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.
15. Ado-trastuzumab Emtansine Fails Phase II/III Gatsby Trial. ADC Review/Journal of Antibody-drug Conjugate. Available online: http://adcreview.com/news/ado-trastuzumab-emtansine-fails-phase-iiiii-gatsby-trial
16. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-43.
17. Janjigian YY. Lapatinib in Gastric Cancer: What Is the LOGiCal Next Step? J Clin Oncol 2016;34:401-3.
18. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-9.
19. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
20. Lux ML, Rubin BP, Biase TL, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. Am J Pathol 2000;156:791-5.
21. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 2001;61:8118-21.
22. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708-10.
23. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660-7.
24. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357-64.
25. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A 2011;108:314-8.
26. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-72.
27. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620-5.
28. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-38.
29. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
30. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 2011;103:117-28.
31. Vogler S, Vitry A, Babar ZU. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. Lancet Oncol 2016;17:39-47.
32. Kantarjian H, Rajkumar SV. Why are cancer drugs so expensive in the United States, and what are the solutions? Mayo Clin Proc 2015;90:500-4.
33. Fox SB, Kumarasinghe MP, Armes JE, et al. Gastric HER2 Testing Study (GaTHER): an evaluation of gastric/gastroesophageal junction cancer testing accuracy in Australia. Am J Surg Pathol 2012;36:577-82.
34. Park T, Griggs SK, Suh DC. Cost Effectiveness of Monoclonal Antibody Therapy for Rare Diseases: A Systematic Review. BioDrugs 2015;29:259-74.
35. Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation

study. Histopathology 2008;52:797-805.
36. Who we are. National Institute for Health and Care Excellence (NICE). Available online: https://www.nice.org.uk/about/who-we-are
37. Cancer Drugs Fund. Cancer Research UK. Available online: http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/cancer-drugs
38. Cancer drugs fund cuts 23 treatments. BBC News. Available online: http://www.bbc.com/news/health-34153136
39. Rüschoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch 2010;457:299-307.
40. Spackman E, Rice S, Norman G, Suh DC, et al. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer: a NICE single technology appraisal. Pharmacoeconomics 2013;31:185-94.
41. 2016 ASP Drug Pricing Files. Available online: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2016ASPFiles.html
42. Holden J, Garrett Z, Stevens A. NICE guidance on trastuzumab for the treatment of HER2-positive metastatic gastric cancer. Lancet Oncol 2011;12:16-7.
43. Shiroiwa T, Fukuda T, Shimozuma K. Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial. Br J Cancer 2011;105:1273-8.
44. Collins IM, King F, O'Byrne K. Cost impact of trastuzumab prescribing in the treatment of advanced Her2 positive gastric cancer in Ireland. Ir J Med Sci 2012;181:451-2.
45. Carter GC, King DT, Hess LM, et al. Health state utility values associated with advanced gastric, oesophageal, or gastro-oesophageal junction adenocarcinoma: a systematic review. J Med Econ 2015;18:954-66.
46. Wadhwa R, Elimova E, Shiozaki H, et al. Anti-angiogenic agent ramucirumab: meaningful or marginal? Expert Rev Anticancer Ther 2014;14:367-79.
47. Gastric cancer (metastatic) - ramucirumab (after chemotherapy) [ID741]. National Institute for Health and Care Excellence. Available online: https://www.nice.org.uk/guidance/GID-TAG500/documents/html-content
48. Goldstein DA, El-Rayes BF. Considering Efficacy and Cost, Where Does Ramucirumab Fit in the Management of Metastatic Colorectal Cancer? Oncologist 2015;20:981-2.
49. Goldstein DA, Ahmad BB, Chen Q, et al. Cost-Effectiveness Analysis of Regorafenib for Metastatic Colorectal Cancer. J Clin Oncol 2015;33:3727-32.
50. Goldstein DA, Chen Q, Ayer T, et al. First- and Second-Line Bevacizumab in Addition to Chemotherapy for Metastatic Colorectal Cancer: A United States-Based Cost-Effectiveness Analysis. J Clin Oncol 2015;33:1112-8.
51. Casali PG, Jost L, Reichardt P, et al. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:64-7.
52. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
53. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093-103.
54. GIST. NCCN Clinical Practice Guidelines in Oncology. Available online: http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
55. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360-7.
56. Phase II Study of Crenolanib (CP-868,596), for the Treatment of Patients With Advanced Gastrointestinal Stromal Tumors With the D842-related Mutations and Deletions in the PDGFRA Gene. Available online: https://clinicaltrials.gov/ct2/show/NCT01243346?term=GIST+and+D842V+mutation&rank=1
57. Zamò A, Bertolaso A, Franceschetti I, et al. Microfluidic Deletion/Insertion Analysis for Rapid Screening of KIT and PDGFRA Mutations in CD117-Positive Gastrointestinal Stromal Tumors. J Mol Diagn 2007;9:151-7.
58. Battochio A, Mohammed S, Winthrop D, et al. Detection of c- KIT and PDGFRA Gene Mutations in Gastrointestinal Stromal Tumors. Am J Clin Pathol 2010;133:149-55.
59. Emile JF, Lemoine A, Bienfait N, et al. Length analysis of polymerase chain reaction products: a sensitive and reliable

technique for the detection of mutations in KIT exon 11 in gastrointestinal stromal tumors. Diagn Mol Pathol 2002;11:107-12.
60. Sanon M, Taylor DC, Parthan A, et al. Cost-effectiveness of 3-years of adjuvant imatinib in gastrointestinal stromal tumors (GIST) in the United States. J Med Econ 2013;16:150-9.
61. Majer IM, Gelderblom H, van den Hout WB, et al. Cost-effectiveness of 3-year vs 1-year adjuvant therapy with imatinib in patients with high risk of gastrointestinal stromal tumour recurrence in the Netherlands; a modelling study alongside the SSGXVIII/AIO trial. J Med Econ 2013;16:1106-19.
62. Wilson J, Connock M, Song F, et al. Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation. Health Technol Assess 2005;9:1-142.
63. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours. NICE technology appraisal guidance [TA326] Published date: November 2014. Available online: https://www.nice.org.uk/guidance/ta326
64. Rubin JL, Taylor DC, Sanon M, et al. Budgetary impact of treatment with adjuvant imatinib for 1 year following surgical resection of kit-positive localized gastrointestinal stromal tumors. J Manag Care Pharm 2010;16:482-91.
65. Contreras-Hernández I, Mould-Quevedo JF, Silva A, et al. A pharmaco-economic analysis of second-line treatment with imatinib or sunitinib in patients with advanced gastrointestinal stromal tumours. Br J Cancer 2008;98:1762-8.
66. Ren H, Zhang J, Dong P. Cost-Effectiveness Of Sunitinib As Second-Line Treatment For Gastrointestinal Stromal Tumor (GIST) In China. Value Health 2015;18:A455.
67. Look Hong NJ, Chang SL, Raut CP. The economic impact of cytoreductive surgery and tyrosine kinase inhibitor therapy in the treatment of advanced gastrointestinal stromal tumours: a Markov chain decision analysis. Eur J Cancer 2014;50:397-405.
68. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. NICE technology appraisal guidance [TA209] Published date: November 2010. Available online: https://www.nice.org.uk/guidance/ta209
69. Sunitinib for the treatment of gastrointestinal stromal tumours. NICE technology appraisal guidance [TA179] Published date: September 2009. Available online: https://www.nice.org.uk/guidance/ta179
70. Sanz-Granda Á, Hidalgo-Figueruela F, Granell M. Estimation of the treshold price of regorafenib in the treatment of unresectable and/or metastatic gastrointestinal stromal tumors after failure on imatinib and sunitinib in Spain: cost-utility analysis. Value Health 2015;18:A464.
71. Deger C, Telli F, Gunaldi M, et al. The cost-effectiveness of regorafenib in the treatment of metastatic/inoperable gastrointestinal stromal tumors in Turkey. Value Health 2015;18:A455.
72. Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal). NICE technology appraisal guidance [TA334] Published date: February 2015. Available online: https://www.nice.org.uk/guidance/ta334
73. Muro K, Bang YJ, Shankaran V, et al. Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab in KEYNOTE-012. J Clin Oncol 2015;33:abstr 3.
74. Bang YJ, Im SA, Lee KW, et al. Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer. J Clin Oncol 2015;33:3858-65.
75. Trent JC, et al. A phase II study of dasatanib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). J Clin Oncol 2011;29:abstr 10006.
76. Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377-83.
77. Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer 2011;117:4633-41.
78. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236-40.
79. Garber AM, Sox HC. The role of costs in comparative effectiveness research. Health Aff (Millwood) 2010;29:1805-11.
80. Durkee BY, Qian Y, Pollom EL, et al. Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin

Oncol 2016;34:902-9.
81. Diaby V, Adunlin G, Ali A, et al. Cost-effectiveness of treatment sequencing of Pertuzumab followed by T-DM1 in metastatic HER2-positive breast cancer. JAMA 2016. In Press.
82. National expenditure data. Centers for Medicare & Medicaid Services. Available online: https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html

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Effectiveness of radiation therapy in GIST: A case report

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Introduction

Over the last decade, gastrointestinal stromal tumor (GIST) became the most commonly diagnosed mesenchymal tumor of the gastrointestinal tract (1,2). Population-based studies suggest an annual incidence of between 11 and 14.5 per million and a prevalence of 129 per million (3). The immunohistochemistry of GIST shows the presence of cell-surface antigen CD117 (KIT), which represents a defining characteristic of GIST (4-7). Immunostaining is essential to differentiate GISTs from other more rare mesenchymal tumors. Differential diagnosis includes leiomyosarcomas, leiomyomas and schwannomas (3). It is believed that GISTs arise from a neoplastic transformation of the intestinal pacemaker cells known as the interstitial cells of Cajal (ICC) (6,8).

Prior to 2002, the only available therapeutic option for patients with localized GISTs was surgical resection (9). Unfortunately, even when excised in negative surgical margins, the recurrence rate for lesions larger than 3 cm was found to be significant. Introduction of the first tyrosine kinase inhibitor, imatinib mesylate, has dramatically changed the management options available for GIST patients (10). The role of radiation therapy in the treatment of GISTs has not been documented (11). In the past, clinicians were reluctant to use radiation therapy due to concerns over the dose received by normal tissues, mostly the potential gastrointestinal toxicity. As such, radiation therapy has been utilized rarely, mostly for palliation purposes (12).

In this report, we describe the successful use of intensity modulated radiation therapy to treat an individual with large intra-abdominal GIST lesions (*Figure 1*), which were deemed unresectable. An initial attempt at systemic treatment with imatinib was not tolerated by the patient and did not produce a significant response.

Case presentation

A 62 year-old African American male presented with complaints of lower abdominal pain for 3 months. He also had complaints of constipation, urinary frequency and weight loss for the same duration. Medical history was positive for hypertension and gallstones. His sister had an unknown malignancy. On physical examination, there was an ill-defined mass in the right lower abdomen. There was no lymphadenopathy or lower extremity edema. The rest of the physical examination was unremarkable. CT scan showed two huge, largely homogenous masses. The superior lesion measured 10.2 cm × 13.3 cm × 12.3 cm, located in the right upper quadrant, and the inferior mass was slightly larger, measuring 14.8 cm × 11.5 cm× 12.3 cm, and was located in the retroperitoneum (*Figure 1*). Biopsy was performed. Histopathological examination revealed a gastrointestinal stromal tumor, epithelioid type, with high risk features (*Figure 2*). Patient was started on systemic therapy with imatinib mesylate (400 mg, po, qd) but developed fluid retention, protracted nausea and lower extremity edema on imatinib. Despite dose adjustments and drug holidays the imatinib was not tolerated, requiring discontinuation. Patient was referred for radiation therapy. Radiation therapy was administered conformally using initially a pair of left anterior oblique (LAO)/right posterior oblique (RPO) field arrangement to 43.2 Gy in 27 fractions, followed by a cone-down setup with an IMRT technique to a total of 63.4 Gy. Despite of the high dose, the radiation therapy was well tolerated and relieved the patient's symptoms with a dramatic reduction

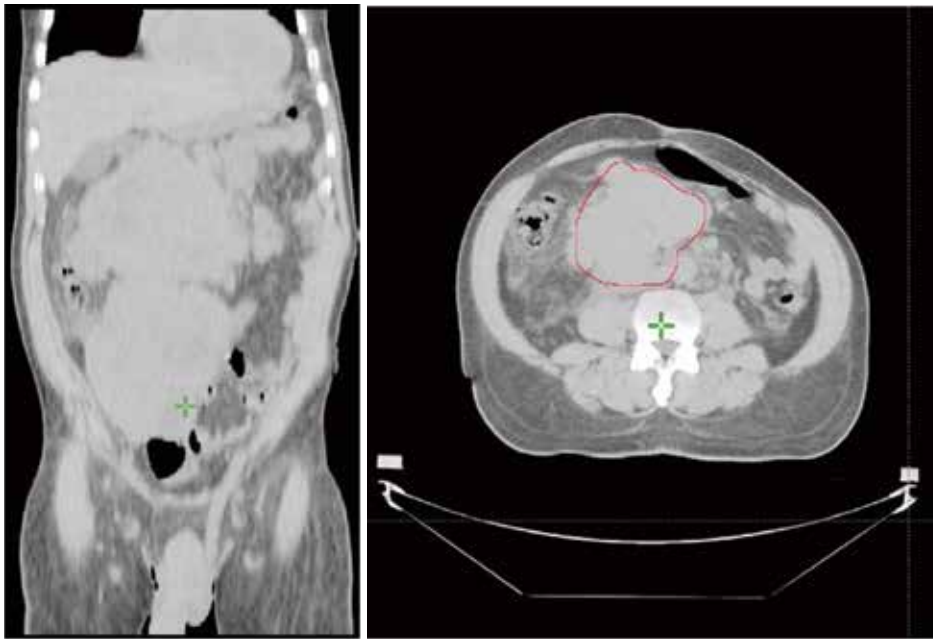

Figure 1 CT images of solid homogenous mass before radiation therapy (8/2/2010).

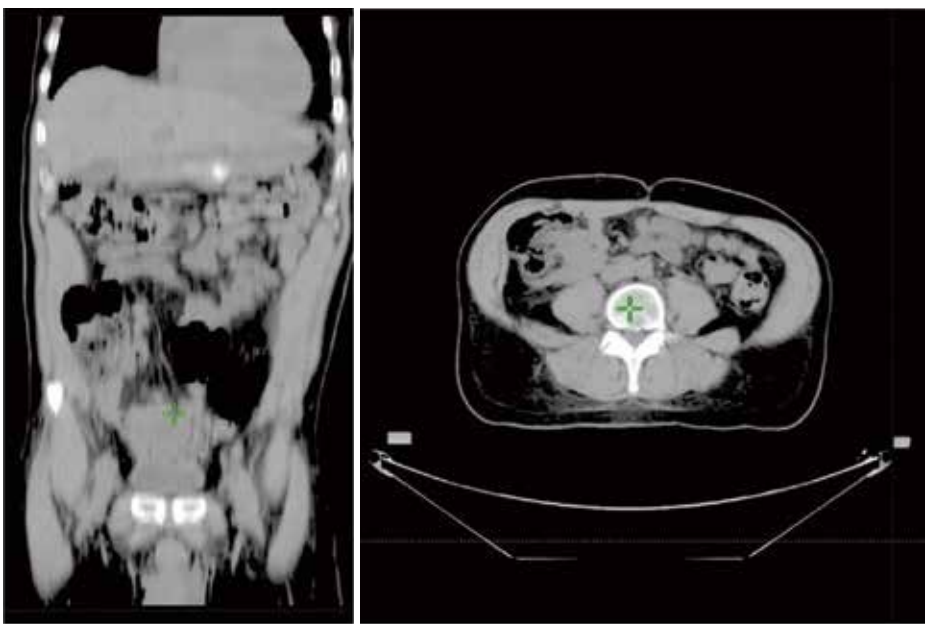

Figure 2 CT scan post radiation therapy (11/1/2010) showing a dramatically reduced solid mass with necrosis after treatment with 63.4 Gy.

in tumor size demonstrated by CT scan (*Figure 1,2*).

Discussion

Gastrointestinal stromal tumors (GIST) account for less than 1% of all gastrointestinal (GI) tumors (13,14). In 1983, Mazur and Clark introduced the term GIST to describe a distinctive subgroup of GI mesenchymal tumor, which had neither neurogenic nor smooth muscle origin (15,16). It is believed that GISTs arise from a neoplastic transformation of the intestinal pacemaker cells known as the interstitial cells of Cajal (ICC) (8).

There is no strong predilection for either sex and these tumors can occur across a wide range of age groups (17). However, men are slightly more affected than women, and 75% of those diagnosed are over the age of 75 (18,19). So far, no link to environmental exposure, or relation with geographic location, ethnicity, or occupation has been established with incidence of GIST (20).

Morphologically, GISTs can appear as epithelioid, spindle cell, or a mixture of the two (21,22). The major histologic marker CD117, an epitope for the extracellular domain of KIT transmembrane receptor tyrosine kinase, stains positively in 95% of GISTs with a characteristic dot-like cytoplasmic pattern (23). Other important histological markers include CD34 (60-70%), ACAT (30-40%), DES (1-2%) and keratin (1-2%) (24).

GISTs show a diverse clinical presentation, with the most common symptoms being the presence of a mass or bleeding (1). The distribution of primary GISTs also varies throughout the gastrointestinal tract, with approximately 60-65% arising in the stomach, 20-25% in the small intestine, 5-10% in the colon or rectum and 5% in the esophagus (8,19).

The current treatment of choice for localized disease is surgical removal of the tumor with careful attention not to rupture the pseudocapsule. Unfortunately, less then 50% of patients have localized disease at diagnosis (18), and even when a curative resection is performed with clear margins the recurrence rate is approximately 50% (25). This recurrence rate can reach as high as 90% for large tumors with high mitotic rates.

In cases where the disease is extensive or the patient is not a surgical candidate, the choice of therapy is molecularly targeted chemotherapy with imatinib. Prior to the use of imatinib, chemotherapy results were dismal with reported success rates of 0-5% (18). The introduction of imatinib as a chemotherapeutic agent has greatly improved the treatment for non surgical candidates, with initial success rates of 70-90% (26). However, patients that do show an initial response are not cured and must stay on the drug indefinitely to prevent relapse (27). Furthermore, most patients eventually relapse and die of the disease (28,29).

Sunitinib malate, an oral agent inhibiting-multiple-tyrosine-kinases including KIT, PDGRF as well as vascular endothelial growth factor receptor is recommended as second line of treatment for patients who experience disease progression while on imatinib treatment or who have life-threatening side effects. Although 20% of patients treated with Sunitinib have been stable for 2 or more years, age above 60 years, poor performance status, pretreatment with higher doses of imatinib and primary resistance to imatinib are predictors for poor response to treatment. Additionally, thrombocytopenia and hand-foot syndrome, frequently leads to poor tolerability (30).

The role of radiation therapy in the treatment of GISTs has not been documented and, in our opinion, it may be underutilized clinically. As stated previously, concerns over the potential side effects have led to a limited role of radiation therapy, mainly for palliative purposes, or in cases of intraperitoneal hemorrhage (1). It has been suggested that radiation may also sensitize GIST tumors to imatinib, although this has not been definitively established (31). The current radiation therapy techniques facilitate the administration of very high and effective doses to the target areas, while protecting efficiently surrounding vital structures. These new radiation technologies have not been explored in GIST tumors and deserve more study.

