Factors Affecting Clinical Outcomes in Women with Non-Gastric Gastrointestinal Stromal Tumors

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Abstract

Background: Knowledge of the clinical outcome of women with non-gastric gastrointestinal stromal tumors (GISTs) is important for preoperative and postoperative consultation, especially for gynecologic oncologist. The aim of this study is to elucidate the factors affecting the clinical outcome of women with non-gastric GISTs.

Methods: Between January 2000 and October 2019, all consecutive women with non-gastric GIST who underwent surgeries in a tertiary referral center were reviewed.

Results: Among 26 women with non-gastric GISTs, eight (31%) women had recurrence or metastasis. Common clinical presentations included abdominal pain/fullness (n=12, 46%) and tarry/bloody stool (n=7, 27%). The primary locations of the tumors included the intestines (n=24) and an undetermined origin (n=2). Five (19%) women were initially admitted to the gynecologic department. Twenty-four (92%) patients underwent laparotomic tumor resection, and 2 (8%) patients underwent laparoscopic tumor resection. The probabilities of recurrence-free survival (RFS) at 60 and 120 months were 65.2% and 55.9%, respectively. Death occurred in seven (26.9%) women. The probabilities of overall survival (OS) at 60 and 120 months were 71.1% and 63.9%, respectively. Cancer stage was the only independent predictor for RFS (hazard ratio=6.00, p=0.007) and OS (hazard ratio=3.88, p=0.04). However, excluding cancer stage, metastasis (hazard ratio=8.74 for RFS, 6.03 for OS) and tumor size (hazard ratio=1.20 for OS) were independent predictors. Tumor size ≥ 13.9 cm was the optimum cut-off value to predict death and had an area under the receiver operating characteristic curve of 0.75 (95% confidence interval=0.53 to 0.98).

Conclusions: Non-gastric GIST may mimic gynecologic adnexal tumors. In addition to cancer stage, metastasis and tumor size (especially ≥ 13.9 cm for OS) remain independent predictors for RFS and OS in women with non-gastric GIST. The above findings may be used for consultation.

Trial registration: ClinicalTrials.gov NCT04256226

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that are generally tyrosine kinase protein KIT (CD117)-positive [1]. They account for 0.1% to 3% of gastrointestinal malignancies, and the locations ordered by frequency are the stomach (51%), small intestine (36%), colon/rectum (12%), and esophagus (1%) [1]. Surgical resection is the most effective treatment for GIST without metastasis [2,3]. Imatinib mesylate is the current mainstay therapy for GIST after surgery or inoperative and metastatic lesions [4].

The clinical presentation of non-gastric GIST might mimic ovarian cancer, and non-gastric GIST might be managed and treated by gynecologists [5,6]. Knowledge of the clinical outcome of women with non-gastric GIST is important for preoperative and postoperative consultation. However, the clinical outcomes

of women with non-gastric GIST have rarely been reported. Thus, the aim of this study is to elucidate the clinical outcomes of women with non-gastric GIST, especially to identify predictors affecting survival.

Methods

Between January 2000 and October 2019, all consecutive women with non-gastric GIST who received surgical treatment in a tertiary referral center were reviewed. The diagnosis of GIST was made according to Asian consensus GIST guidelines [7]. The stage of GIST was defined according to the American Joint Committee on Cancer (AJCC) staging system. Risk classification was defined according to the modified National Institutes of Health criteria [7].

Age, parity, menopausal status, body mass index, tumor markers, clinical presentations, department of admission, tumor location, tumor size, immunohistochemistry analysis of the tumor, mitotic index of the tumor, surgical interventions and adjuvant therapy were reviewed from medical records.

Recurrence of disease was defined according to radiological imaging. Overall survival (OS) was calculated as the time interval from the date of surgery to the date of death from any cause or last follow-up. Recurrence-free survival (RFS) was defined as the time interval from the date of surgery to the date of clinically defined recurrence, disease progression, or last follow-up.

