Gastrointestinal Stromal Tumors in Koreans: It’s Incidence and the Clinical, Pathologic and Immunohistochemical Findings

Seven hundred forty seven cases of gastrointestinal stromal tumors (GISTS) in Koreans who were diagnosed between 2001 and 2002 were analyzed to evaluate their occurrence and their clinical, pathologic and immunohistochemical findings. The most frequent location of tumor was in the stomach (63%), followed by the small intestine (30%), the colorectum (5%), and the esophagus (2%). c-kit expression was found in 93.6% of the cases, while CD34, SMA and S-100 protein was positive in 80.1%, 28.2%, and 20.2%, respectively. c-kit positivity was high in the stomach (94.2%) and small intestine (94.6%), while it was relatively low in the colorectum (85.0%), and esophagus (81.2%). The positivity for CD34 was correlated with the higher risk of GISTS (p=0.04). Follow up of the patients showed that 58 primary GISTs patients died and 20 of these patients were recurrent or metastatic at the time of diagnosis. The pathologic diagnosis to predict the risk of aggressive behavior of GISTS was correlated with the numbers of tumor, clinical stage, epithelioid histologic type, cellularity, cellular atypia, necrosis, and mucosal invasion (p=0.00). GISTS with a poor prognosis were closely related to the clinical stage at presentation, the locations of the tumor, and the ages of the patients.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor of the digestive tract showing lineage differentiation similar to the interstitial cell of Cajal (ICC) and accounts for about 2% of all GI tract neoplasms (1). Their morphology varies from undifferentiated to differentiated tumors having myoid or neural differentiation. So, various kind of diagnosing methods including immunohistochemical stains and electron microscopy were established. And also recent rapid progress has been accomplished for the molecular genetics of GISTS, and studies on the molecular-based classification of GISTS are underway (2).

c-kit (CD117) is a transmembrane tyrosine kinase receptor and its expression appears to play a key role in committing the primitive mesenchymal cells towards ICC differentiation. Some GISTS contain activating mutations in the kit proto-oncogene and this is associated with the expression of the c-kit protein (3). The identification of the mutations that are mostly in exon 11 and to a lesser extent in exons 9 and 13 of the kit proto-oncogene coding for c-kit in many GISTS has resulted in a better understanding of their oncogenic mechanisms. The true neural and smooth muscle neoplasms of the GI tract entirely lack these kit mutations (4). So, c-kit expression has been proposed as being the most sensitive and specific phenotypic marker of GISTS. Although 90% of GISTS were found to be immunohistochemically positive for c-kit (5-12), and the mutations of kit gene have been found in 80% to 85% of these c-kit positive GISTS, a minority of GISTS lack any kit mutations, but nonetheless, c-kit is strongly activated (2, 4, 8). Such GISTS might contain kit mutations that are not readily detected by the conventional screening methods, or alternately, the c-kit might be activated by nonmutational mechanisms. Moreover, in 35% of the GISTS lacking the kit mutations, intragenic mutations in the related receptor for tyrosine kinase, platelet-derived growth factor recep-
tor alpha (PDGFRA), have recently been reported (13, 14). Therefore, the current definition of GISTs as c-kit positive mesenchymal tumors of uncertain malignant potential fails to include a number of GIST cases that have similar histology. Although confirmatory c-kit staining is required for drug therapy and approximately 95% of GISTs stain positively for c-kit (15), the most important tool needed to diagnose GIST is still hematoxylin and eosin-stained section (16), and this will encompass the PDGFRA mutation-positive and c-kit-negative GISTs, both the PDGFRA and kit mutation-negative GISTs, and the rare kit mutation-positive and c-kit-negative GISTs (2).

Immunohistochemical stainings for the other markers are more variable; these include CD34 (47-100%), muscle specific actin (0-50%, usually focal staining), S-100 protein (5-30%), and desmin (2-5%) (15-17). Despite the recent remarkable progress in understanding and treating GISTs, pathologists still have difficulty for predicting behavior of GISTs. Of those GISTs that undergo resection, about half of the cases have possibility of recurrence or metastasis (18). Although a large tumor size and high mitotic activity have been strongly associated with malignancy (17), it can not completely exclude their malignant potential in tumors with small size and no mitosis (19).