Conclusions

The enthusiasm for the targeted therapies in GIST tumors marginalized the use of the more conventional radiation therapy for GIST tumors. In our case, the judicious use of modern techniques of radiation produced an impressive response in a case of large intra-abdominal GIST masses, while being very well tolerated. It is too early to determine the length of response in this patient, yet similar techniques of radiation may prove even more efficient in earlier cases. We recommend, therefore, using radiation therapy more often not only for palliation purposes, but also for definitive treatment, with or without imatinib or sunitinib.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Stamatakos M, Douzinas E, Stefanaki C, Safioleas P, Polyzou E, Levidou G, et al. Gastrointestinal stromal tumor. World J Surg Oncol 2009;7:61.
2. Perez EA, Livingstone AS, Franceschi D, Rocha-Lima C, Lee DJ, Hodgson N, et al. Current incidence and outcomes of gastrointestinal mesenchymal tumors including gastrointestinal stromal tumors. J Am Coll Surg 2006;202:623-9.
3. Joensuu H, Kindblom LG. Gastrointestinal stromal tumors--a review. Acta Orthop Scand Suppl 2004;75:62-71.
4. Badalamenti G, Rodolico V, Fulfaro F, Cascio S, Cipolla C, Cicero G, et al. Gastrointestinal stromal tumors (GISTs): focus on histopathological diagnosis and biomolecular features. Ann Oncol 2007;18 Suppl 6:vi136-40.
5. Aubin F, Blanke CD. Metastatic gastrointestinal stromal tumors. Cancer Chemother Pharmacol 2011;67 Suppl 1:S9-14.
6. Byrd D, Blancke C. Gastrointestinal stromal tumors. Liver metastases 2009;137-8.
7. Gajiwala KS, Wu JC, Christensen J, Deshmukh GD, Diehl W, DiNitto JP, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci U S A 2009;106:1542-7.
8. Papaetis GS, Syrigos KN. Targeted therapy for gastrointestinal stromal tumors: current status and future perspectives. Cancer Metastasis Rev 2010;29:151-70.
9. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol 2004;11:465-75.
10. Pisters PW, Patel SR. Gastrointestinal stromal tumors: current management. J Surg Oncol 2010;102:530-8.
11. Pollock J, Morgan D, Denobile J, Williams J. Adjuvant radiotherapy for gastrointestinal stromal tumor of the rectum. Dig Dis Sci 2001;46:268-72.
12. Siehl J, Thiel E. C-kit, GIST, and imatinib. Recent Results Cancer Res 2007;176:145-51.
13. Howe JR, Karnell LH, Scott-Conner C. Small bowel sarcoma: analysis of survival from the National Cancer Data Base. Ann Surg Oncol 2001;8:496-508.
14. van der Zwan SM, DeMatteo RP. Gastrointestinal stromal tumor: 5 years later. Cancer 2005;104:1781-8.
15. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 1983;7:507-19.
16. Gupta P, Tewari M, Shukla HS. Gastrointestinal stromal tumor. Surg Oncol 2008;17:129-38.
17. Arolfo S, Teggia PM, Nano M. Gastrointestinal stromal tumors: thirty years experience of an institution. World J Gastroenterol 2011;17:1836-9.
18. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51-8.
19. Duffaud F, Salas S, Huyn T, Deville JL. Imatinib as the first and only treatment in Europe for adult patients at significant risk of relapse following gastrointestinal stromal tumor removal. Clinical and Experimental Gastroenterology 2010;3:41-7.
20. Joensuu H. Gastrointestinal stromal tumor (GIST). Ann Oncol 2006;17 Suppl 10:x280-6.
21. Papalambros A, Petrou A, Brennan N, Bramis K, Felekouras E, Papalambros E. GIST suture-line recurrence at a gastrojejunal anastomosis 8 years after gastrectomy: can GIST ever be described as truly benign? A case report. World J Surg Oncol 2010;8:90.
22. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006;30:477-89.
23. Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, Riddell RH. Interstitial cells of Cajal as precursors of gastrointestinal stromal tumors. Am J Surg Pathol 1999;23:377-89.
24. Urbańczyk K, Limon J, Korobowicz E, Chosia M, Sygut J, Karcz D, et al. Gastrointestinal stromal tumors. A multicenter experience. Pol J Pathol 2005;56:51-61.
25. Pierie JP, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ, et al. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. Arch Surg 2001;136:383-9.
26. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
27. Blay JY, Le Cesne A, Ray-Coquard I, Bui B, Duffaud F, Delbaldo C, et al. Prospective Multicentric Randomized Phase III Study of Imatinib in Patients With Advanced Gastrointestinal Stromal Tumors Comparing Interruption

Versus Continuation of Treatment Beyond 1 Year: The French Sarcoma Group. J Clin Onc 2007;25:1107-13.
28. Blay JY, Adenis A, Ray-Coquard I, Cassier PA, Le Cesne A. Is there a role for discontinuing imatinib in patients with advanced gastrointestinal stromal tumour? Curr Opin Oncol 2009;21:360-6.
29. Nannini M, Biasco G, Pallotti MC, Di Battista M, Santini D, Paterini P, et al. Late recurrences of gastrointestinal stromal tumours (GISTs) after 5 years of follow-up. Med Oncol 2012;29:144-50.
30. Nishida T, Omori T, Ueshima S. Evidence-based treatment of gastrointestinal stromal tumor (GIST) with tyrosine kinase inhibitors-imatinib and sunitinib. Gan To Kagaku Ryoho 2011;38:733-7.
31. Ciresa M, D'Angelillo RM, Ramella S, Cellini F, Gaudino D, Stimato G, et al. Molecularly targeted therapy and radiotherapy in the management of localized gastrointestinal stromal tumor (GIST) of the rectum: a case report. Tumori 2009;95:236-9.

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Gastrointestinal stromal tumor with an unusual presentation as an enlarged prostate gland: a case report and review of the literature

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Abstract: We report a case of a 78-year-old male who presented with urinary retention, constipation and an enlarged prostate gland. A transurethral resection of the prostate (TURP) was performed. Pathologic examination revealed a hypercellular-spindled neoplasm with frequent mitoses, nuclear pleomorphism, and multifocal geographic tumoral necrosis. A pathologic diagnosis of gastrointestinal stromal tumor (GIST) was made based on morphologic and immunohistochemical findings, and was later reinforced by molecular study results. This lesion was initially thought to represent a primary prostatic GIST. To the best of our knowledge, there have been only five cases of primary prostatic GISTs. Subsequent imaging studies revealed the mass to be contiguous with the anterior rectal wall, suggesting the possibility of a rectal primary with extension to the prostate gland. The patient was treated with imatinib mesylate, and after twelve months of follow up failed to demonstrate any evidence of progression or metastatic disease. GIST should be considered in cases of prostatic tumors with a spindled or epithelioid morphology, and immunohistochemistry and possible molecular studies are recommended to aid in diagnosis and guide treatment decisions.

Keywords: Gastrointestinal stromal tumor (GIST); prostate; transurethral resection of prostate; transurethral resection of the prostate (TURP)

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Introduction

Primary prostatic gastrointestinal stromal tumor (GIST) is an extremely rare entity that may present with non-specific urinary symptoms (1,2). To the best of our knowledge, there have been only five reported cases of primary prostatic GISTs (1-5). While the vast majority of GISTs occur within the gastrointestinal tract [the stomach is the most frequent site (6)], tumors arising from other locations have been rarely reported, including the retroperitoneum, mesentery, and omentum (5). Rectal GISTs can occur (3rd most frequent site) and secondarily involve the prostate gland; this phenomenon should be excluded before considering a primary prostatic GIST (7).

Case presentation

A 78-year-old male presented with a history of urinary bladder outflow obstruction symptoms. An ultrasound study demonstrated a markedly enlarged prostate gland, estimated to be ~300 grams [expected ~11 grams (8)]. Non-surgical treatments were attempted to reduce the urinary bladder outflow obstructive symptoms, including microwave treatment and medications (finasteride and doxazosin), without significant improvement. Prostate specific antigen levels were within normal range. Rectal examination revealed a large, non-tender prostate pushing against the anterior rectal wall; no discrete nodules were identified. Despite therapy, he continued to experience

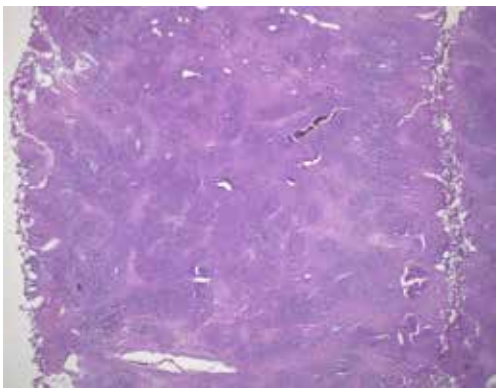

Figure 1 Low-power view shows a mottled appearance with areas of hypercellularity and hypocellularity (H&E, 20×).

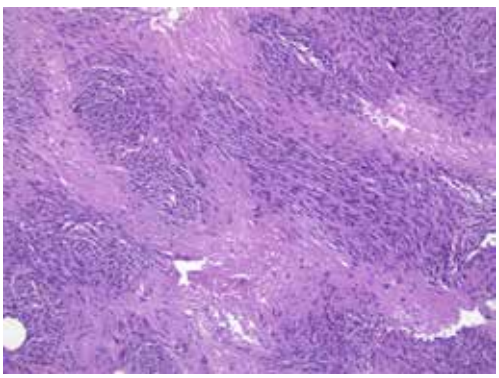

Figure 2 Areas of geographic coagulative tumoral necrosis were present (H&E, 100×).

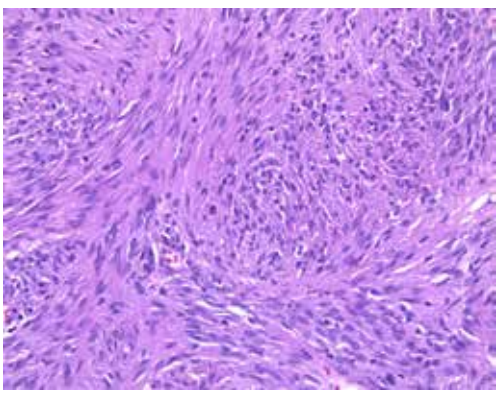

Figure 3 High-power view showing spindled morphology (H&E, 200×).

increased urinary frequency, urinary retention, nocturia, and constipation. Given these findings, a transurethral resection of the prostate (TURP) gland was performed. The procedure was uneventful, and no suspicious findings were encountered at time of surgery. The preoperative and postoperative diagnoses were presumed to be benign prostatic hyperplasia with urinary retention.

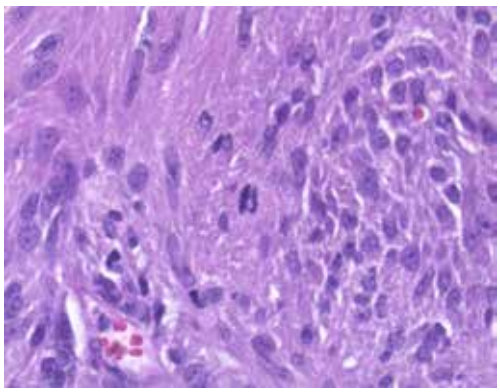

Figure 4 Mitotic figures were easily identified, some atypical. Cytologic atypia was prominent, with prominent nuclear pleomorphism, course granular chromatin, and prominent nucleoli (H&E, 600×).

Pathologic examination of the submitted material demonstrated a 36-gram aggregate of gray-pink firm tissue fragments admixed with clotted blood, measuring 11 cm × 8 cm × 2 cm in aggregate. No discrete lesions were noted. Histologic examination of the hematoxylin and eosin stained sections revealed that many of the tissue fragments comprised an abnormal hypercellular proliferation, with areas of hypocellularity imparting a mottled low-power appearance (*Figure 1*). There were geographic areas of coagulative tumoral necrosis present (*Figure 2*). High-power examined demonstrated tumor cells with elongate, spindled morphology (*Figure 3*), with atypical nuclear features including pleomorphism, course granular chromatin, and prominent nucleoli (*Figure 4*). Mitotic figures were frequently encountered (up to 5 mitoses per 10 high power fields), and atypical mitotic figures were noted (*Figure 4*). By immunohistochemistry, the neoplastic cells were strongly and diffusely positive for CD117 (*Figure 5*), vimentin, and CD34. Immunohistochemical stains for smooth muscle actin, desmin, S-100, and cytokeratin cocktail were negative. Given the morphologic and immunohistochemical findings, a pathologic diagnosis of GIST was rendered. The case was sent out for expert consultation; the consulting pathologist agreed with the diagnosis of GIST. Molecular testing for exons 9 and 11 were performed, revealing a KIT exon 11 mutation. There were scattered benign prostatic glandular elements present, some showing associated calcification. No significant atypia was seen in the native prostatic glandular epithelium.

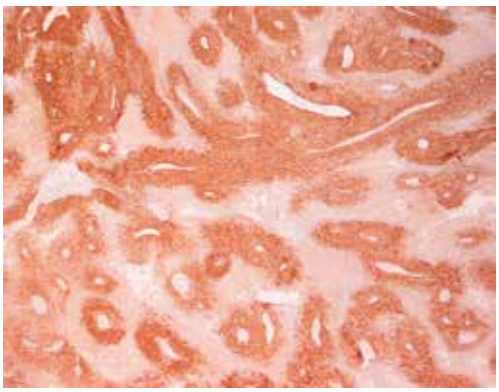

Figure 5 The tumor cells stain diffusely and strongly for CD117 antigen (40×).

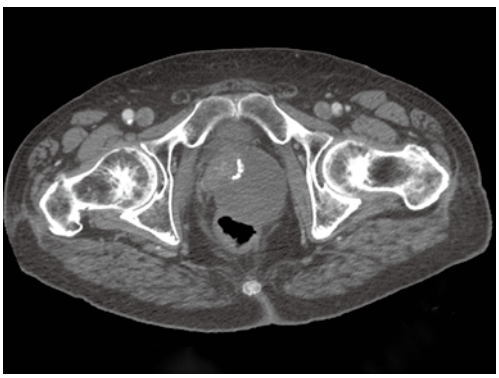

Figure 6 Pelvic CT scan performed following the TURP shows a large mass involving the prostate gland, adherent to the anterior rectal wall. CT, computed tomography; TURP, transurethral resection of the prostate.

In light of the pathologic findings, computed tomography (CT) scans of the pelvis and abdomen were obtained approximately one month after the surgery. The scan demonstrated a mass in the region of the prostate measuring 10 cm × 9.6 cm. This mass was noted to be contiguous with the anterior rectal wall (*Figure 6*). There was no regional lymphadenopathy or hepatic lesions identified on the imaging studies. The patient was started on therapy with imatinib mesylate 400 mg once daily, with the possibility of a surgical resection at a later date. Given the patient's age and potential morbidity, the patient chose not to pursue further surgical treatment. Subsequent imaging studies revealed that the directed therapy with imatinib mesylate had resulted in a significant reduction in the size of the tumor. At twelve months follow-up, there was no evidence of tumor progression or metastatic disease.

Discussion

GISTs are the most frequently encountered primary mesenchymal tumor in the gastrointestinal tract. However, they only account for a small percentage (<2%) of the total gastrointestinal malignancies in the adult population (6). Extra-EGISTs are an exceedingly rare occurrence, accounting for only 5-10% of GISTs (1,3).

Pathologic features that would favor a diagnosis of GIST include cells with spindled and/or epithelioid morphology, perinuclear cytoplasmic vacuolization, and positive immunostaining for CD117, DOG1 and CD34 (5,6). These tumors often show mutations of the KIT or platelet derived growth factor receptor alpha (PDGFRA) genes (9). In addition, BRAF mutations have been reported to occur (9,10). DOG1 immunohistochemical studies may be especially useful, as expression does not appear to be affected by the KIT or PDGFR gene mutation type, and it may be positive in KIT-negative GISTs (9,11).

The pathologic differential diagnosis of spindled neoplasms in the prostate includes schwannoma, melanoma, smooth muscle tumors, solitary fibrous tumor, and prostatic stromal sarcoma. The distinction between GIST and schwannoma can be difficult, as occasional GISTs may show areas suggestive of Verocay bodies. Diffusely and strong immunostaining for S-100 would be typical for schwannoma, while CD117 and smooth muscle markers would be negative. Cytoplasmic clearing and epithelioid cells are typically lacking in schwannoma. While some melanomas may have CD117 positivity, these tumors are DOG1 and CD34 negative, and should stain positively for melanoma tumor markers S100, MART-1, HMB45, and SOX10. Leiomyoma and leiomyosarcoma typically are positive for smooth muscle actin and desmin, and negative for CD117 and CD34. Solitary fibrous tumors are usually CD34 positive, but they should also be BCL-2 positive and CD117 negative. Prostatic stromal sarcoma may be positive for CD34 and progesterone receptor, but has been negative for CD117 in the three reported cases that analyzed this immunostain (5,12,13). A single case has recently been reported implying that prostatic stromal sarcoma may stain positively for DOG1 (12). This suggests that DOG1 positivity should be assessed in combination with other morphologic, immunohistochemical, and molecular studies to achieve the most accurate diagnosis.

In the limited number of primary prostatic GIST described in the literature, the affected patients ranged in age from 31-75 years (mean 51.8 years) (1,2). Other than a single case with liver metastasis, none of the other cases

had metastatic disease (1-3). The PSA levels in the cases described have been within normal range (1,2).

Pathologic features used to predict the prognosis of GISTs are tumor size, mitotic rate and location (11). Distinction between GIST and the other entities within the pathologic differential diagnosis is essential, as specific treatment with tyrosine kinase inhibitors is standard of care (5). GISTs and EGISTs do not appear to be successfully treated by typical radiotherapy or chemotherapy, and lymph node metastases are unusual (2,4). Metastatic GISTs may occur in the liver and anyplace in the abdominal cavity, but also on the odd occasion in the lungs or remote peripheral sites (11).

Before diagnosing a primary prostatic GIST, the possibility of a rectal GIST invading and secondarily involving the prostate should be considered (2). Rectal GISTs account for approximately 4% of GISTs, and may be seen as minute intramural nodules ranging to complex pelvic masses with pelvic extension (6,11). They may be connected to the prostate, and may mimic a prostate tumor clinically and on imaging studies (11). GISTs diagnosed at the time of pathologic examination of prostatic specimens appear to more commonly be of rectal than of prostatic origin, and it is somewhat controversial whether primary prostatic GIST is a true entity (7).

In summary, we have described a case of a GIST involving primarily the prostate gland of a 78-year-old man with urinary retention and constipation, discovered at the time of transurethral prostatic resection. The immunoprofile, morphology, and molecular findings are most consistent with a GIST. This lesion was initially thought to represent a primary prostatic GIST, as rectal involvement was not apparent based on initial ultrasound. However, subsequent imaging studies revealed the mass to be contiguous with the anterior rectal wall, suggesting the possibility of a rectal primary with extension to the prostate. GIST should be considered in cases of prostatic tumors with a spindled and/or epithelioid morphology, and immunohistochemistry and possible molecular studies are recommended to aid in diagnosis and guide treatment decisions.

Acknowledgements

Randy Sosolik, MD was involved in original diagnosis of this case.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Zhang ZH, Feng GW, Liu ZF, et al. A young man with primary prostatic extra-gastrointestinal stromal tumor: a rare case report and review of the literature. Int J Clin Exp Pathol 2014;7:1764-70.
2. Liu S, Yu Q, Han W, et al. Primary gastrointestinal stromal tumor of the prostate: A case report and literature review. Oncol Lett 2014;7:1925-9.
3. Van der Aa F, Sciot R, Blyweert W, et al. Gastrointestinal stromal tumor of the prostate. Urology 2005;65:388.
4. Yinghao S, Bo Y, Xiaofeng G. Extragastrointestinal stromal tumor possibly originating from the prostate. Int J Urol 2007;14:869-71.
5. Lee CH, Lin YH, Lin HY, et al. Gastrointestinal stromal tumor of the prostate: a case report and literature review. Hum Pathol 2006;37:1361-5.
6. Macías-García L, De la Hoz-Herazo H, Robles-Frías A, et al. Collision tumour involving a rectal gastrointestinal stromal tumour with invasion of the prostate and a prostatic adenocarcinoma. Diagn Pathol 2012;7:150.
7. Anagnostou E, Miliaras D, Panagiotakopoulos V. Diagnosis of gastrointestinal stromal tumor (GIST) on transurethral resection of the prostate: a case report and review of the literature. Int J Surg Pathol 2011;19:632-6.
8. Leissner KH, Tisell LE. The weight of the dorsal, lateral and medial prostatic lobes in man. Scand J Urol Nephrol 1979;13:223-7.
9. Hemminger J, Iwenofu OH. Discovered on gastrointestinal stromal tumours 1 (DOG1) expression in non-gastrointestinal stromal tumour (GIST) neoplasms. Histopathology 2012;61:170-7.
10. Hostein I, Faur N, Primois C, et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol 2010;133:141-8.
11. Miettinen M, Lasota J. Histopathology of gastrointestinal stromal tumor. J Surg Oncol 2011;104:865-73.
12. Tang YL, Wong CF, Yap WM, et al. Discovered on gastrointestinal stromal tumours 1 (DOG1) expression in non-gastrointestinal stromal tumour (non-GIST) neoplasms. Histopathology 2014;65:724-6.
13. Zamparese R, Corini F, Braccischi A, et al. Primary sarcoma of the specialised prostatic stroma: a case report and review of the literature. Case Rep Pathol 2011;2011:252805.

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Unusual metastases of gastrointestinal stromal tumor and genotypic correlates: Case report and review of the literature

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Introduction

Gastrointestinal stromal tumors (GISTs) are defined as mesenchymal tumors of the gastrointestinal tract and are characterized by positive CD117 staining, and in most cases positive CD34 staining, with compatible gross features and microscopic findings of a highly cellular mesenchymal tumor of the gastrointestinal tract composed of spindle cells, epithelioid cells or a combination of both (1). They are usually derived from a mutation of the KIT (CD117) or PDGFRA (platelet derived growth factor receptor alpha) gene. Disting uishing GIST from other mesenchymal derived tumors was historically a challenge, since both can arise from the interstitial cells of Cajal, or GI pacemaker cells that form the interface bet ween the autonomic innervation and smooth muscle of the bowel wall (2). The distinction of GISTs based on molecular etiology was described by Hirota et al in 1998, with discovery of a mutation in c-KIT encoding a pro-oncogenic receptor tyrosine kinase (KIT) (3).

It is estimated that 4500 to 6000 new cases of GIST are diagnosed in the United States annually and most occur in the stomach (50%-70%) or small intestine (20%-30%) (4). GISTs are often asymptomatic and discovered incidentally during surgery, endoscopic procedures, or imaging studies. However, the clinical presentation of some GISTs may include overt GI bleeding, abdominal mass, abdominal pain, or bowel obstruction and acute abdomen (2). The most common metastatic sites of gastrointestinal stromal tumors are the liver (65%) and peritoneum (21%); GISTs rarely metastasize to lymph nodes (6%), bone (6%), lung (2%) (2,5), and soft tissue (less than 1%) (6,7). We report the case of a female diagnosed with GIST with subsequent metastases to the liver, peritoneum, lung, bone, and soft tissue.

Case presentation

A 57 year - old Caucasian female, with history of hy per tension and diabetes mellitus, presented to an emergenc y depa r t ment (ED) i n March 2003, with complaints of acute onset of abdominal pain and three month history of fatigue. Her evaluation revealed anemia w it h hemog lobi n of 6.8 gm/d L, a nd a small bowel obstruction by CT imaging of the abdomen/pelvis (*Figure 1*). She underwent a small bowel mass resection. Pathology confirmed a gastrointestinal stromal tumor with a 9 cm primary tumor in the jejunum. Immunohistochemistry revealed spindle cells positive for CD117 (*Figure 2*) and CD34, negative for S-100 protein, cytokeratin, and smooth muscle myosin. Mitotic activity was low (<5/50 per HPF).