Stata software (Version 11.0; Stata Corp, College Station, TX, USA) was used for statistical analyses. Survival curves were generated using the Kaplan-Meier method, and differences in survival curves were calculated with the log-rank test. A p value of less than 0.05 was considered statistically significant. A Cox proportional hazards model was used to identify predictors of RFS and OS. Multivariable backward stepwise Cox proportional hazards modeling was performed by using all variables in the univariate analysis until all remaining variables had $p<0.05$. Receiver operating characteristic (ROC) curve analysis was performed to identify optimal cutoff values. The optimal cutoff value was determined by the point on the ROC curve that was closest to the upper left-hand corner.

Results

There were 26 women with non-gastric gastrointestinal stromal tumors diagnosed between January 2000 and October 2019. Baseline characteristics are tabulated in Table 1.The most common clinical presentation was abdominal pain/fullness (n=12, 46%), followed by tarry/bloody stool (n=7, 27%). The departments at initial admission included general surgery department (n=13), gastrointestinal department (n=6), gynecological department (n=5) and colon and rectal surgery department (n=2).

The mean tumor size was 9.1± 5.3 cm, with a range of 3 to 16 cm. The primary locations of the tumors included the intestines (n=24), and pelvis with undetermined origin (n=2). Twenty-three (89%) patients were classified as high risk, and 3 (11%) patients were classified as low risk.

Twenty-four (92%) patients underwent laparotomic tumor resection, and 2 (8%) patients underwent laparoscopic tumor resection. Sixteen (62%) patients received adjuvant imatinib treatment, and 1 (4%) patient received adjuvant chemotherapy with mitomycin-C, epirubicin and fluorouracil.

Recurrence or metastasis events were noted in 8 (31%) patients. The RFS probabilities at 60 and 120 months were 65.2% and 55.9%, respectively (Fig 1a). Univariate Cox proportional hazards modeling showed that metastasis (hazards ratio=8.74, p=0.002) and cancer stage (hazards ratio=6.00, p=0.007) were predictors of RFS (Table 2). However, multivariable backward stepwise Cox proportional hazards modeling revealed that cancer stage (hazards ratio=6.00, p=0.007) was the only predictor of RFS.

Death occurred in 7 (27%) patients. The OS probabilities at 60 and 120 months were 71.1% and 63.9%, respectively (Fig 1b). Univariate Cox proportional hazards modeling showed that tumor size (hazard ratio=1.17, p=0.04), metastasis (hazards ratio = 4.98, p=0.04) and cancer stage (hazard ratio=3.88, p=0.04) were predictors of OS (Table 3). However, multivariable backward stepwise Cox proportional hazards modeling revealed that cancer stage (hazard ratio=3.88, p=0.04) was the only predictor of OS. Nonetheless, because tumor size and metastasis are components of the GIST AJCC staging system, when we excluded cancer stage as a variable for the multivariable analysis, tumor size (hazard ratio=1.20, p=0.03) and metastasis (hazard ratio=6.03, p=0.03) remained independent predictors of OS.

Tumor size ≥13.9 cm was determined to be the optimum cut-off value to predict death using ROC analysis, which provided an area under the ROC curve of 0.75 (95% confidence interval=0.53 to 0.98; sensitivity=57.1%, specificity=94.7%, Fig 1c).

Among the 5 women with non-gastric GIST who were admitted to the gynecology department, the initial presentations included abdominal pain (n=3), menorrhagia (n=1) and poor appetite (n=1). Abdominal/pelvic solid masses (n=3) or cystic masses (n=2) were found by ultrasonography. Computerized tomography of the tumor showed heterogeneous content in three women, multilobulated cysts in two women, necrosis or mucoid degeneration in one woman, and some coarse calcification in one woman. Preoperatively, four women were diagnosed with adnexal tumors, and one woman was diagnosed with pelvic masses. It is worth mentioning that computerized tomography revealed that tumors were located adjacent or attached to the small intestine in two women, and pelvic GIST was considered one of the probable preoperative diagnoses.

