Neoadjuvant and adjuvant therapy for gastrointestinal stromal tumors

Masaaki Iwatsuki1,2 | Kazuto Harada1,2 | Shiro Iwagami1 | Kojiro Eto1 | Takatsugu Ishimoto1 | Yoshifumi Baba1 | Naoya Yoshida1 | Jaffer A. Ajani2 | Hideo Baba1

1Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
2Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, USA

Correspondence
Hideo Baba, Department of Gastroenterological Surgery, Kumamoto University, Graduate School of Medical Sciences, Kumamoto, Japan. Email: hdebaba@kumamoto-u.ac.jp

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Abstract
Gastrointestinal stromal tumors (GIST) are rare and mesenchymal in origin with a yearly incidence of 10-15 cases per million people. If it is technically resectable, surgical resection is the mainstay of therapy regardless of tumor location. Although complete (R0) resection can be achieved in up to 85% of patients with primary disease, approximately 50% of patients experience recurrence or metastases within 5 years of primary resection. Moreover, prior to 2000, the prognosis of patients with advanced, inoperable GIST was poor because the molecular mechanism had not sufficiently been elucidated, thus effective therapy was lacking. The tyrosine kinase inhibitor imatinib, which selectively inhibits tyrosine kinase KIT, has shown substantial clinical benefit for patients with GIST. In clinical trials, imatinib treatment resulted in response rates of 40%-55% and longer progression-free survival for patients with a KIT-positive unresectable or metastatic GIST. Furthermore, recent clinical trials have shown that giving imatinib after curative resection for high-risk cases prolonged recurrence-free survival and overall survival in an adjuvant setting. Several clinical trials of imatinib treatment in a neoadjuvant setting are ongoing; however, in clinical settings, there are problems to resolve, such as optimal agents, duration of administration, and postoperative management. In this review, we discuss the application of surgical options, combined with adjuvant/neoadjuvant or perioperative imatinib treatment and their potential impact on survival for patients with primary, recurrent, or metastatic GIST.

KEYWORDS
adjuvant, GIST, imatinib, neoadjuvant

1 | INTRODUCTION

Gastrointestinal stromal tumors (GIST) are rare and mesenchymal in origin that are derived from the interstitial cells of Cajal in the gastrointestinal tract.1 With a yearly incidence of 10-15 cases per million people, GIST are the most common sarcomas of the intestinal tract, accounting for approximately 80% of all gastrointestinal mesenchymal neoplasms.2 Prior to 2000, there was no effective therapy for unresectable or metastatic GIST, because the molecular mechanisms of GIST development were not well understood. A significant
breakthrough was achieved with the identification of the expression of the CD117 antigen, which is part of the KIT transmembrane receptor tyrosine kinase (RTK).\textsuperscript{3} Approximately 80% of GIST have KIT gene mutations that lead to constitutive activation of the KIT receptor.\textsuperscript{3–5} Therefore, targeted therapy with imatinib, which is a small-molecule inhibitor of RTK that was originally approved for the treatment of chronic myeloid leukemia, induced dramatic, rapid, and sustained clinical improvement in patients with GIST.\textsuperscript{6} Many clinical trials have subsequently been conducted to confirm the utility of imatinib for patients with metastatic or unresectable GIST, leading to an improved prognosis for these patients.

For patients with a primary localized GIST, complete resection with negative microscopic margins remains the mainstay of therapy and should be the initial therapy if the tumor is technically resectable.\textsuperscript{7,8} However, about half of patients who had a curative complete resection subsequently experienced recurrence after several years.\textsuperscript{9} However, the precise factors responsible for malignant progression and aggressive clinical behavior have been debated for years.\textsuperscript{10} Several risk classifications have been established, which include tumor size, mitotic index, tumor location, and presence of tumor rupture.\textsuperscript{11,12} Most recently, a nomogram was developed to predict recurrence after surgery to help guide patient selection for adjuvant therapy.\textsuperscript{13} To improve the prognosis for patients with a high risk of recurrence after curative surgery, for several years, attempts to use imatinib perioperatively have been made based on the success of this agent in advanced or metastatic GIST. Although these multidisciplinary treatments can improve the prognosis of patients with advanced or high-risk GIST, in the clinical setting, there are several problems to resolve.

