Original Research

Impact of a risk-based follow-up in patients affected by gastrointestinal stromal tumour

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Gastrointestinal stromal tumour;
GIST;
Surgery;

Abstract  Background: Follow-up aims to precociously identify recurrences, metastases or treatment-related adverse events so as to undertake the appropriate therapy. Guidelines admit lack of knowledge on optimal surveillance schedule, but suggest follow-up based on experts’ opinion and risk stratification. To identify the impact, if any, of regular follow-up, we interrogated our prospectively collected database whether early detection of recurrences affected both clinical management and, likely, the outcome.

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1. Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract with an estimated incidence of 1/105 each year [1]. In localised disease, surgery with clear margins remains the only curative treatment [2,3]. Even after optimal surgery, recurrence occurs in nearly 40% of patients [4]. Thus, it is paramount to establish recurrence risk to identify patients deserving adjuvant treatment, and to stratagise patient-specific follow-up. Currently, the most used risk stratification takes into account tumour size, site of origin, and mitotic index [5–8]. Subsequently, risk estimation was improved by integrating tumour rupture and computing mitotic index and tumour size as continuous variables [4]. Quite surprisingly, mutational status is a predictive factor, but as of today, it is absent from all risk classifications [9,10]. Risk stratification tools are used to suggest follow-up strategies in guidelines [11,12]. Unfortunately, no evidence supports the advantage of a regular follow-up. Nevertheless, all patients are equally deemed to be controlled with imaging techniques and clinical examinations for years. Recently, a new model was proposed to optimise the follow-up schedule in high-risk patients treated with adjuvant imatinib [13]. However, the lack of prospective data limits our ability to assess the real benefit of follow-up to both disease course and overall survival (OS). Generally, in the absence of direct evidence of survival benefit, follow-up is deemed worth the effort if earlier recognition of recurrence might affect disease course [14]. In the postoperative GIST setting, indirect evidences suggest follow-up. Indeed, early recurrence detection reduces the likelihood of developing symptoms related to disease extension, lower tumour burden has a prognostic impact in advanced disease, and finally, although of weakly proven benefit, a more precocious diagnosis may increase the likelihood of later tumour resectability [15–17]. This study assessed the ability of a regular follow-up regimen to detect recurrences ahead of symptom appearance and explored the clinical impact, if any, of earlier recurrence detection on eligibility to surgical resection, post-recurrence progression-free survival (PR-PFS) and disease-specific OS.

2. Patients and methods

2.1. Patients

From our prospectively collected database, we identified patients with resectable GIST diagnosed and operated between January 2001 and December 2012. The dataset for analysis included those patients with histologically reviewed diagnosis of GIST ≥ 2 cm, site of origin, dimension, mitotic index, surgical operation description [only R0 (no residual microscopic disease) /R1 (microscopic residual disease) surgeries were included], and ≥3 years of follow-up in the absence of recurrence. Patients treated with neoadjuvant/adjuvant imatinib were excluded. The study was conducted in accordance with Helsinki declaration. All patients provided informed consent for data collection and received routine clinical examinations and computed tomography (CT) of the whole abdomen as follow-up. Patients were stratified...
according to National Institutes of Health (NIH) risk criteria [18] until 2006 when we adopted Armed Forces Institute of Pathology (AFIP) classification [5]. We applied the European Society for Medical Oncology (ESMO) guidelines follow-up schedule based on risk stratification [11]. Consistently, in intermediate/moderate- and high-risk patients, clinical examinations and CT were performed every 3–4 month during the first 3 years, every 6 months in the 4th and 5th years, and annually thereafter. For low- and very low-risk patients, clinical examinations and CT were performed every 6 months for 5 years, and then annually. The incidental diagnosis of other non-GIST malignant tumours was meticulously recorded. Upon recurrence, patients were stratified according to the presence of symptoms related to GIST recurrence (symptomatic versus asymptomatic), and tumour burden (low versus high). We arbitrarily defined ‘low tumour burden’ recurrences as potentially resectable (e.g. involving one surgically amenable site, and <4 lesions in liver or peritoneum with a sum of major diameters ≤10 cm and/or a single lesion ≤10 cm in diameter). ‘High tumour burden’ described lesions not amenable to surgery and/or with widespread abdominal involvement (e.g. both liver and peritoneum and/or adjacent organs and/or widespread at each site, or one lesion ≥10 cm).