Among the above 5 women with non-gastric GIST admitted to the gynecology department, optimal debulking surgery was performed in two women, and small bowel resection was performed in three women. The pathologic examination revealed high risk in all five women, and they were treated with adjuvant imatinib. All patients remained alive without disease until the last follow-up. There were no between-group differences in RFS (Fig 2a, p=0.07) and OS (Fig 2b, p=0.11) regardless of whether patients were admitted to the gynecology department or other departments.

Discussion

Our study showed that cancer stage was the only independent predictor for female non-gastric GIST. The components of the AJCC staging system for GIST include tumor size, lymph node involvement, metastasis and mitotic rate. In our second model, multivariable Cox proportional hazard modeling revealed that tumor size (hazard ratio=1.20 for OS) and metastasis (hazard ratio=8.74 for RFS, 6.03 for OS) were independent predictors (Tables 2 & 3). Therefore, from our study, tumor size and metastasis can be used as independent predictors for RFS or OS in women with non-gastric GIST, as can cancer stage (in our first model: hazard ratio = 6.00 for RFS, 3.88 for OS, Tables 2 & 3). In addition, tumor size ≥13.9 cm can be used as a cut-off value for poor prognosis (Fig 1c).

In our study, the 5-year RFS and OS rates were 65.2% and 71.1%, respectively, for women with non-gastric GIST. Similarly, Lin et al. also reported that the 5-year RFS and OS rates were 76.2% and 83.4%, respectively, for high-risk GIST with complete resection [8]. Thus, our RFS and OS data could be used in postoperative consultation for women with non-gastric GIST.

It is worth mentioning that 20 of 26 (76.9%) women with non-gastric GIST presented after the age of 50, with non-gastric GIST being uncommon in female patients before the age of 50 (6 of 20 patients, 23.1% in our study). In addition, there was no lymph node metastasis in our study (Table 1), and this finding was consistent with a previous study and is probably related to the unique clinical properties of spindle cell; thus, lymph node dissection should be not necessary for GIST surgical treatment [9,10], and this is different to that of ovarian cancer. Complete surgical resection with clear surgical margins along with adjuvant target therapy is the main treatment of GIST [11,12].

Most women with non-gastric GIST underwent surgical interventions by general surgeons or colon/rectal surgeons; however, GIST may mimic adnexal malignancy, and patients with GIST may receive surgical interventions by gynecologists or gynecologic oncologists with or without the aid of general surgeons under the preoperative diagnosis of adnexal tumor. In our study, five women were admitted to the gynecologic department and underwent surgical treatment. However, there were no between-group differences in RFS and OS for women who were admitted to the gynecologic department and those who were admitted to other department (Figs 2a and 2b). Thus, for women with non-gastric GIST who were admitted to the gynecologic department, with multi-disciplinary cooperation, the prognosis seems to not be inferior to that of those patients admitted to other departments.

Two of our five patients with GIST, who were treated by gynecologists, had been suspected as having pelvic GIST preoperatively by computerized tomography because the tumor was located adjacent or attached to the small intestine. Thus, for women with pelvic masses of undetermined origin, computerized tomography should be used for preoperative differential diagnosis to elucidate whether the tumor is located adjacent or attached to the small intestine and/or has features of hemorrhage, necrosis or cystic lesion [13].

As shown in Table 1, abdominal pain and fullness were the main symptoms of non-gastric GIST, and these symptoms are similar to those of gynecologic adnexal tumor. However, tarry/bloody stool was present in 30% of women with non-gastric GIST (Table 1), and this symptom was rarely mentioned as one

of symptoms of gynecologic adnexal malignancy. Thus, for women with abdominal/pelvic tumors, careful history taking with a focus on tarry stool or bloody stool should be important for preoperative differential diagnosis.

Limitations of this study include its retrospective nature and limited sample size. However, we used person-time analysis to elucidate the survival predictors to diminish the limitation of the small sample size.