In the present review, we update and discuss recent progress in the perioperative use of imatinib and other agents for localized GIST. These new data improve our understanding of the multidisciplinary approach for treating advanced and localized GIST. This new information may lead to development of novel clinical targets and improve clinical management of GIST patients.

2 | GENERAL SURGICAL PRINCIPLES

For a resectable GIST (as confirmed by histological examination), surgical resection is the mainstay of therapy regardless of tumor location. The goal of surgery is to remove the tumor macroscopically with an intact pseudocapsule. Lymph node dissection is routinely unnecessary because lymph node metastases are extremely rare. Organ-preserving and function-preserving surgery is oncologically allowed if negative resection margins can be achieved. Bischof et al demonstrated recently that a laparoscopic approach for gastric GIST was associated with low morbidity and a high rate of R0 resection, and the long-term oncological outcome was acceptable. Therefore, they recommended that a laparoscopic approach should be the preferred approach for gastric GIST in well-selected patients.\textsuperscript{14} However, it remains unclear whether this procedure is applicable for larger GIST and for GIST at other sites because the tumor should be handled carefully to avoid rupture, which markedly increases the risk of disease recurrence. Therefore, laparoscopic resection for GIST should currently only be carried out by surgeons with expertise, and prospective studies are required to confirm the utility of the laparoscopic approach for GIST. Furthermore, even if complete resection is achieved for a larger tumor, the rate of recurrence increases with increasing size.\textsuperscript{15} Therefore, adjuvant therapy with imatinib is recommended, as discussed below. For patients with a very large localized GIST, which is considered unresectable without risk of unacceptable morbidity or functional deficit (so-called marginally resectable GIST), preoperative imatinib may be recommended. Preoperative imatinib treatment is also an option to facilitate organ- and function-preserving surgery because esophagectomy for esophageal GIST, pancreaticoduodenectomy for duodenal GIST, and abdominoperineal resection for rectal GIST may be invasive and impair quality of life. Although the goals of neoadjuvant therapy involving imatinib are to preserve organ function, to avoid tumor rupture and to reduce the risk of complication, evidence of safety and efficacy for preoperative imatinib treatment remains to be established.

3 | NEOADJUVANT THERAPY

The high response rate of advanced GIST to imatinib has made it possible to adapt imatinib to the neoadjuvant setting. It is expected that neoadjuvant therapy can achieve organ- or function-preserving surgery, avoid tumor rupture, and reduce postoperative complications. Furthermore, the shrinkage of tumors treated with imatinib permits conservative and less invasive R0 resection, especially for GIST located at the esophagogastric junction, and in the duodenum and rectum. However, as there are few clinical trials of neoadjuvant therapy for GIST, evidence of the efficacy of neoadjuvant therapy remains to be established (Table 1). NCCN guidelines state that neoadjuvant chemotherapy is considered if surgical morbidity could be reduced by downstaging the tumor.\textsuperscript{7} Furthermore, there are several important clinical concerns in the neoadjuvant setting, but not in the adjuvant setting.

3.1 | Clinical trials of neoadjuvant therapy

3.1.1 | Prospective study

The multicenter Radiation Therapy Oncology Group (RTOG) 0132/ American College of Radiology Imaging Network (ACRIN) 6665 trial is the only prospective phase II study yet conducted for neoadjuvant imatinib.\textsuperscript{16} Sixty-three patients with KIT-positive GIST were enrolled, including either primary GIST \( \geq \)5 cm or resectable recurrent or metastatic GIST \( \geq \)2 cm, who received preoperative imatinib (600 mg/day for 8-12 weeks). All patients received adjuvant imatinib for 2 years after surgery. Median follow-up period was 5.1 years. The 5-year progression-free survival and overall survival (OS) rates for localized GIST were 57% and 77%, respectively.\textsuperscript{17}

Recently, a phase II study for a neoadjuvant setting for large gastric GIST was reported from Asia.\textsuperscript{18} Patients with a large gastric GIST (\( \geq \)10 cm) received imatinib (400 mg/day) for 6-9 months before
surgery. Forty-six of 53 patients enrolled in this study completed at least 6 months of dosage. The response rate was 62%, and R0 resection was carried out in 91% of patients. The 2-year OS was 89%. These findings suggest that neoadjuvant imatinib therapy can be beneficial for larger gastric GIST. Operative morbidities of any grade occurred in nine (18%) patients (postoperative bleeding: 2, surgical site infection: 3, anastomotic leakage: 2, bowel obstruction: 1, pyloric stenosis: 1) without treatment-related deaths. However, this study was limited to gastric GIST in a single-arm non-randomized study with a short follow-up period; furthermore, mutation analysis was not carried out before imatinib treatment. Phase III trials are required to confirm the significance of neoadjuvant therapy for advanced GIST. We will discuss the neoadjuvant setting below.