2.2. Statistical analyses

Statistical analyses were performed using SPSS v20.0. A P-value ≤0.05 was considered statistically significant. We analysed descriptive statistics for the following variables: sex, age at diagnosis, tumour site and size, mitotic index, mutational status, and AFIP risk stratification. Qualitative variables were compared using the $\chi^2$ and Fisher’s exact tests.

Survival end-points were estimated by Kaplan and Meier method [19]. Recurrence-free survival (RFS) and OS were calculated from surgery to recurrence/death and death, respectively. PR-PFS and post-recurrence disease-specific OS (PR-OS) were calculated from the date of first recurrence to the date of first subsequent progression/death and death, respectively. Patients who died for causes other than GIST were censored at the day before death for disease-specific OS, but were considered as events for all-cause OS. In the absence of the event, patients were censored at the date of last follow-up.

For comparisons we used log-rank test and hazard ratio (HR) estimates calculated by Cox regression [20]. Multivariate analysis was performed using the Cox proportional hazards model for both PR-PFS and PR-OS with covariates included if P-value ≤0.05 in the univariate analysis. When indicated, tests were two-sided and results were reported with 95% confidence intervals (95%CI) or interquartile ranges (IQR).

3. Results

3.1. Patient and recurrence characteristics

From the 286 patients who underwent surgery for their localised GIST between January 2001 and December 2012, 233 patients were deemed eligible for inclusion and further analyses. Table 1 describes baseline characteristics and exclusion criteria of these patients.

After a median follow-up of 68.3 months (95% CI = 59.8–76.8), 94 (40.3%) patients experienced tumour recurrence and started imatinib. The median RFS was not reached, and estimated 5- and 10-year RFS were 61.8% and 50.4%, respectively (Fig. 1). Table 2 describes recurrence characteristics and both PR-PFS and PR-OS for each variable.

Recurrence was asymptomatic in the majority of patients (73/94 (77.7%)). Among the 21/94 (22.3%) symptomatic recurrences, 17/21 (81.0%) patients experienced abdominal pain, 3/21 (14.2%) dysphagia, and 1/21 (4.8%) melaena.

We stratified patients on the basis of tumour burden at recurrence, and classified 45/94 patients (47.9%) as low tumour burden and 49/94 (52.1%) as high tumour burden. In low tumour burden group, 26/45 (57.8%) patients underwent surgery for their recurrences. Among high tumour burden group, 9/49 patients (18.4%) underwent surgery because the recurrence became resectable (3/49; 6.1%) or because of focally progressing disease under imatinib therapy (6/49; 12.2%). All patients received imatinib before surgery. The probability of having surgery for recurrence was significantly higher in patients with low tumour burden recurrence ($P < 0.001$).

3.2. Post-recurrence progression-free survival

For the 94 recurring patients the median PR-PFS was 49.1 months (95% CI = 31.1–67.0) (Fig. 2A). Disease-related symptoms at first recurrence predicted a higher risk of post-recurrence progression that occurred in 19/21 (90.5%) patients versus 39/72 (54.2%) asymptomatic ones ($P = 0.002$) with a median PR-PFS of 14.1 (95% CI = 0–31.2) versus 67.1 months (95% CI = 38.5–95.8), respectively (HR = 4.60; 95% CI = 2.55–8.28; $P < 0.001$) (Fig. 2B). Likewise, high tumour burden recurrences as compared with low tumour burden ones were associated with higher rate of post-recurrence progression ($P < 0.001$) and significantly lower PR-PFS (31.2 (95% CI = 23.7–38.7) versus 118.8 months (95% CI = 68.2–169.5); HR = 3.98; 95% CI = 2.24–7.07; $P < 0.001$) (Fig. 2C).

