INTRODUCTION

New insights gained in recent years concerning the molecular mechanisms related to GIST (gastrointestinal stromal tumor) pathogenesis were responsible for its identification as a distinct clinicopathologic entity and for the better understanding of its biological behavior (1,2). This new knowledge gave rise to the observation that GIST presents various degrees of behavior (3) and that the clinical outcome is influenced by some prognostic factors (4,5). Therefore, many variables (clinical, pathological and molecular) have been studied in an attempt to identify reliable prognostic factors (6,7).

Among all variables studied, metastatic disease has been identified as one of the most reliable prognostic factors and its presence has been implicated in the reduction of patients' survival (8). In spite of the literature consensus concerning metastatic disease as a reliable prognostic factor (9-11), the influence of lymph node metastasis on GIST carriers' survival remains unknown. The present study aims to evaluate the influence of lymph node metastasis on overall survival and disease free survival in patients with resected gastric GIST.

METHODOLOGY

From 1983-2004, 36 patients with gastric GIST who underwent surgical resection at the Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil were reviewed retrospectively. The prognostic significance of lymph node metastasis was investigated. The endpoints were overall survival and disease free survival.

Results: The median follow-up was 35 months. The 5-years estimate survival rate was 53%. Three patients presented lymph node metastasis and developed recurrence disease. Univariate analysis for overall survival identified the size >13.5cm (p=0.01) and recurrence (p=0.03) as prognostic factors. Size >13.5cm and recurrence were independent factors (p=0.01 and p=0.03, respectively) in the multivariate analysis. Univariate analysis for disease free survival identified the size >13.5cm (p=0.04) and the grade (p=0.04) as prognostic factors but, only the size >13.5cm was an independent factor in the multivariate analysis. Lymph node metastasis had no prognostic significance for overall and disease free survival (p=0.65 and p=0.57, respectively).

Conclusions: GIST lymph node metastasis was not related to poor survival in this study, but more studies are needed to identify the real incidence and the proper role of the GIST metastatic nodal disease.

TABLE 1 Clinicopathological Details of the 29 Cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (34.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (65.6%)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19 (65.6%)</td>
</tr>
<tr>
<td>Palpable mass</td>
<td>16 (55.1%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>Mitotic Index</td>
<td></td>
</tr>
<tr>
<td>&gt;5 mitoses/50 HPFs</td>
<td>19 (65.6%)</td>
</tr>
<tr>
<td>&lt;5 mitoses/50 HPFs</td>
<td>10 (34.4%)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>Distal</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>Spindle</td>
<td>15 (51.8%)</td>
</tr>
<tr>
<td>Epitheloid</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>11 (37.9%)</td>
</tr>
<tr>
<td>Surgery type</td>
<td></td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Subtotal gastrectomy</td>
<td>17 (58.6%)</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>13 (44.9%)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>11 (37.9%)</td>
</tr>
</tbody>
</table>

*GI: Gastrointestinal; "HPFs: High Power Fields
National Cancer Institute (INCA) were reviewed retrospectively. Among these 36 patients, two cases had negative Kit immunostaining and 5 patients did not have complete pathologic data available (the primary tumor was resected in other institutions). Therefore, seven patients were excluded from the analysis, leaving a final study population of 29 patients.

The data related to the patients' characteristics are depicted in Table 1. The median age of the 29 patients at the time of surgical resection was 63 years (range 10-81 years). The median tumor size was 13.5cm. Among the 29 patients, 3 (10.3%) presented lymph node metastasis. The mean lymph node retrieved per surgery was 10. Lymphadenectomy was performed when macroscopically suspicious lymph nodes were identified intraoperatively. The characteristics of the patients with metastatic lymph nodes are shown in Table 2.

Case 1 underwent wedge gastrectomy plus left lateral hepatic segmentectomy because of liver invasion by the tumor. Patient 1 developed multiple hepatic metastases after 4 months from the primary surgery and imatinib mesylate was indicated. Case 2 developed multiple hepatic metastases after 29 months from primary surgery (Figure 1). The microscopic metastatic lymph node features are shown in Figure 2. Case 3 developed hepatic metastasis after 30 months from the primary surgery. None of the three patients used imatinib mesylate as adjuvant therapy after the primary surgery. All three patients are alive with stable disease using imatinib mesylate.