However, in Korea, the incidence and the clinicopathologic features of GISTs have not been characterized because most of the previous studies have been mainly focused on one institution’s experience (20-24), and the multi-institutional studies were focused on the stomach (25, 26). In an attempt to survey the approximate incidence, clinicopathologic characteristics and immunophenotypic features of GISTs in Korea, we conducted a clinicopathologic and immunohistochemical analysis of 747 mesenchymal tumors that had the histologic features of GIST.

**MATERIAL AND METHODS**

Tissue samples were obtained from Korean patients who had mesenchymal tumors of the gastrointestinal tract. The Table 1. Diagnosis of GIST malignancy based on tumor size and mitosis

| Proposed approach for defining risk of aggressive behavior in GISTs (by NIH Consensus Meeting, Hum Pathol 33:459-465, 2002) | Size     | Mitotic count |
|---------------------------------------------------------------|----------|---------------|
| Very low risk                                                | <2 cm    | <5/50 HPF     |
| Low risk                                                      | 2-5 cm   | <5/50 HPF     |
| Intermediate risk                                            | <5 cm    | 6-10/50 HPF   |
|                                                               | 5-10 cm  | <5/50 HPF     |
| High risk                                                     | >5 cm    | >5/50 HPF     |
|                                                               | >10 cm   | Any mitotic rate |
|                                                               | Any size | >10/50 HPF    |

HPF, High power field.

Table 2. Immunohistochemical findings used in the diagnosis of GISTs

| KIT (CD117) | CD34 | SMA | S-100 |
|-------------|------|-----|-------|
| GIST, by definition | +    | + or -  | + or - | + or - |
| (47-100%) | (0-50%) | (5-30%) |
| GIST-like tumors | -    | +    | + or - | + or - |
| - | - | - | - |
| Smooth muscle tumor | -    | -    | +    | rare (+) |
| Schwannoma | -    | -    | -    | + |
RESULTS

Clinical findings

Seven hundred forty seven GISTs were diagnosed among the 849 gastrointestinal mesenchymal tumors that occurred from 2001 to 2002 (334 in 2001 and 413 in 2002). The male to female ratio was 374 to 373. The patients with GISTs ranged in age from 10 to 87 yr (mean 56.3 yr) and the peak age was between 50 and 70 (Fig. 1). According to the operation method, wide resection and excision were performed in 541 cases (71%), and wedge resection or biopsy were performed in 247 cases (20%); and 59 cases (8%) were found incidentally. All incidentally found GISTs were single tumors with sizes ranging from 0.2 cm to 9.5 cm, and most of them were less than 2.0 cm with the mean size being 1.2 cm. They were found during operations for gastric carcinoma in 54 cases, esophageal carcinoma in 2 cases, colon carcinoma in 2 cases and ovarian carcinoma in 1 case.

The sizes of the mass varied from 0.2 cm to 53 cm with the mean size being 6.1 cm (Fig. 2). The most frequent location of the GISTs was in the stomach, followed by the small intestine and the colorectum (Fig. 3). In 11 cases, multiple tumor masses were found after metastatic or recurrent tumor nodules had been excluded. Among these multiple GISTs, eight cases occurred in the small intestine and one case was associated with neurofibromatosis.

The clinical stages of the disease are described in Fig. 4. We found three cases of GIST showing the regional lymph nodes metastasis at the time of operation. These three cases were all male patients. The tumor displayed a high risk of malignant behavior, the mean tumor size was 12.5 cm and the tumors occurred in the small intestine, rectum and stomach, respectively. Although these three cases showed metastasis and recurrent tumor during the follow up, the patients are still alive at more than 36 months after chemotherapy.