The patient was clinically stable and followed by serial imaging until May 2004, when she complained of right upper quadrant abdominal pain and a CT scan of the abdomen revealed liver metastases. The patient began treatment with oral imatinib mesylate (Gleevac) at a dose of 400 mg/day, and a partial response was achieved for two years. The patient then experienced recurrence of right upper quadrant pain and a CT scan demonstrated increase in the size of liver metastases and a new pleural effusion. Subsequent treatment was initiated with oral sunitinib malate at a dose of 50 mg/day, on a schedule of 28 days on and 14 days off. The patient experienced significant side

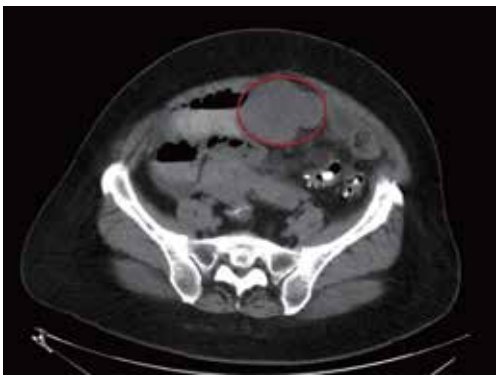

Figure 1 Gastrointestinal stromal tumor of the jejunum with associated small bowel obstruction (red oval marks approxi-mate tumor boundary).

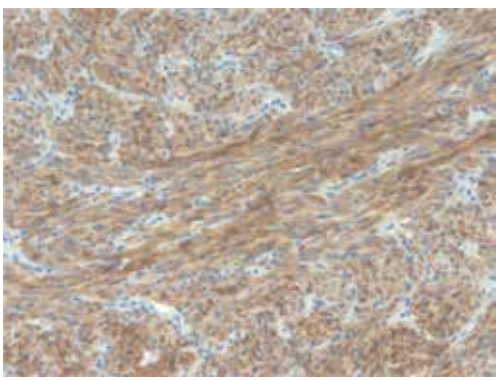

Figure 2 Gastrointestinal stromal tumor: Low-power view of immunohistochemistry showing spindle cells diffusely posi-tive for CD117.

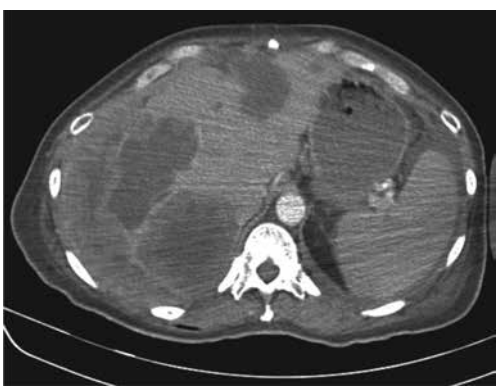

Figure 3 Imaging of the abdomen by CT showing multiple large liver metastases.

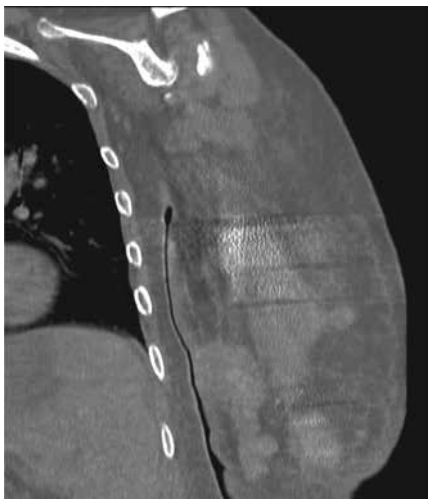

Figure 4 CT imaging of left humerus in the coronal plane showing multiple metastatic soft tissue nodules.

effects including fatigue, severe mouth soreness, decreased appetite, and hand-foot syndrome, necessitating dose reduction to oral sunitinib malate at a dose of 37.5 mg/day after three cycles on the initial dosage. Stable disease was achieved for approximately twelve months while on oral sunitinib.

In April 2007, she had progression of disease in the form of a patholog ica l f racture of the lef t humer us. Biopsy of the left humerus revealed a spindle cell sarcoma morphologically consistent with GIST metastasis, however immunohistochemical stains were negative for CD117 (c-KIT), CD34, and bcl-2. Sunitinib was discontinued pre-operatively, and the patient underwent reconstruction of the left distal humerus. A CT of the abdomen and pelvis in May 2007 showed dramatic progression of liver metastases (*Figure 3*). Given the progression of disease while being off sunitinib and in the absence of other standard of care treatment, she was restarted on oral sunitinib malate at a dose of 37.5 mg/day, on a schedule of 28 days on and 14 days off. In August 2007, she developed hard nodules in the subcutaneous area of the left upper extremity, concerning for tumor recurrence. CT scan of the left humerus revealed multiple soft tissue nodules scattered throughout the humerus (*Figure 4*). She continued sunitinib as systemic therapy and began local radiation therapy of the left humerus for palliation.

In October 2007, the patient was hospitalized for dyspnea, ascites, and lower extremity edema. Imaging showed further metastases to the peritoneum and lungs

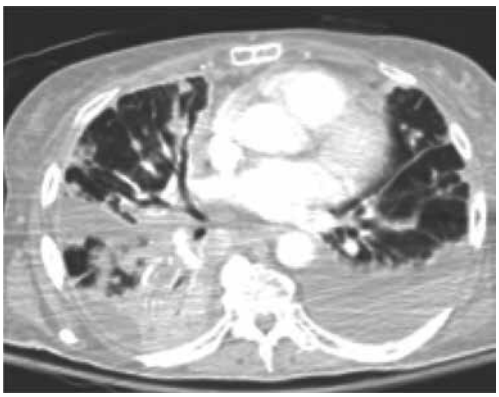

Figure 5 Chest CT image demonstrating multiple pulmonary nodules, compressive atelectasis and associated bilateral pleural effusions.

and bilateral pleural effusions (*Figure 5*). Despite two thoracenteses and pleurodesis, she had progressive symptoms and worsening lung nodules. Her respiratory failure was rapidly progressive and she died in October 2007, approximately 55 months after her initial diagnosis.

Due to unusual sites of metastases, a limited autopsy of the liver, lung and left arm tissue was performed after written consent from her power of attorney. The lung and liver metastatic lesions were morphologically consistent with GIST, and immunohistochemical stains were positive for CD117 (c-KIT). Tumor cells from the left arm subcutaneous nodule were morphologically suggestive of GIST but negative for CD117 by immunohistochemical staining. Molecular analysis demonstrated an in-frame deletion of 74 450 -74 455 (6bp), or del559V-560V (or codons 559/560) in exon 11 of the KIT gene in sequences from metastases of the right lung, left lung, liver, and left arm subcutaneous nodule. No mutation in exon 18 of the PDGFRA gene was identified in these metastases.

Review of the literature

Outside of a retrospective analysis conducted by Schuler *et al* (5), which reported that seventeen out of 307 patients with GIST had bone metastases, there are only a few reported cases in the literature of patients with GIST metastases to the bone, lung, or both (*Table 1*). Kaku *et al* (8) described a case of a 68 year-old woman with intracranial metastasis occurring two years after surgical esection of a GIST tumor of the sacrum. She subsequently developed metastatic tumor involving the lumbar spine and ureter. The intracranial metastasis was resected by right parietal craniotomy and was c-K IT positive by immunohistochemistr y. Biopsy or surger y was not performed on the lumbar spine and ureter lesions. A 37 year-old man with primary GIST of the liver metastatic to the lung is described by DeChiara *et al* (9). The primary tumor was initially diagnosed as a high grade sarcoma, but after further immunohistochemical study, the liver tumor cells stained positively for c-KIT and the tumor was diagnosed as GIST. Fourteen months after this diagnosis, the patient was found to have lung metastases by CT scan, and confirmed by PET. While pathology and immunohistochemistry were not reported on the lung metastases, it was reported that the pulmonary lesions disappeared completely with oral imatinib treatment, suggesting a similar molecular basis of these lesions. Miyake *et al* (10), and Inage *et al* (11), described patients with multiple sites of metastases, with both patients having lung metastases. Ishikawa *et al* (12) reported a patient with liver and bone metastases, in the form of a lumbar vertebral lesion. With the exception of our report, mutational studies of KIT and PDGFRA genes were not reported in these five other cases (8-12).

Even more rare than metastases to bone and lung, metastases of GIST to subcutaneous tissue are reported in less than 1% of cases (6,7). In a series of patients with stomach GIST, five out of 1765 patients (0.04%) developed sk in or sof t tissue metastases (6). No patients were reported to have soft tissue or skin metastases in a series of 906 patients with small intestine GIST (7). Prior to our reported case, the literature includes six case reports (13-18) describing ten patients with cutaneous metastases as a late complication of GIST. The first reported case (13) described a 49 year-old male with multiple skin and subcutaneous metastases to the scalp, anterior jaw, left thigh, and groin, along with liver and splenic metastases. This report did not include description of microscopic, immunoh istochemica l a nd molec u la r feat u res. The patient was treated with gemcitabine and thalidomide, experienced a minimal response and was then lost to follow up. Anagnostoulis *et al* (14) reported a 69 year-old female who presented with synchronous gastric GIST and a subcutaneous paraumbilical metastasis, proven by histology and immunohistochemistry to be consistent with GIST. She died four days postoperatively after gastrectomy and resection of subcutaneous metastasis. Other reports described three patients with subcutaneous metastases in the parietal bone region (15), gluteal region (biopsy proven and immunohistochemistry positive for CD117) (16), and

Table 1. Case Reports describing GIST metastasis to bone, lung, or both.

Author	Age (yr), sex	Location of metastasis	Immunohistochemistry
Kaku S (6)	68 female	Lumbar spine, intracranial (brain), ureter	Intracranial: CD117 and CD34 positive
De Chiara A (7)	37 male	Lung	Primary tumor (l iver): CD117 positive, No immunohistochemistry reported on lung metastases
Miyake M (8)	45 female	Liver, lung, peritoneal	Primary tumor (jejenum): CD117 positive
Inage Y (9)	70 male	Lung, intracranial (left occipital)	Histology and immunohistochemistry showed that both sites were metastases of GIST
Ishikawa A (10)	58 male	Liver, L5 lumbar vertebra	Not reported in abstract
Our case	59 female	Liver, lung, peritoneal, bone	Liver, Lung metastases: positive for CD117, Bone metastases: negative for CD117

right upper arm (biopsy proven, immunohistochemistry positive for CD117) (17) respectively.

Outside of our article, the only other literature to report subcutaneous metastasis of GIST and provide both immunohistochemical and mutational analysis of the subcutaneous metastases is a case series by Wang *et al* (18). They describe two patients with abdominal cutaneous metastases and three extra-abdominal cutaneous metastases (two to scalp and one to cheek). All five cases had multiple concurrent or subsequent abdominal and/or hepatic metastases. Immunohistochemical studies for CD117 expression were performed on the cutaneous metastases in all five cases, and all cases were positive for CD117. In addition to this, four out of the five cases were analyzed for KIT mutations in exons 9, 11, 13, and 17. Two of the four cases had mutations in exon 11, and the remaining two cases were wild-type for exons 9, 11, 13, and 17.

Discussion

The development of molecularly targeted therapy against c-K IT and PDGFR A with imatinib and sunitinib has significantly altered the treatment of GIST. Notably, imatinib has been shown to increase progression free survival in advanced disease (19). Most of the somatic mutations in c-KIT are gain-of-function mutations found in exon 11 and exon 9, with exon 11 mutations showing improved objective responses, time to tumor progression, and overall survival in patients treated with imatinib (19). A mutation in exon 11 was present in our patient's malignancy, and she ex perienced a time to tumor progression of approximately two years while on imatinib. With progression to liver metastases, indicating imatinib resistant GIST, she was started on sunitinib. Despite use of sunitinib, her disease progressed in the form of lung and bone metastases. The clinical activity of sunitinib after imatinib failure has also been correlated with kinase genotype, with progression-free survival and overall survival significantly longer for patients with primary KIT exon 9 mutations or with wild-type genotype, as compared to those with KIT exon 11 mutations (20).

While the relationship between certain kinase genotypes and clinical progression has been described in articles by Heinrich *et al* (19,20), it remains unclear why some patients develop particularly aggressive and unusual metastases. It is also unclear why expression of CD117 in certain metastatic lesions is diminished or absent, such as in our patient's left arm subcutaneous nodule. The absence of CD117 may be related to dedifferentiation of the malignancy or associated with changes induced by tyrosine kinase inhibitor therapy. Loss of CD117 expression has been observed in advanced GIST cases, and may itself be a harbinger of imatinib failure and poor prognosis (21,22). We further postulate that the type of mutation, including point, substitution, deletion, or deletion-insertion, may affect clinical aggressiveness and prognosis, as well as response to imatinib and sunitinib, with exon 11 deletions having a more aggressive course. Additional research is needed to elucidate the relationship between the type of mutant genotypes, and the site of metastases, clinical aggressiveness, and response to tyrosine kinase inhibitors.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Graadt van Roggen JF, van Velthuysen ML, Hogendoorn PC. The histopathological differential diagnosis of gastrointestinal stromal tumours. J Clin Pathol 2001;54:96-102.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130:1466-78.
3. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-KIT in human gastrointestinal stromal tumors. Science 1998;279:577-80.
4. American Cancer Society [Internet]. Detailed Guide: Gastrointestinal stromal tumor (GIST): What are the key statistics about gastrointestinal stromal tumors; c2010 [updated 2010 August 24; cited 2010 October 15]. Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/003103-pdf.pdf
5. Schuler M, Zeile M, Pink D, Tunn A , K retzschmar A , R au B, et al. Incidence of bone metastases in GIST: A single center analysis of 307 patients w ith metastatic disease [abstract]. J Clin Oncol 2008;s26:10565.
6. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29:52-68.
7. Miettinen M, Ma k louf H, Sobin LH, Lasota J. Gastrointestina l st roma l t umors of t he jejenum a nd i leum: a cl i n icopat holog ic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006;30:477-89.
8. Kaku S, Tanaka T, Ohtuka T, Seki K, Sawauchi S, Numoto RT, et al. Perisacral gastrointestinal stromal tumor with intracranial metastasis: case report. Neurol Med Chir (Tokyo) 2006;46:254-7.
9. De Chiara A, De Rosa V, Lastoria S, Franco R, Botti G, Iaffaioli VR, et al. Primary gastrointestinal stromal tumor of the liver with lung metastases successfully treated with STI-571 (imatinib mesylate). Front Biosci 2006;11:498-501.
10. Miyake M, Takeda Y, Hasuike Y, Kashiwazaki M, Mishima H, Ikenaga M, et al. A case of metastatic gastrointestinal stromal tumor developing a resistance to STI571 (imatinib mesylate). Gan To Kagaku Ryoho 2004;31:1791-4. Japanese.
11. Inage Y, Yamabe K, Yamamoto T, Sato Y, Ishikawa S, Onizuka M, et al. Resection for pulmonary metastasis of gastrointestinal stromal tumor of the stomach at 10 years after gastrectomy; report of a case. Kyobu Geka 2002;55:907-11. Japanese.
12. Ishikawa A, Teratani T, Ono S, Ochiai T, Kakinoki N, Kishimoto Y, et al. A case of gastrointestinal stromal tumor with liver and bone metastases effectively treated with radiofrequency ablation and imatinib mesylate. Nippon Shokakibyo Gakkai Zasshi 2006;103:1274-9. Japanese.
13. S habahang M, Living s tone AS. Cutaneous metastasis from a gastrointestinal stromal tumor of the stomach: review of literature. Dig Surg 2002;19:64-5.
14. A nag nostou l is S, Mi m id is K , Papadopou los V, Papa laza rou D, Argyropoulou P, Iakovidis C, et al. Subcutaneous metastasis from a gastrointestinal stromal tumor of the stomach: a case report. J BUON 2007;12:549-52.
15. Bara T, Bancu S, Bara T Jr, Muresan M, Bancu L, Azamfirei L, et al. Gastric stomal tumor with liver and subcutaneous metastasis. Case report. Chirurgia (Bucur) 2009;104:621-4. Romanian.
16. Hughes B, Yip D, Goldstein D, Waring P, Beshay V, Chong G. Cerebral relapse of metastatic gastrointestinal stromal tumor during treatment with imatinib mesylate: Case report. BMC Cancer 2004;4:1-7.
17. Kroep JR, Bovee J, van der Molen AJ, Hogendoorn P, Gelderblom H. Extra-abdominal subcutaneous metastasis of a gastrointestinal stromal tumor: report of a case and a review of the literature. J Cutan Pathol 2009;36:565-9.
18. Wang W, Hornick JL, Mallipeddi R, Zelger BG, Rother JD, Yang D, et al. Cutaneous and subcutaneous metastases of gastrointestinal stromal tumors: A series of 5 cases with molecular analysis. Am J Dermatopathol 2009;31:297-300.
19. Heinrich MC, Owzar K, Corless CL, Benjamin RS, Bramwell VH, Demetri GD, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360-7.
20. Heinrich MC, Maki RG, Corless CL, Antonescu CR,

Harlow A, Griffith D, et al. Primar y and secondar y k inase genot y pes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352-9.
21. Fletcher JA, Corless CL, Dimitrijevic S, Von Mehren M, Eisenberg B, Joensuu H, et al. Mechanisms of resistance to imatinib mesylate (IM) in advanced gastrointestinal stromal tumor (GIST) [abstract]. Proc Am Soc Clin Oncol 2003;22:815.
22. Mearadji A, den Bakker MA, van Geel AM, Eggermont AM, Sleijfer S, Verweij J, et al. Decrease of CD117 expression as a possible prognostic marker for recurrence in the resected specimen after imatinib treatment in patients w ith unresectable gastrointestinal stromal tumors: a clinicopathological analysis. Anticancer Drugs 2008;6:607-12.

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Coexistence of gastrointestinal stromal tumour and colorectal adenocarcinoma: Two case reports

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Abstract: This paper reports two rare cases of patients with synchronous gastrointestinal stromal tumour (GIST) and colorectal adenocarcinoma (CRC) where adjuvant FOLFOX chemotherapy was administered concurrently with imatinib mesylate. The first case is a 67-year-old woman with a large gastrointestinal stromal tumour with metastasis masking a co-existing primary colon cancer, which was diagnosed after tumour response to imatinib mesylate. The second case presents a 61-year-old male with a primary colon cancer and a suspected metastatic lymph node, later confirmed to be a co-existing primary gastric GIST during colon surgery. While colorectal cancer is the third most common cause of cancer-related death in North America, the prevalence of GISTs remains rare. To date, very few cases of synchronous GIST and CRC adenocarcinoma have been reported in the literature. Although the coexistence of these two tumour types is rare, it is im-portant to be aware of their disease patterns.

Keywords: Colonic neoplasms, gastrointestinal stromal tumors, neoplasms, multiple primary

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Case 1

In the fall of 2008, a previously well 67-year-old Caucasian woman, presented with progressive fatigue over three months accompanied by left lower abdominal pain. She reported passage of "darker stools"; however, there was no complaint of bright red blood per rectum or change in stool shape. On physical examination, a minimally tender palpable mass in the left lower quadrant was noted.

Computed tomography (CT) scan imaging revealed a large abdominal mass (*Figure 1*) with multiple hypervascular masses in the liver (*Figure 2*). The abdominal mass, with a large area of internal necrosis, was intimately related to the jejunum with minimal small bowel dilatation. One of the liver lesions in segment 4b was biopsied under ultrasound guidance. Pathology revealed a spindle cell tumour, which was strongly positive for CD117 and CD34 by immunohistochemistry (*Figure 3*). There were no mitotic figures noted. The pathologic diagnosis was consistent with metastatic gastrointestinal stromal tumour and in December 2008, she was started on 400 mg of imatinib mesylate per day.

Subsequently, follow-up CT imaging revealed significant reduction of her primary GIST (*Figure 4*) as well as in the hepatic metastases. The GIST decreased from its initial size of 13.5 x 8.7 cm in November 2008 to 9.0 x 6.0 cm in January 2009. The primary tumour continued to decrease in size from 6.3 x 3.7 cm in June 2009 to 5.2 x 3.5 cm in November 2009.

The CT scan in November 2009 revealed the presence of a colonic mass with mesenteric lymphadenopathy. The presence of the newly identified mass was confirmed on colonoscopy, wh ich revea led t he presence of a n intraluminal mass at 80 cm from the anal verge. Biopsy of this lesion revealed an invasive, moderately differentiated adenocarcinoma of colonic origin.

After discussion at tumor board, a decision was made to resect the primary colonic mass as well as the primary

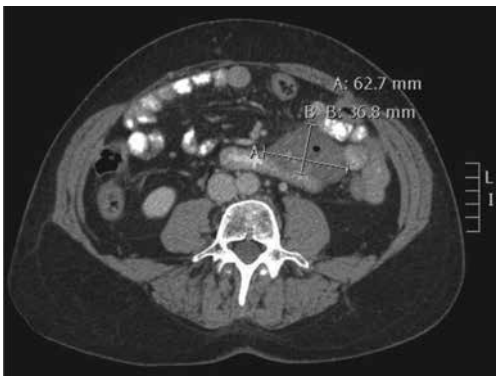

Figure 1 CT of the abdomen revealing a large GIST

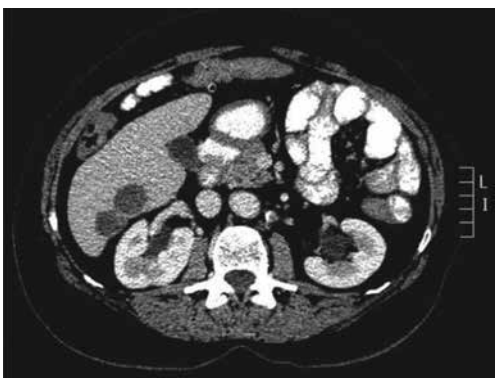

Figure 2 CT scan revealing concomitant liver metastasis

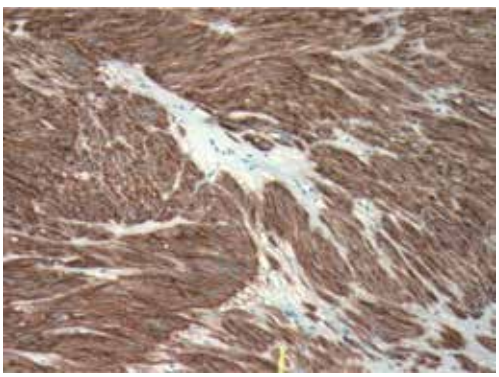

Figure 3 Strongly positive immunochemical CD117 immunostaining (x100) (Dako at a dilution of 1/400)

GIST. In December 2009, the patient underwent a left hemicolectomy in addition to resection of the primary GIST, which originated in the small bowel. The pathology of the colonic mass revealed a moderately differentiated adenocarcinoma with 7 out 12 lymph nodes involved.

