Original Paper

What is the Prognostic Significance of Metastatic Lymph Nodes in GIST?

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ABSTRACT

Background/Aims: So many variables have been identified as prognostic factors influencing survival after curative resection in gastrointestinal stromal tumors (GIST), but the role of lymph node metastasis remains uncertain.

Methodology: Twenty-nine patients with c-Kit positive gastric GIST who underwent surgical resection at the Brazilian National Cancer Institute between 1983 and 2004 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.

KEY WORDS: GIST; lymph node metastases; prognostic factor; survival

ABBREVIATIONS: Gastrointestinal Stromal Tumors (GIST)

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

TABLE 1 Clinicopathological Details of the 29 Cases

Characteristic	Patient number (%)	
Gender	Male	10 (34.4%)
	Female	19 (65.6%)
Clinical presentation	Abdominal pain	19 (65.6%)
	Palpable mass	16 (55.1%)
	Weight loss	12 (41.4%)
	GI* hemorrhage	12 (41.4%)
Mitotic Index	>5 mitoses/50 HPFs**	19 (65.6%)
	<5 mitoses/50 HPFs	10 (34.4%)
Tumor location	Proximal	20 (69%)
	Distal	9 (31%)
Histologic type	Spindle	15 (51.8%)
	Epithelioid	3 (10.3%)
	Mixed	11 (37.9%)
Surgery type	Total gastrectomy	9 (31%)
	Subtotal gastrectomy	7 (24.1%)
	Wedge resection	13 (44.9%)
	Blood transfusion	11 (37.9%)

*GI: Gastrointestinal; **HPFs: High Power Fields

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TABLE 2 Characteristics of the Patients with Metastatic Lymph Node

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

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

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-

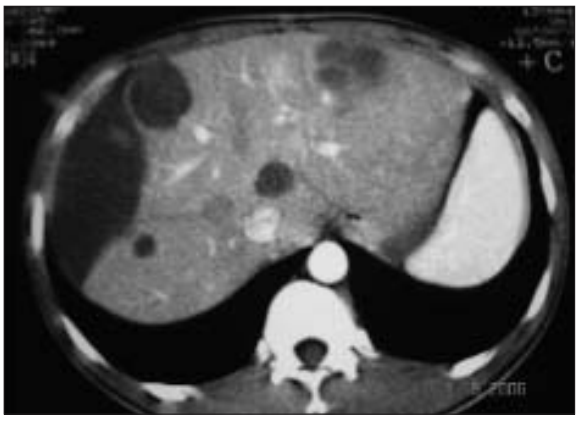

FIGURE 1 Multiple hepatic metastases after 29 months from primary surgery.

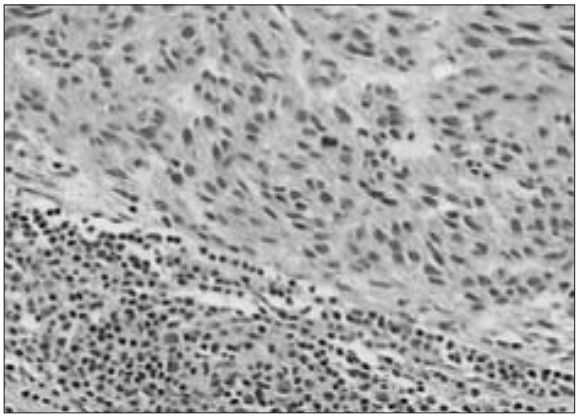

FIGURE 2 Microscopic appearance of the metastatic lymph node (H&E, 200X).

TABLE 3 Univariate Analysis for Overall Survival

VARIABLE	Log-Rank	Df*	*p*-value
Age	1.08	1	0.29
Gender	0.90	1	0.34
Pain	0.37	1	0.54
Palpable mass	2.84	1	0.09
GI hemorrhage	0.0	1	0.99
Weight loss	1.06	1	0.30
Blood transfusion	0.31	1	0.57
Surgery type	1.06	2	0.28
Tumor size (5cm)	0.17	1	0.68
Tumor size (10cm)	0.22	1	0.64
Lymph node metastasis	0.20	1	0.65
Mitotic index	3.0	1	0.05
Tumor location	0.20	1	0.65
Histologic type	1.68	2	0.43
Imatinib mesylate use	2.24	1	0.13
Organs invasion	3.8	1	0.05
Tumor size >13.5cm	5.75	1	0.01
Recurrence	4.46	1	0.03

* Df- Degrees of freedom

TABLE 4 Univariate Analysis for Disease Free Survival

VARIABLE	Log-Rank	Df*	*p*-value
Age	0,01	1	0,90
Gender	0,10	1	0,75
Pain	0,66	1	0,41
Palpable mass	0,04	1	0,84
GI hemorrhage	1,18	1	0,27
Weight loss	0,22	1	0,63
Blood transfusion	0,64	1	0,42
Surgery type	1,60	2	0,44
Tumor size (5cm)	0,48	1	0,48
Tumor size (10cm)	0,19	1	0,66
Lymph node metastasis	0,31	1	0,57
Tumor location	1,40	1	0,23
Histologic type	0,45	2	0,79
Organs invasion	1,12	1	0,29
Mitotic index	3,70	1	0,04
Tumor size >13.5cm	3,70	1	0,04

*Df- degrees of freedom

TABLE 5 Multivariate Analysis for Overall Survival (Cox regression)

VARIABLE	HAZARD RATIO	CI 95%	*p*-value
Recurrence	4,4	0,1-28,9	0,03
Tumor size>13,5cm	5,7	0,08-10,0	0,01

Likelihood Ratio x^2 test: 38,20, Df=1 (p<0,0062>);
CI: Confidence interval

marized in **Tables 3 and 4**. Lymph node metastasis had no prognostic significance for overall and disease free survival (p=0.65 and p=0.57, respectively).

Multivariate analysis using only statistically significant variables found with univariate analysis showed tumor size >13.5cm and recurrence to be independent prognostic factors related to overall survival **(Table 5)**. Univariate analysis for disease free survival identified tumor size >13.5cm (p=0.04) and mitotic index (p=0.04) as prognostic factors but only tumor size >13.5cm was an independent factor in the multivariate analysis (p=0.04; CI 95%=0.7-55.3; hazard ratio 3.9; Likelihood ratio test x^2=28.99; Df=1; p<0.04>).

DISCUSSION

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 conservative 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 reported. 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 metastases 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 specimen was 10 and we strongly believe that this was responsible for the detection of the metastases. Besides this early recurrence in our series, the correlation between lymphatic metastases and overall survival (p=0.65) and disease free survival (p=0.57) fails to demonstrate a poor prognosis in univariate analysis. 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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