Surgeon's role for gastric gastrointestinal stromal tumor in imatinib era

Ji Yeon Park*, Young-Woo Kim

Gastric Cancer Branch, Research Institute & Hospital, National Cancer Center, Goyang, Korea

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor arising in the stomach, which is characterized by the protein-tyrosine kinase KIT (CD117) expression. Historically, surgical resection has been the mainstay of the curative treatment for localized primary tumors. However, more than an half of the patients with GISTs subsequently develop recurrence or metastasis. The discovery of the molecular pathogenesis of GIST led to the remarkable development of the molecular-targeted therapy with imatinib mesylate, a specific tyrosine kinase inhibitor, and the clinical management of GISTs has rapidly evolved during the last decade. As imatinib has demonstrated significant response in most metastatic GIST, it became the standard first line treatment in patients with metastatic or unresectable GISTs. Nonetheless, treating GIST with a single agent alone is proven to have many limitations because of development of imatinib resistance. Surgical resection still remains the only chance for a cure in GIST treatment. A key strategy for prolonging the survival of patients with GIST is to improve the outcome of surgery. Imatinib use in the GIST management may contribute to surgeons’ success in attaining this objective. It is clear that GIST is a complex disease, and a multidisciplinary approach with effective integration of surgery and targeted therapy is crucial to offer a better prognosis to the patients.

Keywords: Gastrointestinal stromal tumors, Surgery, Imatinib

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor that typically arises from the alimentary tract. This tumor is thought to originate from the spindle cells present in the gut wall—the interstitial cells of Cajal.

Prior to 1980s, stromal tumors of the gastrointestinal tract were thought to be neoplasms of smooth muscle origin and were therefore designated as leiomyomas, leiomyosarcomas or leiomyoblastoma. Subsequently, it is revealed that GISTs is a separate entity with distinct ultrastructural features and typical immunophenotype compared with smooth muscle tumors. For years, the only effective treatment available was surgery, but it is seldom curative for high-risk tumors. Postoperative recurrence and metastasis is as high as 40% to 90% of all cases of GISTs treated surgically [1,2]. Surgery in combination with conventional chemotherapy or radiation therapy largely has been ineffective in treating the majority of patients with malignant GIST.

The understanding of the pathobiology of GIST expanded significantly since the landmark work by Hirota et al. [3] in 1998 indicating that gain-of-function mutations in the KIT gene plays early and important role in the development of GIST. The subsequent work by Heinrich et al. [4] in 2003 additionally uncovered intragenic activating mutations in the related receptor tyrosine kinase, platelet-derived growth factor receptor α (PDGFRα). These mutations result in the constitutive activation of transmembrane receptor KIT or PDGFRα and their tyrosine kinase function, which leads to uncontrolled cell proliferation and resistance to apoptosis. The discovery of these tyrosine kinase receptor mutations in GISTs led to the remarkable development of the new molecularly targeted drug therapy with imatinib mesylate (Gleevec, Novartis Pharma, Review

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Correspondence to: Young-Woo Kim
Gastrian Cancer Branch, Research Institute & Hospital, National Cancer Center, 323 Ilsan-ro, Ilsan-dong-gu, Goyang 410-769, Korea
Tel: +82-31-920-1635, Fax: +82-31-920-0696
E-mail: gskim@ncc.re.kr

*Current affiliation: Department of Surgery, Soonchunhyang University Hospital, Seoul, Korea

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Basel, Switzerland), which targets and inhibits the activated KIT tyrosine kinase receptor. This drug has changed the therapeutic landscape of this previously treatment-refractory tumor. Imatinib has been shown to not only prolong survival time but also improve quality of life with generally manageable side-effects as compared to conventional cytotoxic chemoagents. Treatment of GIST is currently regarded as the paradigm of molecular targeted therapy in solid tumors.

