EUROPEAN JOURNAL OF CANCER 43 (2007) 144–148

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain

J. Rubió[a,], R. Marcos-Gragera[b], M.R. Ortiz[c], J. Miró[d], L. Vilardell[b], J. Gironès[e], X. Hernandez-Yagüe[a], A. Codina-Cazador[e], L. Bernadó[c], A. Izquierdo[a,b], R. Colomer[a]*

[a]*Department of Medical Oncology, Catalan Institute of Oncology, Hospital Josep Trueta, Avda. França s/n, 17007 Girona, Spain*
[b]*Epidemiology and Girona Cancer Registry Unit, Catalan Institute of Oncology, Girona, Spain*
[c]*Department of Pathology, Hospital Josep Trueta, Girona, Spain*
[d]*Department of Pathology, Clinica Girona, Spain*
[e]*Department of General Surgery, Hospital Josep Trueta, Girona, Spain*

ARTICLE INFO

Article history:
Received 29 May 2006
Received in revised form
18 June 2006
Accepted 19 July 2006
Available online 18 October 2006

Keywords:
Gastrointestinal stromal tumour,
GIST
KIT
Imatinib
Incidence
Survival
Epidemiology
Cancer registry
Cancer

ABSTRACT

Background: Gastrointestinal stromal tumours (GIST) are rare malignancies characterised by their association with KIT oncogene mutations. Until now, population-based reports of the incidence or survival of kit-confirmed GIST have been rare, and none have originated in Southern Europe.

Materials and methods: We used the Girona Cancer Registry to identify malignant mesenchymal tumours of the digestive tract between 1994 and 2001, and performed c-kit testing in the tumour samples. Age-adjusted incidence rates and survival rates were calculated, and they were also analysed by sex and NIH risk categories.

Results: Forty-six cases were categorised as GIST. Fifty percent were localised in the stomach, 43.5% in small intestine, 4.3% in the omentum, and 2.2% in colon. Thirty-seven percent were classified as high risk of an aggressive behaviour, 30.4% as intermediate risk and 32.6% as low or very low risk. Only one patient received treatment with imatinib mesilate. The annual incidence by 100,000 inhabitants in crude rate, European age-standardised rate and world age-standardised rate was, respectively, 1.09, 0.90 and 0.65 cases. The relative 5-year survival rate was 74.7% for the entire cohort, and it was markedly lower in the high-risk cases (20.3%).

Conclusions: We report the first population-based study of GIST incidence and survival in Southern Europe. The incidence rate is low and comparable with that of cancer registries from Northern Europe. Survival was favourable in our pre-imatinib population although it was low in high risk cases. Prognostic discrimination of the cases with intermediate, low, or very low risk is inadequate, and these categories should be considered jointly in the future. Our results will help researchers in establishing baseline values against which they can compare, in the future, the impact of imatinib and other Kit tyrosine inhibitors on survival.

* *Corresponding author:* Tel.: +34 972940200; fax: +34 972217344.
E-mail address: jrubio@ico.scs.es (J. Rubió).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.07.015

1. Introduction

The natural history of gastrointestinal stromal tumours (GIST) has changed significantly after the combined identification of the activation of the Kit-gene in its pathogenesis, the availability of a test to identify the overexpressed protein,[1] and the development of a successful targeted therapy.[2] Some approaches have evaluated the incidence of GIST in up to 2 cases/100,000 inhabitants per year.[1] The wide spectrum of histological terms that have been used in the past to identify GIST,[3] and the fact that only recently this otherwise heterogeneous type of tumour has been recognised as a clinical entity, has made it difficult to define the real incidence and survival of GIST. In addition, some GIST have been considered as benign tumours, and have not been registered by the population-based cancer registries.

Recent interest in GIST is reflected by the definition of consensus prognostic clinical tool[4] and by the epidemiological studies that have been performed in the United States of America (USA)[5] and in Northern Europe populations.[6–8] C-kit testing however has not always been performed in these studies.