Upon first recurrence, patients treated with imatinib and surgery as compared with those treated with imatinib alone, experienced a borderline-significant trend toward a lower risk of progression and better median
Patients deemed unresectable or who underwent inadequate surgery (gross residual disease (R2)) experienced a significantly lower PR-PFS as compared with those who underwent R0/R1 metastasectomy [median 37.7 (95%CI: 26.0–49.4) versus 98.2 months (95%CI: 61.5–134.9); HR = 2.60; 95% CI = 1.40–4.84; P = 0.003].

### 3.3. Overall survival

After a median follow-up of 115.4 months (95% CI = 98.7–132.2), the median all-cause and disease-specific OS for the entire population were 128.0 months (95% CI not estimated) and not reached, respectively (Fig. 1). Our estimated disease-specific OS at 5- and 10-year time points were 90.7% and 62.1%, respectively. The median PR-OS was 79.1 months (95% CI = 61.0–97.9; HR = 0.56; 95% CI = 0.32–0.97; P = 0.040).
CI = 54.6–103.7) (Fig. 3A). First-recurrence characteristics significantly impacted PR-OS: a symptomatic recurrence correlated with a worse survival [median OS 30.0 (95% CI = 16.5–43.6) versus 96.6 months (95% CI = 53.3–139.8) in asymptomatic patients; HR = 4.51; 95% CI = 2.34–8.71, P < 0.001] (Fig. 3B). High tumour burden recurrences were associated with a higher risk of death when compared to low tumour burden ones.

Table 2

<table>
<thead>
<tr>
<th>Recurrence Characteristics</th>
<th>N = 94 (100)</th>
<th>Median PR-PFS (months; 95%CI)</th>
<th>Log-rank P value</th>
<th>Median PR-OS (months; 95%CI)</th>
<th>Log-rank P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrence site, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Liver only</td>
<td>40 (42.6)</td>
<td>59.6 (0–132.2)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>124.9 (NE)</td>
<td>0.005&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peritoneum only</td>
<td>35 (37.2)</td>
<td>67.1 (45.1–89.1)</td>
<td></td>
<td>91.3 (68.0–114.6)</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; peritoneum</td>
<td>19 (20.2)</td>
<td>30.7 (26.2–35.2)</td>
<td></td>
<td>59.6 (37.1–82.1)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td>0 (0.0)</td>
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<tr>
<td><strong>Time to recurrence, N (%)</strong></td>
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<tr>
<td>&lt;6/12 months</td>
<td>15 (16.0)</td>
<td>40.4 (20.0–60.8)</td>
<td>0.506</td>
<td>57.1 (17.2–96.9)</td>
<td>0.373</td>
</tr>
<tr>
<td>6–12 years</td>
<td>21 (22.3)</td>
<td>67.1 (53.8–80.4)</td>
<td></td>
<td>96.5 (66.1–126.8)</td>
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<tr>
<td>1–2 years</td>
<td>32 (34.0)</td>
<td>36.9 (15.4–58.5)</td>
<td></td>
<td>76.3 (41.8–110.8)</td>
<td></td>
</tr>
<tr>
<td>2–3 years</td>
<td>10 (10.6)</td>
<td>36.8 (22.5–51.1)</td>
<td></td>
<td>78.9 (54.7–103.1)</td>
<td></td>
</tr>
<tr>
<td>3–5 years</td>
<td>10 (10.6)</td>
<td>122.9 (NE)</td>
<td></td>
<td>NR</td>
<td></td>
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<tr>
<td>&gt;5 years</td>
<td>6 (6.4)</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms at recurrence, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>73 (77.7)</td>
<td>67.1 (38.5–95.8)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96.6 (53.3–139.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms</td>
<td>21 (22.3)</td>
<td>14.8 (0–31.2)</td>
<td></td>
<td>30.0 (16.5–43.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour-burden at recurrence, N (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>45 (47.9)</td>
<td>118.8 (68.2–169.5)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>49 (52.1)</td>
<td>31.2 (23.7–38.7)</td>
<td></td>
<td>59.6 (51.0–68.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Quality of surgery for recurrence, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>R0/R1</td>
<td>30 (31.9)</td>
<td>98.2 (61.5–134.9)</td>
<td>0.002&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>R2</td>
<td>5 (5.3)</td>
<td>10.0 (0–23.6)</td>
<td></td>
<td>20.5 (17.6–23.5)</td>
<td></td>
</tr>
<tr>
<td>No Surgery</td>
<td>59 (62.8)</td>
<td>41.0 (27.3–54.7)</td>
<td></td>
<td>61.9 (52.4–71.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery for recurrence by tumour burden, N (total %) (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low tumour burden</td>
<td>26/45 (57.8)</td>
<td>118.8 (49.4–188.2)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR</td>
<td>0.002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>High tumour burden</td>
<td>9/49 (18.4)</td>
<td>29.1 (0–78.3)</td>
<td></td>
<td>54.0 (0–128.1)</td>
<td></td>
</tr>
</tbody>
</table>

