Original Article

Evaluation of Survival and Prognostic Factors in Patients with Gastrointestinal Stromal Tumor

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Abstract

Background: Gastrointestinal stromal tumors (GIST) comprise 1% of primary tumors of gastrointestinal (GI) tract. The aim of this study is to survey overall survival (OS), disease free survival (DFS) and also the effect of some factors such as mitotic count, tumor size, age, gender on prognosis and time of appearing recurrence which is rarely studied in Iran. **Methods**: This study is a type of survival analysis, which was performed on 95 patients who were suffering from GIST during 2004-2017 within Yazd, Shiraz, Kermanshah and Kerman cities. Statistical data were analyzed by SPSS version 21 and the patients· OS and DFS were calculated by Kaplan- meier test. Investigation of risk factors such as age, gender, mitotic count and tumor size on prognosis, time of recurrence (local recurrence or metastasis) were evaluated by log rank test and cox regression model. **Result:** OS and DFS were studied on these patients. In this survey OS was 96%, 94% and 83% in the first year, second year and the fifth year, and DFS was 87%, 81% and 51% respectively. In addition, some factors like mitotic count and tumor size and risk classification were significantly related to disease free survival based on log rank test, and mitotic count and male gender were negative predictor of malignant behavior based on cox regression model ($p<0.05$). **Conclusion**: The survival time in these patients after introduction imatinib remarkably increased and some factors such as mitotic count has prominent effect on prognosis, in comparison with other factors.

Keywords: GIST, survival, prognostic factors

Introduction

Gastrointestinal stromal tumors (GIST) comprise approximately 1% of primary tumors of gastrointestinal tract [1]. In the past, these tumors were categorized as smooth muscle cell tumors like leiomyoma, leiomyoblastoma, leiomyosarcoma. Then the advent of Electronic microscopes in 1970_s and Immuno- histochemical studies in 1980_s showed that a large number of these tumors did not have complete features of muscle cell tumors. And for the first time during 1983and 1984 the term stromal tumor was used [2, 3]. currently, it is crystal clear that GIST tumors originate from cajal cells [1, 4]. These cells act as pace maker of GI system. They are also a link between anatomic nervous system and smooth muscles of GI tract And adjust peristalsis of GI system [5, 6]. GIST tumors can take place in any part of GI tract. The most prevalent places are stomach, then small intestine and after that colon and rectum and finally esophagus [7, 8]. This tumor is reported rarely in some other locations outside of gastrointestinal system such as uterus, recto vaginal septum, vagina, mesentery, omentum and retroperitonea which is known as extra gastrointestinal stromal tumor [9-11].

GIST has different and various degrees of aggression and various factors effect on the biological behavior of these tumors, prognosis and survival time. These factors include

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tumor size, mitotic count, tumor location [12], histological features like tumor necrosis, existence of symptoms [13], tumor histological structure [14], immunohistochemical factors [15]. Tumor size, mitotic activity and anatomic site are used to predict malignant courses according to CAP guideline edition 7th classification [16].

In addition, in the treatment process of GIST, the cooperation between oncology surgeon and medical oncologist is required. cytotoxic chemotherapy in GIST treatment is ineffective and before using of tyrosine kinase inhibitors the patients with metastasis had poor prognosis and average overall survival was less than 2 years [17]. the prognosis of these patients were changed remarkably after introduction of imatinib. The use of imatinib was confirmed after clinical trial study in 2000, and approved as adjuvant therapy in 2008 [18-20]. This study is about evaluation of survival and also association of some factors such as mitotic count, tumor size, age, gender on prognosis, local recurrence and metastasis. Studies like this rarely carried in Iran.

METHODS:

This study is a type of survival analysis which was performed on 95 patients suffering from GIST. GIST was approved according to pathological and immunohistochemical characteristics of these tumors. The patients referred to specialized oncologists in Yazd, Shiraz, Kermanshah and Kerman cities for treatment. After patients satisfaction, the demographic data such as age, gender, family history of cancer, sign and symptoms, tumor location, tumor histological characteristics, local recurrence, metastasis and current status of patients were registered via questionnaire. All patients were under surgery for tumor removal. 2 patients were excluded from the study because they were suffering from adenocarcinoma and GIST at the same time, and intervene the treatment process. Nine patients were also excluded due to inadequate data.

All cases were classified according to guideline CAP edition 7th with regard to mitotic count, tumor size, tumor location into four groups: very low risk, low risk, moderate risk and high risk.