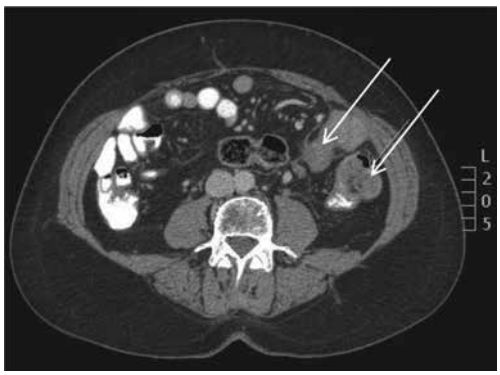

Figure 4 CT scan of the abdomen following treatment with imatinib mesylate revealing a reduction of GIST (top arrow). The colon mass is now visible (bottom arrow)

The small bowel pathology revealed a spindle cell lesion consistent with a GIST, which was positive for CD117 and CD34. The Ki67 stain showed positivity in less than 1% of tumour cells. The mitotic count was less than 1 per 50 High Power Fields (HPF). The tumour showed large hypocellular areas of hyalinization, an area of necrosis, and several areas of hemorrhage as well as a focal hemangiopericytoma-like pattern, consistent with treatment (imatinib mesylate) effect. Of note, the laboratory findings did not include a pre-operative CEA, however, a CEA level was drawn shortly after the surgery, measuring 2.5 ug/L.

She subsequent ly received 12 cycles of modif ied FOLFOX-6 chemotherapy while remaining on imatinib for her metastatic GIST. She did not experience any unexpected toxicity from either the imatinib or chemotherapy and rema ins wel l w it h continued reg ression of her l iver metastasis (GIST).

Case 2

A 61-year-old Caucasian gentleman presented with a change in bowel habits and rectal bleeding in March 2009. He reported no associated anorexia or weight loss. Colonoscopy and biopsy revealed an adenocarcinoma at the splenic flexure. A staging CT scan also revealed a few subcentimeter lymph nodes and a 5 cm mass at the gastrohepatic ligament also suspected to be an enlarged metastatic lymph node (*Figure 5*).

In May 2009, at the time of surgery, the gastrohepatic mass was resected. Once confirmed on a frozen section to be a spindle cell tumour consistent with a GIST, a partial gastrectomy was performed.

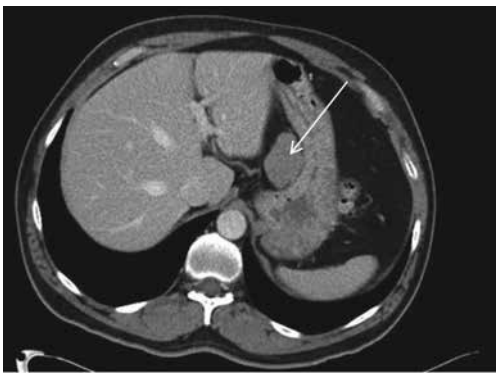

Figure 5 CT scan demonstrating a mass later confirmed to be a primary gastric GIST

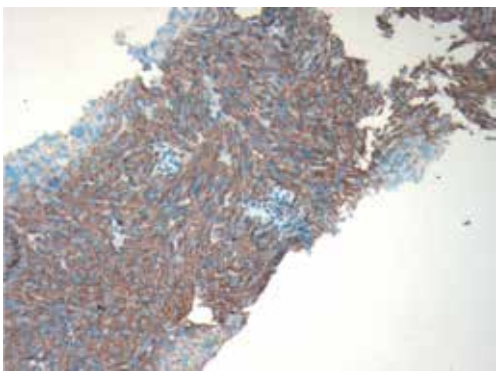

Figure 6 Patient 2: Positive CD117 staining (x100) (Dako at a dilution of 1/400)

During the same operation, the patient also underwent a left hemicolectomy. Final pathology revealed a 4 x 3.5 x 1.1 cm moderately differentiated adenocarcinoma with 4/22 lymph nodes being positive.

The gastric-based mass was a primary GIST measuring 5.5 cm. Histopathological examination revealed a spindle cell lesion with a high mitotic index of 7 mitoses per 50 high power fields (HPF) with negative resection margins. The immunohistochemistry was positive for CD34 and CD117 (*Figure 6*) and negative for S100 and desmin. Ki67 stained 10% of tumor cell nuclei. A pre-operative CEA level was normal at 1.3 ug/L.

Post-operatively, he received 10 cycles of adjuvant FOLFOX chemotherapy for his stage III colon cancer as well as one year of adjuvant imatinib therapy for the GIST. Imatinib (400 mg per day) was started after he had received two cycles of modified FOLFOX-6.

Discussion

Defined as cellular spindle cell, epithelioid, or pleomorphic mesenchymal tumour of the gastrointestinal (GI) tract, the term gastrointestinal stromal tumour (GIST) was introduced by Mazur and Clark in 1983 to differentiate GISTs from leiomyomas (1,2). The putative origin of these tumours is believed to be the interstitial cells of Cajal, the GI pacemaker cells (2-4). Approximately 95% of GISTs are positive for expression of the KIT (CD117, stem cell factor receptor) protein and as well as 70-80% of GISTs expressing CD34, the human progenitor cell antigen (2,5).

Although GISTs are the most common mesenchymal tumours of the digestive tract, they remain rare. They represent 0.1-3% of all GI cancers and have an incidence of 10-20 cases/million (2,4). Conversely, colorectal cancer is the third most common cause of cancer-related death in North America (6). While the incidence of synchronous occurrence of other tumours with GISTs is on the rise, there is no evidence of a common etiology (4,7). Based on the prevalence of both tumours, an incidental occurrence is more likely. What remains important, however, is the need to be aware of their coexistence.

The first case outlines the presentation of a metastatic small bowel GIST masking a colonic adenocarcinoma. As the primary GIST decreased in size in response to treatment with imatinib mesylate, the colonic mass and enlarged mesenteric lymph node was unmasked. As lymph node involvement with GIST is rare, the lymphadenopathy was consistent with metastasis from a second primary tumour. It also highlights that metastatic GIST should not preclude the potential curative treatment of other secondary cancers. The second case details a man with a primary colonic neoplasm and an unidentified gastrohepatic mass that was initially suspected to be a metastatic node but later confirmed to be a GIST. Given the atypical location of the suspected lymph node, the patient underwent primary surgery rather than systemic therapy. These cases highlight the importance of being aware of second primary cancers throughout the course of treatment for both colon cancer and GISTs.

GISTs a re most common ly found in the stomach and small intestine. The coexistence of GISTs a nd adenocarcinoma at two separate locations in the GI tract is uncommon (7). Both colon cancer and GISTs are infrequently associated with a genetic disposition and in this report, neither patient reported a family history of any malignancies.

Surgery is the primary treatment modality for both nonmetastatic GISTs and colon cancer (3). For metastatic GIST, imatinib mesylate is the standard first-line treatment (8). Imatinib mesylate, a selective tyrosine kinase inhibitor, has been shown to have a tumor response rate of greater than 50% (3,9). Continuous treatment with imatinib in the metastatic setting is the standard treatment as interruptions have been shown to result in rapid disease progression (10). Although surgery for patients with metastatic disease is considered investigational, if the patient has disease responsive to imatinib, surgical excision of a primar y tumor or an isolated metastasis that has progressed can be associated with a good outcome (11).

Treatment w it h imatinib in the adjuvant setting , however, is now established as the standard of care for those with resected primary GISTs (8). A phase III trial, ACOSOG Z9001, was the first to demonstrate that one year of imatinib as compared to placebo in the adjuvant setting, is effective in decreasing recurrences. The trial included 713 patients with a resected GIST measuring at least 3 cm in maximal diameter. Mitotic count was not an inclusion criterion for this study. In this report, patient two had a tumour greater than 3 cm and received adjuvant imatinib therapy for one year consistent with the recommendations of the major cancer societies (12,13). Although adjuvant imatinib is recommended for a minimum of one year, the optimal duration of administration remains unknown. The Intergroup EORTC 62024 trial is a randomized study comparing two years of imatinib versus observation alone. The Scandinavian Sarcoma Group (SSG) trial XV III is investigating three years versus one year of adjuvant imatinib. Although both studies have completed accrual, the results have not yet been presented. Hence, until the results of these two studies are known, the recommended duration of adjuvant treatment remains one year.

A unique feature common to the two cases presented is the concurrent treatment of adjuvant FOLFOX chemotherapy with imatinib mesylate. Dexamethasone is a steroid that is commonly included as part of the antiemetic reg i men w it h a seroton i n 5HT-3 antagonist in the FOLFOX regimen. Both imatinib and dexamethasone are metabolized by the cytochrome P450 (CYP450) isoenzyme CYP3A4. Imatinib is a potent competitive inhibitor of the CYP450 isoenzyme CYP3A4 while dexamethasone is an inducer (14). There is a high possibility of a drug interaction as the plasma concentration of imatinib may decrease when administered with dexamethasone. While case two presents a patient who received concurrent treatment for ten cycles of FOLFOX, the patient in case one was administered concurrent treatment for all twelve cycles. Although there were no ill effects noted in either case, perhaps due to the brief exposure of both dexamethasone and imatinib, a more prolonged exposure of the two medications may benef it from possible monitoring of plasma imatinib levels especially in the setting of metastatic GIST (case one). Mod i f icat ions to t he treatment cou ld include increasing the dosage of imatinib, decreasing the dosage of dexamethasone, or administering another anti-emetic in lieu of dexamethasone.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Conclusion

There have been ver y few incidences of synchronous colorectal cancer and GISTs reported in literature. Most of the cases described were found due to other malignancies or discovered incidentally during surgery (3,5,15). The two cases presented above underline the importance of being aware of this particular coexistence as well as the unlikely metastatic spread of GIST to lymph nodes, development of other primary tumours during treatment of metastatic GIST, and the importance of a multidisciplinary approach to cancer treatment.

References

1. Mazu r MT, Cla rk HB. Gast r ic st roma l t umors. Reappra isa l of histogenesis. Am J Surg Pathol 1983;7:507-19.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438:1-12.
3. Melis M, Choi EA, Anders R, Christiansen P, Fichera A. Synchronous colorectal adenocarcinoma and gastrointestinal stromal tumor (GIST). Int J Colorectal Dis 2007;22:109-14.
4. Efstathios P, Athanasios P, Papaconstantinou I,

Alexandros P, Frangisca S, Sotirios G, et al. Coexistence of gastrointestinal stromal tumor (GIST) and colorectal adenocarcinoma: A case report. World J Surg Oncol 2007;5:96.
5. Kosmidis C, Efthimiadis C, Levva S, Anthimidis G, Baka S, Grigoriou M, et al. Synchronous colorectal adenocarcinoma and gastrointestinal stromal tumor in meckel's diverticulum; an unusual association. World J Surg Oncol 2009;7:33.
6. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
7. Gopal SV, Langcake ME, Johnston E, Salisbur y EL. Synchronous association of small bowel stromal tumour with colonic adenocarcinoma. ANZ J Surg 2008;78:827-8.
8. DeMatteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-104.
9. Spinel li GP, Miele E , Tomao F, Rossi L , Pasciuti G, Zul lo A , et al. The synchronous occurrence of squamous cell carcinoma and gastrointestinal stromal tumor (GIST) at esophageal site. World J Surg Oncol 2008;6:116.
10. Le Cesne A, Ray-Coquard I, Bin Bui N, Adenis A, Rios M, Duffaud F, et al. Time to onset of progression after imatinib interruption and outcome of patients with advanced GIST: Results of the BFR14 prospective french sarcoma group randomized phase III trial [abstract]. J Clin Oncol 2010; s28:10033.
11. Mussi C, Ronellenfitsch U, Jakob J, Tamborini E, Reichardt P, Casali PG, et al. Post-imatinib surgery in advanced/metastatic GIST: Is it worthwhile in all patients? Ann Oncol 2010;21:403-8.
12. Nccn.org [Internet]. Washington: National Comprehensive Cancer Network. c2010 [cited 2010]. Available from: http://www.nccn.org/.
13. Casa l i PG, Jost L , Reicha rdt P, Sch lemmer M, Blay J Y, ESMO Guidelines Working Group. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20:s64-7.
14. Scripture CD, Figg WD. Drug interactions in cancer therapy. Nat Rev Cancer 2006;6:546-58.
15. Tzilves D, Moschos J, Paikos D, Tagarakis G, Pilpilidis I, Soufleris K, et al. Synchronous occurrence of a primary colon adenocarcinoma and a gastric stromal tumor. A case report. Minerva Gastroenterol Dietol 2008;54:101-3.

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A 26-year-old female with metastatic primary gastrointestinal malignancy presenting as menorrhagia

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Abstract: Krukenberg tumor is a metastatic malignant tumor of the ovary arising from a wide variety of primary sources, with the stomach being the most common. The presenting symptoms are non-specific and the primary source is often un-identified. Here, we describe a case of a 26-year-old Hispanic gravida 4, para 3 female who presented to our hospital with dysuria, pelvic pain and irregular, heavy menstrual cycles for three months duration. An endometrial biopsy was suggestive of carcinosarcoma. The patient underwent debulking surgery with partial cystectomy and bladder repair. A week later, she presented with hematemesis and an endoscopic biopsy revealed a diagnosis of poorly differentiated gastric adenocarcinoma. The tissue specimen obtained during the initial surgery was identified as Krukenberg tumor. The patient underwent adjuvant chemotherapy with FOLFOX along with gastrectomy with intraperitoneal chemotherapy.

Keywords: Krukenberg tumor; menorrhagia

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Introduction

Krukenberg tumor is a rare metastatic ovarian carcinoma with a usual underlying gastrointestinal primary tumor, the commonest being gastric cancer (1). The presentation is similar to other ovarian tumors, often with vague symptoms of abdominal pain and distension, menstrual cycle changes and dyspareunia in a young patient. Occasionally, the primary tumor may manifest with life threatening complications such as in our case.

Case report

A 26-year-old Hispanic gravida 4, para 3 female presented to the gynecology clinic at our institution for heavy vaginal bleeding for the preceding 3 months. The patient also reported irregular menstrual cycles, bilateral pelvic pain, dysuria and suprapubic discomfort with urination for 3 months. Her pelvic examination revealed a firm fixed cervix with bilateral enlarged ovaries. A transvaginal ultrasound showed bilateral enlarged ovaries, right measuring 6.21 cm and left measuring 7.28 cm, irregularly shaped with free fluid in cul-de-sac. Computed tomography (CT) scan of the abdomen and pelvis showed severe bilateral hydronephrosis, worse on the right and enlarged uterus of mixed density. Large heterogeneous mass is noted in the pelvis that appeared bi-lobed measuring 6.7 cm on right and 7.8 cm on left. Positron emission tomography (PET) scan revealed a small bladder nodule measuring 2.3 cm × 1.8 cm, small amount of free fluid in the pelvis and adjacent to the liver, severe right-sided hydronephrosis and hydroureter, bilateral moderate to severely enlarged ovaries. PET scan official reading did not mention any abnormal activity in the stomach. She underwent bilateral ureteral stents placement. At that time, bladder, endometrial and endocervical biopsies were obtained.

Pathology from the cervical biopsy revealed fragments infiltrated by malignant neoplasm, with a differential diagnosis that included carcinosarcoma. The tissue specimen was send to a tertiary institution for a second

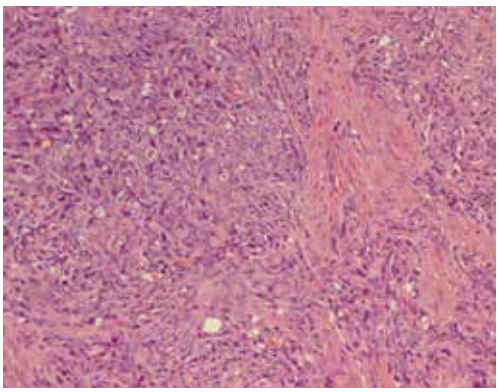

Figure 1 Hematoxylin and eosin stain (20×) showing ovaries being completely replaced by a spindle cell neoplasm in a fibrotic background. Intermixed are ovoid epithelial cells with lumen formation.

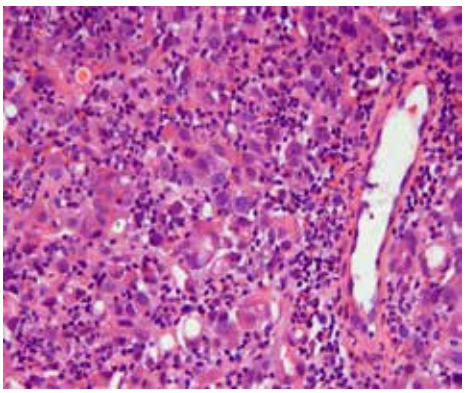

Figure 2 Hematoxylin and eosin stain (20×) showing gastric tissue replaced by poorly differentiated adenocarcinoma formed by single neoplastic cells. The neoplastic cells have eccentric hyperchromatic pleomorphic nuclei with cytoplasmic mucin.

opinion and was reported as "cervical mucosa with diffuse infiltration by spindle and epithelioid appearing cells with hyperchromatic and pleomorphic round and spindle nuclei". Immunostaining revealed diffuse positivity for pancytokeratin, SMA, vimentin and focal positivity for CD10. The tissue staining was negative for P63, CK5/6, and calretinin. These findings were supportive of a likely diagnosis of carcinosarcoma. She underwent exploratory laparotomy with radical hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymph node dissection, tumor debulking and partial cystectomy with bladder repair. The tissue specimen revealed extensive malignant neoplasm in right (8 cm) and left (9 cm) ovaries, fallopian tubes, myometrium and cervix. The pathological specimen was reported as poorly differentiated tumor with extensive lymphovascular and perineural invasion with the largest tumor burden noted in the ovaries (*Figure 1*). Immunostaining showed diffuse positivity for AE1/3 and smooth muscle actin (AMA), and focal positivity for inhibin. Differential diagnosis included carcinosarcoma. The pathologic specimen was send to another tertiary care center for second opinion.

The patient returned to our emergency department within a week after her discharge, with multiple episodes of hematemesis. Shortly after her presentation, the results of pathological examination of the specimen from her debulking surgery were received, and showed Krukenberg tumor, with primary site being indeterminate. An esophagogastroduodenoscopy (EGD) showed a single, five centimeter, broad based, friable mass along the greater curvature of the stomach, three centimeters below the gastro-esophageal junction. The mass was found to be actively bleeding. The bleeding was controlled by embolization of the left gastric and left gastroepiploic arteries. Tissue biopsy of the gastric mass revealed poorly differentiated adenocarcinoma, diffuse type, with signet ring cells, identified as the primary source of the Krukenberg tumor (*Figure 2*). Immunostaining was positive for cytokeratin AE1/AE3 and negative for HER2/neu and CD 20. HER-2 fluorescence in situ hybridization was positive. She was started on adjuvant chemotherapy with folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) a month later. The patient underwent gastrectomy with heated intraperitoneal chemotherapy 3 months later with subsequent removal of the left ureteral stent 2 months later. A follow-up PET scan showed no residual or recurrent neoplasm and residual left sided hydronephrosis. The patient completed 12 cycles of FOLFOX chemotherapy without major side effects. PET/CT scan done 1 month after the completion of chemotherapy showed left-sided pelvic activity that was felt to be associated with the bowel. The patient underwent colonoscopy one year after her initial presentation. This revealed an inflammatory mass in the rectum. Biopsy revealed poorly differentiated adenocarcinoma; a subset of cells showed signet ring cell morphology, similar to the prior studies confirming metastatic tumor in the rectum. The patient underwent low anterior resection with re-anastomosis. A repeat PET/CT scan now showed a new focus of increased metabolic activity within the vaginal cuff concerning for tumor recurrence with a plan for surgery, along with administration of adjuvant herceptin.

Table 1 Immunohistochemistry in Krukenberg tumor (3,6,10)

Tumor	Immunohistochemistry
Primary ovarian	CK7+/CK20–
Primary ovarian tumors with primary from	
Gastric adenocarcinoma	CK7–/CK20+/CDX2+/Hep Par 1+/ER–
Colorectal adenocarcinoma	CK7–/CK20+/CDX2+/Muc 2+/Muc 5AC+
Pancreatic, biliary and pulmonary adenocarcinoma	CK7+/CK20–
Breast adenocarcinoma	CK7+/CK20–/Muc 1+, ER+
Adenocarcinoma of appendix	CK7+/CK20+

Discussion

Krukenberg tumor is commonly defined as an ovarian carcinoma that contains a significant component of mucin-filled signet-ring cells lying within a cellular stroma of ovarian origin, accounting for 1% to 1.5% of all ovarian tumors (1). Krukenberg tumor is primarily seen in the young, with the average age ranging from 40 to 46 years (2). Recent case reviews have reported that 35-45% of patients are younger than 40 years of age, similar to our patient. With the young age at presentation, an association with pregnancy is not uncommon and may present a diagnostic challenge (2,3).

Nearly all Krukenberg tumors are considered to be metastatic, with rare cases labeled as primary tumors. The existence of the latter has been challenged in recent literature and is thought to be the result of occult primary tumors (4). The most common sites of origin include the stomach (76%), colon (11%), breast cancer (4%), biliary system (3%) and the cecal appendix (3%). A minority (3%) come from the pancreas, cervix, bladder and renal pelvis (5). In our case, on re-review of the initial PET scan with the radiologist, an FDG-avid mass was found in the stomach. Given the rarity of the tumor, it was misread as normal gastric activity. While the exact mode of transmission remains to be elucidated (6), it is widely accepted that the most likely routes are lymphatic, hematogenous and peritoneal spread. Early lymphatic invasion followed by subsequent spread into the systemic circulation, is postulated as the predominant metastatic pathway. The close relation of the retroperitoneal lymph nodes draining the upper abdominal organs, with lymphatic vessels from the ovary is often thought to account for the frequent bilateral involvement (up to 80% at time of diagnosis) by the tumor (6). In context of the hematogenous route, it has been suggested that the relatively early age at diagnosis is a result of the high ovarian vascularity, facilitating vascular metastasis (7). Peritoneal spread has not been shown as a predominant mode for metastasis to the ovaries with the near universal absence of evidence of peritoneal involvement such as seeding, adhesions, implantations, or tumor infiltration on the external ovarian surface.