### 3.1.2 Retrospective study

Several retrospective studies of neoadjuvant therapy have been reported.19,20 However, few data are available for primary GIST in the neoadjuvant setting, because most of these studies included both primary and recurrent or metastatic resectable GIST. Recently, in a larger retrospective study, 161 patients with locally advanced GIST who received preoperative imatinib (400 mg daily) was reported.19 The primary tumor was located in the stomach (55%), rectum (20%), small intestine (11%), duodenum (10%), or esophagus (3%). Median duration of preoperative imatinib was 40 weeks. Although the rate of R0 resection was 83%, two cases had disease progression before surgery. Five-year disease-specific survival and disease-free survival rates were 95% and 65%, respectively. Only 56% of patients received imatinib after surgery for at least 1 year. The findings of this study suggested that neoadjuvant imatinib therapy was feasible and effective for locally advanced GIST. It is possible that the benefit from neoadjuvant therapy depends on tumor location. Neoadjuvant therapy can be beneficial for GIST located at the esophagogastric junction, duodenal, and rectum because complete resection for these tumors requires extensive organ disruption through esophagectomy, pancreaticoduodenectomy, or abdominal perineal resection. For rectal GIST, in particular, several studies indicated the efficacy of neoadjuvant imatinib therapy. Jakob et al showed that the rate of the negative surgical margin in patients after neoadjuvant therapy was significantly higher than that in patients without neoadjuvant therapy.21 Also, all patients with a positive surgical margin who experienced recurrence after surgery did not receive imatinib before surgery. Tielen et al also showed that complete resection was achieved in 77% of patients given preoperative imatinib for rectal GIST.22 Furthermore, sphincter-preserving surgery is achieved more often in patients who received imatinib, also leading to a reduction of local recurrence. Although Wilkinson et al also showed that neoadjuvant imatinib therapy can decrease both tumor size and mitotic activity,23 suggesting that neoadjuvant therapy is a promising strategy for locally advanced GIST, a larger prospective study is required to resolve the clinical questions.

### 3.2 Agents as neoadjuvant therapy

Only imatinib has been evaluated in previous studies. It remains unclear whether other agents including sunitinib and regorafenib are effective in the neoadjuvant setting as well as the adjuvant setting, although there is one case report using sunitinib as an active neoadjuvant therapy as a result of severe adverse events from imatinib.24 Regarding the dose of imatinib, in the RTOG0132A/ACRIN6665 trial, 600 mg was given daily.16 Most retrospective studies of neoadjuvant therapy used a dose of 400 mg daily. However, in the European Society For Medical Oncology (ESMO) guidelines, 800 mg imatinib daily is recommended for KIT exon 9 mutation cases, based on the finding that cases with KIT exon 9 mutation have an inferior response to imatinib in metastatic disease.25 Therefore, it is necessary to evaluate the optimal dose of imatinib as neoadjuvant therapy in the context of the safety of subsequent surgery.

The optimal duration of imatinib treatment also remains unclear. The best timing of surgery is the point of best response by the agent before secondary resistance to the agent is acquired. Median time of response to imatinib is 3 months, as reported in a phase II trial of imatinib for unresectable GIST, and the rate of response reached a plateau at 6 months.26 Given these data, the optimal duration of neoadjuvant imatinib therapy appears to be 3-6 months.

