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ORIGINAL PAPER

Late recurrences of gastrointestinal stromal tumours (GISTs) after 5 years of follow-up

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Abstract In practice, relapses of gastrointestinal stromal tumours after long time of surgical resection occur. However, few published data are available for duration, intensity and imaging sources of follow-up in radically excised patients with localized disease. Therefore, every single institution chooses the surveillance schedule according to its experience. The aim of this study was to describe the late recurrences of disease 5 years after the primary tumour's excision in a series of patients with recurrent GIST from our institution. We retrospectively reviewed 42 patients with "recurrent" GIST, collected since 2001. Ten patients were always followed at our institution, and 32 patients came to our attention at the time of recurrence. The analysed series were divided into two groups: patients who developed recurrence before 5 years and patients who developed recurrence 5 years after the primary tumour's excision. Among 42 patients, 36 patients developed the recurrence within 5 years of the primary tumour excision, whereas 6 patients developed the recurrence 5 years after primary tumour excision diagnosed during follow-up or casually for other reasons. All patients had distant recurrence, involving liver and peritoneum, whereas no local relapse was observed. These patients were heterogeneous in primary tumour site, risk classification and molecular analysis. Duration of the follow-up for radically excised patients with GIST remains still unsettled; however, the integration of every clinical, pathological and molecular parameter is essential to optimize the duration and intensity of the follow-up for each single patient.

Keywords GIST · Follow-up · Late recurrences · Risk stratification · Mutational analysis

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Introduction

In the last years, great efforts have been made to improve management of gastrointestinal stromal tumours (GISTs), especially in diagnosis, surgical and medical treatment and finally molecular biology. Tyrosine kinase inhibitors have dramatically modified the natural history of these rare tumours and represent nowadays the standard treatment for advanced and recurrent disease [1, 2]. More recently, imatinib has been approved also in the adjuvant setting for patients with substantial risk of relapse [3]. Finally, molecular biology is now playing an important role in medical decisions, such as patients' selection, dose and type of drugs administration, and in the discovery of new targets [4–6]. Novel criteria, combining tumour size and tumour density, have been suggested in tumour response evaluation [7].

On the contrary, few published data are available for duration and timing of follow-up in radically excised patients with localized disease. NCCN guidelines recommend history, physical examination and abdominal/pelvic CT scan every 3–6 months for 3–5 years, then annually for significant risk of recurrence, while ESMO guidelines recommend a routine follow-up with CT scan every 3–4 months for 3 years, then every 6 months until 5 years, and yearly afterwards for high- and intermediate-risk tumours and with CT scan every 6 months for 5 years for low-risk tumours [8, 9].

Thus, until now, the intensity and the duration of surveillance are guided by the relapse risk assessment, based on tumour size, mitotic count and tumour site [10]. According to the US National Institute of Health (NIH) consensus criteria, which as been represented the first approach to estimate the risk of aggressive GISTs, the high-risk category consists of GISTs larger than 10 cm in diameter (regardless of the tumour mitotic count), of tumours of any size when the mitotic count exceeds ten per 50 high-power fields (HPFs) and of tumours larger than 5 cm when the mitotic count exceeds five per 50 HPFs [11]. The more recent US Armed Forces Institute of Pathology (AFIP) prognostic criteria also account for tumour site and provide a more detailed risk stratification [12]. As suggested, the follow-up programmes have the standard overall duration of 5 years, which should be prolonged in case of high- to intermediate-risk patients.

In practice, relapses of disease long time after surgical resection occur and, consequently, clinicians are experiencing difficulties on defining the exact duration, intensity and imaging sources of follow-up. The lack of large clinical data makes every single institution to choose the surveillance schedule according to its experience. We believe that a debate on this topic may help clinicians in everyday clinical practice. The aim of this study was to describe the late recurrences of disease 5 years after the primary tumour's excision in a series of patients from our single institution.