On gross pathology, these tumors often present bilaterally as asymmetrically enlarged ovaries with a bosselated surface. The capsular surface is typically smooth and devoid of implants (7). Cut sections show yellow or white, hard, solid masses ranging from just a few to more than twenty centimeters across, which may have grayish-red gelatinous areas of cystic degeneration (5,7). Light microscopy reveals a diffuse infiltration of a stroma made of large spindle shaped cells by mucin laden 'signet ring' cells with eccentric hyperchromatic nuclei. Evidence of stromal edema forming pseudocysts or an intense desmoplastic response may be noted as well (7). The signet ring cells may occur singly or in nests, clusters, tubules, acini, trabeculae or cords, often many of these in the same tumor (4). As a result, the histology does not always correspond to that of the primary tumor.

Presenting symptoms are often vague and include abdominal pain and distension, menstrual cycle changes and dyspareunia, as in our patient. Virilization may be a presenting feature in some (8). Ascites is a late feature, but is noted in up to half of those diagnosed (5). The Pseudo-Meig syndrome of accompanying right hydrothorax may be rarely seen (4).

Krukenberg tumors are usually suspected with a CT scan showing solid ovarian tumors with well demarcated cystic lesions, often with strongly contrast enhancing walls (9). However, diagnosis relies on the characteristic histology with identification of intra-cytoplasmic mucin in the signet ring cells. Immunohistochemistry is often helpful in distinguishing between a primary ovarian tumor and a metastatic tumor, and also between different primary sites of origin (*Table 1*) (11).

Most patients with Krukenberg tumors die within a year

of the diagnosis (5). Very rarely, longer survival of up to 7 years has been described (12,13). Prognostic factors are not yet well established. The prognosis is poor when the primary tumor is identified after the ovarian metastasis and even poorer if there is no primary identified (14). CA-125 levels have also been used for prognostication. Kikkawa and his colleagues found that the 5-year survival rate was lower in patients in whom preoperative serum CA-125 levels were greater than 75 U/mL compared with those with levels less than that (14). Our patient's initial CA-125 was 275 U/mL, decreasing to 107 U/mL after 6 months, following surgery and 11 cycles of FOLFOX.

The optimal treatment strategy remains unclear. Surgical resection of metastatic ovarian tumor has been associated with improved survival in patients with metachronous Krukenberg tumor from gastric cancer in the absence of distant metastasis other than that to the ovaries (15). Advanced gastric cancer which has invaded the gastric serosa carries a very poor prognosis, as peritoneal dissemination frequently occurs even after curative surgical resection (16). To date, various attempts have been made to treat peritoneal dissemination of gastric cancer, including aggressive surgery (17), peritonectomy for cytoreduction, intraperitoneal chemotherapy and/or hyperthermia, and systemic chemotherapy (18-21). However, contributions of these therapies to patient survival have been unsatisfactory. Recent clinical trials have revealed that chemotherapy with the anticancer agent S-1, which is composed of FT (tegafur), CDHP (5-chloro-2,4-dihydroxypyridine, which inhibits the 5-FU degradation enzyme dihydropyrimidine dehydrogenase), and Oxo (otastat potassium, which reduces 5-FU gastrointestinal toxicity) might be a promising therapy for patients with advanced gastric cancer (10).

Conclusions

Krukenberg tumor like other ovarian tumors presents with vague symptoms but at times presents with manifestations of the primary tumor, most often a gastric cancer. Treatment is largely surgical, with removal of both the tumor as also any identified primary. Prognosis is exceedingly poor, and a combination of novel chemotherapeutic and biological agents along with surgery may lead to better outcomes, although data on this is lacking.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Scully RE, Young RH, Clement PB. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. In: Rosai J, Sobin LH. eds. Atlas of Tumor Pathology, 3rd series, fascicle 23. Washington, DC: Armed Forces Institute of Pathology, 1995.
2. Kiyokawa T, Young RH, Scully RE. Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol 2006;30:277-99.
3. Byun S, Kim HK, Kim GW, et al. Bone metastasis with paraplesia of Krukenberg tumor in pregnancy. Korean J Obstet Gynecol 2012;55:830-3.
4. Al-Agha OM, Nicastri AD. An in-depth look at Krukenberg tumor: an overview. Arch Pathol Lab Med 2006;130:1725-30.
5. Gómez Zuleta M, Benito LF, Almonacid C. Friedrich Krukenberg of Krukenberg's Tumor: Report of a series of cases. Rev Col Gastroenterol 2012;27:119-24.
6. Israel SL, Helsel EV Jr, Hausman DH. The challenge of metastatic ovarian carcinoma. Am J Obstet Gynecol 1965;93:1094-101.
7. Young, Robert H. From Krukenberg to today: the ever present problems posed by metastatic tumors in the ovary: part I. Historical perspective, general principles, mucinous tumors including the Krukenberg tumor. Adv Anat Pathol 2006;13:205-27.
8. Ances IG, Ganis FM. Metabolism of testosterone by virilizing Krukenberg tumor of the ovary. Am J Obstet Gynecol 1968;100:1062-70.
9. Megibow AJ, Hulnick DH, Bosniak MA, et al. Ovarian metastases: computed tomographic appearances. Radiology 1985;156:161-4.
10. Koizumi W, Kurihara M, Nakano S, et al. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. Oncology 2000;58:191-7.
11. Chu PG, Weiss LM. Immunohistochemical characterization of signet-ring cell carcinomas of the stomach, breast, and colon. Am J Clin Pathol

2004;121:884-92.
12. Kiyokawa T, Young RH, Scully RE. Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol 2006;30:277-99.
13. McGoogan LS, Hatch KD. Krukenberg tumor--report of two cases. Nebr Med J 1972;57:409-15.
14. Kikkawa F, Shibata K, Ino K, et al. Preoperative findings in non-gynecologic carcinomas metastasizing to the ovaries. Gynecol Obstet Invest 2002;54:221-7.
15. Cheong JH, Hyung WJ, Chen J, et al. Survival benefit of metastasectomy for Krukenberg tumors from gastric cancer. Gynecol Oncol 2004;94:477-82.
16. Mori T, Fujiwara Y, Yano M, et al. Prevention of peritoneal metastasis of human gastric cancer cells in nude mice by S-1, a novel oral derivative of 5-Fluorouracil. Oncology 2003;64:176-82.
17. Fujimura T, Yonemura Y, Nakagawara H, et al. Subtotal peritonectomy with chemohyperthermic peritoneal perfusion for peritonitis carcinomatosa in gastrointestinal cancer. Oncol Rep 2000;7:809-14.
18. Yu W, Whang I, Suh I, et al. Prospective randomized trial of early postoperative intraperitoneal chemotherapy as an adjuvant to resectable gastric cancer. Ann Surg 1998;228:347-54.
19. Nakajima T, Nishi M, Kajitani T. Improvement in treatment results of gastric cancer with surgery and chemotherapy: experience of 9,700 cases in the Cancer Institute Hospital, Tokyo. Semin Surg Oncol 1991;7:365-72.
20. Yonemura Y, Bando E, Kawamura T, et al. Cytoreduction and intraperitoneal chemotherapy for carcinomatosis from gastric cancer. Cancer Treat Res 2007;134:357-73.
21. Yonemura Y, Kawamura T, Bandou E, et al. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. Br J Surg 2005;92:370-5.

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Rare gastrointestinal stromal tumors (GIST): omentum and retroperitoneum

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms that arise in the gastrointestinal tract and rarely elsewhere in the abdomen. GISTs that develop outside the digestive tract are called extra-GISTs (EGISTs). The incidence of EGISTs is reported to be approximately 10% of all GISTs, and the median age is younger than that of conventional GISTs. EGISTs have similar histology and immunohistochemical features as conventional GISTs, with the majority of them in the omentum and mesentery. Most GISTs harbor a kinase-activating mutation in either KIT or PDGFRA. For EGISTs, the incidence of this type of mutation is 40–50%, which is somewhat lower than for conventional GISTs. EGISTs may have a worse prognosis compared with conventional GISTs with high mitotic indices, large size, and distant metastasis including lymph node involvement. In large abdominal tumors, the visceral origin is almost impossible to discern.

Keywords: Gastrointestinal stromal tumors (GIST); extra-gastrointestinal stromal tumor (EGISTs); omentum; retroperitoneum; mesentery

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Introduction

Gastrointestinal stromal tumors (GISTs) typically originate from interstitial cells of Cajal (ICC), which are pacemaker cells that control gastrointestinal track (GIT) peristalsis and the only cells that exhibit the KIT or CD34 immunochemical positive reaction in the GIT, which is the diagnostic hallmark of a GIST (1). The tumors can occur anywhere that these cells exist in the GIT, including the stomach (60–70%, which has a preferable prognosis), ileum and jejunum (25–30%), colon and rectum (5–15%), duodenum (5%) and esophagus (2%) (2,3). Some GISTs occur outside the digestive tract, such as in the omentum or retroperitoneum. These types are called extra-GISTs (EGISTs) (4,5). Other less frequent anatomical locations have been reported as primary sites, such as the liver (6), mediastinum (7), pharynx (8) and gall bladder (9). ICC-like cells, which are KIT-positive mesenchymal cells, have been reported in the omentum (10). Similarly, ICC-like cells have been identified in many other organs, such as the urinary bladder, gall bladder, omentum, uterus, prostate and myocardium (11); thus, it is reasonable to assume that EGISTs originated from a common precursor that differentiated into ICC-like cells outside of the GIT. Therefore, EGISTs may theoretically arise from outside of the GIT. Miettinen *et al.* first defined soft tissue tumors, which originate outside of the GIT and present clinicopathological features and molecular characteristics similar to those of GISTs, as EGISTs (4). While the clinicopathological and biological features and prognosis of conventional GISTs are widely known, those of EGISTs have not been thoroughly investigated due to their sparsity.

Incidence

While the annual incidence of GISTs is estimated at 10–15 per 1 million in the general population (12), the incidence of EGISTs is reported to be approximately 10% or less of all GISTs. Miettinen *et al.* found that the

incidence of EGISTs accounted for approximately 5–10% of GISTs and approximately 4–7% of soft tissue tumors in the abdominal cavity (4). Castillo-Sang M *et al.* showed that EGISTs accounted for 4.5% of all stromal tumors (22/486), with a male to female ratio of 1.4:1 and a median onset age of 45.5 years (13). Du *et al.* reported the incidence of EGISTs as 15 out of 141 (10.6%) cases (14). Cho *et al.* (15) also described similar incidences of the disease (10.1%). In a report of SEER data, 323 out of 2812 (11.5%) cases were found to be EGISTs (16).

Occurrence sites

Cho *et al.* (15) also showed the most common site for these tumors was the mesentery (45.1%) followed by intra-abdominal (34.3%), pelvis (9.8%), retroperitoneum (3.9%) and abdominal wall (3.9%). Zhou *et al.* reported that the incidence of tumors in the mesentery was 50% (11/22), in the retroperitoneum was 36.4% (8/22) and in the omentum was 13.6% (3/22) (17). It has been reported that EGISTs are often found in the mesentery, omentum and retroperitoneum, and they can also occur in the pancreas, bladder and female reproductive system (18).

Pathology

EGISTs are a group of rare tumors with similar histology and immunohistochemical features as conventional GISTs, occurring outside the GIT, with a majority of them in the omentum and mesentery or in the retroperitoneum (4,19,20). Like their digestive counterparts, most omental tumors are typically positive for KIT and less consistently for CD34, positive for α-smooth muscle actin (α-SMA) and negative for desmin and S100 protein (4). These tumors have low mitotic activity and, similarly to GISTs, present as elongated spindle cells, epithelioid cells or mix cells with high cellularity (21). Analyzing 48 EGISTs (40 omental and mesenteric and 8 retroperitoneal), Reith *et al.* found that the tumors expressed KIT 100%, CD34 50%, neuron-specific enolase (NSE) 44%, α-SMA 26%, desmin 4% and S100 protein 4% (5).

Approximately two-thirds of patients with a conventional GIST have a *c-kit* mutation at exon 11 (22). Although the ratio of c-kit and PDGFRA gene mutations is similar to ordinary GISTs, their frequency is lower than conventional GISTs. The incidence of EGISTs mutated at exon 11 is reported to be approximately 40–50% (14,19). As this mutation is expected to have a good response to imatinib, a greater number of mutation analyses for EGISTs are required. To our best knowledge, there are two definite reports of EGIST responding to imatinib (23,24). Exon 11 mutation was indicated in one of the reports (24).

Malignant potential

The clinical outcomes of EGISTs are not fully understood due to their sparsity. However, compared with a conventional GIST, an EGIST is considered to have a less favorable prognosis (5,15,16). This is because EGISTs are frequently accompanied by unfavorable prognostic factors, such as high mitotic indices, large size and distant metastasis including lymph node involvement. Zhou *et al.* (17) reported on the survival of EGIST patients. Comparing the survival of conventional GIST patients, the 1-, 3- and 5-year overall survival rates of EGIST patients were 91.7%, 61.1% and 48.9%, respectively; the 1-, 3- and 5-year recurrence-free survival rates were 72.2%, 28.9% and 19.3%, respectively. The overall survival rate of EGIST patients was significantly lower than that of conventional GIST patients (with 1-, 3- and 5-year overall survival rates of 94.0%, 88.1% and 82.4%, respectively); however, EGIST and conventional GIST patients did not show a statistically significant difference in recurrence-free survival. Other investigators have shown that the prognosis of an EGIST is less favorable (5,15). Zhou *et al.* (17) speculated that the significant differences between the two groups in survival might be related to the following two points. First, tumor size is thought to be an important factor affecting the prognosis of stromal tumors. The median tumor diameter of an EGIST is typically greater than that of a GIST, which may be due to available space at occurrence sites; thus, the clinical symptoms occur only when the tumor size becomes large, leading to the observation that EGISTs are relatively larger. Second, compared with a typical GIST, an EGIST does not affect the digestive tract; therefore, it is rare to identify early symptoms, such as gastrointestinal bleeding, that are observed in GISTs. This is also an important factor causing the relatively larger size and more advanced staging when an EGIST is discovered.

Prognostic factors

Tumor size, mitotic index and primary tumor sites are important factors affecting the prognosis of GISTs; therefore, they have been included in the risk grading system for GISTs. A high mitotic index [5/50 high-power

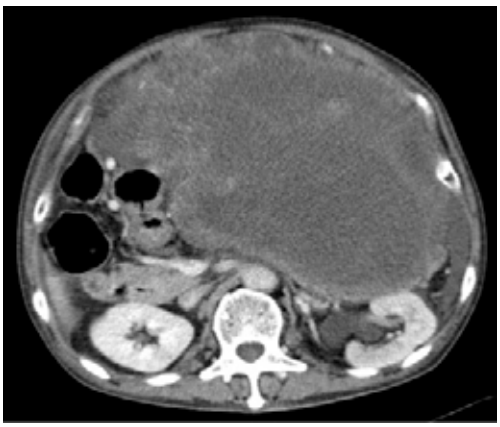

Figure 1 Huge abdominal tumor. This tumor was resected *en bloc* with a part of stomach, small intestine and peritoneum. It was pathologically diagnosed as a GIST and had connection to these adjacent organs. The origin is unknown though it was pathologically investigated. GIST, gastrointestinal stromal tumor.

field (HPF)] or a high Ki-67 labeling index (10%) were associated with poor prognosis in the case of an EGIST (19). Tumor size is an important prognostic factor in both the National Institute of Health (NIH) and the Armed Forces Institutes of Pathology criteria (25). EGISTs are often a large size due to their anatomic site which has enough space to grow before producing symptoms. Guye *et al.* reported that tumor size was not an adverse prognostic factor in a multivariate survival analysis of a large GIST cohort composed of 2,489 patients (88.5%) with GISTs and 323 patients (11.5%) with EGISTs (16). Therefore, tumor size might not be associated with adverse outcomes because most of EGISTs were found a large size. Another explanation is that tumor size itself may not express the biological characteristics of an EGIST because the tumor size has different clinical implications at different anatomical sites (3). Further examination should be required to the prognostic role of tumor size in EGISTs. Therefore, a grading system for conventional GIST using a combination of mitotic index and tumor size may not be completely applicable for EGISTs.

Difficult diagnosis

Agaimy and Wünsch reported that tumors labeled initially as primary EGISTs were instead GISTs (26). Acritical reevaluation of the surgical report and a careful search for original muscular tissue from the gut wall in the tumor pseudocapsule of 14 EGISTs, made it possible to reclassify most of these cases as either GISTs with extramural growth (8/14) or as metastases from a GIST (3/11). This study emphasized the focal attachment or adhesions to the gut wall that must be documented intraoperatively and the paramount role of the pathologist in searching for any residual muscle tissue in the tumor pseudocapsule. The clinical presentation of EGISTs depends on the primary location and dimensions. In very large abdominal tumors, the visceral origin is almost impossible to determine (*Figure 1*).

Conclusions

Compared with conventional GIST patients, EGIST patients have a younger onset age, larger tumor size and poorer prognosis. The clinical symptoms of EGISTs are often manifested as common digestive symptoms. Because it does not typically affect the GIT, an EGIST rarely causes gastrointestinal bleeding, obstruction or other typical clinical manifestations. A survival analysis showed that the primary tumor site and mitotic indices are important factors, but tumor size is controversial in affecting the prognosis of EGIST patients. Due to the low incidence of EGISTs, multi-center collaborative investigations combining basic research with clinical studies are required to expand the sample size and further study the biological characteristics of EGISTs.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Sircar K, Hewlett BR, Huozinga JD, et al. Interstitial cells of Cajal as precursors of gastrointestinal stromal tumors. Am J Surg Pathol 1999;23:377-89.
2. Emory TS, Sobin LH, Lukes L, et al. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. Am J Surg Pathol 1999;23:82-7.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83.

4. Miettinen M, Monihan JM, Sarlomo-Rikala M, et al. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol 1999;23:1109-18.
5. Reith JD, Goldblum JR, Lyles RH, et al. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol 2000;13:577-85.
6. Hu X, Forster J, Damjanov I. Primary malignant gastrointestinal stromal tumor of the liver. Arch Pathol Lab Med 2003;127:1606-8.
7. Lee JR, Anstadt MP, Khwaja S, et al. Gastrointestinal stromal tumor of the posterior mediastinum. Eur J Cardiothorac Surg 2002;22:1014-6.
8. Siddiq MA, East D, Hock YL, et al. Gastrointestinal stromal tumour of the pharynx. J Laryngol Otol 2004;118:315-6.
9. Park JK, Choi SH, Lee S, et al. Malignant gastrointestinal stromal tumor of the gallbladder. J Korean Med Sci 2004;19:763-7.
10. Sakurai S, Hishima T, Takazawa Y, et al. Gastrointestinal stromal tumors and KIT-positive mesenchymal cells in the omentum. Pathol Int 2001;51:524-31.
11. Min KW, Leabu M. Interstitial cells of Cajal (ICC) and gastrointestinal stromal tumor (GIST): facts, speculations, and myths. J Cell Mol Med 2006;10:995-1013.
12. Mucciarini C, Rossi G, Bertolini F, et al. Incidence and clinicopathologic features of gastrointestinal stromal tumors. A population-based study. BMC Cancer 2007;7:230.
13. Castillo-Sang M, Mancho S, Tsang AW, et al. A malignant omental extra-gastrointestinal stromal tumor on a young man: a case report and review of the literature. World J Surg Oncol 2008;6:50.
14. Du CY, Shi YQ, Zhou Y, et al. The analysis of status and clinical implication of KIT and PDGFRA mutations in gastrointestinal stromal tumor (GIST). J Surg Oncol 2008;98:175-8.
15. Cho MY, Sohn JH, Kim JM, et al. Current trends in the epidemiological and pathological characteristics of gastrointestinal stromal tumors in Korea, 2003-2004. J Korean Med Sci 2010;25:853-62.
16. Guye ML, Nelson RA, Arrington AK, et al. The prognostic significance of extra-intestinal tumor location for primary nonmetastatic gastrointestinal stromal tumors. In: 2012 Gastrointestinal Cancers Symposium. J Clin Oncol 2008;30:2.
17. Zhou J, Yan T, Huang Z, et al. Clinical features and prognosis of extragastrointestinal stromal tumors. Int J Clin Exp Med 2016;9:16367-72.
18. Krokowski M, Jocham D, Choi H, et al. Malignant extragastrointestinal stromal tumor of bladder. J Urol 2003;169:1790-1.
19. Yamamoto H, Oda Y, Kawaguchi K, et al. c-kit and PDGFRA mutations in extragastrointestinal stromal tumor (gastrointestinal stromal tumor of the soft tissue). Am J Surg Pathol 2004;28:479-88.
20. Gun BD, Gun MO, Karamanoglu Z. Primary stromal tumor of the omentum: report of a case. Surg Today 2006;36:994-6.
21. Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol 2000;13:1134-42.
22. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer 2011;11:865-78.
23. Rediti M, Pellegrini E, Molinara E, et al. Complete pathological response in advanced extra-gastrointestinal stromal tumor after imatinib mesylate therapy: a case report. Anticancer Res 2014;34:905-7.
24. Joyon N, Dumortier J, Aline-Fardin A, et al. Gastrointestinal stromal tumors (GIST) presenting in the liver: Diagnostic, prognostic and therapeutic issues. Clin Res Hepatol Gastroenterol 2017. [Epub ahead of print].
25. Goh BK, Chow PK, Yap WM, et al. Which is the optimal risk stratification system for surgically treated localized primary GIST? Comparison of three contemporary prognostic criteria in 171 tumors and a proposal for a modified Armed Forces Institute of Pathology risk criteria. Ann Surg Oncol 2008;15:2153-63.
26. Agaimy A, Wünsch PH. Gastrointestinal stromal tumours: a regular origin in the muscularis propria, but an extremely diverse gross presentation. A review of 200 cases to critically re-evaluate the concept of so-called extra-gastrointestinal stromal tumours. Langenbecks Arch Surg 2006,391:322-9.