The patients’ survival status was followed up for 12-36 months by using the data obtained from the Korea National Statistical Office. Seventy one patients had died by December 31, 2003, and 13 of them had incidentally found GISTs during their operations for disease other than the GISTs. Of the remaining 58 primary GISTs, the small intestine and the stomach were the most common locations with 28 and 25 cases, respectively, while the colorectum and the esophagus comprised the remaining 5 cases. Among 58 patients who died of GISTs, 20 of them showed recurrent or metastatic tumor nodules at the time of diagnosis. Their pathologic

![Fig. 1. Distribution of the ages of the patients with gastrointestinal stromal tumors in 747 patients.](image1)

![Fig. 2. Distribution of the sizes of the gastrointestinal stromal tumors.](image2)

![Fig. 3. Anatomic locations of the gastrointestinal stromal tumors.](image3)

![Fig. 4. Clinical stages of the patients at the time of diagnosis.](image4)
Fig. 5. Photograph of the representative findings of gastrointestinal stromal tumors. (A) Epithelioid type GIST. (B) Spindle cell type GIST. (C) Mixed epithelioid and spindle cell type GIST. (D) Hyaline changes observed in GIST. (E) Myxoid changes observed in GIST. (F) Ischemic tumor necrosis observed in GIST. (G) Mucosal invasion observed in the small intestinal mucosa. (H) Skeinoid fibers observed in the small intestinal GIST. (I) Paraganglioma-like patterns observed in the small intestinal GIST.
diagnosis included 50 high risk tumors, 4 intermediate risk tumors and 4 low risk tumors. Forty nine (84.5%) of the 58 cases showed c-kit protein expression. In this study, prognosis of the GISTs were closely related to the clinical stages at presentation, pathologic diagnosis of GISTs, and the locations (<0.05).

The breakdown of the low risk GISTs patients having a poor prognosis showed 2 small intestinal, 1 esophageal and 1 rectal tumor location with the patients’ ages being over 65 yr; there were multiple tumors in 2 cases and diffuse cytoplasmic staining for c-kit protein in 3 cases.

Histopathologic findings

Of the total 849 cases of mesenchymal tumors of the gastrointestinal tract, 747 cases were diagnosed as GISTs including 48 GIST-like tumors that met the criteria described in the materials and methods section. When all the GISTs were classified according to the pathologic factors that define the risk of aggressive behavior in GISTs, very low risk, low risk, intermediate risk and high risk were found in 112 (13.6%), 216 (29.1%), 159 (21.4%), and 255 (34.4%) cases, respectively. The increasing aggressive risk of GISTs was correlated with increased number of tumors, higher clinical stage, epithelioid histology, high cellularity, severe cellular atypia, the presence of necrosis, and mucosal invasion (<0.00).

For histology, spindle cell type was found in 578 cases (77.4%) (Fig. 5A), epithelioid cell type was found in 66 cases (8.8%) (Fig. 5B), and mixed type was found in 103 cases (13.8%) (Fig. 5C). Benign cellular patterns such as hyaline changes (Fig. 5D), cystic changes and myxoid changes (Fig. 5E) were observed in 267 cases, which included 46 cases of very low risk, 97 cases of low risk, 48 cases of intermediate risk and 76 cases of high risk. The benign cellular pattern was inversely correlated with the risk level of the GISTs (<0.007).

Dystrophic calcification was found in 2 cases of GISTs with low and very low risk of malignant potential, respectively. Skeinoid fibers (Fig. 5H) were almost exclusively found in the small intestinal GISTs. Paraganglioma-like histologic features were observed in five cases of small intestinal GISTs as well as 8 gastric GISTs of the mixed spindle and epithelioid histologic types (Fig. 5I). These paraganglioma-like features were apparent in the superficial areas of the mass that possessed plump vascular structures.