Patients and methods

We retrospectively reviewed 42 patients with "recurrent" GIST, collected since 2001 and included in our GIST database. Ten patients were always followed up at our institution, and 32 patients came to our attention at the time of recurrence. All patients' characteristics are listed in Table 1. The group was made up of 27 (65%) men and 15 (35%) women. Age had a unimodal distribution, with a

Table 1 Patients' characteristics

Number of patients	Total 42
Sex	
Male	27 (65%)
Female	15 (35%)
Age	
Median	59 years
Range	31–83 years
Primary tumour site	
Stomach	18(43%)
Small intestine	22(52%)
Rectum	2(5%)
Mitotic index	
≤5/50 HPF	11(26%)
>5/50 HPF	19(45%)
NA	12(29%)
Tumour size	
≤2 cm	0(0%)
>2 ≤ 5 cm	5(12%)
>5 ≤ 10 cm	15(36%)
>10 cm	17(40%)
NA	5(12%)
Risk	
Very low	1(2%)
Low	2(5%)
Intermediate	6(14%)
High	22(53%)
NA	11(26%)
Surgical margins	
R0	36 (86%)
R1	5 (12%)
NA	1 (2%)
Adjuvant treatment	
No	39 (93%)
Yes	3(7%)

median of 59 years (range 31–83). Primary tumour site was stomach in 18 patients (43%), small intestine in 22 patients (52%) and rectum in 2 patients (5%). Risk stratification was the following: 22 patients (53%) had a high-risk tumour, 6 patients (14%) an intermediate-risk tumour, 2 patients (5%) a low-risk tumour and 1 (2%) patient a very low-risk tumour. In 11 patients (26%), tumour risk was not assessable because histological specimens were not suitable for review and in the original histological reports was used a non-standardized mitotic count. All patients underwent surgical excision of primary tumour: surgical margins were negative in 37 patients (88%) and microscopically positive in 5 patients (12%). Adjuvant therapy was performed in 3 patients (7%), while 39 patients (93%) did not receive any adjuvant treatment.

The histological examination of primary tumour and/or relapse was reviewed again and confirmed by the same pathologist. Mutational analysis was performed in all samples: 20 patients harboured an exon 11 c-KIT mutation, 3 patients harboured an exon 9 c-KIT mutation, 4 patients harboured an exon 18 PDGFRA mutation and 5 patients were wild type. In 10 patients, mutational analysis was not assessable. Primary tumour risk stratification was defined according to NIH and Miettinen classification [11, 12] (Table 2).

The analysed series were divided into two groups: patients who developed recurrence within 5 years of primary tumour excision and patients who developed recurrence 5 years after primary tumour excision.

Results

Among 42 patients, 36 patients developed the recurrence within 5 years of the primary tumour excision, whereas 6 patients developed the recurrence 5 years after primary tumour excision: one patient after 6 years, one after 7 years, one after 9 years, two patients after 11 years and one after 12 years. Late recurrent patients' characteristics are summarized in Table 3. The group included one man

Table 2 GIST risk stratification systems

Tumour size	Mitotic count	NIH risk (Fletcher 2002)	Miettinen risk (Miettinen 2006)			
		All sites	Stomach	Jejunum/ileum	Duodenum	Rectum
≤2 cm	≤5/50 HPF	Very low	None	None	None	None
>2 ≤ 5 cm		Low	Very low	Low	Low	Low
>5 ≤ 10 cm		Intermediate	Low	Intermediate	High	High
>10 cm		High	Intermediate	High	High	High
≤2 cm	>5/50 HPF	Intermediate (>5 to ≤10/50 HPF) High (>10 HPF)	None	High	NA	High
>2 ≤ 5 cm		Intermediate (>5 to ≤10/50 HPF) High (>10 HPF)	Intermediate	High	High	High
>5 ≤ 10 cm		High	High	High	High	High
>10 cm		High	High	High	High	High