PR-PFS, post-recurrence progression-free survival; PR-OS, post-recurrence overall survival; NR, not reached; NE, not estimated.

<sup>a</sup> Liver & peritoneum versus other.

<sup>b</sup> R0/R1 surgery versus R2 or no surgery.
Fig. 2. Post-recurrence progression-free survival. Panel A, post-recurrence progression-free survival for the 94 recurring patients; Panel B, post-recurrence progression-free survival according to symptoms at first recurrence (symptomatic green line, asymptomatic blue line); Panel C post-recurrence progression-free survival according to tumour burden at first recurrence (high-tumour-burden green line, low tumour burden blue line).
Fig. 3. Disease-specific Overall Survival after first recurrence. Panel A, disease-specific overall survival for the 94 recurring patients; Panel B, overall survival according to symptoms at first recurrence (symptomatic green line, asymptomatic blue line); Panel C, overall survival according to tumour burden at first recurrence (high-tumour-burden green line, low tumour burden blue line).
[median OS 59.6 months (95% CI = 51.0–68.3) versus not reached; HR = 3.78; 95% CI = 1.89–7.54, P < 0.001] (Fig. 3C). The role of surgery was more controversial. Indeed, a borderline-significant difference in median PR-OS was observed between patients treated with surgery and those who were not [96.4 (95% CI not estimated) versus 64.9 months (95% CI = 47.1–82.7); HR = 0.55; 95% CI = 0.29–1.06, P = 0.077]. However, patients who underwent adequate surgery (R0/R1) for their recurrences showed a significantly better PR-OS when compared with patients who did not or those who had R2 metastasectomy [median not reached versus 60.2 months (95% CI = 51.1–69.4); HR = 0.31; 95% CI = 0.14–0.67, P = 0.003].

3.4. Univariate and multivariate analyses

Risk group, symptoms, tumour burden, and radical surgery at first recurrence were the four significant prognostic factors for PR-PFS included as covariates in the multivariate analysis. Symptoms, tumour burden, and radical surgery at time of first recurrence were included in the multivariate analysis for PR-OS. Symptoms and high tumour burden at recurrence remained the only statistically significant prognostic factors of both worse PR-PFS (HR 3.19 and 2.80, respectively) and PR-OS (HR 3.65 and 2.38, respectively) (Table 3).

3.5. Radiological exams and exposure

In a 10-year follow-up course, ESMO guidelines suggest a total of 20 and 15 CT scans in high-/intermediate- and in low-/very low-risk GIST patients, respectively. In our series, high-/intermediate- and low-/very low-risk patients underwent a median of 10 (IQR: 4–15) and 10 (IQR: 8–11) CT scans respectively. Given a median radiation dose per exam of 8 mSv, our patients were exposed to a median total radiation dose of 80 (IQR: 32–120) and 80 (IQR: 64–88) mSv, respectively.

