A study of histopathological assessment criteria for assessing malignancy of gastrointestinal stromal tumor, from a clinical standpoint

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Key words: GIST, new criteria for malignancy, hemorrhage and necrosis, tumor size, Ki-67

Introduction

It is currently apparent that gastrointestinal stromal tumors (GISTs) account for many mesenchymal tumors that originate in the gastrointestinal tract and consist of spindle-shaped or epitheloid cells.1–3 Because CD117 (c-kit) is expressed by the interstitial cells of Cajal (ICC), which are pacemaker cells in the digestive tract, GISTs would appear to arise from these cells.4–7 Of interest, imatinib mesylate (STI571), a tyrosine kinase inhibitor developed for the treatment of chronic myeloid leukemia, is very effective in the treatment of GIST,8,9 a finding that has increased the level of interest in this tumor. However, there are no clear criteria for assessing the malignancy of GIST, with recurrence or metastasis occasionally being observed in some tumors histopathologically diagnosed as benign.10 The objective of the present study was, therefore, to find new histopathological criteria for assessing the malignancy of GIST, from a clinical standpoint.

Methods

Between February 1994 and August 2002, 34 patients had surgical treatment, at the Surgical Department of Nippon Medical School Chiba Hokusoh Hospital, for tumors diagnosed as gastrointestinal mesenchymal tumor (GIMT) by a pathologist (Y. O.) at that hospital. GIMT was defined as a mesenchymal tumor originating in the gastrointestinal tract, and consisting of spindle-shaped or epitheloid cells. All 34 of these patients were followed up for more than 2 years. The subjects of this study were 22 of these patients who had GIST (defined

Background. As no established histopathological criteria exist for assessing the malignant potential of gastrointestinal stromal tumor (GIST), recurrence or metastasis is occasionally observed in lesions diagnosed histopathologically as benign. The present study aimed to clarify the histopathological criteria for assessing the malignancy of GIST, from a clinical standpoint.

Methods. The subjects were 22 patients with GIST expressing CD117 (c-kit) and/or CD34, who were followed up for more than 2 years. Clinically, GIST malignancy was diagnosed if any of the following criteria were met: peripheral invasive growth, lymph node metastasis, metastasis to another organ, peritoneal dissemination, recurrence, or death. GIST was also categorized as either benign or malignant by a new histological malignancy classification system, based on the determination of significant factors indicating malignancy in the clinical classification system above.

Results. Significant factors for malignancy identified in the clinical malignancy classification were: tumor hemorrhage/necrosis (present vs absent; P = 0.0053), tumor size (<5 cm vs ≥5 cm; P = 0.0022), and Ki-67 labeling index (<3% vs ≥3%; P = 0.0002). A new histological malignancy classification, based on a combination of these three factors, was developed. A significant correlation existed between the clinical system and the new histological malignancy classification system (P = 0.0008). The recurrence-free survival rate was 100% in the histologically benign cases and 37.5% in the histologically malignant cases (P = 0.0012). Conclusions. The new histological malignancy classification for GIST was demonstrated to be useful from a clinical standpoint.
as a subgroup of GIMT expressing CD117 and/or CD34, as assessed by immunohistochemical staining, regardless of myogenic and neurogenic markers).

GIST was diagnosed as clinically malignant when any of the following criteria were met: peripheral invasive growth, lymph node metastasis, metastasis to another organ, peritoneal dissemination, recurrence, or death. The following clinicopathological factors were analyzed: age, sex, primary site, tumor size, ulceration, growth pattern, peripheral invasive growth, lymph node metastasis, metastasis to another organ, peritoneal dissemination, hemorrhage/necrosis, cellularity, nuclear atypia, mitotic count, α-smooth muscle actin (SMA), S-100 protein, CD117, CD34, bcl-2, and the Ki-67 labeling index (LI). With tumor size defined by maximum diameter, GIST was classified into two groups with four different cutoff values: 2, 3, 4, and 5 cm. Macroscopic growth pattern was classified as intramural (Im), intraluminal (II), exoluminal (El), or combined (C). Cellularity was classified as low (L), moderate (M), or high (H), and nuclear atypia as mild (L), moderate (M), or severe (H). Mitotic count was determined by totaling the number of mitoses in 50 high-power fields (HPF), at three locations for each sample, with the highest value being used. Presence or absence of intratumoral hemorrhage/necrosis was assessed histopathologically.