|/Gastrointestinal Stromal Tumors in Koreans 981|

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### Table 3. Immunohistochemical staining results in GISTs

|        | GIST         | GIST-like Tumor | Total |
|--------|--------------|----------------|-------|
| C-kit  | positive     | 699 (100.0%)   | 444   |
|        | negative     | 0 (0.0%)       |       |
| CD34   | positive     | 571 (82.0%)    |       |
|        | negative     | 125 (18.0%)    |       |
| SMA    | positive     | 203 (29.2%)    |       |
|        | negative     | 493 (70.8%)    |       |
| S-100  | positive     | 141 (20.2%)    |       |
|        | negative     | 556 (79.8%)    |       |

### Table 4. Relationship between organ site and classification of GISTs according to differentiation

| Organ Site | GIFT | GILT | GINT | GIDT | Total |
|------------|------|------|------|------|-------|
| Stomach    | 336  | 66   | 52   | 15   | 469   |
| Small Int | 80   | 68   | 35   | 39   | 222   |
| Colon     | 24   | 10   | 5    | 1    | 40    |
| Esophagus | 4    | 7    | 1    | 4    | 16    |
| Total     | 444  | 151  | 93   | 59   | 747   |

GIFT, Gastrointestinal stromal tumor with fibroblastic differentiation; GINT, Gastrointestinal stromal tumor with neural differentiation; GILT, Gastrointestinal stromal tumor with smooth muscle differentiation; GIDT, Gastrointestinal stromal tumor with dual smooth muscle and neural differentiation.

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Fig. 6. c-kit expression according to the pathologic diagnosis defining the risk of aggressive behavior for the gastrointestinal stromal tumors.
Immunohistochemical findings

Of the 747 GISTs, c-kit expression was found in 699 cases (93.6%) and its expression, according to the histologic diagnosis, for defining the risk of aggressive behavior is depicted in Fig. 6. c-kit was positive in 90.2% of very low risk, 94.0% of low risk, 93.7% of intermediate risk, and 95.3% of high risk GISTs \(p<0.05\). The c-kit expression was noted to be diffuse in the cytoplasm and along the cytoplasmic membrane of the tumor cells; in 24 cases, a dot-like c-kit expression was predominant rather than the membranous staining. Focal c-kit expression was observed in a total of 34 cases with cyttoplasmic (29 cases) and a dot-like pattern (5 cases). In most of these cases, the malignant potential and their histologic types were spindle cell type in 20 cases, epithelioid cell type in 5 cases, and mixed cell type in 5 cases.

CD34, SMA and S-100 protein were positive in 597 (80.2%), 209 (28.1%), and 153 (20.5%) cases, respectively (Table 3). The GISTs with c-kit expression were related with CD34 positivity and with high cellularity of GISTs \(p<0.05\). But patients' gender, age, resection range, size of tumor, clinical stage, histologic type, presence of benign cellular pattern, necrosis and expression of S-100 protein were not related with the c-kit expression status \(p>0.05\). According to the locations of GISTs, c-kit positivity was high in the stomach (94.2%) and the small intestine (94.6%), while it was relatively low in the colorectum (85.0%), and the esophagus (81.2%). Additionally, all three cases with lymph node metastasis showed diffuse c-kit staining.

When dividing the GISTs according to their differentiation based on the immunophenotypic features, GIFT was the most common type (59.4%), followed by GILT (20.2%), GINT (12.5%), and GIDT (7.9%), respectively (Table 4). Fibroblastic differentiation (GIFT) was most frequent in the highly cellular and epithelioid GISTs, and it was more prevalent in the stomach and colorectum. Neural differentiation (GINT) was common in the small intestine, while smooth muscle differentiation (GILT) was common in the esophagus (Table 4).

**DISCUSSION**

Although several papers describing the clinicopathologic characteristics (20-22, 25, 26), the genetic (23, 24), and ultrastructural findings (27) of GISTs in Koreans have been reported, this multi-institutional study provides much more information on the clinical and immunophenotypic characteristics of GISTs in Koreans. In this study, we found that small intestinal GISTs were more common while colorectal and esophageal GISTs were less frequent in Koreans than in the Western countries (9, 17, 18). Like the previous reports suggesting the aggressive behavior of small intestinal GISTs, our survival data showed that the small intestinal GISTs comprised the most common cause of death by GISTs, although they made up only 30% of the total GISTs.