The purpose of our research was to define the incidence rates and survival of kit-confirmed GIST in Girona, an area representative of Southern Europe, and to evaluate the NIH pronostic classification.

2. Materials and methods

The Girona Cancer Registry is a population-based cancer registry located in Northeast Spain.[9] The population covered by the Registry in 2001 was 553,661 inhabitants. The information sources of the cancer registry are the regional and community hospitals, the haematology and pathology departments, and death certificates. Tumours registered are those considered malignant or borderline. The completeness of the registry is 96.3%.[10]

We searched for all histologies of mesenchymal tumours of the digestive tract in the database of the Girona Cancer Registry between 1994 and 2001. As the terminology GIST is of recent use and did not have a specific code until the third edition of ICD-O, which was published in 2000,[11] we searched terms such as leiomyoma, leiomyosarcoma, leiomyoblastoma, gastrointestinal autonomic nerve tumour, epitheloid leiomyoma or leiomyosarcoma, mesenchymoma, stromal sarcoma and sarcoma not otherwise specified (NOS) of the gastrointestinal tract, as described by Miettinen and colleagues.[3] We reviewed all cases of mesenchymal tumours registered using the pathological codes of the ICD-O second edition.[12] The tumour site codes used were those of the gastrointestinal tract, from c17 to c26. We confirmed that liposarcoma or rhabdomyosarcoma of the gastrointestinal tract were correctly classified. Since some GIST are considered as benign tumours, and therefore were not registered, we additionally asked the pathology departments of the area to review all the suspected cases, benign or malignant.

We obtained paraffin-embedded samples and performed the immunohistochemical detection of c-kit. Immunohistochemistry was performed on available formalin-fixed, paraffin-embedded tissue blocks in two pathology laboratories. Standard haematoxylin and eosin stained sections were used to evaluate tumour cytology and the number of mitoses. Mitotic figures were counted in 50 consecutive high power fields (HPF; ×400 magnification) using an Olympus BX 41 TF microscope. The immunostains were performed using the Envision non-avidin-biotin based polymer system (Dako) in 44 cases and with the avidin biotin peroxidase complex in ten cases. Diaminobenzidine was used as the cromogen in all of them. The primary antibody source dilution was Kit (CD 117), polyclonal, Dako, Carpinteria, CA 1:400. Heat-induced epitope retrieval with EDTA buffer was performed as a pre-treatment.

We classified GIST using the risk criteria for aggressive behaviour defined at the National Institutes of Health GIST Workshop in April 2001,[4] which is based on the tumour size and mitotic rate per 50 high power field (hpf) according to four groups: very low risk (< 2 cm and < 5 mitoses/50 hpf), low risk (2–5 cm and < 5 mitoses/50 hpf), intermediate risk (< 5 cm and 6–10 mitoses/50 hpf or 5–10 cm and < 5 mitoses/50 hpf) and high risk (> 5 cm and > 5 mitoses/50 hpf or > 10 cm regardless of mitotic activity or any size and > 10 mitoses/50 hpf).

Incidence was calculated as crude rate and also as World and European age-standardised rates (ASR).[13] Survival was obtained by active follow-up, and was calculated from the date of biopsy until July of 2004 or last follow-up. Record linkage to the Catalan Mortality Registry was made in the case of incomplete follow-up. Relative survival (RS) was defined as the ratio between observed survival (OS) and expected survival, and was calculated to express the probability of cancer survival after adjustment for competing causes of death.[14] Relative survival rates at 1, 3, and 5 years were calculated using the Hakulinen method[15] by means of WAERS,[16] a web-assisted application developed by the Catalan Institute of Oncology which permits the estimation of the relative survival of a cohort of patients. Expected survival was estimated using the mortality life tables of Catalonia.