Statistical methods:

All calculations were performed with the spss version 21 software. Furthermore, overall survival (OS), disease free survival (DFS) curves were analyzed using the Kaplan-meier test. OS was calculated from the date of diagnosis until they died or time of doing study and DFS was calculated using the time of local recurrence or metastasis or time of doing study.

Local recurrence was defined as the reappearance of tumor at the initial site of primary tumor. metastasis was recorded when the tumor spread to the liver, lymph node or other sites. Local recurrence and metastasis of these patients were considered, approved and studied via radiological, pathological and clinical data.

The relations of age, gender, mitotic count, tumor size, and risk groups to OS and DFS were tested by univariate and multivariate analysis. The log rank test was used to compare various groups and cox regression hazards model was used to assess the prognostic significant of these factors and estimate the hazard ratios and 95% confidence interval (CI) of prognostic factors.

A value of $p< 0.05$ was considered statistically significant.

RESULT:

This study was done on generally, 84patients referred oncologists of Yazd, Shiraz, Kermanshah and Kerman cities between 2004-2017.GIST was found to be more common in males with slight male predominance (54.76% were men and 45.24% were women). almost 40 % of these patients had a cancer history in their families. Based on tumor location, the stomach was the most prevalent site (61.9%, n=52) and after that small intestine (27.38%, n=23) and other sites (10.71%, n=9).

According to sign and symptoms, the most common clinical presentation was fatigue (83.33%, n=70) and after that melena and hematochezia (63.09%, n=53), anemia (57.14%, n=48), loss of appetite (53.57%, n=45), abdominal pain (50%, n=42), losing weight (42.85%, n=36), nausea and vomiting (23.80%, n=20), hematemesis (13.09%, n=11), dysphagia (9.52%, n=8) and sense of mass (7.14%, n=6).

Tumor necrosis occurred in 26.19% of patients and tumor hemorrhagic occurred in 13.09% of patients and 7.14% of patients had cystic tumor.

Local recurrence occurred in 15.47% of patients (n=13) and 17.86% of patients had metastasis (n=15). metastasis was seen in liver and pelvic in (11.9%, n=10) and lung in (23%, n=2) and omentum in (3.57 %, n=3).

Among these patients, 11.90% of patients died because of this disease, 2.38% died due to other disease like MI and 85.71% of patients were alive.

OS was investigated and studied (figure 1). OS was 96%, 94% and 83% in the first year, second year and the fifth year. Furthermore, DFS was studied as shown (figure 2). DFS was 87%, 81% and 51% in the first year, second year and the fifth year.

On univariate analysis (table 1), size of tumor, mitotic rate and risk group were significant predictors of survival. The disease free survival of patients who were in very low and low risk groups, statistically differs significantly from the survival of patients who were in high risk groups ($p<0.00001$). Patients with tumor size< 10cm fared better than those with tumor size ≥ 10cm ($p<0.005$) and also mitotic rate was an important predictor. Patients with mitotic rate<5 per 50 HPF did markedly better than those with mitotic rate ≥ 5 per 50 HPF ($p<0.0005$). There was no difference on DFS

between patients with stomach GIST and small intestine GIST and other places (p>0.05). Age and gender didn't predict disease free survival (p>0.05).

These factors didn't predict overall survival, by univariate analysis. However, we believe that, it is associated with the increase of OS in patients after using imatinib and low number of death in this study or inadequate number of cases.

Multivariate analysis showed that (table 2), tumor size (H.R:1.048, P: 0.219), mitotic count (HR:1.043, P:0.066), tumor site (small intestine: H.R 1.109, P:0.868 and other site HR:2.796, p:0.177), older age (HR:1.015, P:0.381) were poor prognostic sign on DFS but they aren't statically significant. Also in the study of OS according to these factors, mitotic count (HR:1.12, P:0.014) was the most significant factor and female gender (HR:0.047, P:0.047) had better prognosis, and tumor size (HR:0.961, P:0.606), age (HR:0.998, P:0.948) and tumor site (small intestine: H.R ;0.956, P:0.958 and other site HR:0.234, P:0.245) were not significantly correlated with the OS.

We did not enter risk groups into multivariate analysis, as they were depended to the tumor size, mitotic count and tumor site.

Discussion:

The most prevalent sign and symptom indicated in our study on 84 patients was fatigue and other symptoms based on tumor location were different. Like other studies, stomach was most prevalent site in which tumors were indicated. Then small intestine ranked the second [21].