Conclusions

Non-gastric GIST may mimic gynecologic adnexal tumors. In addition to cancer stage, metastasis and tumor size (especially ≥ 13.9 cm for OS) remain independent predictors for RFS and OS in women with non-gastric GIST. The above findings may be for consultation.

Abbreviations

GIST = gastrointestinal stromal tumor

AJCC = American Joint Committee on Cancer

OS = overall survival

RFS = recurrence-free survival

ROC = receiver operating characteristic

Declarations

Ethics approval and consent to participate: This study was approved the Research Ethics Review Committee of Far Eastern Memorial Hospital (No:108174-E), which waived the requirement for informed consent.

Consent for publication Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: SMH and KHC contributed to the study design. PHH wrote the manuscript. SMH and HHL revised the manuscript. PHH, HHC, WHT and YYC collected the data. SMH analyzed the data. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics and clinical outcome of women with non-gastric gastrointestinal stromal tumors (n=26)

Variables	Values
Age (years)	59.4±12.8
Parity	2.1±1.3
Menopause	19 (73)
Body mass index (kg/m^2)	24.1±4.2
Clinical presentations	
Abdominal fullness/pain	12 (46)
Tarry / bloody stool	7 (27)
Dizziness / poor appetite	3 (12)
Miscellaneous	4 (15)
CA125 (units/ml)	149.4±200.3
CEA (ng/ml)	1.6±1.4
CA199 (units/ml)	24.1±32.4
Average tumor size (cm)	9.1±5.3
Tumor size	
≤2 cm	0 (0)
>2 - ≤5cm	5 (19)
>5 - ≤10cm	12 (46)
>10cm	9 (35)
Spread to lymph node	0 (0)
Metastasis at initial diagnosis	4 (15)
Mitotic rate (per 50 high power fields)	
Low (≤5)	12 (46)
High (>5)	11 (42)
No data	3 (12)
Stage	
I	3 (12)
II	6 (23)
IIIA	0 (0)
IIIB	13 (50)
IV	4 (15)
Location	
Intestine	24 (92)
Undetermined	2 (8)
Immunochemistry profile	
CD117	26 (100)
†CD34	16 (80)
†DOG1	7 (100)
Imatinib treatment	16 (62)
Recurrence	8 (31)
Death	7 (27)

Values were expressed as mean ± standard deviation or number (percentage).

†CD34 and DOG 1 data was available in 20 and 7 women, respectively.

Table 2. Cox proportional-hazards modeling for predicting factors affecting recurrence-free survival of women with non-gastric gastrointestinal stromal tumors (n=26)

Variables	Univariate			Model 1 Multivariable			Model 2 Multivariable		
	Hazard ratio	95% CI	†P	Hazard ratio	95% CI	‡P	Hazard ratio	95% CI	‡P
Age (years)	1.02	0.96 to 1.08	0.54	-	-	-	-	-	-
Parity	0.84	0.34 to 2.13	0.72	-	-	-	-	-	-
Menopause	0.68	0.16 to 2.86	0.60	-	-	-	-	-	-
Body mass index (kg/m2)	0.98	0.82 to 1.18	0.85	-	-	-	-	-	-
CA125 (units/ml)	1.003	0.996 to 1.009	0.40	-	-	-	-	-	-
CEA (ng/ml)	1.27	0.74 to 2.15	0.38	-	-	-	-	-	-
CA199 (units/ml)	1.00	0.97 to 1.04	0.79	-	-	-	-	-	-
Tumor size (cm)	1.04	0.90 to 1.20	0.62	-	-	-	-	-	-
Metastasis	8.74	2.15 to 36.62	0.002	-	-	-	8.74	2.15 to 36.62	0.002
Immunochemistry									
CD34	0.68	0.14 to 3.37	0.64	-	-	-	-	-	-
Imatinib treatment	3.15	0.38 to 26.0	0.29	-	-	-	-	-	-
Mitotic rate (Low vs. high mitotic rate)	5.65	0.65 o 49.35	0.12	-	-	-	-	-	-
Stage (i.e., I = 1, II = 2, IIIA = 3, IIIB = 4 and IVA = 5)	6.00	1.61 to 22.29	0.007	6.00	1.61 to 22.29	0.007			

CI = confidence interval.