3.6. Other non-GIST tumours

Overall, we detected 94 recurrences by performing a total of 2230 CT scans, which equates to one recurrence detected in every 24 exams. We then calculated the CT number needed to detect one recurrence by risk group. Thirteen exams for high-, 28 for intermediate/moderate-, 98 for low-, and 414 for very low-risk patients were needed to identify one recurrence. Finally, to detect one RFS event, we needed to follow-up 1.4, 2.4, 10.4, and 41 high-, intermediate-, low- and very low-risk patients respectively. Further details and cost analysis are provided in Table 4.

Table 4

<table>
<thead>
<tr>
<th>Cost analysis and radiation exposure.</th>
<th>Number of exams</th>
<th>Radiation exposure (mSv)</th>
<th>Cost (euros)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT abdomen and pelvis</td>
<td>1</td>
<td>8</td>
<td>158</td>
</tr>
<tr>
<td>10-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High- and intermediate/</td>
<td>20</td>
<td>160</td>
<td>3160</td>
</tr>
<tr>
<td>moderate-risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low- and very-low-risk group</td>
<td>15</td>
<td>120</td>
<td>2370</td>
</tr>
<tr>
<td>Number of CT scans needed to detect one recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk-group</td>
<td>13</td>
<td>104</td>
<td>2054</td>
</tr>
<tr>
<td>Intermediate/</td>
<td>28</td>
<td>224</td>
<td>4424</td>
</tr>
<tr>
<td>moderate-risk-group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk-group</td>
<td>98</td>
<td>784</td>
<td>15,484</td>
</tr>
<tr>
<td>Very-low-risk-group</td>
<td>414</td>
<td>3312</td>
<td>65,412</td>
</tr>
</tbody>
</table>

mSv, millisievert; CT, computed tomography.

Table 3

| Univariate and multivariate analyses for post-recurrence progression-free survival and disease-specific overall survival.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Post-Recurrence Progression-free Survival</th>
<th>Disease-specific Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Risk group (high versus non-high)</td>
<td>2.77 (1.19–6.45)</td>
<td>0.018</td>
</tr>
<tr>
<td>Symptoms at recurrence (yes versus no)</td>
<td>4.60 (2.55–8.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumour-burden (high versus low)</td>
<td>3.98 (2.24–7.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adequate surgery for recurrence (no surgery or R2 surgery versus R0/R1 surgery)</td>
<td>2.60 (1.40–4.84)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

HR, hazard ratio; 95% CI, 95% confidence interval.
(P < 0.001). On the contrary, second tumours had no impact on all-cause OS for recurring patients (P = 0.379).

4. Discussion

Recurrence after complete resection continues to concern both patients and clinicians. Our study showed that asymptomatic, and low tumour burden recurrences were detected by regular follow-up and associated with lower risk of further progression and disease-specific death. Second, earlier recurrence detection increased the chances to become eligible for surgery for residual disease. Furthermore, asymptomatic metachronous secondary tumours were incidentally diagnosed during follow-up. Finally, we estimated the number, radiation exposure [21] and cost of CT scans required to detect one recurrence according to risk group.

To our knowledge, these data are the first to provide evidence supporting the effort of a regular follow-up in radically resected GIST patients [11,12]. Indeed, even if risk assessment has been undoubtedly refined in the last few years [4], this improvement did not generate evidence on whether or not, and/or how to follow-up the individual patient. Despite the lack of proof, experts consensus actually suggests a follow-up scheme that was adopted to control our patients over years [11,12]. Of course, not all authors agree with the aforementioned schedule [14,22]. Nonetheless, several clinicians suggest to follow-up patients because they hypothesize that earlier recurrence diagnosis might prelude to a minor amount of disease and eventually lead to a more favourable outcome [14,22]. Despite the fact that we cannot exclude a lead-time bias, our data argue in favour of such a strategy in terms of both PR-PFS and PR-OS.

In general, clinical experts may answer differently as to where to set the risk bar when determining which patients warrant follow-up as is the case when identifying patients who deserve adjuvant treatment [23]. One may predict that patients having the highest recurrence risk would benefit most from follow-up. For example, our data indicated following 41 very low-risk patients would anticipate one recurrence. Clearly, such numbers are interpreted differently among the varied perspectives of oncologist, health administrator, or patient. In other medical settings, it is considered worthwhile to pursue a course of care capable of identifying one event in every 41 patients, such as mammography and breast cancer [24].