Table 3 Late recurrent patients' characteristics

Series	Sex	Age	Year of diagnosis	Primary tumour site	Risk	Mutational analysis	Adjuvant treatment	Year of recurrence	Site of recurrence
G_1	F	63	2003	Small intestine	High	Wild type	Yes	2009	Liver
G_2	F	52	1997	Small intestine	High	Wild type	No	2006	Liver
G_3	F	54	1997	Small intestine	Low	PDGFRA exon 18 Ins	No	2008	Liver and abdomen
G_4	F	65	1996	Small intestine	NA	c-KIT exon 11 del VYIDPTQL 569-576	No	2008	Liver
G_5	M	60	1998	Rectum	High	c-KIT exon 11 c1669-1647 del (pTrp557_Lys558del)	No	2009	Liver
G_6	F	66	1999	Stomach	High	c-KIT exon 11 (1728_1729dupCCTTATGATCACAinsTT)	No	2006	Liver

Table 4 Prognostic parameters' evaluation in late recurrent patients

Series	Primary site of lesion	Primary tumour dimension (cm)	Mitotic count	Tumour rupture	Surgical margins	Mutational analysis
G_1	Small intestine	6.2	5.6/50 HPF	No	R0	Wild type
G_2	Small intestine	7	>5/50HPF	No	R0	Wild type
G_3	Small intestine	3	Low (not counted)	No	R0	PDGFRA exon 18 Ins
G_4	Small intestine	7	0–1/30 HPF	No	R0	c-KIT exon 11 del VYIDPTQL 569-576
G_5	Rectum	4	16/50 HPF	No	R1	c-KIT exon 11 c1669-1647 del (pTrp557_Lys558del)
G_6	Stomach	12	9/50 HPF	No	R0	c-KIT exon 11 (1728_1729dupCCTTATGATCACAinsTT)

Table 5 Medical history of late recurrent patients

Series	Surgical treatment	Current therapy	Reason	ECOG
G_1	Yes (R0)	None	Wild type	0
G_2	Yes (R0)	None	Wild type	0
G_3	No	Sunitinib 37.5 mg daily	Disease progression after imatinib 400 and 800 mg	0
G_4	No	None	Disease progression after imatinib 400, 800 mg and sunitinib 37.5 mg	1
G_5	No	Imatinib 400 mg daily	Prolonged stable disease	0
G_6	Yes (R0)	None	Severe imatinib intolerance	0

and five women, with a median age of 60 years (range 52–66). The primary tumour was diagnosed from 1996 to 2003 and localized in small intestine (4 pts), rectum (1 pts) and stomach (1 pts). According to NHI and Miettinen classification, four patients had a high-risk primary tumour, one patient had a low-risk primary tumour, and in one patient, tumour risk stratification was not assessable because histological specimen was not suitable for review. Five patients had negative microscopic margins (R0), while 1 patient had positive microscopic margins (R1). Tumour's relapse was developed from 2006 to 2009, involving liver in five patients and liver and abdomen in one patient. Site of recurrence was single in two patients and multiple in the remaining four patients. In mutational analysis performed on primary tumour specimens, three patients harboured an exon 11 c-KIT mutation, one patient harboured an exon 18 PDGFRA mutation, and two patients were wild type. Only one patient received imatinib with adjuvant intent for 2 years, even though it was not approved at that time.

Recurrence was asymptomatic in all patients: for 4 patients, it was detected during annual follow-up by an abdominal US examination, whereas for 2 patients, the recurrences detection was casual, in one during MRI due to a low back pain not related to the disease and for another one during the follow-up of a second more recent bladder cancer. A subsequent CT–PET evaluation was performed in five patients: tumour relapse was confirmed in four patients, while in one patient, with a WT kinase genotype both on primary tumour and relapse, recurrent sites were CT–PET negative, probably related to its mutational status.

About prognostic parameters evaluation in late recurrent patients, the most relevant ones were the predominance of small intestine tumour primary site (4/6 pts) and primary tumour size greater than 5 cm (3/6 pts). Only one patient had positive surgical margins (1/6 pts), and no patients had tumour rupture whether spontaneous or at the time of surgical resection (0/6 pts; Table 4).