3. Results

We identified 61 cases fulfilling the screening criteria diagnosed during the previously specified period. We performed the c-kit immunostaining in 54 cases. Forty-three tumours were positive. Eleven were negative; five of these were reclassified as benign leiomyoma and six to true leiomyosarcoma c-kit and CD 34 negative. Paraffin-embedded samples were not obtained in seven cases. Of those, three were diagnosed by cytology only in the context of an advanced disease, and were considered GIST in the final analysis due to their clinical characteristics, course and histological description.

Therefore, we categorised 46 cases as GIST for the analysis, 22 of which (47.8%) occurred in males and 24 (52.2%) in females. Table 1 shows the different histological terms and codes initially used to register those cases.

The primary sites of GIST were the stomach in 23 cases (50%), the small intestine in 20 cases (43.5 %) the colon in one case (2.2%) and the omentum in two cases (4.3 %).We assessed the mitotic index and size in 43 of the 46 tumours. The three cases diagnosed by cytology only were included in the high risk category. The number of mitoses per 50 hpf was

Table 1 – ICD-O codes used to refer true GIST to Girona Cancer Registry

ICD-O	Description	No.
8004/3	Malignant fusocellular tumour	3
8800/0-8800/1	Soft tissue tumour benign	2
8800/3	Sarcoma NOS	3
8804/3	Epitheloid sarcoma	1
8890/0-8890/1	Leiomyoma-leiomyomatosis	11
8890/3	Leiomyosarcoma	7
8891/0	Epitheloid leiomyoma	5
8891/3	Epitheloid leiomyosarcoma	3
8935/0-8935/1[a]	Stromal tumours benign or NOS	3
8936/0-8936/1[a]	Gastrointestinal stromal tumour benign or NOS	5
8936/3[a]	Gastrointestinal stromal sarcoma	3
		46

All codes ICD-O 2nd edition except otherwise specified.
a Codes from ICD-O 3rd edition (published in 2000 and used in CGR since coding year 1998).

<5 in 30 cases, 5–10 in eight cases and >10 in five cases. The distribution of sizes were <2 cm in one case; 2–5 cm in 12 cases; 5–10 cm in 20 cases and >10 cm in ten cases. Tumours were classified as high risk (HR) of aggressive behaviour in 17 cases (37.0%), as intermediate risk (IR) in 14 cases (30.4 %), low risk (LR) in 14 cases (30.4%), and very low risk (VLR) in one case (2.2%).

The median age at diagnosis was 63 years, with a range between 26 and 90 years. The median age of patients with high risk tumours was 63 years, 64 years in the intermediate risk, and 63 years in the combined low and very low risk categories.

Of the fifteen GIST that were not registered originally in the cancer registry, because they were initially considered as benign tumours, four were reclassified as high risk, four as intermediate risk and seven as low or very low risk of an aggressive behaviour.

All of our patients were diagnosed before the end of 2001, and only one was treated with imatinib mesilate. He was diagnosed with an advanced GIST that became refractory to chemotherapy, and later received imatinib during almost 2 years.

The incidence of GIST in Girona 1994–2001 is showed in Table 2. The annual crude rate, the annual European ASR, and the annual World ASR were 1.09, 0.90 and 0.65 per 100,000 inhabitants/year for both sexes. For males they were 1.05, 0.94 and 0.68 respectively. For females they were 1.12, 0.86 and 0.60.

The median time of follow-up for the whole group is 4.5 years with a range from 3 months to 10.3 years. In patients alive, the median follow-up is 5.7 years with a range between 2.6 and 10.3 years. Sixteen patients in our cohort have died (34.8%). The median survival time for the GIST with high risk of aggressive behaviour was 3.0 years, and it is not reached for each of the intermediate, low, or very low groups.

The 5-year observed survival for all patients of this cohort was 63.6 % and the relative survival was 74.7% (Table 3). In males, the 5-years OS and RS were 52.1% and 60.6%. In females, the 5-years OS and RS were 74.8% and 81.7% respectively.There is not a statistically significant difference in the survival between sexes.