### 3.3 Evaluation of response

It remains controversial as to which is the best modality to evaluate the response of GIST to tyrosine kinase inhibitors (TKI). Contrast-
enhanced computed tomography (CT) is useful to assess not only tumor size but also tumor viability, evaluated by blood supply. When imatinib is effective, it is often observed that tumor density decreases without a change in tumor size. Therefore, it is possible that the response evaluation criteria in solid tumors (RECIST) criteria are likely to underestimate the efficacy of imatinib. Choi criteria, which consider CT density, are useful to evaluate the response to imatinib for GIST.\(^{27}\) Positron emission tomography scanning using fluorodeoxyglucose (FDG-PET) is highly sensitive for GIST, which have high glucose metabolism. A prompt response is often observed (within days) without a change in tumor size. Recently, Farag et al. reported that carrying out PET for early evaluation of response can result in a change of treatment strategy in GIST patients treated with neoadjuvant intent.\(^{28}\) However, it is critical to conduct FDG-PET evaluation before treatment because in baseline surveillance, 20% of GIST do not display abnormal FDG uptake by the tumor. An earlier radiological assessment may be required in the neoadjuvant setting, because curative resection or sunitinib as second-line therapy should be considered if imatinib is not effective.

3.4 | Postoperative management

There is no consensus on postoperative management for patients receiving neoadjuvant therapy. High-risk GIST patients are recommended to receive adjuvant imatinib therapy, as described above. However, it may be desirable that patients with neoadjuvant therapy receive adjuvant imatinib therapy for several years, because the behavior of the original tumor before treatment may require adjuvant therapy. Notably, most patients in the RTOG0132 trial experienced recurrence within 2 years after discontinuation of imatinib.\(^{16}\) Therefore, further study is needed to determine the risk factor for recurrence after neoadjuvant therapy.

3.5 | Clinical concerns for neoadjuvant therapy

Although neoadjuvant therapy appears beneficial for locally advanced GIST, several clinical problems need to be resolved as follows. First, histological confirmation of a GIST is necessary prior to neoadjuvant therapy according to the National Comprehensive Cancer Network (NCCN) and ESMO guidelines.\(^{7,8}\) Furthermore, testing for mutation in c-kit and platelet-derived growth factor receptor alpha (PDGFRalpha) mutational analysis is strongly recommended before neoadjuvant therapy to ensure the tumor has a genotype that is likely to respond to treatment.\(^{7}\) However, tissue samples can sometimes be obtained by an endoscopic procedure, depending on tumor location. Sampling tissues by laparotomy should be avoided because of the possibility of intraoperative tumor spillage, leading to peritoneal dissemination. Second, risk stratification cannot be reliably evaluated after neoadjuvant therapy because tumor size and mitotic count can differ from those of the tumor before treatment. Therefore, the neoadjuvant strategy can make it difficult to select appropriate patients. Finally, we should provide patients with the following information: (i) we may miss the opportunity for curative resection as a result of disease progression if the GIST does not respond; (ii) postoperative complications may increase as a result of neoadjuvant therapy; and (iii) preoperative complications may arise, including tumor necrosis, perforation, and/or hemorrhage. In these circumstances, it is possible that surgery will be required when the patient is in poor condition. It is critical to establish a system to promptly deal with an emergency situation.

### TABLE 2
Clinical relevance of adjuvant treatment for GIST (prospective trials)

| Phase          | Journal          | Year | Cases | Agent/Dose          | Patients                  | Duration | Notes               |
|----------------|------------------|------|-------|---------------------|---------------------------|----------|---------------------|
| Prospective study |                 |      |       |                     |                           |          |                     |
| ACOSOG Z9000 (P-II) | Ann Surg        | 2013 | 107   | Imatinib/400 mg     | High-risk GIST            | 1 y      | 5-y RFS: 40%        |
| ACOSOG Z9001 (P-III) | J Clin Oncol  | 2014 | 713   | Imatinib/400 mg     | GIST (≥3 cm, mitosis>5 ≥ 50HPF) | 1 y      | 1-y RFS: 98% (imatinib) vs 83% (placebo) |
| SSGXVIII/AIO (P-III) | JAMA            | 2012 | 400   | Imatinib/400 mg     | High-risk GIST (>10 cm, high mitosis) | 1 vs 3 y | 5-y RFS: 66% (3 years) vs 48% (1 y) |
| EORTC 62024 (P-III) | J Clin Oncol   | 2015 | 908   | Imatinib            | Intermediate- or high-risk GIST | 2 y      | 5-y RFS: 69% (imatinib) vs 63% (surgery alone) |

GIST, gastrointestinal stromal tumor; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.
endpoints, namely the rates of 1-, 2-, and 3-year recurrence-free survival (RFS), were 96, 60, and 40%, respectively. In an analysis according to specific mutations, the median RFS of patients with KIT exon 9 mutation and exon 11 mutation were 19 months and 42 months, respectively. In a multivariate analysis for prognosis, KIT exon 9 mutation and high mitotic rate were significantly associated with poorer prognosis. This latter finding is consistent with a previous report that some mutations, including KIT exon 9, were associated with a poorer response to imatinib in the setting of advanced or metastatic disease.