Medical history of all six patients after recurrence diagnosis is summarized in Table 5. Three patients underwent complete surgical resection of metastases and none of them is now receiving medical treatment due to mutational status (two patients had a wild-type GISTs) and imatinib severe intolerance in one case. One patient is currently treated with imatinib 400 mg daily with a stable hepatic disease. One patient experienced disease progression under imatinib 400 mg and 800 mg daily and is now receiving sunitinib 37.5 mg daily reaching stable disease. Finally, one patient was treated with imatinib 400 mg, imatinib 800 mg and sunitinib 37.5 mg daily, and because of further disease progression, the patient is now under evaluation for nilotinib treatment.

Discussion

In practice, risk assessment based on mitotic count, tumour size and tumour site may help in choosing the routine follow-up strategy. Therefore, even if there are no published data indicating the optimal routine follow-up policy of surgically treated patients with localized disease,

european and US guidelines suggest a routine follow-up with CT scan every 3–4 months for 3 years, every 6 months until fifth year, then yearly afterwards for intermediate- to high-risk patients and a CT scan every 6 months for 5 years for low-risk tumours [8, 9].

In our study, we analysed a series of patients with recurrent GIST at our single institution focusing on patients who have developed a late recurrence after 5 years from the primary tumour's excision. Among 42 patients, 6 experienced a disease relapse after 6–11 years from the primary, diagnosed during follow-up or casually for other reasons. All patients had distant recurrence, involving liver and peritoneum, whereas no local relapse was observed. These patients were heterogeneous in primary tumour site, risk classification and molecular analysis. Similarly, the remaining 36 patients who relapsed within 5 years from the primary tumour's excision were heterogeneous in clinical and pathological main features. Most of them had an high-risk primary tumour, equally located in the stomach (18 patients) and in the small intestine (16 patients). Liver and peritoneum were the most representative site of recurrences, even if other sites such as lung and bone were involved (Table 5).

Although the case study is small, the observation of six cases of late recurrent GIST would open the debate about this topic also for this disease.

First of all, since a late recurrence can rarely occur, how long should be the follow-up? Who are the patients that need a long follow-up in GIST? The small series of our study and the heterogeneity in known tumour characteristics such as primary lesion site, risk classification and molecular analysis do not allow to identify which factors may be more strictly correlated with delayed recurrence development, even if the prevalence of small intestine primary GIST and of lesions greater than 5 cm may confirm their already known negative prognostic value. Recently, it has been shown that KIT exon 11 mutations negatively affect relapse-free survival of patients with GIST not treated with adjuvant therapy and that the difference in relapse-free survival between WT patients treated or not with adjuvant imatinib is not statistically different [13]. Our series, even if small, seems to be in agreement with this evidence: among five patients who did not receive adjuvant treatment, three harbour a c-KIT exon 11 mutation, while the only one patient treated with adjuvant imatinib was WT for KIT and PDGFRA mutations. However, we think that mutational status only, without the integration of other clinical–pathological parameters, should not guide oncologists for planning the duration of the follow-up. It may require a study on a large population during a long period, stratified according to each clinical, morphological and biological feature, in order to identify possible prognostic and predictive factors of late recurrence. It is likely that the improvement in disease-free survival, thanks to adjuvant treatment, leading to a reduction of early relapses, makes necessary a prolongation of the surveillance programme in order to identify delayed recurrences. This may be true for patients with significant risk of relapse who are candidates to an adjuvant treatment and are followed up more intensively, while for low-risk patient, the question remains unsettled.

Secondly, which biological significance may have a GIST late recurrence? The theory of "tumour dormancy", defined as a protracted stage in tumour progression in which tumours remain occult and asymptomatic for a prolonged period of time, is already known, and delayed recurrence seems to be consistent with this concept [14]. Different mechanisms have been involved in tumour dormancy and in tumour escape from dormancy, such as angiogenesis, biochemical and biophysical relation with the microenvironment and immune system [14]. In particular, it has been recently shown that different types of dormant and fast-growing tumour cells (human breast carcinoma, glioblastoma, osteosarcoma and liposarcoma) have a different molecular signature, and angiogenesis-related genes were those most differentially expressed [15]. Tumour dormancy has been reported in many solid tumours, especially in breast cancer and melanoma, for which late relapses occurring more than 10 years after primary diagnosis is documented [16–21]. No evidence on tumour dormancy in GIST cells have been reported by now; however, it may be interesting to investigate this aspect in order to identify critical components involved in GIST cells quiescence, to select patients with higher risk of occult micrometastases and to develop novel strategies aimed at maintaining tumour cells in dormant stage.