**EPIDEMIOLOGY AND CLINICAL PRESENTATION**

According to a population-based sample, the annual incidence of GIST was estimated at 10-20 cases million [5]. Based on this figures, the annual incidence in South Korea can be estimated at 500-1,000 cases. Of these, 20%-30% are malignant tumors. GISTs are known to demonstrate fairly similar distribution between genders, but some series showed a slight male predominance [6]. Although GIST has been reported in patients of all ages, most of the people affected by the disease are between 40 and 80 years old at the time of diagnosis, with the median age of 60 years. Pediatric GISTs represent 1%-2% of all GISTs with a predilection in females, and 85%-90% of these GISTs fall under wild-type GIST lacking KIT or PDGFRA mutations [6]. The majority of GISTs are sporadic, but there are several case reports of familial germline mutations in the KIT or PDGFRA proto-oncogenes. Approximately 60%-70% of the GISTS arise in the stomach, 20%-30% in the small intestine, 5% in the colon and in the rectum and less than 5% in the esophagus [1]. Rarely, they can also develop in the omentum, mesentery, pancreas, or other retroperitoneal organs [7].

The majority (70%) of the patients diagnosed with GIST has non-specific symptoms, which are commonly related to mass effect or bleeding from a large-sized tumors, such as abdominal discomfort, gastrointestinal bleeding from a mucosal erosion, or an abdominal mass. GISTS can also rupture into the peritoneum causing peritonitis or life-threatening intraperitoneal hemorrhage. Asymptomatic small GISTS are often detected incidentally during surgery or endoscopy for other conditions, during rectal examination, or occasionally as incidental radiologic findings. 10% of the cases are detected only at the time of autopsy.

**DIAGNOSIS**

**Clinical diagnosis**

Contrast-enhanced computed tomography (CT) of the abdomen and pelvis is useful to evaluate the primary tumor as well as to assess the extent of the disease and whether metastatic disease is present. The liver and peritoneal surface are the most common sites of the metastatic disease. On CT scan, GISTS typically appear as hyperdense, enhancing masses, closely associated with the stomach. Magnetic resonance imaging or contrast-enhanced ultrasound may be alternatives. Hypermetabolic uptake in fluorodeoxyglucose-positron emission tomography (PET) is highly sensitive, but not specific enough for the diagnosis of GIST. PET can be used to monitor the clinical response of tumor to treatment.

Endoscopy may be useful in the diagnosis of gastric GIST. On endoscopy, GIST appears as a submucosal mass, since it originated from the bowel wall and not the mucosa. This can be confirmed via endoscopic ultrasound (EUS). EUS can also be used to guide fine needle aspiration (FNA) for pathologic confirmation. Recent studies have shown that endoscopic FNA for the diagnosis of GIST has a sensitivity as high as 80% [8]. However, biopsies by either percutaneous or endoscopic techniques theoretically can precipitate tumor rupture and lead to tumor dissemination or hemorrhage. Preoperative tissue diagnosis is usually not necessary for primary localized tumors unless diagnosis is in doubt. Biopsy may be useful when another diagnosis, such as lymphoma, that would not benefit from surgical resection is entertained. Biopsy is also recommended for metastatic disease or in cases where the mass is marginally resectable and neoadjuvant imatinib is under consideration.

**Pathologic diagnosis**

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry. GISTs are monotonous tumors that can be divided into 3 principal subtypes depending on the microscopic morphology. The majority of GISTS (approximately 70% of cases) are spindle cell type, and about 20% of cases are composed of epithelioid cells, which are commonly seen in pediatric GISTs. The remaining 10% of GISTS have a mixed spindle and epithelioid cell morphology [2].