Besides lymph node metastasis, others clinicopathological variables were analyzed and the influence of these variables on overall survival and disease free survival was investigated. Statistical analysis was performed using SPSS version 8.0 software. For assessment of prognostic significance of the individual variables, log-rank test and Cox proportional hazard model were used with univariate and multivariate analysis. Survival was estimated by Kaplan-Meier Method. The level of statistic significance considered was $p<0.05$.

RESULTS
The median follow up was 35 months (range 6-134 months). At the time of census, 19 of the 29 patients were still alive and 9 had no disease evidence. The overall 5-year survival rate was 53%. Recurrence rate was 62% (18 patients). Patients with recurrent disease had statistically significantly poorer survival ($p=0.03$). Among the patients who developed recurrent disease (18 patients), 7 received imatinib mesylate, but 5 patients have not completed 1 year of imatinib mesylate treatment.

The results of the univariate analysis are sum-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Lymph node resected (number)</td>
<td>3</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Metastatic lymph node (number)</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Surgery type+hepatic resection</td>
<td>Wedge gastrectomy</td>
<td>Total gastrectomy</td>
<td>Subtotal gastrectomy</td>
</tr>
<tr>
<td>Tumor size</td>
<td>27 cm</td>
<td>9 cm</td>
<td>8.5cm</td>
</tr>
<tr>
<td>Mitotic Index</td>
<td>2 mitoses/50 HPFs$^*$</td>
<td>25 mitoses/50 HPFs</td>
<td>18 mitoses/50 HPFs</td>
</tr>
<tr>
<td>Lymph node resected (number)</td>
<td>3</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Distal</td>
<td>Proximal</td>
<td>Distal</td>
</tr>
<tr>
<td>Histologic type</td>
<td>Spindle cell</td>
<td>Spindle cell</td>
<td>Spindle cell</td>
</tr>
<tr>
<td>Resection type</td>
<td>R0$^*$</td>
<td>R0</td>
<td>R0</td>
</tr>
</tbody>
</table>

$^*$HPFs- High power fields; $^*$R0- No microscopic residual disease

FIGURE 1 Multiple hepatic metastases after 29 months from primary surgery.

FIGURE 2 Microscopic appearance of the metastatic lymph node (H&E, 200X).
multivariate analysis using only statistically sig-
ificant variables found with univariate analysis
showed tumor size >13.5 cm and recurrence to be
independent prognostic factors related to overall
survival (Table 5). Univariate analysis for disease free
survival identified tumor size >13.5 cm (p=0.04) and
mitotic index (p=0.04) as prognostic factors but only
tumor size >13.5 cm was an independent factor in the
multivariate analysis (p=0.04; CI 95%: 0.7-5.5; hazard
ratio 3.8; Likelihood ratio test x²=28.99; Df=1;
p<0.04).

DISSCUSSION
GISTs may behave in different ways (manners),
varying from indolent to extreme aggressive tumors
(3). The stage at the diagnosis is recognized as the
most important prognostic factor and the median
survival in the presence of metastases is around 20
months (8). The presence of lymphatic metastases is
not yet defined as a prognostic factor. This might be
related to under notification due to a more conserva-
tive treatment in which lymphadenectomy is not
indicated.

De Matteo et al. (12) reported the incidence of
lymphatic metastases to be 6% in 200 GISTs of the
gastrointestinal tract. But, the localization and type
of surgery performed of those 6 cases was not report-
ed. Crosby et al. (13) published a cohort of 50 cases of
small bowel GISTs. The lymph node status could be
evaluated only in 15 of the specimens and 4 cases had
lymphatic metastases. Aparicio et al. (14) reported 2
cases out of 59 GISTs of the whole gastrointestinal
tract. Tashiro et al. (15) reported a series of gastric
GISTs operated on at the NCC-Tokyo and found 2
cases (1.1%) in 177. We believe that lymphatic metas-
tases might be under estimated considering that the
surgery is sometimes D0 making the analysis of this
prognostic variable very difficult.

In our series of 29 gastric GISTs, we found 3 cases
of lymphatic metastases and all developed distant
metastases in a short period of follow up. All patients
underwent D1 surgeries and so all had lymph node
analysis. The mean number of lymph nodes per spec-
imen was 10 and we strongly believe that this was
responsible for the detection of the metastases.
Besides this early recurrence in our series, the corre-
lation between lymphatic metastases and overall sur-
rvival (p=0.65) and disease free survival (p=0.57) fails
to demonstrate a poor prognosis in univariate analy-
sis. The worst prognosis was related to size and
mitotic index (high risk). So, the real importance of
the lymphatic metastases is not yet fully established.

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