The 5-year OS and RS in intermediate risk GIST were similar to that of low or very low risk GIST(80% and 94.9% in LR/VLR group and 93% and 100% in IR group), and was significantly poorer in high risk GIST (20.3% OS and 21.4% RS at 5 years).

4. Discussion

GIST originate from the interstitial cells of Cajal of the gastrointestinal tract.[17] Hirota and colleagues[18] defined a characteristical mutation of the Kit gene, and the associated c-kit protein overexpression which can in turn be detected by immunohistochemistry. This has become the most useful test in the diagnosis, since it is positive in 95% of GIST, in contrast to other markers with a more variable positivity rate, such as CD34 (70%), smooth muscle actin (35%) or S-100 (10%).[19] The nomenclature of GIST has changed in recent years. Before 1983, the terms used were leiomyoma, leiomyosarcoma and leiomyoblastoma. In 1983, the term GIST was introduced, although it was not widely used until 1990.[19] In 1998, the term gastrointestinal pacemaker cell tumour (GIPACT) was proposed by Kindblom and colleagues.[17]

Table 2 – Incidence of GIST in Girona (Spain) 1994–2001

	No.	CR	ASR Europe	ASR Europe CI95%	ASR World	ASR World CI95%	Cumulative risk 0–74
All	46	1.09	0.90	(0.76–1.04)	**0.65**	(0.55–0.75)	0.070
Male	22	1.05	0.94	(0.74–1.14)	**0.68**	(0.54–0.82)	0.070
Female	24	1.12	0.86	(0.66–1.06)	**0.60**	(0.46–0.74)	0.066

CR: crude rate; ASR: age-standardised rate.

Table 3 – Observed and relative survival at 1, 3 and 5 years

	1 year			3 year			5 year		
	n	OS	RS (95%CI)	*n*	OS	RS (95%CI)	*n*	OS	RS (95%CI)
All	46	84.8	87.3 (77.2–98.6)	35	71.7	78.7 (65.5–94.4)	24	63.6	74.7 (59.5–93.8)
By sex									
Males	22	81.8	85.0 (69.8–103.4)	15	63.6	69.8 (50.9–95.8)	11	52.1	60.6 (39.8–92.3)
Females	24	87.5	88.6 (76.2–101.3)	20	79.2	82.7 (67.3–101.5)	13	74.8	81.7 (64.7–103.3)
By risk groups									
HR	17	70.6	71.8 (52.8–97.6)	10	47.1	48.9 (29.6–81.0)	4	20.3	21.4[a] (6.8–67.2)
IR	14	92.9	94.4 (81.6–101.7)	13	92.9	97.9 (84.7–105.5)	10	93.0	100 (89.1–110.9)
LR/VLR	15	93.3	97.1 (84.8–104.0)	12	80.0	88.7 (68.9–110.9)	10	80.0	94.9 (73.3–118.6)

HR: high risk; IR: intermediate risk; LR: low risk; VLR: very low risk; RS: relative survival in %; OS: observed survival in %; *n*: number of patients at risk.

a Statistical differences between HR and the other risk categories.

The Consensus Conference at the National Institutes of Health in April 2001 defined the criteria to apply in the diagnosis of GIST.[4] The positivity in the detection of kit-protein expression was considered the main characteristic with some exceptions due to sampling errors, processing problems, or an imatinib treatment before the histologic diagnosis. At the ESMO Consensus Meeting of March 2004,[20] panelists agreed that GIST could be c-kit negative in 5% of cases.

A strength of the epidemiologic analysis of GIST is that some of them are considered benign and not included in a register focused on malignant tumours. An important finding in our study was that 32% of the cases were not initially registered, because they were considered benign cases in the registration process. Half of them were reclassified as high or intermediate risk. This registraton bias should be addressed by using a specific ICD-O code for GIST.