Immunohistochemical characteristics of GIST have proven very helpful in diagnosis. KIT (CD117) expression is a specific and sensitive marker for GIST, and approximately 95% of GISTS are immunoreactive for KIT. Most GISTS show a strong and diffuse cytoplasmic staining for KIT, although there is a variability in the level of KIT expression. KIT overexpression is usually related to mutations in the KIT gene, although PDGFRA mutations and other unknown mechanism also appear to result in KIT overexpression without KIT gene mutation. Although KIT-positivity is a major defining feature for GIST, KIT-positivity alone may not be sufficient for diagnosis because there are non-GISTS that are positive for KIT. GIST can be confidently diagnosed if the morphology and immunophenotype are concordant; however, tumors with any unusual features should
be sent to a referral institution with special expertise. In addition to KIT (CD117), 60%-70% of GISTs express CD34, but several other mesenchymal neoplasms, which enter into the differential diagnosis of GISTs, stain with CD34. 30%-40% of GISTs express smooth muscle actin and nuclear and cytoplasmic positivity for S100 protein occurs in 5%-10%, while a small minority of GISTs (2%) express desmin [9,10].

Traditional microscopy and immunohistochemistry are usually sufficient to establish the diagnosis of GIST. However, in tumors where the diagnosis remains uncertain, real-time polymerase chain reaction testing for KIT or PDGFRA gene mutations may be useful. KIT gene mutations are detectable in 75%-80% of all GISTs. PDGFRA mutations represents a minority of the overall GISTs (5%-7%) and PDGFRα mutant GISTs are generally limited to the stomach, particularly with an epithelioid morphology, and clinically less aggressive [4,11]. The diagnosis of KIT-negative GIST (in the 5% range of all GISTs) depends on tissue morphology as well as genotyping the tumor for a KIT or PDGFRA mutation as some tumors negative for KIT by immunohistohemistry have been shown to have either mutation [12,13]. A subset of 7%-14% of GISTs is negative for detectable KIT and PDGFRA mutations. These are quite rare, but nearly all of them are represented in the stomach. GISTs associated with Carney’s triad (paraganglioma, pulmonary chondroma, and gastric GIST) also appear to lack kinase gene mutations.

### Table 1. Risk of aggressive behavior is dependents on size and mitotic degree in a GIST

<table>
<thead>
<tr>
<th>Risk</th>
<th>Size (cm)</th>
<th>Mitotic count (/50 HPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt; 2</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Low risk</td>
<td>2–5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&lt; 5</td>
<td>6–10</td>
</tr>
<tr>
<td></td>
<td>5–10</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt; 5</td>
<td>&gt; 5</td>
</tr>
<tr>
<td></td>
<td>&gt; 10</td>
<td>Any mitotic rate</td>
</tr>
<tr>
<td>Any size</td>
<td></td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumor; HPF, high-power field. Adopted from Fletcher et al. [9] with permission from Elsevier.

### Table 2. Risk stratification of primary GIST by sites

<table>
<thead>
<tr>
<th>Mitotic index</th>
<th>Tumor parameter</th>
<th>Stomach</th>
<th>Jejunum/ileum</th>
<th>Duodenum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 per 50 HPF</td>
<td>≤ 2</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>&gt; 2, ≤ 5</td>
<td>Very low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>&gt; 5, ≤ 10</td>
<td>Low</td>
<td>Moderate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&gt; 10</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>&gt; 5 per 50 HPF</td>
<td>≤ 2</td>
<td>None</td>
<td>High</td>
<td>-</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>&gt; 2, ≤ 5</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>High</td>
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<td></td>
<td>&gt; 5, ≤ 10</td>
<td>High</td>
<td>High</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>&gt; 10</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Adopted from Miettinen and Lasota [14] with permission from Elsevier. GIST, gastrointestinal stromal tumor; HPF, high-power field.

### PROGNOSIS

The best indicator of malignancy is the confirmation of metastatic disease. When there is no evidence of distant metastasis, the risk of relapse of operable disease is estimated on the bases of mitotic rate, tumor size, tumor location, surgical margins and whether tumor rupture occurred. Tumor size and mitotic count are considered by the 2002 consensus risk classification (Table 1) [9]. Importantly, neither small size nor low mitotic rate completely excludes the potential for malignant behavior of the GIST.