4.2 | ACOSOG Z9001 (phase III)

In this trial, 713 patients who underwent a complete resection for KIT-positive primary GIST ≥3 cm were randomly assigned to a 1-year dosage of either imatinib (400 mg daily) (N = 359) or placebo (N = 354). When an interim analysis showed that few patients in the imatinib group experienced recurrence, this trial was stopped. The 1-year RFS rate, the primary endpoint, was 98% in the imatinib group and 83% in the placebo group (HR: 0.35, 95% CI: 0.22-0.53). In subgroup analysis, imatinib significantly improved RFS in all categories, including tumor size, mitotic rate, and tumor location. Notably, however, adjuvant imatinib therapy did not affect OS, perhaps because of the short duration of follow up, the limited number of relapses, or the high efficacy of imatinib for patients experiencing recurrence. Importantly, the findings in this trial bring several key clinical questions to light. One is the appropriate duration of imatinib treatment after complete resection; another is the definition of subsets of patients who should receive adjuvant imatinib therapy.

4.3 | SSGXVIII/AIO (phase III)

The Scandinavian Sarcoma Group (SSG) XVIII trial was a large randomized controlled trial comparing 2 vs 3 years of adjuvant imatinib therapy (400 mg daily) or observation after complete resection for intermediate or high-risk GIST patients. In this trial, high-risk was defined as having at least one of the following: tumor size >10 cm, mitotic count >10/50 high-power field (HPF), tumor size >5 cm with mitotic rate >5/50 HPF, or tumor rupture. There was a significant improvement in primary endpoint RFS in patients who received imatinib for 3 years compared with 1 year (5-year RFS: 66% vs 48%, HR: 0.46, 95% CI: 0.32-0.5). OS in patients treated for 3 years was also significantly improved compared to those patients treated for 1 year. Recent long-term follow-up results demonstrated that patients who received imatinib for 3 years had significantly greater RFS (71% vs 52%) and OS (92% vs 85%). Adverse events related to imatinib treatment were observed more frequently in patients treated for 3 years and included periorbital edema and muscle cramps. Most adverse events were grade 1 or 2, and the rate of severe adverse events ≥grade 3 was similar in both groups. However, the rate of discontinuation of imatinib for reasons other than disease progression was more frequent in patients treated for 3 years (26% vs 13%). Based on this trial, 3 years of adjuvant imatinib treatment is standard for high-risk GIST patients.

4.4 | EORTC 62024 (phase III)

The EORTC 62024 trial was an open-label randomized study comparing 2 years of adjuvant imatinib therapy (400 mg daily) or observation after complete resection for intermediate or high-risk GIST patients. Nineteen-eight intermediate- or high-risk patients, including those having experienced tumor rupture or intraoperative tumor spillage, were randomly assigned. Primary endpoint was imatinib-free survival (IFS: the time to death or starting treatment with other TKI). Five-year IFS was 87% in the treatment arm compared with 84% in the observation arm (HR: 0.79, 95% CI: 0.52-1.25). The difference in 5-year IFS between the treatment arm and the observation arm was not statistically significant even in limited high-risk or high-risk patients based on the modified National Institutes of Health (NIH) risk criteria, including tumor site.