It is known that the epithelioid GISTs, which are the same as leiomyoblastomas of Stout, comprise about 10% of the gastric GISTs (9). In our series, 50 out of the 470 gastric GISTs (10.6%) were of epithelioid type. The spindle cell type was more frequent than epithelioid type and these results are in good agreement with the previous data (1, 5, 17).

In immunohistochemistry, c-kit was positive in 81-100% of the GISTs arising in the esophagus, stomach, small intestine and colon. The GISTs with either spindle cell or epithelioid type were both positive for c-kit, though the staining was less intense in the latter. The predominant membranous staining that can be observed in fibroblasts or myofibroblasts with the rabbit polyclonal antibody manufactured by Dako (28) was not observed in any of the cases we examined. CD34 was positive in 47-100% of the GISTs and its expression varied with the location of the tumor within the gastrointestinal tract. Miettinen et al. (10) found that among the c-kit positive tumors that they studied, 100%, 90%, 47%, 65%, 96% and 64% of the cases were CD34 positive in the esophagus, stomach, small intestine, colon, rectum and extraintestinal locations, respectively. In this study, CD34 expressions were 90%, 78%, 63% and 62% of the cases in the stomach, colorectum, small intestine and esophagus, respectively. Although CD34 positivity in the stomach was the same as that of previous study, its expression was somewhat different in the esophagus and small intestine. There have been some reports that CD34 is, perhaps, more often negative in malignant GISTs (29), although the opposite was found by Wang et al. (30). In our study, CD34 expression was positively correlated with the higher risk of malignancy in GISTs and this result may have been caused by higher positivity of CD34 in the small intestine and the lower CD34 expression in the esophagus. SMA was found only focally in 0-47% of the total cases and its expression rate was inversely correlated to that of CD34 (15-19). In our study, SMA was positive in 28.1% of the cases and it was most frequently expressed in the esophageal GISTs. Moreover, SMA expression was inversely correlated with the higher risk of malignancy in GISTs. However, the expression of S-100 protein in this study was higher than in the previous western studies, which were reported to be less than 10% of the cases with S-100 protein expression (1, 5, 17), and our findings were correlated well with the previous Korean reports (20). In the previous reports, the S-100 protein expression in GISTs was different according to the location of the tumor; it was more frequently expressed in the small intestinal GISTs (12, 31), and it was rarely expressed in the large intestine (11). The possible reasons for this high positivity may have been the higher incidence of small intestinal GISTs (20% vs. 30%), the lower incidence of colorectal GISTs (10% vs. 5%), the higher percentage of multiple and malignant GISTs in Koreans, and the differ-
ences in the interpretation of the results.

With this study, we found that expressions of CD34 and SMA were positively and inversely correlated with the higher risk of malignant potential in GISTs. The focal positivity of c-kit was associated with lower risk of malignant potential. According to the immunophenotypic features, GIFTs were common in the stomach and the colon. GILTs were common in the esophagus and the colon. GISTs were common in the small intestine. The higher incidence of GISTs with high risk of malignant potential and the more frequent small intestinal GISTs in Korean resulted in a higher death rate.

For further study, we need to continue with a) following up on these patients and completing the clinical data on GISTs in Korean, resulting in a higher death rate.

