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Using the recurrence risk score by Joensuu to assess patients with gastrointestinal stromal tumor treated with adjuvant imatinib

A retrospective cohort study

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Abstract

In 2014, Joensuu and colleagues devised the first recurrence risk score (RRS) to identify the risk factors for gastrointestinal stromal tumor (GIST) recurrence. However, there are scarce data available on RRS effectiveness and efficiency. Therefore, we retrospectively analyzed clinical data to validate Joensuu's RRS in patients treated with adjuvant imatinib.

In this retrospective cohort study, data were collected from patients with GIST who were treated with adjuvant imatinib between December 2005 and May 2017 in the West China Hospital. The study consisted of 137 patients, after application of inclusion and exclusion criteria. Recurrence-free survival (RFS) was the primary end point.

The RRSs for 137 patients were divided into 3 groups: low (n = 46), medium (n = 48), and high (n = 43). The RFSs of the 3 groups were significantly different ($P < .001$). In patients who received adjuvant imatinib for <36 months, the RFS difference was also significant ($P < .001$), and the result was similar in patients treated with adjuvant imatinib for ≥36 months ($P = .03$). The area under the curve of the RRS was 0.84 ([95% confidence interval] 0.76–0.92, $P < .001$), suggesting that the RRS method could accurately assess recurrence risks for patients with GIST who were treated with adjuvant imatinib.

It is appropriate to apply the RRS method to assess recurrence risks for patients with GIST who were treated with adjuvant imatinib. A longer adjuvant imatinib duration is recommended for high-risk patients with GIST. It is also important to identify a more effective treatment for patients who are resistant to imatinib.

Abbreviations: AUC = area under the curve, CI = confidence interval, GIST = gastrointestinal stromal tumor, HR = hazard ratio, IQR = interquartile range, RFS = recurrence-free survival, ROC = receiver-operating characteristics, RRS = recurrence risk score.

Keywords: adjuvant imatinib, GIST, high-risk, retrospective analysis, risk factors

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal soft tissue malignancy.[1,2] Approximately 80% of GISTs contain an activating mutation in the *KIT* oncogene, whereas 5% to 10% have a mutation in the gene encoding *PDGFRα*.[3–6] Complete surgical resection is the standard treatment for localized, primary GISTs, but approximately 40% to 50% of patients experience recurrence.[7] Imatinib can reduce the relapse of patients with GIST who undergo complete resection, and this has been confirmed by many studies.[8–12] Imatinib is recommended as the standard first-line treatment for GIST,[13,14] and ≥ 3 years of adjuvant imatinib is the recommended treatment for high-risk patients with GIST who undergo complete resection, based on the Scandinavian Sarcoma Group SSGXVIII/AIO randomized phase III trial (NCT00116935).[13,15–18] Therefore, many guidelines suggest that 3 years of adjuvant imatinib for high-risk patients with GIST after complete resection effectively decreases recurrence.[19–22] Many high-risk patients with GIST have received adjuvant imatinib for 3 years after surgery, and some patients have even been treated for >3 years. However, some patients experience disease recurrences soon after stopping imatinib, and scarce data are available about the recurrence risk factors in high-risk patients treated with adjuvant imatinib.

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JT and RZ equally contributed to this study.

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Individual contributions: MZ and JT conceived the study together. All of the authors contributed to the research and development process that resulted in this article. JT, RZ, XZ, LX, YW, LF, SR, PW, and MX performed patient follow-up, together. JT wrote the manuscript under the guidance of MZ. All of the authors read and approved the final manuscript.

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In 2014, Joensuu and colleagues first identified the GIST recurrence risk factors in this setting and devised the recurrence risk score (RRS), based on the SSGXVIII/AIO and ACOSOG Z9001 trials.[18] RRSs can be used to guide follow-ups, counseling, and treatments for high-risk patients with GIST who are treated with adjuvant imatinib. Currently, relevant RRS research is sparse and lacks results from prospective studies. Therefore, we retrospectively analyzed clinical data to validate the Joensuu's RRS in patients treated with adjuvant imatinib.