Based on long-term follow-up of more than 1,600 patients, Miettinen and Lasota [14] proposed risk partitioning scheme which incorporated primary tumor location in addition to the mitotic count and tumor size (Table 2). In particular, it reflects the fact that gastric GISTs have a better prognosis than small bowel or rectal GISTs. According to these guidelines, gastric GISTs that are 2 cm or smaller with a mitotic index of 5 or less per 50 high-power field (HPF) can be regarded as essentially benign, but lesions larger than 2 cm with the same mitotic index have a risk for recurrence. Data are lacking on the prognosis of patients with GISTs smaller than 2 cm with a mitotic count of more than 5 per 50 HPF.

Recently, a nomogram utilizing the same criteria has been developed by Gold et al. [15] from Memorial Sloan-Kettering Cancer...
Center to predict recurrence-free survival (RFS) after resection of localized primary GIST (Fig. 1). This nomogram was shown to accurately predict RFS after resection, and may be useful for patients care, interpretation of trial results, and selection of patients for postoperative imatinib therapy.

**TREATMENT**

Successful treatment of GIST requires assessment of the extent and progression of disease, and integration of surgery and molecular-targeted therapy. Thus, a multidisciplinary team that includes radiologists, medical oncologists, pathologists, and surgeons is paramount for the effective care of these patients. A proposed algorithm for treatment of primary and recurrent metastatic GIST is outlined (Fig. 2).

**Primary localized GIST**

**Surgical resection**

Complete surgical resection is the mainstay of the treatment modality for GIST with no evidence of metastasis, and should be initial therapy if the tumor is technically resectable and associated with acceptable risk for morbidity. The objective of surgery is to remove all gross tumors and achieve negative microscopic margins (R0 resection). Wide margins have not been shown to be associated with better prognosis. En-bloc resection of the GIST and its pseudocapsule, if present, should be performed, and adjacent organs adhered to the tumor should also be completely resected en bloc. Care should be exercised to avoid excessive tumor manipulation, which can disrupt what may be a friable tumor and lead to bleeding and intraperitoneal dissemination. Avoidance of tumor rupture is imperative. Resection can usually be accomplished with only a wedge resection of the stomach, but it may require total or subtotal gastrectomy, depending on tumor location and size. Lymphadenectomy is not routinely necessary unless locoregional lymph nodes are enlarged, because regional lymph node involvement is rare in GIST.

All GISTs 2 cm or larger should be resected. Although a 2 cm cutoff is somewhat arbitrary, recent data suggest that it is reasonable [14]. However, the management of incidentally encountered GISTs smaller than 2 cm remains controversial. For a subset of patients with very small gastric GISTs (<2 cm) with no high-risk EUS features, endoscopic surveillance at 6- to 12-month intervals may be considered [16].

Successful use of laparoscopic techniques for the resection or small (<5 cm) primary GISTs has been reported in small series, reporting technical feasibility with favorable oncologic outcomes when performed by skilled surgeon [17-19]. Intraoperative endoscopy or laparoscopic ultrasound may be used to assist the laparoscopic procedure as needed. Advantages of laparoscopic resection also included minimal manipulation of the tumor as well as better cosmesis. However, long-term data for patients who have under-

![Fig. 2. Algorithm for the treatment of gastrointestinal stromal tumor in imatinib era. RFA, radiofrequency ablation. If all gross disease or all imatinib-resistant disease is treatable. Adopted from Gold and DeMatteo [20] with permission from Lippincott, Williams, and Wilkins.](image-url)
gone laparoscopic resection for GIST are generally lacking.

Complete gross resection of the tumor is the most significant factor for outcome and can be accomplished in 85% of patients with primary localized disease [21-23]. Prognosis of low risk GIST after complete resection is excellent. However, high-risk GISTs have a high rate of recurrence [23]. Without any further treatment, at least 50% of patients develop tumor recurrence and 5-year survival rate is approximately 50% [1,19].