We decided to focus on kit-positive tumours, unless the clinical characteristics strongly suggested this diagnosis and not enough sample could be obtained. The 17% of the tumours of our series initially considered as probably GIST by histological features, were c-kit negative and reclassified to true leiomyoma or leiomyosarcoma, now considered rare in the digestive tract except in the oesophagus.[21] As reported,[18] 5% of GIST could be negative in c-kit immunostaining and 90% of them will have a KIT mutation. Performing the screening for mutation of exon 9,11,13 and 17 in the kit gene in the cases in doubt, might improve the accuracy in the diagnosis of these tumours. As some new immunohistochemical markers could arise to identify the c-kit negative GIST,[22,23] the rules of classification of these tumours could change considerably in the future and somehow vary future estimations of incidence.

The organ distribution of GIST in our patients series is comparable to others reported,[1,5–7] confirming that approximately half of GISTs arise in the stomach.

In our study, 37% of GIST were classified in the high risk for malignant behaviour group. This figure is higher than that of the studies from Sweden[6] (21%) or Iceland[7] (22.8%) and lower than that published from The Netherlands[8] (45%).

4.1. *Incidence*

The GIST incidence in our series is the first published in Southern Europe. Tran and colleagues[5] published recently the analysis of the Surveillance, Epidemiology and End Results (SEER) registries, with an incidence of 0.6 per 100,000 inhabitants/year. Their data, however, was not reported in World standardised rate, and therefore makes comparisons difficult. In the SEER study only tumours coded as having a malignant behaviour were included and the true incidence was possibly underestimated because morphologically benign GIST was not registered. Furthermore, in the SEER study the KIT immunopositivity is not required in the diagnosis and some true leiomyosarcomas can have been incorrectly considered GIST. The Swedish group[6] published an incidence of 1.46 per 100,000 inhabitants/year, considering all benign and malignant GIST with unequivocal immunoreactivity for KIT. Although it is a crude rate, this incidence is slightly higher than ours. Our results are closer than those published by Tryggvason and colleagues[7] in a nationwide study on Iceland with annual incidence of 0.9 per 100,000 inhabitants in men, 1.4 in women and 1.1 for both sex. Recently, Goettsch and colleagues[8] published the population-based incidence of GIST in The Netherlands showing an increase from 0.21/100,000 inhabitants in 1998 to 1.27/100,000 in 2003, with a decrease on the incidence of other GIST-like tumours as leiomyosarcomas. The immunohistochemical staining with anti-CD117 was performed in 87% of the tumours considered GIST and the 93% were positive. This trend of the incidence reflects the evolution of the diagnostic pathway, and we agree with the authors that the incidence could be slightly underestimated.

4.2. *Survival*

The median survival of the intermediate and low or very low risk patients has not been reached in our series and in the high risk group is 3.0 years. These results are very close to those estimated by the Swedish group (with a median survival of 3.4 years for the patients with high risk GIST),[6] and also similar to the results of the study from The Netherlands, that published a median survival of the patients with high risk tumours of 1.5–3.4 years. The data of 5-year relative survival of the SEER study (41% in men and 50% in women) is not comparable to ours because only cases with malignant behaviour by histologic criteria are included in it, but the 5 year relative survival of patients with regional or distant disease (33%

and 13% respectively) are closer to our results in high risk tumors. In the USA the median survival time for all GIST is 2.97 years, similar to our median survival for the high risk tumours group.

Our results in relative survival of GIST of very low, low and intermediate risk show that there are not important differences in survival between those patients and the normal population. As far as we know, the relative and observed survival of c-kit immunopositive GIST has not been formally published before.

The 5-year relative survival of the high risk group is statistically different from that of intermediate risk and low and very low risk groups. In contrast, we could not discriminate in our series the prognostic value of intermediate versus low and very low risk categories. This finding is similar to what has been observed in other reports. For example, Nilsson and colleagues[6] found estimated median survival values of 14.2 years and 16 years in the intermediate and low risk groups and 3.4 years in the high risk tumours. Taken together, this data suggest that prognostic categories in the future should focus on high risk versus all other groups combined. This however, should be confirmed in future series in which imatinib has been used to treat patients with advanced GIST.