REFERENCES

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. Pol J Pathol 2003; 54: 3-24.
2. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004; 22: 3813-25.
3. Hirota S, Isozaki K, Mortyama Y, Hashimoto K, Nishida T, Isihiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998; 279: 577-80.
4. Lasota J, Jasinski M, Sarlomo-Rikala M, Miettinen M. 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: 33-60.
5. Miettinen MM, Sarlomo-Rikala M, Kovatch AJ, Lasota J. Calponin and h-caldesmon in soft tissue tumors: consistent h-caldesmon immunoreactivity in gastrointestinal tumors indicates traits of smooth muscle differentiation. Mod Pathol 1999; 12: 756-62.
6. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152: 125-8.
7. Sakurai S, Fukasawa T, Chong JM, Tanaka A, Fukayama M. Embryonic form of smooth muscle myosin heavy chain (SMemb/MHC-B) in gastrointestinal stromal tumor and interstitial cells of Cajal. Am J Pathol 1999; 154: 23-8.
8. Rubin BP, Singer S, Tsao C, Duensing A, Lux ML, Ruiz R, Hibbard MK, Chen CJ, Xiao S, Tuveson DA, Demetri GD, Fletcher CD, Fletcher JA. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 2001; 61: 8118-21.
9. Miettinen M, Lasota J. Gastrointestinal stromal tumors: definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001; 438: 1-12.
10. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 1999; 30: 1213-20.
11. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. 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.
12. Miettinen M, Kopczynski J, Makhlouf HR, Sarlomo-Rikala M, Gyorffy H, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. Am J Surg Pathol 2003; 27: 625-41.
13. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003; 299: 708-10.
14. Hirota S, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, Kitamura Y. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003; 125: 660-7.
26. Kwon SJ; Korean Gastric Cancer Study Group. Surgery and prognostic factors for gastric stromal tumor. World J Surg 2001; 25: 290-5.
27. Park SH, Kim MK, Kim HS, Song BJ, Chi JG. Ultrastructural studies of Gastrointestinal stromal tumors. J Korean Med Sci 2004; 19: 234-44.
28. Yantiss RK, Spiro JJ, Compton CC, Rosenberg AE. Gastrointestinal stromal tumor versus intra-abdominal fibromatosis of the bowel wall. Am J Surg Pathol 2000; 24: 947-57.
29. 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.
30. Wang L, Vargas H, French SW. Cellular origin of gastrointestinal stromal tumors: a study of 27 cases. Arch Pathol Lab Med 2000; 124: 1471-5.
31. 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.

**APPENDIX**

**Hospitals that participated in this study**

Seoul National University Hospital, Chungnam National University Hospital, Yonsei University Hospital, Yong-Dong Severance Hospital, Yonsei Wonju University Hospital, Korea University Anam Hospital, Korea University Guro Hospital, Korea University Ansan Hospital, University of Ulsan Asan Medical Center, Sungkyunkwan University Samsung Seoul Hospital, Sungkyunkwan University Kangbuk Samsung Hospital, The Catholic University of Korea Kangnam St. Mary’s Hospital, The Catholic University of Korea St. Mary’s Hospital, The Catholic University of Korea St. Paul’s Hospital, The Catholic University of Korea Our Lady of Mercy Hospital, The Catholic University of Korea St. Vincent’s Hospital, The Catholic University of Korea Holy Family Hospital, The Catholic University of Korea Uijongbu St. Mary’s Hospital, The Catholic University of Korea Daejeon St. Mary’s Hospital, Kyung Hee University Hospital, Soonchunhyang University Hospital, Soonchunhyang University Chunan Hospital, Soonchunhyang University Puchon Hospital, Inje University Seoul Paik Hospital, Inje University Ilsan Paik Hospital, Inje University Pusan Paik Hospital, Ajou University Hospital, Eulji University Hospital, Nowon Eulji General Hospital, National Cancer Center Hospital, Korea Cancer Center Hospital, Seoul Municipal Boramae Hospital, Pundang Jesaeng Hospital, Pusan National University Hospital, Dong-A University Hospital, Kosin University Hospital, Pusan Maryknoll Hospital, Pusan Wallace Memorial Baptist Hospital, Kyungpook National University Hospital, Keimyung University Hospital, Yeungnam University Hospital, Daegu Catholic University Hospital, Taegu Fatima Hospital, Chosun University Hospital, Chonbuk National University Hospital, Wonkwang University Hospital, Chonju Presbyterian Medical Center, Konyang University Hospital, Chonbuk National University Hospital, Cheongju St. Mary’s Hospital.