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Two cases of gastrointestinal stromal tumor of the small intestine with liver and bone metastasis

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. These tumors most commonly occur in the stomach (60%), jejunum and ileum (30%). Metastasis is characteristically the malignant behavior of the GISTs. GISTs most frequently metastasize to the liver and peritoneum, whereas bone and lung metastases are uncommon sites. Here, we described two cases of bone and liver metastases in patients with advanced GISTs. Both of them showed liver metastasis at disease presentation and bone metastasis in early time after the diagnosis. Bone metastases involved the lumber spine and right femur in first patient and L2 vertebral body in the second case. All of the lesions presented a lytic pattern. These cases are presented because of the rare incidence of bone metastasis to femur and vertebral bodies. More attention should be paid to the diagnosis of bone metastases from GISTs in clinical practice despite the shortage of available data on the sensitivity and specificity of bone scintigraphy and PET-CT.

Keywords: Gastrointestinal stromal tumor (GIST); bone; metastasis

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Most gastrointestinal soft tissue neoplasms were classified as leiomyomas, schwannomas, leiomyoblastomas, or leiomyosarcomas. They are now classified as GISTs based on immunohistochemistry, histology and molecular study. They originate from the multipotential mesenchymal stem cells and differentiate to interstitial Cajal's cells (1).

Based on size, mitotic index and anatomic location, GISTs are categorized as low, intermediate, and high risk. GISTs are generally defined as c-KIT (CD117; a tyrosine kinase receptor) positive tumors with a characteristic set of histologic features. CD34 (70%), variable expression of smooth muscle actins (SMA) (20-30%) and S100 protein (10%) are commonly positive and desmin is almost uniformly negative (only 2-4% of GISTs are positive) (2).

The incidence of GIST is in the range of 20 to 40 cases per million. Over 90% of GISTs occur in adults over 40 years old, in a median age of 63 years and rarely in children in the second decade (<1%). Most GISTs are benign; malignant tumors account for 20-30% of cases. The most common location of GIST is stomach (50-60%) and small intestine (30-40%), Other less common locations are duodenum (4-5%), rectum (4%), colon and appendix (1-2%), and esophagus (<1%). Patients have different symptoms, such as abdominal pain and swelling, weakness and anemia (3).

Cases

Case 1

A 56-year-old male patient was examined with an abdominal swelling. The examinations and abdomen CT showed the presence of a mass in small intestine and a lesion in the liver. It was unclear whether the tumor was primary or metastatic. Sectional resection of the jejunum, ileum and liver biopsy was performed on September 2012. Histopathological

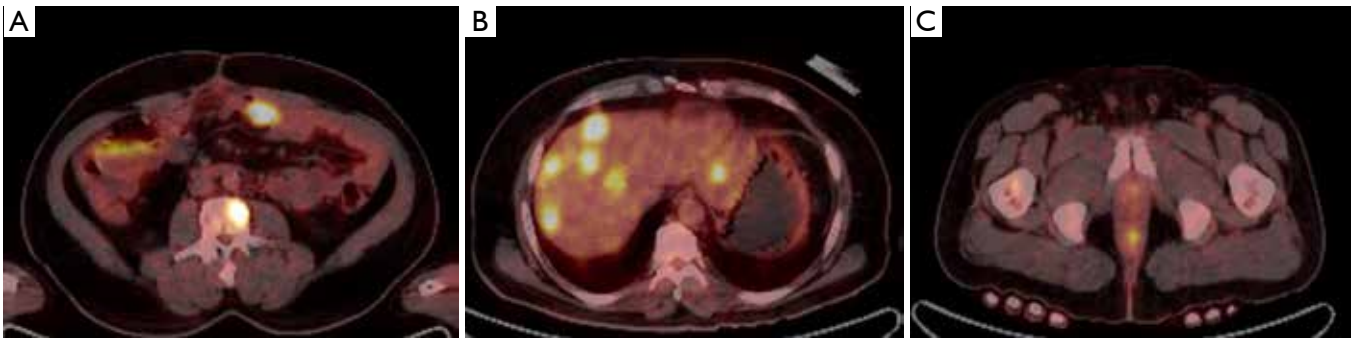

Figure 1 (A) Vertebral metastasis of case 1; (B) multiple liver metastasis of case 1; (C) right femur metastasis of case 1.

examination showed epithelioid and spindle cells, 12 mitoses at 50× magnification, infiltrative growth pattern and mild cytological atypia. There was no necrosis. In the immunochemical analysis, CD 117, CD 34, SMA, EMA, CD 99 and Pan CK were positive, CK 5/6 and Glut 1 were focally positive, S100 and desmin were negative, and the Ki-67 index was 80%. Tumor diameter was 9 cm, muscle and serosal invasion were positive and the tumor persisted at the surgical margin. Pathological examination showed high-risk gastrointestinal stromal tumor of the small intestine and liver metastasis. After the surgery, Imatinib mesylate 400 mg/day was given to the patient as an adjuvant treatment. Four months after the operation, the patient had a complaint of pain in dorsal and lumbar area and right hip. MR imaging of the thorocal-lumbar vertebra and hip showed that there were metastatic lesions on the L1-L3 vertebral body and proximal of right femur. Furthermore, a PET-CT scan was performed on the patient. The results showed the existence of multiple metastatic lesions in the liver, a relapse lesion in small intestine area and increased activity in the right femur and L1-L3 vertebral body (SUV_{max}: 12.64). PET-CT images of patient showed in *Figure 1*. Palliative radiotherapy was performed at a fraction of 3 Gray (Gy) with a total dose of 30 Gy on the bone metastasis in the right femur and L1-L3 vertebral body. Afterwards, zoledronic acid 4 mg i.v. was started. Pain complaint significantly decreased after the radiotherapy. We can not take any new images after the radiotherapy because of the patient's clinical status and he was died 2 months after the radiotherapy.

Case 2

A 70-year-old male patient was examined with an abdominal pain. Examinations showed the presence of a mass in small intestine and a lesion in the liver. Afterwards, resection of the ileum and liver biopsy was performed on August 2012. Histopathological examination showed epithelioid and spindle cells, 20 mitoses at 50× magnification, infiltrative growth pattern, mild cytologic atypia and necrosis. In the immunochemical analysis, CD 117, CD 34 and SMA were positive, S100 and desmin were negative, and the Ki-67 index was 6%. Tumor diameter was 15 cm, muscle and serosal invasion were positive. Pathological examination showed high-risk gastrointestinal stromal tumor of the small intestine and liver metastasis. After the operation, Imatinib mesylate 400 mg/day was given to the patient as an adjuvant treatment. Five months after the operation the patient had a complaint of pain in lumbar area. MR imaging of the lumbar vertebras showed that there were metastatic lesions on the L2 vertebral body. MR images of patient showed in *Figure 2*. He had received palliative radiation therapy at the bone metastasis with a total dose of 30 Gy. Afterwards zoledronic acid 4 mg i.v. was started. Pain complaint significantly decreased after the radiotherapy. We can not take any new images, because he was died 45 days after the radiotherapy.

Discussion

Metastasis is characteristically the malignant behavior of the GIST. GISTs most frequently make metastasis to the liver and peritoneum, whereas bone and lung metastases are uncommon sites (4).

Jati *et al.* reported 190 GIST patients, six (3.2%) had bone metastases, four patients had multiple bone metastases, and two patients had a solitary metastasis (5).

Di Scioscio *et al.* reported 3 GIST cases with bone metastasis and two of them showed bone and liver metastasis at the time of disease presentation (6). In the

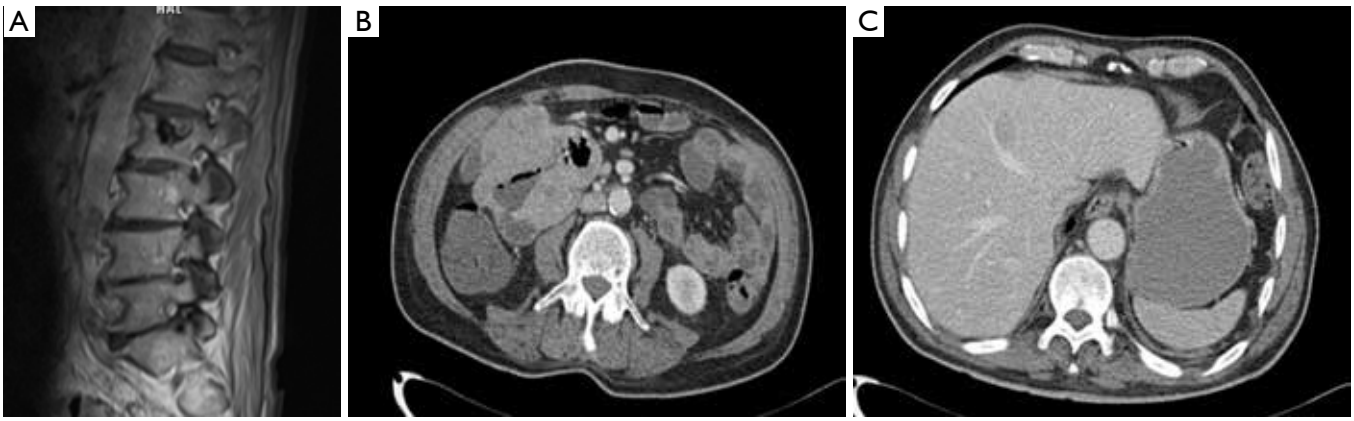

Figure 2 (A) L2 metastasis of case 2; (B) primer tumor of case 2; (C) liver metastasis of case 2.

study of Schuler *at al.*, out of the 309 consecutive patients with metastatic GIST, 17 (5.5%) were identified to have bone metastases, 5/17 patients had synchronous metastatic disease and 17/17 patients had hepatic manifestations (7).

Our patients had liver metastasis at the time of disease diagnosis and bone metastasis in early time after the diagnosis. In our previous case study, we showed one case of GIST with bone metastasis approximately one year after diagnosis (8). CT, MRI, and especially PET-CT can be used for staging in the diagnosis and metastases scanning of GIST because of the metastasis at the same time of diagnosis and may enhance the diagnosis of tumor bone metastasis and provide more information for cancer treatment (9). Initial reports suggest F-FDG PET-CT in staging, evaluation of early response to imatinib mesylate therapy and follow-up in recurrent or metastatic GIST (10). PET-CT shows the increased metabolic activity of tumor cells and can detect both osteoblastic and osteolytic lesions at an earlier stage and useful in characterizing bone lesions that require biopsy (11). In case one, we used PET-CT after diagnosis and imatinib treatment. The results showed multiple metastatic lesions in the liver, bone metastasis and a relapse lesion in small intestine.

Limited data can be found in literature on the treatment of bone metastases in GISTs. Imatinib mesylate (Kit-selective tyrosine kinase inhibitor) can be used in the treatment of advanced, recurrent, unresectable or metastatic GIST. Imatinib mesylate has also proven efficacy in bone metastases of GIST (12,13). Other treatments include radiofrequency ablation and embolization. Radiotherapy can be used in patients with bone metastasis for palliative reasons (8).

Zoledronic acid is a bisphosphonate and penetrates osteoclast cells selectively and promotes their apoptosis by reducing bone resorption. That is the current standard therapy for osteoporosis and is used to combat hypercalcemia and bone metastases from solid tumors in the colon, breast, lung, prostate and renal cell carcinoma (14). We used zoledronic acid in both cases and the previous case.

Conclusions

In our opinion, more attention should be paid to the diagnosis of bone metastases from GIST's in clinical practice despite the shortage of available data on the sensitivity and specificity of bone scintigraphy and PET-CT. These imaging studies must be done especially for the high-risk GISTs during the diagnosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sornmayura P. Gastrointestinal stromal tumors (GISTs): a pathology view point. J Med Assoc Thai 2009;92:124-35.
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn

Pathol 2006;23:70-83.
3. Miettinen M, El-Rifai W, H L Sobin L, et al. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. Hum Pathol 2002;33:478-83.
4. Bashir U, Qureshi A, Khan HA, et al. Gastrointestinal stromal tumor with skeletal muscle, adrenal and cardiac metastases: an unusual occurrence. Indian J Pathol Microbiol 2011;54:362-4.
5. Jati A, Tatlı S, Morgan JA, et al. Imaging features of bone metastases in patients with gastrointestinal stromal tumors. Diagn Interv Radiol 2012;18:391-6.
6. Di Scioscio V, Greco L, Pallotti MC, et al. Three cases of bone metastases in patients with gastrointestinal stromal tumors. Rare Tumors 2011;3:e17.
7. Schuler M, Zeile M, Pink D, et al. Incidence of bone metastases in GIST: A single center analysis of 307 patients with metastatic disease. J Clin Oncol 2008;26:10565.
8. Tezcan Y, Koç M. Gastrointestinal stromal tumor of the rectum with bone and liver metastasis: a case study. Med Oncol 2011;28 Suppl 1:S204-6.
9. Van den Abbeele AD. The lessons of GIST--PET and PET/CT: a new paradigm for imaging. Oncologist 2008;13 Suppl 2:8-13.
10. Gayed I, Vu T, Iyer R, et al. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. J Nucl Med 2004;45:17-21.
11. Peller PJ. Role of positron emission tomography/computed tomography in bone malignancies. Radiol Clin North Am 2013;51:845-64.
12. Stamatakos M, Douzinas E, Stefanaki C, et al. Gastrointestinal stromal tumor. World J Surg Oncol 2009;7:61.
13. Murakami M, Ebisui C, Okada K, et al. A case of liver and bone metastasis from gastrointestinal stromal tumor treated using imatinib. Gan To Kagaku Ryoho 2014;41:99-101.
14. Machado M, Cruz LS, Tannus G, et al. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. Clin Ther 2009;31:962-79.

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Gastric inflammatory fibroid polyp tumor with acute intestinal obstruction—Vanek's tumor can mimick a giant gastrointestinal stromal tumor or a gastric lymphoma

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Abstract: An inflammatory fibroid polyp (IFP) is a solitary rare benign neoplasm of the gastrointestinal tract, frequently located in the gastric antrum. IFPs account for about 0.1% of all gastric polyps. We report a case of a giant gastric inflammatory polyp of 2.5 cm × 7 cm that determines a gastric outlet obstruction called "ball valve syndrome" mimicking a gastrointestinal stromal tumor (GIST) and a gastric lymphoma, with an intestinal obstruction of high origin. Therefore, due to acute presentation we have decided to submit the patient to a subtotal gastrectomy. The patient was discharged two weeks later, asymptomatic. At 14 months of follow-up, patient is disease free at abdominal CT and OGDS. Depending on their size and location, IFPs can be associated with unspecific symptoms. Giant IFPs of the gastric antrum or the duodenum can determine an intermittent gastric outlet obstruction called "ball valve syndrome". Endoscopic biopsies are unhelpful and right diagnosis can be reached only with resection. In fact, only about 10% of the gastric lesions are diagnosed correctly prior to resection. Surgical treatment with complete resection with safe margins is curative. Giant IFPs are rare benign lesions whose atypical presentation can mimic GISTs, lymphomas or carcinomas. Clinical and radiological findings may not clarify the right diagnosis until histopathological evaluation aided with immunohistochemical analysis. The resection of IFPs with negative margins is curative with a good clinical outcome. In acute presentation, like in our case, surgery is the mainstay of treatment.

Keywords: Inflammatory fibroid polyp (IFP); Vanek's tumor; ball valve syndrome; gastrointestinal stromal tumor (GIST); acute gastric outlet obstruction

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Introduction

An inflammatory fibroid polyp (IFP) is a rare benign neoplasm of the gastrointestinal tract, frequently located in the gastric antrum. IFPs account for about 0.1% of all gastric polyps (1). The correct preoperative diagnosis is often difficult and delayed, due to IFP' rarity and to the variety and non-specificity of symptoms depending on its location and size. Thanks to the growing use of endoscopy, these lesions are increasingly identified in absence of symptoms. We report a case of a giant gastric inflammatory polyp of 2.5 cm × 7 cm that determined an acute gastric outlet obstruction called "ball valve syndrome" mimicking a gastrointestinal stromal tumor (GIST) and a gastric lymphoma.

Case presentation

We report a case of a 64-year-old woman that came to our observation for recurrent episodes of abdominal colic pain in the epigastrium and in the right hypochondrium,

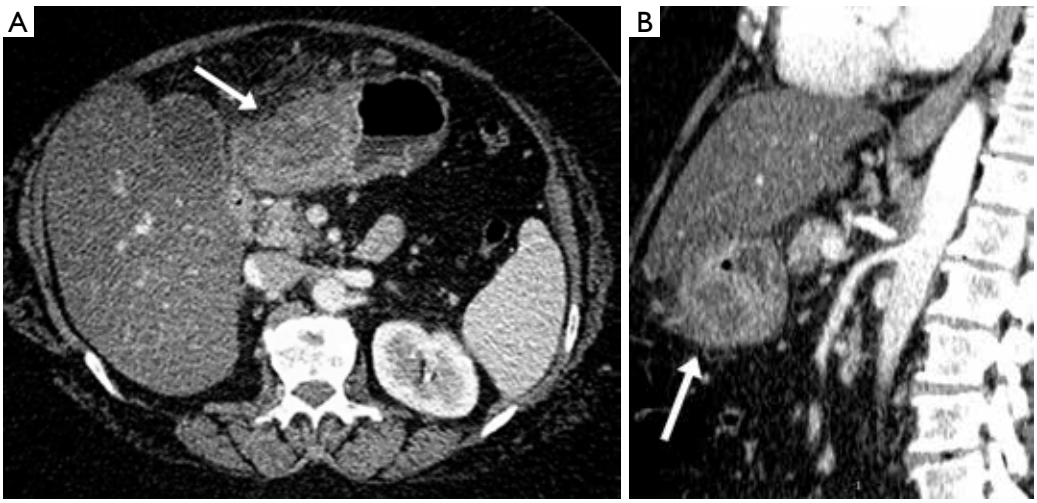

Figure 1 On transverse (A) and sagittal (B) plane, at CT imaging there was evidence the presence of a pathologic tissue between the region of the body and gastric antrum, along the greater curvature, in the anterior wall (gray arrows). This tissue presented a multiloculated aspect with an extension of 7 cm × 5 cm and it appeared to grow in the context of the gastric wall resulting in marked narrowed lumen. The lesion presented markedly uneven structure, showing impregnation of its peripheral components and branches intralesional and hypodensity of the central portions as for cystic and/or necrotic-colliquative process. The lesion was developed mainly on the serous side and in the context of the omentum there were located some adenopathies globose with maximum dimensions of 14 mm. CT, computed tomography.

increasing immediately post-prandially, treated with analgesic and antispasmodic therapy with temporary advantage.

The medical history of the patient reported only arterial hypertension and severe obesity body mass index (BMI) =46.8 kg/m^2. The laboratory data revealed a microcytic anemia (Hb. 12.1 gr%) with normal value of lactate dehydrogenase (LDH), a mild increase of gammaglobulin, and a diagnosis of diabetes with 9.30% glycated hemoglobin level.

Tumor markers were negative: CEA 2.60 ng/mL; AFP 3.20 ng/mL, CA19-9 18.50 UI/mL; CA125 94.10 U/mL; CA15-3 14.20 U/mL; CA50 38.80 U/mL; CA72-4 2.60 U/mL; Beta 2 microglobulin 2,125.00 ng/mL (range, 1,010.00–2,150.00 ng/mL); immunoglobulin IgA 4 mg/dL; IgM 337 mg/dL; IgG 1,522 mg/dL.

Therefore, the patient was submitted to an upper endoscopy [Oesophagogastroduodenoscopy (OGDS)] with evidence of a deformation of the antropyloric region similar to an *ab extrinsico* compression without evidence of mucosal lesions, with the impossibility of performing an endoscopic biopsy.

Abdominal computed tomography (CT) (*Figure 1*) confirmed the presence of pathologic tissue between the region of the body and the gastric antrum, along the greater curvature, in the anterior wall. The tissue showed a multiloculated aspect with an extension of 7 cm × 5 cm and it appeared to grow in the context of the gastric wall resulting in marked narrowed lumen. The lesion showed markedly uneven structure, with impregnation of its peripheral components, intralesional branches and hypodensity of the central portions as for cystic and/or necrotic-colliquative process. The lesion developed mainly on the serous side and in the context of the omentum some globose adenopathies were located with maximum dimensions of 14 mm. Moreover, a severe steatosis was present. Therefore, for this clinical picture we took into consideration the hypothesis of a GIST or a lymphoma without, however, being able to exclude other neoplastic diseases.

Within few days during the hospital stay the patient had developed an intestinal obstruction of high origin. We have submitted the patient to an endoscopic ultrasonography (EUS), which could not be performed due to the impossibility to distend the gastric lumen in correspondence of the deformation of the antro-pyloric region and without the possibility to study the gastric wall layers.

Therefore, due to acute presentation we have decided to submit the patient to an exploratory laparoscopy with extemporary biopsy of the perigastric tissue of the

antral region. We performed a subtotal gastrectomy with lymphadenectomy and reconstruction of the digestive tract with a Roux-en-Y anastomoses and total omentectomy.

The extemporary biopsy of the perigastric tissue demonstrated only lymphoid tissue with infiltration of the adjacent adipose tissue. Even the extemporary biopsy of the falciform ligament highlighted the infiltration of the adipose tissue by lymphoid elements.

The definitive histological examination has revealed chronic inflammatory infiltration of the falciform ligament, of the gastric wall and of the greater omentum.