Obviously, follow-up strategy efficiency improvement is an unmet medical need. For example, despite the fact that the relapse risk is not homogeneously distributed among different genotypes. Our data are consistent with the evidences pointing out the higher recurrence risk associated with KIT exon 9 mutations and deletions affecting exon 11 codons 557–558 [9,25,26]. Nonetheless, this is not yet taken into account to modulate follow-up intensity. In the same way, tumour cell DNA detection in plasma [27,28], has been demonstrated to be highly sensitive and reproducible to track GIST in advanced disease [29–31]. Notwithstanding, it needs validation showing its potential to integrate with or substitute for present follow-up imaging techniques.

Consistently with previous series, we detected the majority of recurrences within the first 5 years after surgery, and only 6/94 (6.4%) patients experienced a late recurrence (>5 years) [22,32].

Unfortunately, there are no data to indicate when it is safe to stop follow-up. This is a decision to be shared with patients considering many factors: life expectancy, basal risk of recurrence, psychological distress, and economic sustainability.

Our work, along with others, advances the idea that follow-up utility relies on the concept that earlier identification of recurrence may improve subsequent management of relapsed patients. As in other tumours (e.g. colorectal cancer, germinal tumours), preventing recurrence growth before it causes symptoms and/or organ failure may lead to a curative surgery with/without other medical treatments [14]. We suggest that this practice might also be applicable to recurred GIST. Retrospective analyses in advanced GIST studies demonstrated a direct correlation between tumour size and imatinib resistance [15], likely related to a greater number of tumour clones harbouring resistant mutations, a number that grows with tumour mass [33,34]. On this basis, we speculated that tumour burden at recurrence detection could be considered a negative prognostic factor, possibly affecting the natural course of the disease. Indeed, we demonstrated a statistically significant advantage in terms of both PR-PFS and PR-OS for patients with a low tumour burden as compared to those with a high one at recurrence. Several reasons could explain these results. First, patients with low tumour burden recurrence had a higher likelihood of obtaining longer disease control with imatinib [15,35]. Second, patients with low tumour burden may be eligible to complete surgery, as supported by several series that showed improved outcome with this strategy [16,17,36].

Our study has limitations related to the absence of a randomised control group and, though collected prospectively, its retrospective nature. For instance, we cannot exclude that both higher tumour burden and symptomatic relapse might be related to an intrinsically more aggressive biology of the tumour. That said, a randomised prospective trial on follow-up is highly unlikely to take place in GIST, as in several other more common cancers [37]. Prospectively collected data might, in fact, be the only source capable of addressing this kind of issue, at least in the near future [37]. Furthermore, our series is very homogenous and consistent with regard to control planning (images and exams) and commonly adopted guidelines. This last aspect makes the results informative for clinicians choosing a like follow-up. A
second limitation is related to the exclusion of patients treated in the adjuvant setting with imatinib. We acknowledge that today imatinib represents the standard-of-care for high-risk patients [11,12,38]. Within this specific population, a modulated follow-up strategy might be preferred during and after imatinib [13,22]. However, long-term adjuvant imatinib role is left to be demonstrated outside the high-risk group, and we believe our study provides information for the non-negligible proportion of patients that refuse, or are not deemed suitable for adjuvant treatment.

In conclusion, our data support risk-tailored clinical-radiological follow-up for GIST patients aimed at reducing the impact of recurrence. As it is difficult to foresee a prospective randomised trial, confirmatory studies in different series will strengthen these results.

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Conflict of interest statement

Dr. Grignani reported consulting/advisory role for PharmaMar, Novartis, Pfizer, Bayer, Eisai, and Eli Lilly outside the submitted work. Dr. Dei Tos received personal fees from PharmaMar, Pfizer, and Eli Lilly outside the submitted work. All remaining authors have declared no conflicts of interest.

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References