†Cox proportional-hazard modeling

‡In model 1, multivariable backward stepwise Cox proportional-hazard modeling is performed by using all variables in the univariate analysis till all remaining variables with $p<0.05$. In model 2, stage is excluded as a variable. Multivariable backward stepwise Cox proportional-hazard modeling is performed by using all the other variables in the univariate analysis till all remaining variables with $p<0.05$.

Table 3. Cox proportional-hazards modeling for predicting factors affecting overall survival of women with non-gastric gastrointestinal stromal tumors (n = 26)

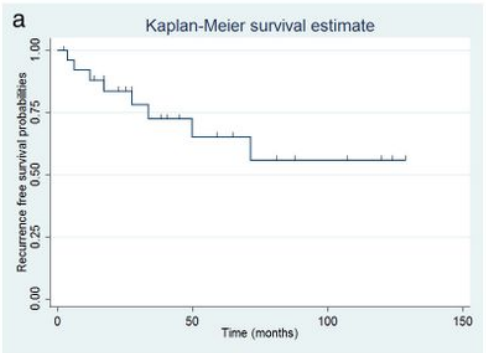
Variables	Univariate			Model 1 Multivariable			Model 2 Multivariable		
	Hazard ratio	95% CI	†P	Hazard ratio	95% CI	‡P	Hazard ratio	95% CI	‡P
Age (years)	1.03	0.97 to 1.09	0.37	-	-	-	-	-	-
Parity	0.53	0.23 to 1.22	0.13	-	-	-	-	-	-
Menopause	0.97	0.19 to 5.02	0.97	-	-	-	-	-	-
Body mass index (kg/m2)	0.93	0.77 to 1.14	0.49	-	-	-	-	-	-
CA125 (units/ml)	1.001	0.995 to 1.009	0.59	-	-	-	-	-	-
CEA (ng/ml)	1.12	0.63 to 1.97	0.70	-	-	-	-	-	-
CA199 (units/ml)	0.99	0.96 to 1.03	0.74	-	-	-	-	-	-
Tumor size (cm)	1.17	1.01 to 1.35	0.04	-	-	-	1.20	1.01 to 1.41	0.03
Metastasis	4.98	1.10 to 22.54	0.04	-	-	-	6.03	1.20 to 30.35	0.03
Immunochemistry									
CD34	0.63	0.12 to 3.27	0.58	-	-	-	-	-	-
Imatinib treatment	1.06	0.20 to 5.53	0.95	-	-	-	-	-	-
Mitotic rate (Low vs. high mitotic rate)	5.12e+15	0 to -	1.00	-	-	-	-	-	-
Stage (i.e., I = 1, II = 2, IIIA = 3, IIIB = 4 and IV = 5)	3.88	1.05 to 14.29	0.04	3.88	1.05 to 14.29	0.04			

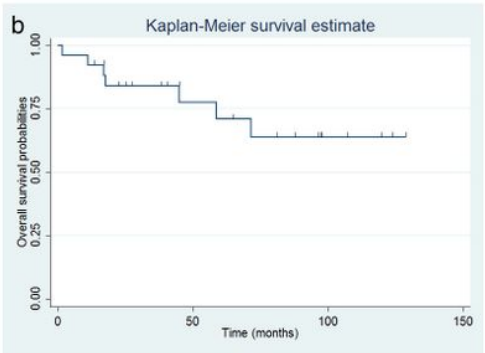
CI = confidence interval.

†Cox proportional-hazard modeling

‡In model 1, multivariable backward stepwise Cox proportional-hazard modeling is performed by using all variables in the univariate analysis till all remaining variables with p<0.05. In model 2, stage is excluded as a variable. Multivariable backward stepwise Cox proportional-hazard modeling is performed by using all the other variables in the univariate analysis till all remaining variables with p<0.05.