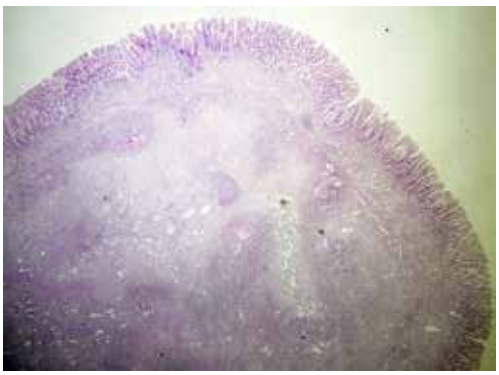

Figure 2 Polypoid appearance determined by submucosal mesenchymal proliferation, with vascular and fibroblastic components (HE, ×80).

At the definitive histological examination, a neoplasm of the antrum was identified in the anterior wall measuring 2.5 cm × 7 cm. The neoplasm showed a diffuse inflammatory infiltration with prevalent eosinophils and polypoid intramural protrusion. The perivisceral infiltrator presented subacute character of lipophagic gigantocellular (*Figures 2,3A*). The features were in favor of IFP with a differential diagnosis of GIST.

Immunohistochemical staining showed positive CD34 (*Figure 3B*) and negative: CK AE1/AE3, Desmin, AML, S-100, CD20. Therefore, the neoplasm was compatible with the diagnosis of an IFP-tumor of Vanek. The patient was discharged 2 weeks later, asymptomatic. At 14 months of follow-up, the patient is disease-free at abdominal CT and OGDS.

Discussion

IFPs are rare submucosal growths in the gastrointestinal tract. They are benign mesenchymal gastrointestinal tumors. IFPs mainly occur in the gastric antrum and in the duodenum, but also in the small and large intestine. IFPs are solitary submucosal lesions with perivascular onion skinning and prominent eosinophilic infiltrates (1).

In 1920 Konjetzny described the first case of IFP as a "polypoid fibroma", successively in 1949 Vanek reported six cases of gastric lesions which he referred to as gastric

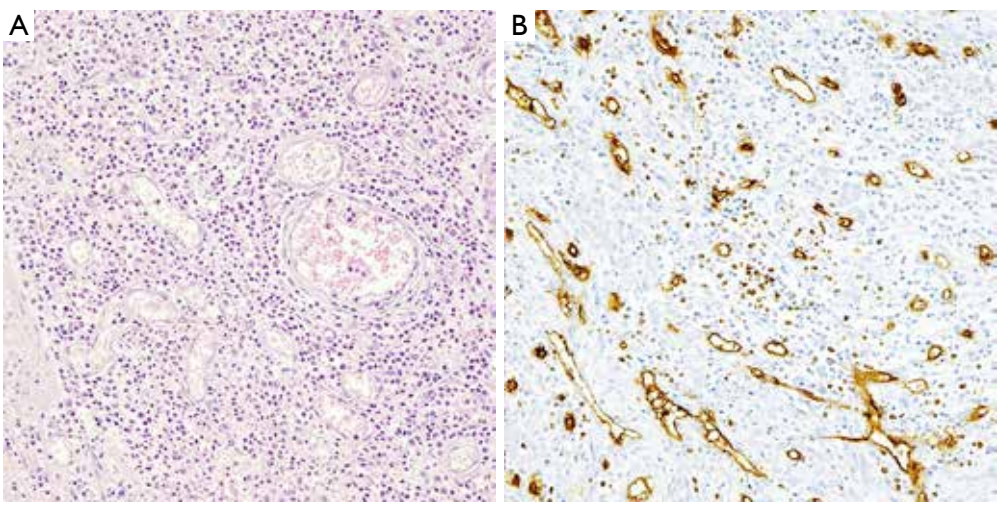

Figure 3 At higher magnification, the polyp presented mononuclear, spindle-shaped cells, arranged in whorls. An inflammatory infiltration includes blood vessels, eosinophil granulocytes, lymphocytes, macrophages and mastocytes. (A) The rich eosinophilic infiltrate is the classic one as originally described by Josef Vanek (HE, ×320); (B) CD34 showed the vascular network inside the lesion (Mayer's haemalum counterstain, ×320).

submucosal granuloma with eosinophilic infiltration (2). Helwig and Ranier introduced the term "inflammatory fibroid polyp" in 1953 (3).

They are usually asymptomatic, often diagnosed as incidental finding during endoscopy examinations. Depending on their size and location, IFPs can be associated with unspecific symptoms such as abdominal pain, weight loss, dyspeptic symptoms, iron deficiency anemia, intestinal obstruction, and rarely massive digestive hemorrhage (4). Giant IFPs of the gastric antrum or the duodenum can determine an intermittent gastric outlet obstruction called "ball valve syndrome" (5).

The peak age incidence occurs between 60 and 70 years (6) with a moderate male predominance. Upon the first diagnosis, the asymptomatic IFP usually measures between 2 and 5 cm. An ileal location is most frequently responsible for intestinal intussusception (7). However, giant IFPs have been reported with a size of up to 12.5 cm in diameter (8).

Regarding whether the lesion is neoplastic or not, nowadays authors agreed in favor of it being a benign reactive phenomenon similar to a granuloma occurring in response to an unknown irritant agent (9). Different hypotheses have been proposed to explain the etiology of these uncommon subtype of gastric polyps: possible role of *H. pylori infection*, physical or metabolic factors, parasites, and allergic cause, but to date the pathogenesis of IFPs remains unclear (9-11).

Endoscopic biopsies are unhelpful and right diagnosis can be reached only with resection. In fact, only about 10% of gastric lesions are diagnosed correctly prior to resection (10,12-14). Therefore, the diagnostic role of endoscopy is to identify a solitary lesion with an intramural growth.

EUS can be useful to better identify the submucosal lesion. At EUS, IFPs appear hypoechogenic and homogeneous, with indistinct margins, located within the second and third sonographic layers of the gastric wall. The numerous blood vessels within the lesion give internal echoes. EUS can support the differential diagnosis: GIST have a transmural growth with well-defined margins (13,15,16).

Several differential diagnoses have to be considered. The most common benign lesions are adenomatous polyps, which are usually small. The presence of fat within the lesion characterizes intestinal lipomas at CT and magnetic resonance imaging (MRI). Lymphomas account for 20% to 40% of malignant small bowel lesions typically seen as a voluminous endoluminal tumor. GISTs have a similar appearance to IFPs but generally show partial extraluminal growth with irregular margins and a heterogeneous appearance (17).

The radiological appearance of IFPs is not specific and is scarcely reported in literature. An IFP is often described at imaging exam as an intestinal tumor growing in the lumen of the digestive tract. Balci *et al.* (18) have reported the MRI appearance on a T2-weighted HASTE sequence.

The peripheral enhancement is probably related to the hypervascularized nature of the IFP. On the diffusion sequence, the spherical aspect appears similar to the pathological anatomy findings: from the periphery to the center, a fleshy bud (external ring with accelerated diffusion), a fibrous ring (ring with restricted diffusion) and a central edematous and myxoid area (homogeneous diffusion).

IFPs appear either sessile or pedunculated on endoscopic examination, and may present superficial erosion/ulceration. Differential diagnosis has often to be made with GISTs, which have an incidence of 1% of all gastrointestinal tumors (19), but also with various benign mesenchymal tumors such as inflammatory pseudotumor, hemangioendothelioma, hemangiopericytoma, spindle cell carcinoid, T-cell lymphoma and solitary fibrous tumor.

Immunohistochemistry can differentiate between the two tumors, which are both positive for CD34, but only GISTs express CD117 (c-kit). Moreover, IFP is typically associated with a mutation of exon 12 of the *PDGFR-A* gene (20).

Wille *et al.* (9) have described the histologic features of IFPs, which present submucosal proliferations of spindle cells, often arranged in an onion-like pattern not only around blood vessels but sometimes also around mucosal glands. Besides proliferation of numerous capillary vessels of varying size, there were always irregularly shaped blood vessels which were often ectatic and with varying thickness of the muscular walls. Overall, there was an inflammatory reaction of varying degree, dominated by eosinophils and macrophages. Focal inflammation was seen in and around the wall of few medium-sized venous vessels. Moreover, due to the immunohistochemical similarities and since IFPs and GISTs occur exclusively in the gastrointestinal tract, Wille *et al.* have suggested the possibility that IFPs can be the non-neoplastic counterparts of true GIST tumors emerging from the same primitive perivascular stem cell that seems to be specific for the gastrointestinal tract.

Endoscopic polypectomy can be performed if the lesion is polypoidal and accessible. However, endoscopic resection

may result in perforation or incomplete resection and in an increased risk of local recurrence due to its typical submucosal growth with sessile aspect. Therefore, in case of large tumors, surgical treatment with complete resection is often necessary. IFPs do not usually recur or metastasize and wedge resection with safe margins is curative.

In our case, we have had to perform a subtotal gastrectomy due to the large size of the neoplasia, which had produced an intestinal obstruction syndrome. We had not the possibility to better characterize the lesion with an EUS, first of all due to acute presentation, secondly for the impossibility to distend the gastric lumen. Therefore, we needed to resolve the obstruction syndrome and to better characterize the lesion that we thought was probably a GIST, as suggested preoperatively at the CT imaging.

Conclusions

Giant IFPs are rare benign lesions whose atypical presentation can mimic GISTs, lymphomas or carcinomas. Clinical and radiological findings may not clarify the right diagnosis until backed by histopathological evaluation through immunohistochemical analysis. The resection of IFPs with negative margins is curative with a good clinical outcome. In acute presentation, like in our case, surgery is the mainstay of treatment.

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Footnote

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References

1. Carmack SW, Genta RM, Schuler CM, et al. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. Am J Gastroenterol 2009;104:1524-32.
2. Vanek J. Gastric submucosal granuloma with eosinophilic infiltration. Am J Pathol 1949;25:397-411.
3. Helwig EB, Ranier A. Inflammatory fibroid polyps of the stomach. Surg Gynecol Obstet 1953;96:335-67.
4. Zhang C, Cui M, Xing J, et al. Massive gastrointestinal bleeding caused by a giant gastric inflammatory fibroid polyp: A case report. Int J Surg Case Rep 2014;5:571-3.
5. Yazumi S, Nakase H, Matsushima Y, et al. The "scarf-ring sign" of ball valve syndrome. Gastrointest Endosc 2002;55:560.
6. Liu TC, Lin MT, Montgomery EA, et al. Inflammatory fibroid polyps of the gastrointestinal tract: spectrum of clinical, morphologic, and immunohistochemistry features. Am J Surg Pathol 2013;37:586-92.
7. Nonose R, Valenciano JS, da Silva CM, et al. Ileal Intussusception Caused by Vanek's Tumor: A Case Report. Case Rep Gastroenterol 2011;5:110-6.
8. Harned RK, Buck JL, Shekitka KM. Inflammatory Fibroid Polyps of the Gastrointestinal Tract: Radiologic Evaluation. Radiology 1992;182:863-6.
9. Wille P, Borchard F. Fibroid polyps of intestinal tract are inflammatory-reactive proliferations of CD34-positive perivascular cells. Histopathology 1998;32:498-502.
10. Albuquerque A, Rios E, Carneiro F, et al. Evaluation of clinico-pathological features and Helicobacter pylori infection in gastric inflammatory fibroid polyps. Virchows Arch 2014;465:643-7.
11. Park DY, Lauwers GY. Gastric polyps: classification and management. Arch Pathol Lab Med 2008;132:633-40.
12. Stolte M, Finkenzeller G. Inflammatory fibroid polyp of the stomach. Endoscopy 1990;22:203-7.
13. Sadamoto Y, Tanaka M, Harada N, et al. Gastrointestinal: gastric inflammatory fibroid polyp. J Gastroenterol Hepatol 2001;16:1069.
14. Zinkiewicz K, Zgodzinski W, Dabrowski A, et al. Recurrent inflammatory fibroid polyp of cardia: a case report. World J Gastroenterol 2004;10:767-8.
15. Chan JK. Images in pathology: myxoglobulosis of the appendix. Int J Surg Pathol 2001;9:303.
16. Matsushita M, Hajiro K, Okazaki K, et al. Gastric inflammatory fibroid polyps: endoscopic ultrasonographic analysis in comparison with the histology. Gastrointest Endosc 1997;46:53-7.
17. Bensimhon D, Soyer P, Boudiaf M, et al. Imaging of gastrointestinal stromal tumors. J Radiol 2009;90:469-80.
18. Balci NC, Radjazi S, Polat H. Adult intussusception secondary to inflammatory fibroid polyp: demonstration by MRI. Eur Radiol 2000;10:1708-10.

19. Ridolfini MP, Cassano A, Ricci R, et al. Gastrointestinal stromal tumors. Ann Ital Chir 2011;82:97-109.
20. Daum O, Hatlova J, Mandys V, et al. Comparison of morphological, immunohistochemical, and molecular genetic features of inflammatory fibroid polyps (Vanek's tumors). Virchows Arch 2010;456:491-7.

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Is a "wait-and-see" policy the best for small gastric gastrointestinal stromal tumor (GIST)?

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Several months ago, a middle-aged female patient presenting with a gastrointestinal stromal tumor (GIST) visited me at Sanjo General Hospital to seek a second opinion of her disease. The patient was asymptomatic and a diagnosis of submucosal tumor (SMT) in the stomach was made on the basis of barium swallow in a health examination. The incidentally found SMT was located at the gastric fornix and not associated with ulceration. Endoscopic ultrasonography (EUS) and computed tomography (CT) both showed that the tumor had a homogenous content and measured approximately 1.8 cm in maximal diameter. EUS-guided fine-needle aspiration (FNA) disclosed KIT-positive spindle cells. A diagnosis of GIST was made, and the attending physician recommended that she undergo surgical resection of the tumor. The query of the patient was whether surgery was mandatory or not although she preferred not to. I informed her of the potentially malignant nature of GIST and the very low risk of metastasis in her case and advised that resection was essentially recommended although she could take a wait-and-see strategy with regular follow-up. The patient finally chose watchful waiting and was scheduled for another CT 6 months later.

With gastric surveillance becoming more widespread, asymptomatic, incidentally found GISTs are becoming more common, and we occasionally encounter gastric GISTs smaller than 2 cm in diameter, named "small gastric GISTs" (SGGs). Owing to the lack of clinicopathological data, however, an unanswered clinical question remains: how can we manage SGGs?

In a study published in Medicine, Shen and colleagues offered new evidence for managing patients with SGGs (1). They analyzed the clinical outcomes of 54 patients who underwent endoscopic and surgical resections of gastric GISTs measuring 2 cm or smaller at the authors' institution. The study of Shen *et al.* provided two pieces of clinically useful information. First, endoscopic resection was safe and feasible. Second, SGGs included a considerable number of tumors with significant metastatic risk. By comparing two patient groups divided according to selected treatment, Shen *et al.* showed that endoscopic resection was a more preferable procedure than surgical resection in terms of operative time, blood loss, use of analgesics, time of nasogastric tube retention, and hospital stay. Conventional open surgery was selected in all patients of the surgical group. The results are, therefore, not surprising. Nevertheless, the data of 32 SGG patients who underwent endoscopic resection were regarded as clinically valuable.

Advances in endoscopic technology, including endoscopic submucosal dissection (ESD), have enabled the resection of large and submucosa-invasive gastric carcinomas. Nevertheless, concerns remain whether or not endoscopic resection is applicable to gastric SMTs, because in such cases, the tumors are mainly located beneath the mucosa, which presumably increases the risk of operative morbidities, including perforation and bleeding. Indeed, the reported incidence of perforation ranged from zero to 28% in early studies of endoscopic resection of gastric SMTs (2-6). In the current study by Shen *et al.*, perforation and postoperative bleeding occurred in one (3%) and two patients (6%), respectively. The findings suggested that endoscopic resection for SGGs was relatively safe and feasible. It should be noted, however, that the authors selectively used endoscopic resection in patients with tumors exhibiting intraluminal growth, not in patients with extramural and mixed-type GISTs. Ye *et al.* (5) have reported a higher risk of perforation in tumors located at

the deep muscular layer than in those at the superficial muscular layer (70% *vs.* 1.3%). Careful selection of patients according to intramural location may be critical for achieving safe endoscopic resection of GISTs.

Despite increasing evidence pointing to the safety of endoscopic resection, it also should be noted that the current study of Shen *et al.* has corroborated the technical feasibility of endoscopic resection for SGGs but has not ensured an oncological one. They made no mention of the histological status of the endoscopically excised tumors although they reported no macroscopic tumor residue. Joo *et al.* (6) reported conducting endoscopic resection in 90 GIST patients, 23 (25.6%) of whom microscopic complete resection with histologically negative margins was achieved. Although only one patient showed recurrence after the median follow-up of 31.5 months in Shen *et al.*'s study, delayed local recurrence is not rare in GIST (7). We should wait longer to determine whether endoscopic resection with possible microscopic injury of tumor capsules increases the risk of *in situ* recurrence or not.

The clinicopathology of SGGs was another important finding in Shen *et al.*'s study. Of the 54 SGGs that were endoscopically or surgically excised, of which median tumor size was 1.7 or 1.82 cm, respectively, seven tumors showed 6–10 mitoses per 50 high power fields (HPF) and four showed more than 10 mitoses per 50 HPF. Patients presenting with tumors showing high mitotic activities should be regarded as being at a significant risk of metastasis, and tumor resection should be recommended. Studies by refined histopathological analysis have revealed that subclinical minute GISTs (micro GISTs), which are smaller than 10 mm in diameter, are unexpectedly common in the general population. Micro GISTs were found in 22.5% of autopsy cases (8) and 35% of gastric cancer patients who underwent stomach resection (9). On the contrary, population-based studies have estimated that the annual incidence of clinically diagnosed GISTs is 11–14.5 per million (10-12). According to observations of the large differences between the incidences of micro and clinical GISTs, there is widespread understanding that many of the micro GISTs are self-limiting and only a small population of micro GISTs develop into clinically diagnosed GISTs. Thus, it remains undetermined how earnestly we should remove asymptomatic SGGs, which are borderline lesions of the two categories. According to expert consensus, clinical guidelines recommend that endoscopic surveillance be conducted at 6- to 12-month intervals (wait-and-see approach) for SGGs that show no possible high-risk features based on endoscopy and ultrasonography, because data on SGG pathology are limited (13,14).

The current study of Shen *et al.* has shown that SGGs include a considerable number of GISTs with significant metastatic potential. In a recent study from Italy (15) in which 170 GISTs measuring 2 cm or smaller were analyzed, mitotic activity was found to be very low in tumors smaller than 1 cm, but the activity dramatically increased once the tumor size exceeded 1 cm. These findings suggested that SGGs were not self-limiting lesions in contrast to micro GISTs, strongly supporting that timely histological diagnosis should be made even in small SMTs. On the other hand, Sekine *et al.* (16) reported a significant increase in the mean diameter of SGGs from 1.14 cm to 2.27 cm after a 12-month follow-up of 18 patients with tumors histologically diagnosed by FNA. The wait-and-see approach could be a practical choice for making decisions on the necessity and timing of tumor resection as EUS-FNA is difficult for small gastric SMTs. Patients who select regular follow-up would have to continue undergoing endoscopic examinations at 6- to 12-month intervals and sustain psychological and financial burden because their disease has yet to be essentially eradicated. Endoscopic resection may be suitable for the management of patients with small gastric SMTs because the procedure is not only diagnostically useful but also potentially curable. Although more data are needed, the study of Shen *et al.* has opened doors to a new approach for small gastric SMTs.

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Footnote

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References

1. Shen C, Chen H, Yin Y, et al. Endoscopic versus open resection for small gastric gastrointestinal stromal tumors: safety and outcomes. Medicine (Baltimore) 2015;94:e376.
2. Huang WH, Feng CL, Lai HC, et al. Endoscopic ligation and resection for the treatment of small EUS-suspected gastric GI stromal tumors. Gastrointest Endosc 2010;71:1076-81.
3. Bai J, Wang Y, Guo H, et al. Endoscopic resection of

small gastrointestinal stromal tumors. Dig Dis Sci 2010;55:1950-4.
4. Huang ZG, Zhang XS, Huang SL, et al. Endoscopy dissection of small stromal tumors emerged from the muscularis propria in the upper gastrointestinal tract: Preliminary study. World J Gastrointest Endosc 2012;4:565-70.
5. Ye LP, Zhang Y, Mao XL, et al. Submucosal tunneling endoscopic resection for small upper gastrointestinal subepithelial tumors originating from the muscularis propria layer. Surg Endosc 2014;28:524-30.
6. Joo MK, Park JJ, Kim H, et al. Endoscopic versus surgical resection of GI stromal tumors in the upper GI tract. Gastrointest Endosc 2016;83:318-26.
7. Papalambros A, Petrou A, Brennan N, et al. GIST suture-line recurrence at a gastrojejunal anastomosis 8 years after gastrectomy: can GIST ever be described as truly benign? A case report. World J Surg Oncol 2010;8:90.
8. Agaimy A, Wünsch PH, Hofstaedter F, et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol 2007;31:113-20.
9. Kawanowa K, Sakuma Y, Sakurai S, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 2006;37:1527-35.
10. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. Cancer 2005;103:821-9.
11. Tryggvason G, Gíslason HG, Magnússon MK, et al. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer 2005;117:289-93.
12. Rubió J, Marcos-Gragera R, Ortiz MR, et al. Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. Eur J Cancer 2007;43:144-8.
13. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41.
14. Nishida T, Hirota S, Yanagisawa A, et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. Int J Clin Oncol 2008;13:416-30.
15. Rossi S, Gasparotto D, Toffolatti L, et al. Molecular and clinicopathologic characterization of gastrointestinal stromal tumors (GISTs) of small size. Am J Surg Pathol 2010;34:1480-91.
16. Sekine M, Imaoka H, Mizuno N, et al. Clinical course of gastrointestinal stromal tumor diagnosed by endoscopic ultrasound-guided fine-needle aspiration. Dig Endosc 2015;27:44-52.