2. Methods

2.1. Patients

In this retrospective cohort study, data were collected from patients with GIST who were treated with adjuvant imatinib between December 2005 and May 2017 in the West China Hospital. Our study included 1021 patients, all of whom were confirmed by immunohistochemistry. The inclusion criteria met the requirements of the RRS and were as follows: patients were *KIT* (CD117) positive by immunohistochemistry; underwent complete resection; began adjuvant imatinib between 1 and 8 weeks after surgery; had a high-risk of recurrence that was confirmed by modified NIH criteria, which is a generally accepted risk-stratification scheme.[23–25] The exclusion criteria included patients who received preoperative treatment with imatinib, did not receive adjuvant imatinib therapy after surgery, and had metastatic or recurrent GIST. To validate the Joensuu's RRS in patients treated with adjuvant imatinib, the time of GIST recurrence must be accurate. If the time was not clear, such as in patients with irregular follow-ups, the patients were not included in this study. For patients who died, the time of recurrence was included, but the time of death was not included. Finally, the study enrolled 137 patients who fulfilled the inclusion and exclusion criteria.

2.2. Follow-up

Professional researchers postoperatively followed-up the patients, and the follow-ups included CT or MRI of the abdomen and pelvis and CT of the chest or chest x-ray. A CT or MRI scan was performed at 3-month intervals for first 2 years and subsequently at 6-month intervals. Blood cell counts and chemistries were performed at 1- to 3-month intervals during the treatment period, and subsequently at 6-month intervals after stopping imatinib. All patients were closely followed, and the follow-up periods ranged from 5 months to 8.3 years, with a mean duration of 45.6 months. The primary end point was recurrence-free survival (RFS).

2.3. Ethics statement

The study protocol was approved by the ethics committee of the West China Hospital, Sichuan University. Written informed consent was obtained from the patients and families of the patients, even though the study was retrospective in nature. Patient records/information was anonymized and deidentified before analysis, and the methods were performed in accordance with approved guidelines.

2.4. Statistical analyses

All statistical analyses were performed using SPSS version 20.0 (for window, IBM). We used the χ^2 test to compare categorical data and the *t* test or ANOVA to compare continuous data. The survival data were compared using the Kaplan–Meier method, and the log-rank test model was used to detect differences in the survival curves of the various subgroups. The Cox proportional hazards model (hazard ratios [HRs]) was used to analyze the prognostic factors associated with RFS and relationships among various factors. Receiver-operating characteristics (ROC) curves were constructed to assess sensitivity, specificity, and respective areas under the curves (AUCs), with 95% confidence intervals (CIs). All *P* values were 2-sided, and *P* values of $<.05$ were considered statistically significant.

Table 1

Characteristics of patients and tumors.

Factor	No.	%
Sex		
Female	63	46
Male	74	54
Age, y		
≤52 (mean)	67	49
>52	70	51
Duration of adjuvant imatinib, mo		
<35	67	49
≥36	70	51
Tumor size, cm		
≤5.0	53	39
5.1–10.0	67	49
>10.0	17	12
Tumor mitotic (count per 50 HPFs)		
≤5	47	34
6–10	37	27
>10	53	39
Tumor site		
Gastric	68	50
Non-gastric	69	50
Tumor rupture		
No	94	69
Yes	43	31

3. Results

3.1. Characteristics

The baseline characteristics of the patients and tumors are shown in Table 1. The most frequent location of the primary tumor was the stomach (n = 68, 49.6%), followed by the small intestine (n = 40, 29.2%). The mean of tumor size was 7.6 ± 0.4 cm (interquartile rang [IQR] of 5.0–10.0 cm), and the mean of tumor mitosis was 12.3 ± 1.3 per 50 high-power fields of the microscope (IQR: 4.0–16.0). The tumor site, tumor rupture statistics, and duration of adjuvant imatinib therapy are shown in Table 1.