Targeted adjuvant therapy
Since conventional adjuvant chemotherapy and radiation therapy has been proved ineffective in treating the majority of patients with malignant GIST, imatinib is being studied to determine whether it reduces recurrence. Adjuvant imatinib is provided in order to enhance the eradication of microscopic lesions after the complete gross resection, and proposed as an option for those patients with a substantial risk of recurrence. In a phase III trial by American College of Surgeons Oncology Group (ACOSOG, Z9001), 713 patients were randomized to imatinib 400 mg/day or placebo for 1 year after complete resection of primary GISTs (>3 cm) [24]. Imatinib demonstrated a significant increase in RFS as compared with a placebo, although no difference in overall survival (OS) between the two treatment arms was noted. Results from the recently completed randomized controlled Scandinavian Sarcoma Group XVIII (SSG-XVIII/AIO) trial suggested that adjuvant imatinib administered for 36 months improved RFS and OS, as compared to adjuvant imatinib administered for 12 months, for patients with a high estimated risk of recurrence of surgery [25]. Based on these results, it is recommended to use imatinib as an adjuvant treatment for at least 36 months for patients with high-risk GISTs (tumor greater than 5 cm in size with high mitotic rate >5 mitoses/50 HPF), but an optimal duration of adjuvant imatinib treatment has yet to be determined [26]. Estimation of risk of recurrence is important in selecting patients who would benefit from postoperative imatinib after complete resection. In addition to risk assessment, mutational analysis may guide the selection of those patients who are more likely to benefit from the treatment.

In the case of tumor rupture at the time of surgery, there has been spillage of tumor cells in the peritoneal cavity, so that occult peritoneal disease can be assumed. This puts the patients at a very high risk of peritoneal relapse [27]. Therefore, these patients should be considered for imatinib therapy either in adjuvant setting or in palliative setting. The optimal duration of treatment in these cases is unknown.

Neoadjuvant therapy
Neoadjuvant imatinib can be particularly attractive for patients with large or poorly localized primary tumors that would otherwise require extensive surgery or sacrifice of a large amount of normal tissue causing functional deficit. Neoadjuvant imatinib can be used to downstage the marginally resectable tumors. In these cases, a careful pretreatment and rapid treatment response assessment by CT and/or PET scan should be performed in multidisciplinary discussion. Duration of the neoadjuvant imatinib therapy may vary according to treatment response, and surgery should be performed after sufficient shrinkage of the tumors (typically between 4 and 6 months, up to 12 months) [17]. For patients who have undergone complete resection after neoadjuvant imatinib, continuation of imatinib following resection is warranted.

Most recurrence occurs within 2 years after surgery, and the most common sites for disease recurrence are liver and peritoneum. Although there is no evidence that earlier detection of recurrent GIST improve survival, the consensus statements advocate the intense surveillance during this period. For high and intermediate risk, CT scans of the abdomen and pelvis are recommended every 3 to 4 months for 3 years, then every 6 months until 5 years, and yearly thereafter. For patients with low or very low risk disease, CT scans are recommended every 6 months for 5 years after surgery [17,28].

Recurrent or metastatic GIST
The majority of the patients undergoing complete resection of primary GIST would develop tumor recurrence, and the median time to recurrence after surgery ranges from 18 to 25 months [1, 17, 22, 29, 30]. The most commonly involved site of recurrence is liver, and peritoneal dissemination follows next. Metastases to extra-abdominal sites such as lung or bone sometimes occur with disease progression [1,29]. Local recurrence limited to gastric wall of gastric GISTs is infrequent.

Because of the lack of any alternative therapies, surgical resection was considered for patients with recurrence after primary resection and for those with metastatic GIST in the pre-imatinib era. Patients with limited hepatic metastasis or isolated peritoneal recurrence were sometimes treated with surgical resection. The results of the surgical management for these patients have been variable depending on the factors such as tumor size, risk profile, completeness of tumor resection and the disease-free interval after initial surgery [30]. However, outcome was usually very poor: the median survival of such patients only ranged from 6 months to 19 months [1, 30-32]. The literatures in the era before the introduction of imatinib clearly demonstrate that surgery alone is not sufficient to provide long-term survival for GIST patients.