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Extra Gastrointestinal Stromal Tumor treated with imatinib in a patient with Neurofibromatosis type 1

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Introduction

Neurofibromatosis type 1 (NF1) , also known as Von-Recklinghausen's disease is one of the most commonly transmitted hereditary autosomal dominant diseases, with an estimated birth incidence of 1:3,000. The pathogenesis is thought to be due to a mutation in the NF1 tumor suppressor gene that is found on chromosome 17. This mutation leads to the loss of tumor suppressor function, which then results in the development of benign and malignant tumors. In addition to cutaneous, soft tissue, and visceral (plexiform) neurofibromas, this syndrome is connected with several types of gastrointestinal (GI) and abdominal tumors. Examples of such include the following: neuronal hyperplasia (neuromas), ampullary carcinoid, pheochromocytoma, and gastrointestinal stromal tumor (GIST). The latter has been suggested to be the most common NF1-associated GI tumor. Here we present the case of a NF1 patient who was found to have extra gastrointestinal stromal tumor (EGIST) which is seen in <5% cases of GIST.

Case report

A 64-year-old man with known Neurofibromatosis type 1 was brought to the hospital after he was found unconscious and pulseless. He had multiple cutaneous neurofibromas (*Figure 1*). He was revived with CPR and defibrillation. He then underwent cardiac catheterization which revealed three-vessel coronary artery disease and was recommended to undergo coronary artery bypass graft (CABG) surgery. During the course of acute management, CT scans of the thorax and the abdomen and pelvis were obtained to rule out any hemorrhage or aortic dissection. Note was made of a large inhomogeneous pelvic mass with dimensions of 8.6 cm × 10 cm × 7.8 cm (*Figure 2*). A CT-guided biopsy of the mass revealed palisaded-appearing long spindle cells (*Figure 3*). A schwannoma was considered on morphologic grounds, but an S-100 stain was negative. There was focal, weak staining for smooth muscle actin (SMA). The neoplastic cells were strongly and diffusely positive for CD117 (c-KIT) (*Figure 4*) and CD34 (*Figure 5*), indicating a GIST. The KIT and PDGFR mutations were found to be negative on the mutational analysis. The tumor was considered to be marginally resectable and so the patient was started on imatinib 400 mg daily with the hope of making subsequent surgery feasible. A repeat CT abdomen/pelvis done after 3 months of imatinib therapy, showed multiple foci of air suggestive of necrosis, though the size of the tumor remained stable. The tumor was then resected en-bloc. A cavity was noted within the tumor along with fistula formation necessitating excision of part of the small intestine. After the surgery he was restarted on imatinib 400 mg daily with surveillance CT scans planned every six months.

Discussion

Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms that are related to the interstitial cells of Cajal of the myenteric plexus. These tumors express the cell-surface transmembrane receptor c-KIT that has tyrosine kinase activity and is the protein product of the *KIT* proto-oncogene (1).

GIST are rare tumors with an incidence of 1.5/100,000/year with EGIST being <5% of the total. There is a well-known correlation between NF1 and GIST as GIST

Figure 1 Cutaneous neurofibromas

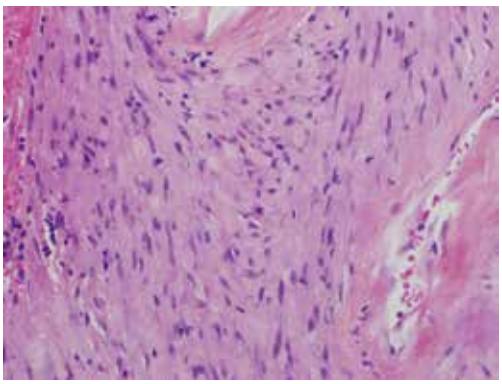

Figure 2 Palisaded appearing long spindle cells

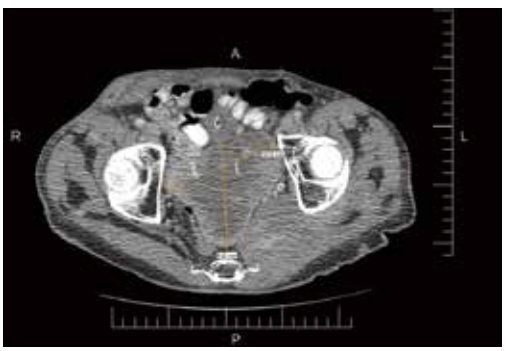

Figure 3 CT image of the pelvic mass

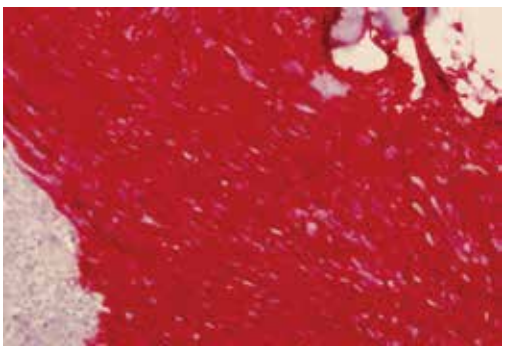

Figure 4 CD117 positive

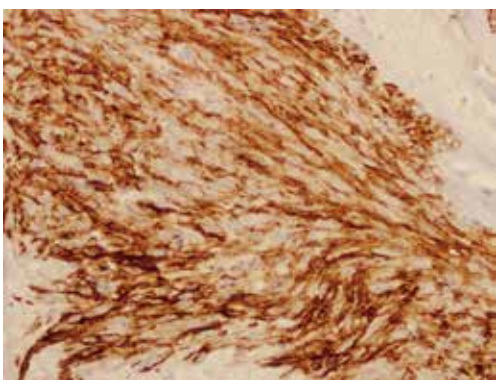

Figure 5 CD34 positive

develops in 7% of patients with NF1. The occurrence of NF1 is 150-180 times more frequent in GIST than in the general population. However, it is known that NF1-associated and sporadic GIST have different pathogenesis.

EGIST are very rare mesenchymal tumors which originate in sites outside the gastrointestinal tract, with clinico-pathological and molecular profiles similar to GIST. The most common sites of EGIST are the retroperitoneum, the mesentery and the omentum (2). However, other less frequent sites have also been reported such as the gallbladder, the pancreas and the recto-vaginal septum. The EGIST comprise a group of aggressive stromal tumors; their behavior is similar to those of GIST of distal location. It is unusual to diagnose EGIST when they are small due to their atypical location and vague symptomatology (2). Goh *et al.* in a series of 8 cases found average tumor size of 14.8 cm at the time of diagnosis (3).

NF1-associated GIST appears to be a different entity than sporadic GIST (4). NF1 patients develop GIST at a younger age (median, 49 years) than individuals with sporadic GIST (median, 56 years). There is some female predominance for NF1-associated GIST, in contrast to a weak male predominance for patients with sporadic GIST. Also in terms of distribution, GIST in NF1 occur predominantly in the small intestines, unlike sporadic GIST of which 60% arise in the stomach (4). The occurrence of

multiple GIST is notably common in NF1 patients, and it is very uncommon among patients with sporadic GIST (4).

It has been reported that c-KIT activation occurs in all cases of GIST, regardless of the mutational status of *KIT* (4). In a study by Miettinen et al, no mutations were detected in the genomic DNA of KIT (exons 9, 11, 13, 17) or *PDGFRA* (exons 12, 18) in NF1 associated GIST, whereas sporadic GIST have a high frequency of such activating mutations (4). In sporadic GIST, these mutations are thought to be central events in tumorigenesis, and their occurrence even in minimal GIST <1 cm in diameter indicates them to be an early pathogenetic event. In regard to *KIT* mutations, Kinoshita *et al*. also reported no *KIT* mutations in 21 GIST in 7 patients with NF1 (such as in our patient described above). Lack of GIST-specific mutations suggests that the pathogenesis of GIST in NF1 patients is different from that of *KIT* or *PDGFRA*-driven GIST.

The diagnosis of GIST relies on morphology and immunohistochemistry. In 95% of GIST CD117 is positive (5).

Risk stratification is done on the basis of prognostic factors, which include: mitotic rate, tumor size, tumor site, surgical margins (including whether tumor rupture occurred) (5).

Contrast-enhanced abdominal and pelvic CT-scan is the preferred imaging for staging and follow-up. Recent studies have demonstrated that Response Evaluation Criteria In Solid Tumors (RECIST) is an insensitive tool in evaluating GIST treated with imatinib. Another means of assessment, the Choi criteria, describes a 10% decrease in unidimensional tumor size or a 15% decrease in tumor density on contrast-enhanced CT as an early indicator of response (6). This appears to be more sensitive and more precise than RECIST in assessing the response of GIST to imatinib after 3 months of therapy. This was seen in our case as the patient's tumor size remained stable after 3 months of imatinib but there was a decrease in tumor density with multiple foci of air seen in the follow up CT scan. So, CT assessment is a sensitive and specific method to assess the response of GIST to imatinib if evaluated by Choi criteria. Evaluation of FDG uptake using PET scan is useful mainly when early detection of tumor response to imatinib treatment is of special concern.

The standard treatment of localized GIST is complete surgical excision, without dissection of clinically negative lymph nodes (5). If complete resection is not feasible, or if cytoreduction is desired to allow less aggressive surgery, initial imatinib pretreatment is recommended (5). Following maximal tumor response, surgery is performed. Mutational analysis may help to exclude less sensitive mutational status (e.g., *PDGFRA D842V* mutations) from therapy with imatinib. PET scan is particularly useful to assess tumor response very rapidly, so that surgery is not delayed in the case of non-responding disease. In patients with locally advanced or metastatic disease, imatinib is the preferred treatment with the standard dose being 400 mg daily (5). Patients with exon 9 *KIT* mutations fare better in terms of progression free survival on higher doses, i.e. 800 mg daily, which is therefore standard treatment in this subgroup. Treatment should be continued indefinitely since treatment interruption is generally followed by rapid tumor progression. Close monitoring of tumor response should be continued throughout treatment, since the risk of secondary progression persists over time. The standard approach in the case of tumor progression is to increase the imatinib dose to 800 mg daily. In case of progression or intolerance on imatinib, the second-line standard treatment is sunitinib. This drug was proved effective in improving progression free survival following a '4 weeks on -2 weeks off' regimen. After failing on sunitinib, patients with metastatic GIST should be considered for participation in a clinical trial (5).

Conclusions

With the significantly higher incidence of GIST in NF1 patients, we suggest that guidelines be considered to screen for GIST in such patients in order to treat at an earlier stage of the disease. In addition it is important to note that fistula formation between the tumor and the small intestine, as seen in our case, is a possible complication of tyrosine kinase inhibitors. There is one reported case of vesicocutaneous fistula formation (7) and another reported case of colonic perforation (8) both during treatment with sunitinib. Clinicians need to be alert for this complication while treating GIST with tyrosine kinase inhibitors.

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Footnote

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References

1. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
2. Barros A, Linhares E, Valadão M, et al. Extragastrointestinal stromal tumors (EGIST): a series of case reports. Hepatogastroenterology 2011;58:865-8.
3. Goh BK, Chow PK, Kesavan SM, et al. A single-institution experience with eight CD117-positive primary extragastrointestinal stromal tumors: critical appraisal and a comparison with their gastrointestinal counterparts. J Gastrointest Surg 2009;13:1094-8.
4. Miettinen M, Fetsch JF, Sobin LH, et al. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol 2006;30:90-6.
5. Casali PG, Jost L, Reichardt P, et al. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20:64-7.
6. Benjamin RS, Choi H, Macapinlac HA, et al. We should desist using RECIST, at least in GIST. J Clin Oncol 2007;25:1760-4.
7. Watanabe K, Otsu S, Morinaga R, et al. Vesicocutaneous fistula formation during treatment with sunitinib malate: Case report. BMC Gastroenterol 2010;10:128.
8. Hur H, Park AR, Jee SB, et al. Perforation of the colon by invading recurrent gastrointestinal stromal tumors during sunitinib treatment. World J Gastroenterol 2008;14:6096-9.

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Durable response with a combination of imatinib and sorafenib in KIT exon 17 mutant gastrointestinal stromal tumor

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Abstract: Imatinib, a selective KIT tyrosine-kinase inhibitor is considered standard first line therapy in metastatic gastrointestinal stromal tumors (GISTs). However, up to 40-50% of patients develop resistance to imatinib resulting in progression of disease. Other kinase inhibitors such as sunitinib, and most recently regorafenib have been approved as second and third line options respectively. Sorafenib has also been used following progression on standard therapies. Here we present the case of a patient with stage IV GIST of the rectum who had a rare exon 17 mutation treated prior to the approval of regorafenib. Therapy initially consisted of single agent imatinib, followed by sunitinib then sorafenib. Following continued progression of disease, the patient went on to develop stable disease for close to two years on a combination of sorafenib and imatinib.

Keywords: Gastrointestinal stromal tumor (GIST); c-kit mutation; imatinib; sorafenib

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Case report

A 54-year-old white male presented to his primary physician for routine examination. He was found to have a persistently increasing PSA (>20) and he subsequently underwent a prostate biopsy. Pathology was reported as CD117 positive (CD34, S100, smooth muscle actin and keratin negative) spindle cell neoplasm consistent with a gastrointestinal stromal tumor (GIST). There were 10 mitoses per 50 HPF and subsequent gene sequence analysis demonstrated N822K mutation at c-kit exon 17. Staging CT scan of his abdomen and pelvis demonstrated a 13 cm × 6 cm lesion extending down from his rectum to the level of the prostate as well as a 3 cm hepatic lesion concerning for metastatic disease (*Figure 1*). Treatment was initiated with imatinib 400 mg daily with follow-up CT scans every 3-4 months.

Six months after commencement of imatinib, CT scan showed interval increase in the size of the pelvic mass to 19 cm × 9 cm as well as several enlarged mesenteric lymph nodes and peritoneal metastases. Imatinib was increased to 800 mg daily. Additionally, he developed multiple right lower extremity deep venous thrombosis (DVTs) and started anticoagulation therapy with warfarin. Repeat CT scan three months later showed necrosis within multiple tumors, however the patient developed a new 3.2 cm × 2.3 cm lesion consistent with progression of disease. Imatinib was stopped and the patient was started on sunitinib 50 mg four weeks on and two weeks off.

While on sunitinib, he developed significant anemia with hemoglobin of 4.9 requiring admission to the hospital and multiple transfusions. Work-up revealed Coombs positive autoimmune hemolytic anemia managed with steroids. Additionally he developed new bilateral lower extremity DVTs while on coumadin and an IVC filter was placed. CT scan during that admission showed progression of disease.

Sunitinib was stopped and he began treatment with sorafenib 400 mg twice daily. CT scans after three months of treatment showed marked decrease in size of the primary tumor (*Figure 2*), but follow-up CT scans after six months on sorafenib revealed a new soft tissue mass in the left lower abdomen, as well as enlargement and necrosis of multiple soft tissue masses along the right paracolic gutter. There was also decrease in two masses in the right lower quadrant.

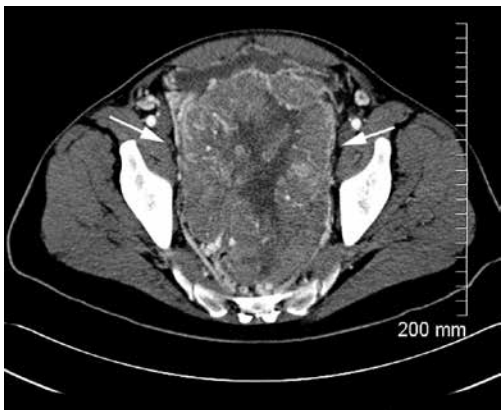

Figure 1 CT scan at diagnosis.

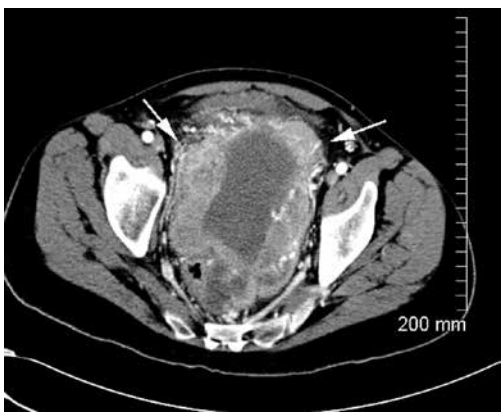

Figure 2 CT scan after three months of sorafenib 400 mg twice daily.

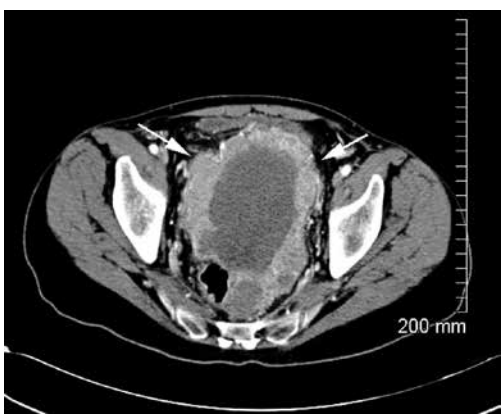

Figure 3 CT scan while on sorafenib and imatinib combination therapy.

At that time imatinib, 400 mg every other day was added to sorafenib 400 mg twice daily. Follow-up CT scans showed stable disease for almost one year after which he developed numerous peritoneal lesions (*Figure 3*). Imatinib was increased to 400 mg daily and surveillance CT scans have since remained stable over the last one year using combination treatment of imatinib and sorafenib.

Discussion

While a relatively rare gastrointestinal malignancy, GISTs are the most common primary mesenchymal tumor arising in the GI tract. Eighty five to ninety percent of all GISTs arise in the stomach and small intestine and approximately 4% arise in the rectum (1).

This group of tumors is believed to be derived from the interstitial cells of Cajal, which are responsible for coordinating peristaltic contractions throughout the GI tract. Studies have demonstrated that these cells commonly express KIT tyrosine kinase (CD117). Sixty eight percent of mutations to KIT occur in the juxtamembrane portion (exon 11) while only 1% are believed to occur in exon 17 (2).

Surgical resection remains the only potential curative treatment of GIST. However, recurrence rates following surgical resection have been reported from 40-90% (3).

Understanding of the molecular oncogenesis of GIST has prompted investigations in the use of targeted therapy to block the function of this tyrosine kinase. The first of these medications, imatinib produced significant responses with median progression free survival in the US S0033 phase 3 trial of 18 months and median overall survival of 55 months (4). Additionally, there was no significant difference in outcome between doses of imatinib 400 mg daily and 800 mg daily except in exon 9 mutated patients where the estimated risk of progression or death was reduced by 42% in the high dose arm compared to the lower (5). Twelve to fourteen percent of GIST patients have primary resistance to imatinib while 40-50% develop secondary resistance with progression of disease within 2-3 years (6,7). Resistance to tyrosine kinase inhibitors is of special consideration in exon 17 mutations in both the primary and secondary settings (8). Imatinib has been demonstrated to be more effective in juxtamembrane mutations like KIT exon 11 and PDGFR exon 12 and less effective in those mutations affecting activation loops like KIT exon 17 and PDGFR exon 18 (8).

Exon 17 mutants have also been shown to develop cross-resistance to sunitinib. Sunitinib has been approved as second line treatment following development of resistance or treatment failure with imatinib (9). A 2012 retrospective analysis of sorafenib as third or fourth line therapy in advanced GIST demonstrated a median overall survival of 13.5 months (10). Sorafenib, with its antagonism of the activation loop in exon 17 mutants, has provided rationale for its use in imatinib-resistant patients (11). Studies have suggested a role for intermittent imatinib in exon 17 mutant GIST (12). Liegl *et al.* reported on the heterogeneity of kinase inhibitors resistance mechanism in GIST, in a study of 53 GIST metastases in 14 patients, 6 out of 14 patients had two to five different secondary mutations in separate metastases. Furthermore, three patients were found to have two secondary KIT mutations within the same metastasis thus potentially raising the question of a consideration for studies evaluating combining TKI monotherapies if deemed tolerable and beneficial (13). While our patient developed resistance to imatinib six months after initiating therapy, he has had quite durable responses to sorafenib plus imatinib lasting more than two years. Recently, regorafenib has been approved for 3rd line treatment of GIST following progression after imatinib and sunitinib. GRID—a randomized phase 3 trial of 133 patients treated with regorafenib 160 mg once daily three out of four weeks showed a significantly improved PFS of 4.8 versus 0.9 months in the placebo arm (n=66) (14). Further studies are warranted to understand the role of regorafenib in patients with exon 17 mutations.

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Footnote

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References

1. Zhao X, Yue C. Gastrointestinal stromal tumor. J Gastrointest Oncol 2012;3:189-208.
2. Corless CL, Heinrich MC. Molecular pathobiology of gastrointestinal stromal sarcomas. Annu Rev Pathol 2008;3:557-86.
3. Rossi CR, Mocellin S, Mencarelli R, et al. Gastrointestinal stromal tumors: from a surgical to a molecular approach. Int J Cancer 2003;107:171-6.
4. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008;26:626-32.
5. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 2010;28:1247-53.
6. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
7. Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. J Clin Oncol 2005;23:5795-804.
8. Wozniak A, Floris G, Debiec-Rychter M, et al. Implications of mutational analysis for the management of patients with gastrointestinal stromal tumors and the application of targeted therapies. Cancer Invest 2010;28:839-48.
9. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci U S A 2009;106:1542-7.
10. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: a retrospective analysis. Eur J Cancer 2013;49:1027-31.
11. Guo T, Agaram NP, Wong GC, et al. Sorafenib inhibits the imatinib-resistant KITT670I gatekeeper mutation in gastrointestinal stromal tumor. Clin Cancer Res 2007;13:4874-81.
12. Revheim ME, Kristian A, Malinen E, et al. Intermittent and continuous imatinib in a human GIST xenograft model carrying KIT exon 17 resistance mutation D816H. Acta Oncol 2013;52:776-82.
13. Liegl B, Kepten I, Le C, et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J Pathol

2008;216:64-74.
14. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.

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