For immunohistochemical staining, formalin-fixed paraffinized sections were prepared; after deparaffinization, the resulting sections were stained with labeled streptavidin biotin. The following primary antibodies were used: vimentin (V9, code no. M 0725; DAKO, Glostrup, Denmark), α-SMA (1A4, code no. M 0851; DAKO Japan, Tokyo, Japan); desmin (D33, code no. M 0760; DAKO, Denmark), S-100 (code no. Z 0311; DAKO, Denmark); CD117 (code no. A 4502, DAKO Japan), CD34 (NU-4A1, code no. 312012; Nichirei, Tokyo, Japan); bcl-2 (124, code no. M 0887; DAKO, Denmark); and Ki-67 (MIB-1, code no. M 7240; DAKO, Denmark). With bcl-2, slight brownish coloration of the cytoplasm was considered a positive reaction, and for Ki-67, the number of cells with brownish nuclei per 1000 cells (×400 magnification) was counted to determine the Ki-67 LI (%). Tumors were classified into two groups on the basis of a Ki-67 LI cutoff level of 3%.

For statistical analysis, the Mann-Whitney U-test, χ² test, or t-test was used to compare data between two groups, while the Kruskal-Wallis test was used to compare data among more than two groups. The Cox proportional hazards model was used for multivariate analysis. Survival and recurrence-free survival rates were calculated using the Kaplan-Meier method, and significant differences were assessed with the log rank test. Stat View software (1998; SAS Institute Cary, NC, USA) was used in all analyses, and the level of significance was set at P < 0.05.

Results

Clinicopathological features

Of the 34 GIMT patients, 22 were diagnosed with GIST, with the remaining 12 patients being diagnosed with benign leiomyoma (n = 9) and benign schwannoma (n = 3). In the 22 GIST patients who served as subjects, the tumors were diagnosed as benign in 17 (77.3%), and as malignant in 5 (22.7%), according to the clinical classification system (Table 1). Age ranged from 37 to 74 years (mean ± SD, 55 ± 11.4 years) for all subjects, from 37 to 74 years (56.5 ± 11.3 years) in the benign group, and from 41 to 71 years (53.2 ± 12.7 years) in the malignant group. Hence, patients in these two groups were similar in age. The subjects comprised 9 men (40.9%) and 13 women (59.1%). No significant difference in sex ratio was observed between the benign and malignant groups, with male-to-female ratios of 7:10 and 2:3, respectively. For the 22 subjects, the primary sites were as follows: esophagus, n = 0 (0%); stomach, n = 14 (63.6%); small intestine, n = 7 (31.8%); colon, n = 0 (0%), and rectum, n = 1 (4.6%). In the benign and malignant groups, respectively, the breakdown of the primary site was as follows: stomach, 13 vs 1; small intestine, 3 vs 4; rectum, 1 vs 0. The proportion of benign GISTs originating in the stomach was significantly higher than that of malignant GISTs (P = 0.0210), while the proportion of malignant GISTs originating in the small intestine was significantly higher than that of benign GISTs (P = 0.0085).

The maximum tumor diameter was normally distributed, ranging from 0.3 to 26 cm (mean ± SD, 6.8 ± 6.8 cm) in the subjects overall; it ranged from 0.3 to 23 cm (4.9 ± 5.4 cm) in the benign group, and from 7.5 to 26 cm (13.2 ± 7.4 cm) in the malignant group. Hence, maximum tumor diameter was significantly larger in the malignant group (P = 0.0112), and the level of significance was highest with a cutoff value of 5 cm (P = 0.0022). In the group as a whole, ulceration occurred in 7/22 patients, being apparent in 4/17 (23.5%) of the benign group and in 3/5 (60%) of the malignant group. While no significant difference was apparent between the two groups, the incidence of ulceration tended to be higher in the malignant group. None of the 22 patients exhibited lymph node metastasis. Intratumoral hemorrhage/necrosis was observed in 10 of the 22 patients in the whole group and in 5/17 of the benign group (29.4%), and in 5/5 of the malignant group (100%). The incidence of hemorrhage/necrosis was clearly higher for the malignant group (P = 0.0053). Malignancy assessed using the clinical classification system showed no significant correlation with cellularity, nuclear atypia, or mitotic count.