Figures





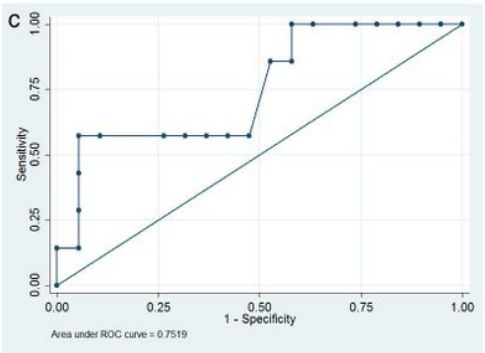


Figure 1

Probabilities of (a) recurrence-free survival and (b) overall survival inwomen with non-gastric gastrointestinal stromal tumors. (c) The receiver operating characteristic curve for tumor size as a predictor of death in women with non-gastric gastrointestinal stromal tumors.

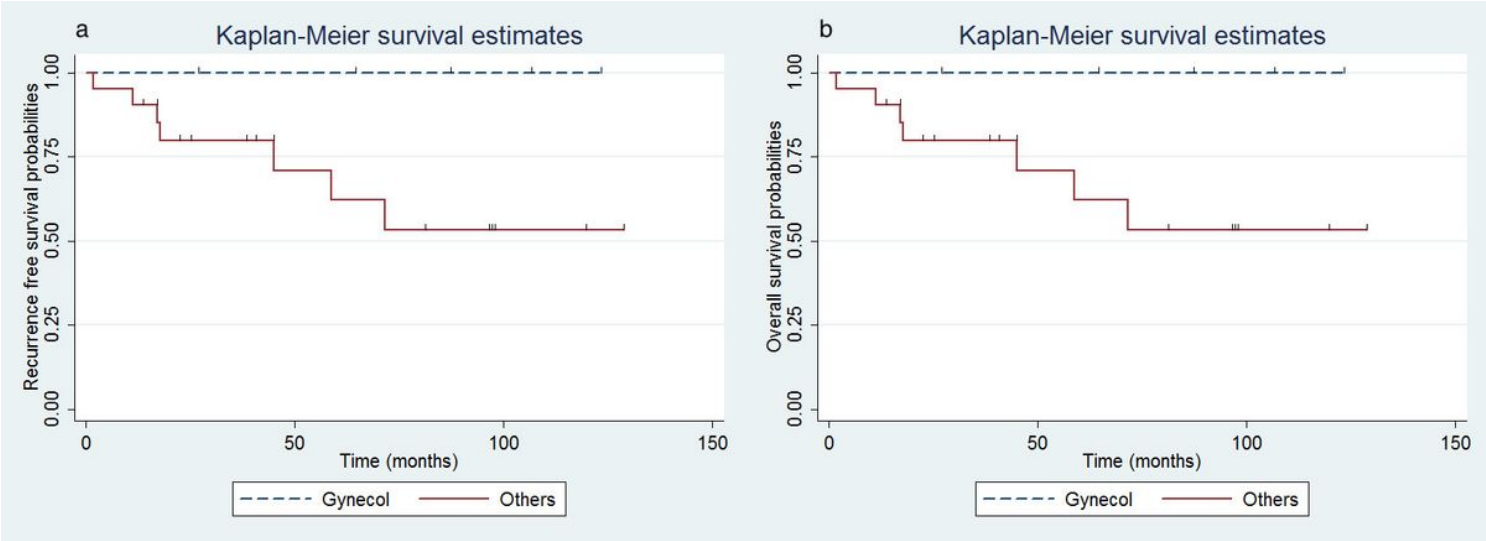


Figure 2

Probabilities of (a) recurrence-free survival and (b) overall survival in women with non-gastric gastrointestinal stromal tumors between those seen in the gynecologic department and those seen in other departments.