The aim of this study was to analyze 37 patients with malignant primary gastrointestinal stromal tumors and to compare the findings and their therapeutic implications with those previously reported. The medical records of 37 patients who were diagnosed and operated on between January 1996 and December 2002 were retrospectively reviewed. The patients’ age, tumor size, type of surgery, histologic type, mitotic counts, presence of necrosis, Ki-67 proliferative index, National Institutes of Health 2001 consensus classification, immunohistochemical staining, and recurrence were examined to analyze factors affecting survival. Overall actuarial survival for all patients was 46%. When analyzed by type of resection, the complete resection group (R0 resection) had a mean overall survival of 48.2 ± 6.18 months compared with the patients with incomplete resection (R1–R2) who survived a mean of 10.8 ± 3.2 months (P < 0.00).

Univariate analysis showed development of recurrence (P = 0.00), tumor size of 8 cm or greater (P = 0.05), Ki-67 proliferative index greater than 0.82 (P = 0.0448), desmin staining (P = 0.0076), age younger than 49 years (P = 0.0009), and incomplete resection (P = 0.00) to be significantly correlated with a poor survival. In multivariate analysis, desmin staining (P = 0.031), tumor size (P = 0.033), age (P = 0.01), recurrence (P = 0.038), and R0 resection (P = 0.02) were significant independent prognostic factors. We recommend that more careful preoperative and more frequent postoperative follow-up examinations be performed for patients with large tumors, age of younger than 49 years, and Ki-67 proliferative index greater than 0.82. (J GASTROINTEST SURG 2005;9:418–429) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Gastrointestinal stromal tumors, prognostic factors, survival analysis, recurrence, surgery

Gastrointestinal (GI) stromal tumors (GISTs) are relatively rare tumors of the GI tract. GISTs constitute 1–2% of all GI malignancies and are considered to originate from neoplastic transformation of intestinal pacemaker cells (Cajal cells). Until recently, mesenchymal tumors of the GI tract were termed smooth muscle tumors (leiomyomas, leiomyoblastomas, and leiomyosarcomas) or schwannomas. Recently, GISTs have been defined as mesenchymal tumors of the GI that express c-kit proto-oncogene product (CD-117), a transmembrane tyrosine kinase receptor molecule. Immunohistochemical findings have made it clear that GISTs may have smooth muscle differentiation, neural differentiation, dual smooth muscle and neural differentiation, or no obvious differentiation. They are nearly uniformly c-kit-positive and frequently express the myeloid stem cell antigen CD34. A significant subset of GISTs also express some other cell-type markers like SMA, desmin, vimentin, and S100, among others.1–3

GISTs have a wide clinical spectrum from benign to frankly malignant, and clinical behavior is difficult to predict in an individual patient. Among the various prognostic factors studied, mitotic index and tumor size are considered to provide the most useful prognostic information. Data from literature suggest that any GIST greater than 5 cm in diameter and greater than five mitoses per 50 high-power fields (HPFs) should be considered as the strongest pathologic predictors of malignant behavior. GISTs larger than
10 cm in diameter have a high risk of aggressive behavior regardless of the mitotic count, and GISTs of any size with a high mitotic count are also deemed to be high-risk tumors.4–7 Although many studies have tried to identify prognostic factors, an accurate method to determine the patients at risk for survival has not been generally accepted.

Different studies have shown controversial results probably related to the different criteria used for selection of cases, different methods used, few number of patients contained, long time periods, and benign tumors. Studies about GISTs are increasing in journals. However, a few of these include almost all clinicopathologic findings, including immunohistochemical markers, to evaluate indicators of survival. Data from the studies of different centers that aimed to evaluate prognostic factors may be beneficial for solution of this confusion. This study was designed to analyze clinical presentation and histopathologic examination, to evaluate prognostic factors that affect survival after surgery in our series of 37 GIST patients with malignant potential, and to compare the findings and their therapeutic implications with those previously reported.

METHODS

Patients

The medical records of 37 patients who were diagnosed and operated on for malignant GISTs between January 1996 and December 2002 at the Department of Surgery, Uludag University Medical School, were retrospectively reviewed. Pathologic investigations of all patients were performed at the Department of Pathology in our medical school. Systemic chemotherapy and radiation therapy were excluded from the analyses in this report because they were used in sporadic fashion. Microscopically, tumors with a mitotic count greater than 5, which were determined by counting the mitotic cells seen in 50 consecutive HPFs of the most active areas of tumor, and/or tumor size larger than 5 cm and/or hypercellularity and/or presence of invasion to adjacent tissue metastases was accepted criteria for malignancy.

Clinical and Surgical Findings

Patient charts, operative reports, and histopathologic slides were reviewed to determine clinical presentation, demographic data, histologic type and immunohistochemical features, tumor size, location, type of surgical resection, operative morbidity and mortality, pattern of recurrence, and survival. Follow-up was obtained by chart review and via telephone.

Resections are classified as follows:

1. Incomplete resection (R1–R2) if tumor is non-resectable at exploration or if gross residual disease is present after resection.
2. Complete resection (R0) if excision of all gross disease with negative histopathologic margins is performed. Complete resection is subdivided into two groups: radical resection and limited resection. The limited resection group includes subtotal or wedge gastric resection and segmental bowel resection. The radical resection group includes resection of stomach or bowel with wide margin and removal of contiguous organ involvement.

Pathologic and Immunohistochemical Findings

Mitotic counts were obtained from the areas where mitotic activity was maximum in hematoxylin and eosin–stained preparations. The following variables were examined to analyze factors affecting survival: age, tumor size, type of surgery, histologic type, mitotic counts determined by counting 50 HPFs covering the most active areas, presence of necrosis, Ki-67 proliferative index, National Institutes of Health (NIH) 2001 consensus classification, immunohistochemical staining, and recurrence.

In each case, one representative block was chosen for immunohistochemical staining using the streptavidin-biotin technique. Paraffin sections, 4 µm thick, were deparaffinized with xylene (20 minutes) and then rehydrated through serial baths of ethanol solution to water. Endogenous peroxidase activity was blocked by incubation for 20 minutes with 3% hydrogen peroxide in methanol. The selected sections were autoclaved for 15 minutes in 500 ml of 0.01 mol/L sodium citrate buffer, pH 6.0. They were washed with phosphate-buffered saline solution (pH 7.4) before immunohistochemical staining. The sections were incubated with monoclonal antibodies at room temperature for 20 minutes. The antibody-treated slides were rinsed in phosphate-buffered saline solution and incubated with a biotinylated secondary antibody (Labvision Co., Fremont, CA). The slides were washed in phosphate-buffered saline and then incubated with a biotinylated secondary antibody (Labvision Co., Fremont, CA). The slides were washed in phosphate-buffered saline and then incubated with an avidin-biotin-peroxidase complex (Ultra-streptavidin/Anti-Polyvalent, Labvision Co.) for 30 minutes. As chromogen, 3,3′-diaminobenzene tetrahydrochloride was used with hydrogen peroxide. The sections were counterstained with hematoxylin.

The antigens visualized with antibodies were c-kit protein (clone 117 CO5, ready for use; Neo