3.2. RFS by RRS

RRS was used to analyze the RFS for 137 patients who were treated with adjuvant imatinib and met the RRS requirements.[18]

RRS = 0.05316 × tumor mitotic index (/50 HPEs) + 0.00000 (if gastric GIST) + 1.17607 (if nongastric GIST) + 0.00000 (adjuvant imatinib for ≥36 months) + 0.89619 (adjuvant imatinib for <36 months) + 0.68533 (if the tumor ruptured) + 0.04460 × tumor size (cm).

The RRSs for the 137 patients were divided into 3 groups: low (RRS≤1.62, n = 46), medium (RRS>1.62, <2.61, n = 48), and high (RRS≥2.61, n = 43), and these thresholds were estimated by

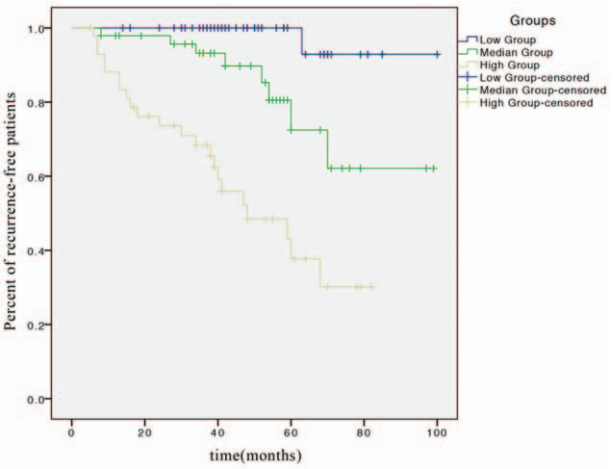

Figure 1. Kaplan–Meier analysis of RFS in different RRS groups.

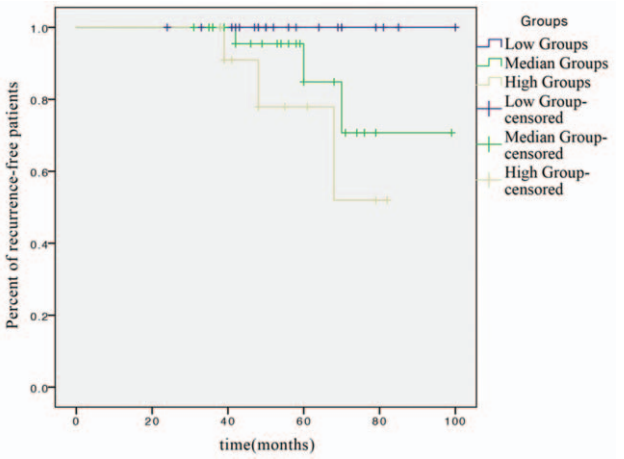

Figure 3. Kaplan–Meier analysis of RFS of patients who received adjuvant imatinib for ≥36 months.

Joensuu and colleagues. The RFS values of the 3 groups were significantly different ($P < .001$; Fig. 1). The RFS of the medium group was better than that of the high group ($\chi^2 = 6.5$ $P = .01$), and the RFS of the low group was the best of the 3 groups ($\chi^2 = 12.1$ $P = .001$) (Fig. 1).

In the patients treated with adjuvant imatinib for <36 months, the differences of RFS vales were also significant ($P < .001$; Fig. 2), and the results were similar to those of patients who were treated with adjuvant imatinib for ≥36 months ($P = .03$; Fig. 3).

The ROC analysis showed that RRS strongly associated with the RFS of high-risk patients with GIST who were treated with adjuvant imatinib. The AUC of RRS was 0.84 ([95% CI] 0.76–0.92, $P < .001$; Fig. 4), suggesting that the RRS method can accurately assess recurrence risks in patients with GIST who are treated with adjuvant imatinib.