In our series, molecular analysis was performed on primary tumour in all patients and also on metastatic lesions in two patients. In these two cases, no secondary mutations were found and the mutational status of relapse was the same as the primary, suggesting that a change in mutational status may be not considered as a potential mechanism involved in the escape of GIST from dormancy but, as is well known, only a potential mechanism of treatment resistance.

It is likely that the risk of developing early and late recurrence may arise from different mechanisms and thus may be predicted by different factors. It may be presupposed that the molecular mechanisms involved in GIST pathogenesis, even if still unsettled, are the same involved in micrometastases dormancy escape. In fact, there are some evidences on the occurrence of putative precursor lesions found as sporadic, incidental, multifocal or small GISTs, with a different pattern of kinase genotype, mutated or not [22–28]. Most authors suggested that the acquisition of activating KIT mutations occur very early and represent

an essential step for the transformation of these microlesions in macrolesions. Therefore, because the incidence of precursor lesions is high and GISTs represent a rare finding in clinical practice, their potential to become a clinical GIST is very low and specific molecular mechanisms or genetic/epigenetic alterations other than KIT/PDGFRA kinase mutations may be involved in this step. Probably the same molecular mechanisms, even if unknown, may be involved in the escape of GIST from dormancy.

The patient risk stratification may be even more complex and may be differentiated between adjuvant treatment planning, based on relative risk of early relapse and long-term surveillance programme planning, based on relative risk of late relapse. A wide genomic study on primary tumour may be addressed to the discovery of a specific gene signature belonging to patients with late recurrent GIST, in order to select which patients may be candidate for a longer follow-up.

Finally, can a prolonged follow-up be useful for detecting a second primary cancer? In other malignancies such as colorectal cancer, breast cancer and melanoma, it has been already shown that patients have a higher risk of developing second primary lesions than general population and even if the underlying causes for metachronous cancers are to be elucidated yet, a long-term follow-up is thus justified [29–31]. On the contrary, the risk of developing a second metachronous GIST has not been assessed yet, as if other factors than genetic susceptibility, reiterated environmental exposure and lifestyle may be involved in GIST pathogenesis. However, multifocal synchronous GISTs have been reported and most of them are defined as sporadic multiple primary GIST not related to syndromic diseases [25–28]. This finding supports the possibility that widespread tumour priming of GIST precursor mesenchymal cells may be implicated in these patients [26].

It may be interesting to evaluate the molecular relationship between metachronous primary GISTs of a same patient in order to understand whether metachronous lesions maintain the same molecular profile or whether there is a clonal evolution between each other.

Some evidences reported that GISTs may be associated with other types of cancer, either synchronous or metachronous [32]. It is likely that the association of GIST with other malignancies may be related to syndromic diseases [33]. Therefore, even if the risk of second primary GIST may be a rare event compared to other malignancies, a prolonged follow-up may be useful not only for the detection of late recurrent cancer, but also for the early diagnosis of other metachronous cancers.

In conclusion, the duration of the surveillance programme of radically excised patients with GIST remains still unsettled; however, some remarks may arise from this small study. First of all, the integration of all clinical, pathological and molecular parameters is essential for optimizing duration and intensity of the follow-up for each single patient. Secondly, large studies specifically addressed to this topic may be required in order to well know the long-term natural history of this rare disease, helping medical oncologists to identify those subgroups of patients with higher risk to develop late recurrence. However, each single institution should be invited to signal own experience and bring own clinical suggestions for offering other cues of reflection to the scientific community. Finally, we should continue to lean on molecular biology that, through the identification of individual genomic fingerprints, will be probably the best key of knowledge for cancer in the future.

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