In this study OS was 96%, 94% and 83% in the first year, second year and the fifth year, and DFS was 87%, 81% and 51% respectively, which indicates the increase of OS and DFS time in using imatinib in comparison with studies before introduction of imatinib [21-23]. as like as other researches which performed after using imatinib on survival [24, 25]. On the other hand, this can also be caused by the heterogeneity of study populations. For example, some studies only included malignant GISTs, but others might also include benign GISTs.

In the assessment of DFS, it has been observed that, tumor size, mitotic count and risk groups predicted outcome on univariate evaluation. as the same several studies identified tumor size and mitotic rate as prognostic variables [23, 26, 27]. However, in our study, tumor location did not predict disease free survival, it has been observed that gastric GIST generally has a more favorable course than small intestine GIST [28-30] and patients with colon or rectum GIST had a high rate of recurrence [25].

In the evaluation of overall survival, in multi variable assessment, mitotic count was associated with worse overall survival as like as other studies [31-33].

Although many studies showed that, tumor size is a negative predictor of survival [31-33], In the current study, tumor size did not correlate with overall survival. It is unclear why such a discrepancy occurs. This can be caused by the increase of OS in patients after using imatinib and low number of death in this study or inadequate number of cases.

The impact of gender and tumor location on survival are still controversial. some studies argued that, they were not prognostic factors of GIST [31, 34, 35]. However, in our study the cox multivariable analysis revealed that gender was significant independent predictor of survival of GIST patients. Male gender was identified as a negative predictor of survival, which was consistent with findings in other studies [29, 36, 37].

Moreover, age did not correlate with overall survival and disease free survival, as the same other studies [23, 25]

Conclusion:

Survival time in GIST patients increases remarkably after introduction of imatinib. Some factors such as mitotic count, tumor size, risk classification have effect on disease free survival and mitotic rate, has prominent effect on prognosis in comparison with other factors. However, it needs more studies in Iran.

Abbreviations:

Gastrointestinal tumor (GIST), overall survival (OS), disease free survival (DFS), gastro intestinal (GI)

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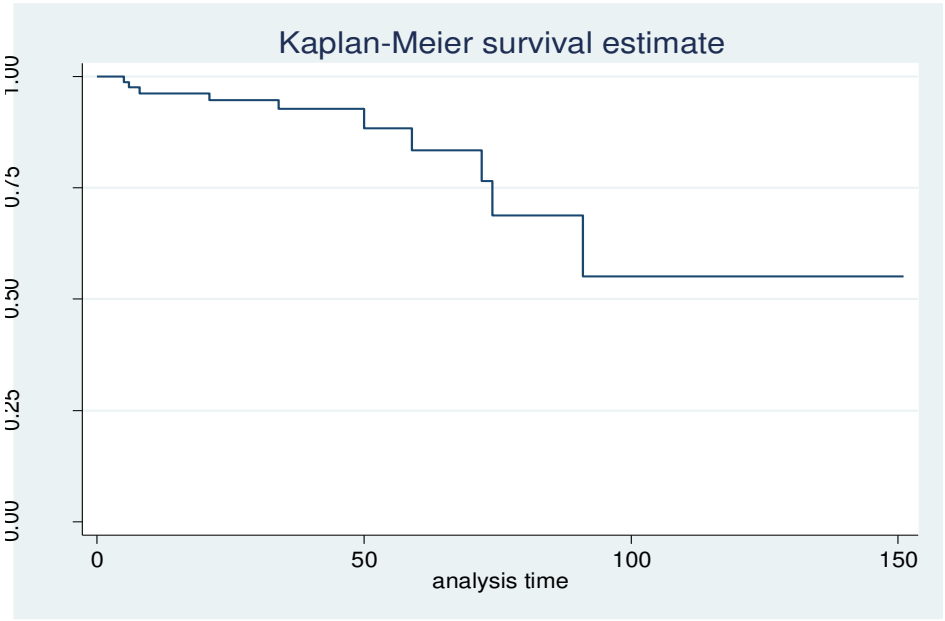

Figure 1. Kaplan–Meier analysis describing overall survival (OS) in patients with GIST