In conclusion, GIST are tumours of low incidence in Girona, a region of Southern Europe, although it is comparable to others in Northern Europe. The survival of GIST of very low, low and intermediate risk of malignant behaviour is favourable, but high risk GIST had a poor survival. The current classification of risk is useful, although the discrimination beetween intermediate, low or very low risk groups is poor, and these three categories should perhaps be considered jointly in the future.

Conflict of interest statement

None declared.

Acknowledgement

This research was supported by a prize from the Sociedad Española de Oncología Médica (SEOM).

REFERENCES

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors-definition, clinical, histological, imunohistochemical and molecular genetic features and differential diagnosis. *Virchows Arch* 2001;**438**:1–12.
2. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;**347**(7):472–80.
3. Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GIST): a review. *Eur J Cancer* 2002;**38**(suppl):39–51.
4. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002;**33**:459–65.
5. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1458 cases from 1992 to 2000. *Am J Gastroenterol* 2005;**100**(1):162–8.
6. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course and pronostication in the pre-imatinib mesylate era: A population based study in Western Sweden. *Cancer* 2005;**103**(4):821–9.
7. Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. The Icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer* 2005;**117**:289–93.
8. Goettsch WG, Bos SD, Breekveldt-Postma N, Casparie M, Herings R, Hogendoorn P. Incidence of gastrointestinal stromal tumors is underestimated:Results of a nation-wide study. *Eur J Cancer* 2005;**41**:2868–72.
9. Viladiu P, Izquierdo A, Marcos R, et al. Cancer incidence in Girona (Spain) 1993-1997. In: Cancer incidence in five continents vol. VIII. IARC scientific publication n° 155; 2002.
10. Viladiu P, Izquierdo A, Marcos R, et al. El cáncer en Girona, 1994-1997. 1st ed. Institut d'Asistència Sanitaria edition; 2000.
11. Frit A, Jack A, Percy C, et al. *International classification of diseases for oncology*. third ed. Geneva: World Health Organisation edition; 2000.
12. Percy C, Van Holten V, Muir CS. *International classification of diseases for oncology*. second ed. Geneva: World Health Organisation edition; 1990.
13. Esteve J, Benhamou E, Raymond L. Statistical methods in cancer research, vol.IV. Descriptive epidemiology. Lyon: IARC Scientific Publications. World Health Organisation, 1994.
14. Esteve J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival. Elements for further discussion. *Stat in Med* 1990;**9**:529–38.
15. Hakulinen T. Cancer survival corrected for heterogeity in patients withdrawal. *Biometrics* 1982;**38**:933–42.
16. Clèries R, Ribes J, Gàlvez J, Melià A, Moreno V, Bosch FX. Cálculo automatizado de la supervivencia relativa vía web. *El proyecto WAERS del Instituto Catalán de Oncología*. *Gac Sanit* 2005;**19**:71–5.
17. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemarker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interticial cells of Cajal. *Am J Pathol* 1998;**152**:1259–69.
18. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998;**279**:577–80.
19. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004;**22**:3813–25.
20. Blay JY, Bonvalot S, Casali P, et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. *Ann Oncol* 2005;**16**:566–78.
21. Miettinen M, Kopczynski J, Makhlouf HR, et al. Gastrointestinal stromal tumors, intramural leiomyomas and leiomyosarcomas in the duodenum. *Am J Surg Pathol* 2003;**27**(5):625–41.
22. Motegi A, Sakurai S, Nakayama H, Sano T, Oyama T, Nakajima T. PKC theta, a novel immunohistochemical marker for gastrointestinal stromal tumors (GIST), especially useful for identifying KIT-negative tumors. *Pathol Int* 2005;**55**(3):102–6.
23. Rossi G, Valli R, Bertolini F, et al. PDGFR expression in differential diagnosis between KIT-negative gastrointestinal stromal tumours and other primary soft-tissue tumours of the gastrointestinal tract. *Histopathology* 2005;**46**:522–31.