3.3. Multivariable survival analyses

In a stepwise Cox multivariable analysis of the 137 patients who were included in our study, the duration of adjuvant imatinib treatment was the only protective factor associated with RFS (HR [95% CI], 0.92 [0.89–0.94], $P < .001$) (Table 2). Tumor size, tumor mitotic index, tumor rupture, and tumor site were, respectively, important independent factors that were associated with RFS (HR [95% CI], 1.13 [1.04–1.23], $P = .005$; HR [95% CI], 1.01 [1.00–1.03], $P = .002$; HR [95% CI], 1.52 [0.65–3.55], $P = .03$; HR [95% CI], 2.70 [1.15–6.37], $P = .02$) (Table 2).

4. Discussion

The incidence of GIST has been increasing,[1,26,27] and imatinib is recommended as the first-line targeted therapy for GIST by Clinical Practice Guidelines.[28,29] Surgery and adjuvant imatinib therapy after surgery are important treatments for high-risk GIST. However, there is scarce data about the recurrence risks of patients with GIST who are treated with adjuvant imatinib. The following interesting discoveries were identified by our investigation.

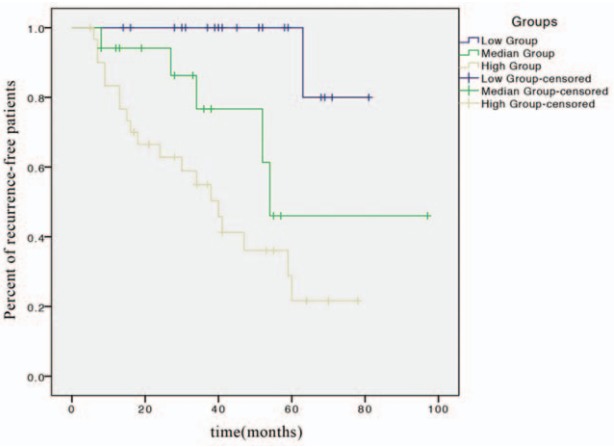

Figure 2. Kaplan–Meier analysis of RFS of patients who received adjuvant imatinib for <36 months.

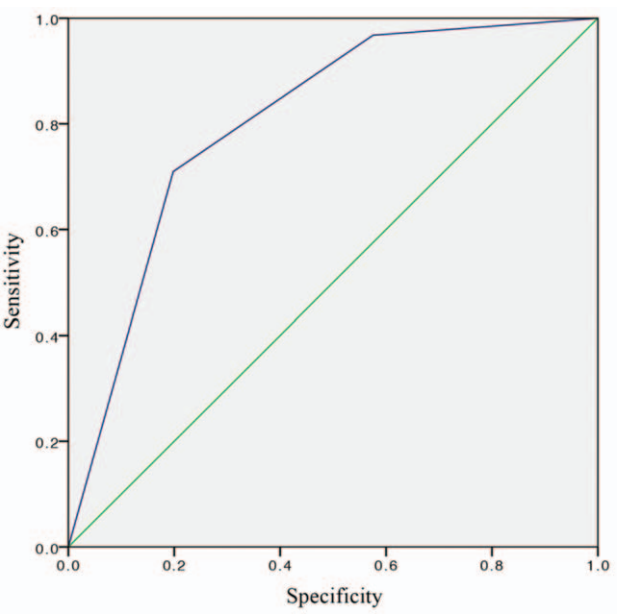

Figure 4. The ROC curve of RRS with RFS for all patients.

Table 2

Multivariate analyses of risk factors for RFS.

Factors	Hazard ratio	95% CI	*P*
Duration of adjuvant imatinib, mo	−0.92	−0.89–0.94	<.001
Tumor size, cm	1.13	1.04–1.23	.005
Tumor rupture (Y/N)	1.01	1.00–1.03	.002
Tumor site (gastric/nongastric)	1.52	0.65–3.55	.03
Tumor mitotic (/50 HPF)	2.70	1.15–6.37	.02

CI = confidence interval, RFS = recurrence-free-survival.