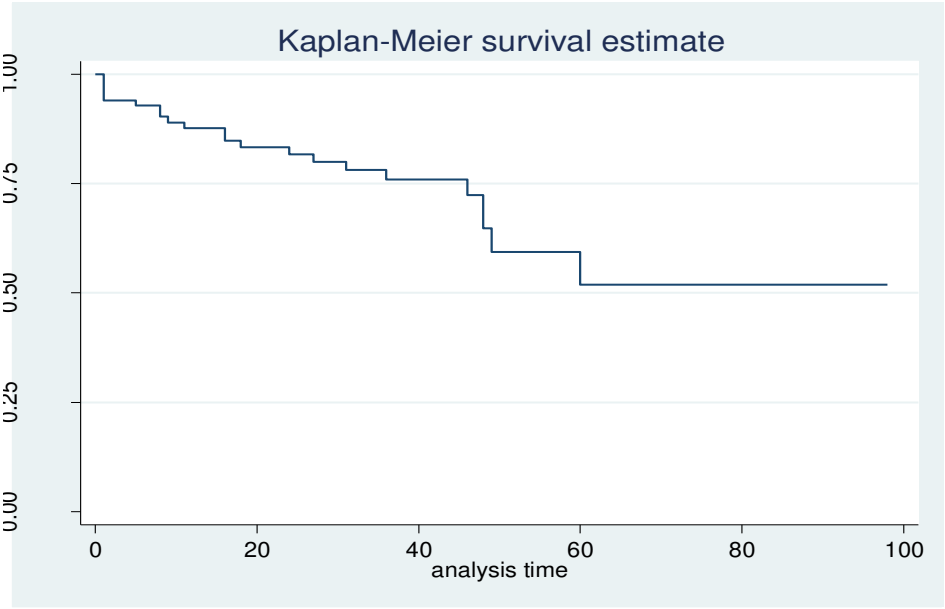

Figure 2- Kaplan–Meier analysis describing disease-free survival (DFS) in patient with GIST

Table 1- association of prognostic factors with disease free time and survival time by univariate analysis (log rank test)

	Effect of factors on disease free time							Effect of factors on overall survival time						
variable	n	Mean of disease free time	SE	CI		Recurrence number	P value	n	Mean of survival time	SE	CI		death number	P value
Age<60	52	74	6	61	84	11		52	127	10	107	147	5	
Age≥60	32	49	5	39	58	11	0.3501	32	75	8	59	90	5	0.1393

Female	38	63	6	52	74	8		38	90	4	83	98	3	0.3086
Male	46	64	7	49	79	14	0.2626	46	107	14	79	134	7	
Tumor Size <10cm	51	79	6	67	91	8		51	116	14	88	143	5	
Tumor Size ≥10cm	33	39	5	30	48	14	0.0049	33	82	56	70	943	5	0.6322
Stomach	52	62	5	52	72	11		52	83	7	69	96	4	
Small intestine	23	54	6	42	66	7	0.2819	23	77	7	63	91	5	0.4104
Other sites	9	52	16	20	83	4		9	135	15	105	165	1	
Mitotic count<5 HPF	41	87	6	75	99	3		41	120	18	84	155	2	0.2093
Mitotic count≥5 HPF	43	43	5	34	53	19	0.0003	43	80	5	70	91	8	
Very low risk group	10	65	7	52	78	1		10	-	-	-	-	0	
Low risk group	23	88	7	75	101	2		23	114	21	73	155	2	
Moderate risk group	27	67	4	58	75	3	0.000	27	-	-	-	-	0	0.0853
High risk group	24	30	5	21	40	16		24	72	8	57	87	8	

Table 2- association of prognostic factors with disease free time and survival time by multivariate analysis (cox regression model)

		Effect of factors on disease free time						Effect of factors on overall survival time					
variable	Sub group	Haz.ratio	CI		S.E	Z	P-value	Haz.ratio	CI		S.E	Z	P-value
Age	-	1.015	0.982	1.048	0.017	0.88	0.381	0.998	0.950	1.048	.0248	-0.06	0.948
gender	male	reference	-	-	-	-	-	-	-	-	-	-	
	female	0.530	0.190	1.483	0.525	-0.634	0.227	0.047	0.002	0.958	1.536	-3.053	0.047
Tumor Size	-	1.048	0.972	1.130	0.040	1.23	0.219	0.961	0.827	1.116	0.073	-0.52	0.606
Tumor site	stomach	reference	-	-	-	-	-	-	-	-	-	-	
	Small intestine	1.109	0.326	3.765	0.692	0.17	0.868	0.956	0.178	5.119	0.818	-0.05	0.958
	Other sites	2.796	0.627	12.452	2.130	1.35	0.177	0.234	0.020	2.708	0.292	-1.16	0.245
Mitotic count	-	1.043	0.997	1.090	0.024	1.84	0.066	1.12	1.023	1.23	0.053	2.46	0.014