Imatinib is now the first line treatment in patients who develop recurrent metastatic disease. Imatinib therapy has significantly improved the prognosis of patients with metastatic GIST. Imatinib is
reported to achieve partial tumor response or stable disease in approximately 80% in advanced GISTs [33,34]. Remarkably, the median survival has improved to nearly 5 years [35]. The majority of patients with metastatic GIST achieve a response within 6 months of imatinib therapy with a median time to response of approximately 3 months [33,34]. However, positive responses after imatinib therapy alone in metastatic GIST are not maintained indefinitely, and the median interval to disease progression is less than 2 years [34]. Thus, a multimodal approach utilizing surgical resection in conjunction with imatinib therapy to treat recurrent and metastasis GIST in multidisciplinary team is highly desirable.

It is well recognized that the clones of resistant tumor cells develop continuously after initiation of imatinib therapy. The most common mechanism of the acquired resistance is additional point mutation in the KIT kinase domains [36,37]. The risk of disease progression on imatinib and developing imatinib resistance seems to be proportional to the amount of residual viable tumor. Therefore, once maximal response to imatinib occurs (generally after 2-6 months of therapy), metastatic disease can be evaluated by a multidisciplinary team for the chance of complete resection. Selected patients with metastatic GIST who have responsive disease or focal resistance to imatinib may benefit from elective surgical resection [38,39]. Imatinib therapy should be continued postoperatively, since treatment interruption is generally followed by rapid tumor regrowth in virtually all cases, even when lesions have been surgically excised [17,40].

However, surgery is generally not indicated in patients with generalized disease progression under imatinib treatment, unless to provide symptomatic relief [38,39]. In patients with overt diffuse progression, increasing the dose of imatinib or using other tyrosine kinase inhibitors, such as sumatinib, are more appropriate options [17].

**POSTOPERATIVE SURVEILLANCE**

As mentioned above, median time to tumor recurrence ranges from 18 to 25 months in patients who have undergone surgical resection. Although there is no evidence that earlier detection of recurrent GIST improves survival, imatinib therapy may suspend the tumor progression in most patients. Abdominal CT is an excellent imaging modality to monitor disease during the course of treatment and surveillance after surgery, and the National Comprehensive Cancer Network guidelines recommend CT scans should be obtained every 3 to 6 months for 3-5 years, then annually afterward [16]. For very low-risk GISTs, less-frequent surveillance with interval of 6 to 12 months could be allowed.

**CONCLUSION**

In 2001, Joensuu et al. [41] published their first experience with imatinib mesylate to treat metastatic GIST in a single patient who exhibited dramatic tumor regression. Since then, numerous clinical trials formally assessed the efficacy of imatinib in metastatic GIST, and they have reported approximately an 80% response rate, compared with a dismal 5% response to conventional chemotherapy. Imatinib mesylate has truly revolutionized the treatment of GIST. The treatment of GIST has evolved rapidly, and dramatic changes in clinical practice have been observed during the last decade. Nonetheless, it is also revealed that treating GIST with a single agent alone carries many limitations, as resistance to imatinib has become a significant clinical dilemma.

Surgical resection still remains the only chance for a cure in GIST treatment. A key strategy for prolonging the survival of patients with GIST is to improve the outcome of surgery, and imatinib use in the GIST management can aid attaining this objective successfully. It is clear that GIST is a complex disease. A multidisciplinary approach with close collaboration between the medical oncologist, the gastroenterologist, the radiologist, and the surgeon is essential to offer a better prognosis to the patients.

Furthermore, there are some points to be clarified. Notably, the ideal duration of adjuvant imatinib after surgery is still unclear. It is difficult to determine the exact place of surgery in metastatic or recurrent GIST patients. It is also unclear whether surgery makes any difference in outcomes in patients with metastatic GIST. Future and ongoing studies will further delineate the feasibility of multimodal treatment of this disease.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**