The RRS AUC was 0.84 ([95% CI] 0.76–0.92, $P < .001$), which illustrates that the RRS by Joensuu is appropriate for assessing the recurrence risk of patients with GIST who are treated with adjuvant imatinib. RRS can guide clinic doctors in the follow-up, counseling, and treatment of patients with GIST who were treated with adjuvant imatinib. Adjuvant imatinib therapy for <36 months can reduce recurrences in high-risk patients with GIST, but for some patients with high scores, adjuvant imatinib for <36 months was insufficient (Fig. 2). The 5-year RFS of patients with high scores who were treated with adjuvant imatinib for <36 months was lower than those with low scores (Fig. 2). Meanwhile adjuvant imatinib therapy for 36 months can also reduce recurrences for many patients, but for those with high scores, this therapy was not enough, and the 5-year RFS of patients with high scores was the lowest among included patients (Fig. 3).

The RRS values demonstrate that recurrences in high-risk patients with GIST who were treated with adjuvant imatinib were different (Figs. 1 and 3). For example, the outcomes of high-risk patients with gastric GISTs were more favorable than those of high-risk patients with nongastric GISTs, although the risk stratifications were same. This suggests that the patient outcomes were greatly different among those with the same degree of risk. Based on previous studies and our retrospective data, adjuvant imatinib therapy for 3 years is insufficient for all high-risk patients with GIST, and longer durations of adjuvant imatinib therapy might decrease recurrence for some high-risk patients with high RRSs.[30,31] Therefore, when high-risk patients with GIST finish adjuvant imatinib therapy after 36 months, we should use the RRS to reassess the risk of GIST recurrence, and a longer duration of adjuvant imatinib should be used to decrease recurrence for some patients with high RRSs.

In 2017, results from the PERSIST-5 study, which were reported by the ASCO conference, indicated that 5-year adjuvant therapy might further prolong disease-free survival for intermediate and high-risk patients. However, resistance to imatinib restricts long-term treatments. Imatinib resistance can be divided in 2 categories. One, primary resistance, is caused by an overrepresentation of *KIT* exon 9 mutation or no detectable kinase mutation (wild-type tumor) within 6 months of an initial clinical response.[5,32–34] Secondary resistance involves new acquired kinase mutations in *KIT* or *PDGFRα* after >6 months of clinical resistance.[33–36] Typically, there is slight primary resistant to imatinib, but secondary resistance eventually develops in most patients treated with imatinib.[37,38] Secondary resistance is frequently observed and found in 50% to 70% of patients who show late progression.[39] Although knowledge of imatinib resistance mechanisms has rapidly increased in recent years, the entire spectrum of resistance mechanisms has not been fully elucidated.[40] Therefore, it is important to develop more effective and new treatments for high-risk patients with GIST who experience resistance to imatinib.

There are certain limitations to our study. First, this was a retrospective study with a limited sample size, and some patients were censored during follow-up. Second, this study was conducted in one single central hospital. Third, the mutational analysis of our data was incomplete before 2010, which caused a lack of mutational status data. Finally, the short follow-up time might cause bias. Thus, a larger scale, multicenter, prospective study with a longer-term follow-up investigation is warranted. Despite these caveats, it appears that our findings could contribute to the follow-up and individualized treatments of patients with GIST.

5. Conclusions

The RRS method is appropriate for assessing recurrence risks in patients with GIST who are treated with adjuvant imatinib. In summary, based on the RRS, longer durations of adjuvant imatinib are necessary for high-risk patients with GIST. It is also important to develop more effective and new treatments for high-risk patients with GIST who are resistant to imatinib and did not undergo long durations of adjuvant imatinib therapy.

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