### TABLE 3 Clinical concerns of neoadjuvant and adjuvant treatment for GIST

| Clinical concern | Note |
|------------------|------|
| **Neoadjuvant therapy** | |
| Agent | Only imatinib evaluated in previous studies. No trials whether sunitinib and regorafenib are effective in the neoadjuvant setting. |
| Optimal duration | At least 3-6 months prior to surgery may be required, but before secondary resistance (within 2 y). |
| Evaluation of response | PET may give indication of imatinib activity after 2-4 weeks of therapy for early evaluation of response. |
| Postoperative management | There is no consensus on adjuvant therapy for patients receiving neoadjuvant therapy. It may be desirable because the behavior of the original tumor before treatment may require adjuvant therapy. |
| **Adjuvant therapy** | |
| Optimal imatinib dose | Only the 400 mg daily dose was given in all previous phase III trials. |
| Optimal duration | At least 3 y of imatinib treatment is recommended for high-risk GIST patients, but phase II trial of 5-year dose of adjuvant imatinib was reported. |
| Patient selection | High-risk patients based on tumor size, mitotic rate, tumor location, and tumor rupture, mutation subtypes should also be considered during patient selection (PDGFRA exon 18 D842V mutation). |

GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; PET, positron emission tomography.
Collectively, the data from the above trials suggest that adjuvant imatinib therapy is effective for high-risk GIST patients. However, the following clinical questions remain unclear.

### 4.5 Optimal imatinib dose and duration

Only the 400 mg daily dose was given in all previous trials. However, an 800 mg daily dose of imatinib led to an improved outcome, compared to 400 mg daily, for patients with KIT exon 9 mutation in an advanced or metastatic setting. Further study is needed to clarify the optimal dose according to the molecular features and to evaluate the feasibility of high-dose therapy in an adjuvant setting.

Data from the SSG XVIII trial established that at least 3 years of imatinib treatment is recommended for high-risk GIST patients. Duration of imatinib dose may be a factor influencing the prognosis. Therefore, we anticipate that a longer duration of imatinib treatment may improve the prognosis for high-risk GIST patients. However, adverse events including secondary cancer induced by longer-term imatinib dose should be considered.

### 4.6 Patient selection

Patient selection was different in all of the above trials, and optimal selection of patients who will derive the most benefit from adjuvant imatinib remains unestablished. Although several risk-stratification tools were available based on tumor size, mitotic rate, tumor location, and tumor rupture, mutation subtypes should also be considered during patient selection. Patients with a KIT exon 9 mutation, PDGFRα exon 18 D842V mutation, and wild-type (lacking KIT or PDGFRα mutation) had an inferior response to imatinib in several clinical trials for advanced or metastatic GIST. In the ACOSOG Z9001 trial, imatinib therapy was associated with higher RFS in patients with a KIT exon 11 deletion of any type, but not with a KIT exon 11 insertion or point mutation, a KIT exon 9 mutation, a PDGFRα mutation, or a wild-type tumor. In clinical practice, there is consensus that patients with PDGFRα D842V mutation should not be treated with adjuvant therapy. Therefore, mutational analysis is critical to make a decision for adjuvant therapy. Joensuu et al investigated the risk factors for GIST recurrence despite adjuvant therapy after curative resection using the SSG XVIII trial database. The factors identified were also validated using the database of the ACOSOG Z9001 trial. Five factors (high tumor mitotic count, non-gastric location, large size, rupture, and adjuvant imatinib for 12 months) were independently associated with unfavorable RFS in a multivariable analysis in the SSG XVIII cohort. These variables were strongly associated with RFS in the Z9001 cohort. Collectively, further trials are required to elucidate the optimal dose, duration, and patient selection for adjuvant imatinib therapy.

## 5 Conclusion

We review and summarize the clinical relevance and issues of neoadjuvant and adjuvant therapy for localized GIST (Table 3). Although imatinib as neoadjuvant and adjuvant therapy clearly contributes to improving the prognosis for high-risk GIST, the optimal dose, duration, and patient selection for clinical settings remain controversial. Furthermore, molecular biological research including detailed mutational analysis will help guide personalized therapy for advanced GIST.

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### DISCLOSURE

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### ORCID

Masaaki Iwatsuki [http://orcid.org/0000-0002-8447-5278](http://orcid.org/0000-0002-8447-5278)
Yoshifumi Baba [http://orcid.org/0000-0003-3657-2388](http://orcid.org/0000-0003-3657-2388)
Naoya Yoshida [http://orcid.org/0000-0002-0886-4618](http://orcid.org/0000-0002-0886-4618)
Hideo Baba [http://orcid.org/0000-0002-3474-2550](http://orcid.org/0000-0002-3474-2550)

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