Clinicopathological significance of c-KIT mutation in gastrointestinal stromal tumors: a systematic review and meta-analysis

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Many types of KIT mutations have been observed in gastrointestinal stromal tumors (GISTs), but their prognostic and predictive significance are still unclear. A meta-analysis and literature review were conducted to estimate the contribution of KIT mutations in prognostic parameters and clinicopathological significance of GISTs. A total of 18 relevant articles from PubMed, EMBASE and Web of Science databases were included in this study. The frequency of KIT mutation was significantly increased in the GIST patients with higher mitosis (≥5/50 high-power fields (HPFs) and larger size (≥5 cm) of tumors than in those with lower MI (≤5/50HPFs) and smaller size (≤5 cm) of GISTs respectively. The rate of KIT mutation was not significantly changed between GISTs in stomachs and in small intestines. KIT mutational status has prognostic significance for patients’ outcome. GIST patients with KIT exon 9 mutations have higher risk of progression than those with exon 11 mutations. 5 year relapse-free survival (RFS) rate was significantly higher in patients with KIT exon 11 deletion than in those with other type of KIT exon 11 mutations. The deletion involving KIT exon 11, particularly codons 557–558, is a valuable predictor of prognosis for patients with GISTs.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal (GI) tract. The population-based studies showed that the annual incidence of GISTs ranges from 11 to 19.6 per million population1,2. It has been a considerable debate regarding their cellular origin and diagnosis3. After gain-of-function mutations in the c-KIT protooncogene were discovered in 1998, GISTs were reliably distinguished from other histopathological subtypes of GI mesenchymal tumors4. GISTs occur primarily in older patients of either sex5, which are present anywhere along the GI tract from esophagus to the rectum, most commonly located in stomach (60%) and small intestine (25%)5. Local recurrence and metastasis are frequently observed in patients with GISTs after adequate resection and adjuvant therapy with tyrosine kinase inhibitor (TKIs)6. In addition, metastasis to the lung and bones occurs in patients with advanced disease6. Therefore, it is critical to identify risk criteria to predict their recurrence and metastasis.

c-KIT, the cellular homologue of the oncogene v-KIT, was isolated from feline fibrosarcoma, the Hardy-Zuckerman 4 feline sarcoma virus (HZ4-FeSV). The viral genome of HZ4-FeSV contains a new oncogene that was designated v-KIT, which encodes a transmembrane tyrosine kinase receptor called KIT7. Huizinga et al. revealed that mice with mutations in the KIT gene lacked the network of interstitial...
cells of Cajal which was associated with Auerbach’s nerve plexus and intestinal pacemaker activity, indicating that the interstitial cells of Cajal express the KIT receptor. Mutations of the KIT gene in GISTs occur most frequently in KIT exon 11 (juxtamembrane domain), followed by KIT exon 9 (extracellular domain), less frequently, mutations occur in the adenosine triphosphate (ATP)-binding pocket (exon 13) or activation loop (exon 17) (Fig. 1). Many types of KIT mutations have been observed in GISTs, but controversy still exists concerning their prognostic and predictive value. Deletions in the KIT exon 11 most frequently involve the 5' portion between codons 550 and 560. A few studies have shown that tumors containing deletion in this area are clinically more aggressive than tumors with other type of mutations. However, several studies have reported inconsistent results. The aim of this study is to estimate the contribution of different types of KIT mutations in prognostic parameters and clinic-pathological significance of GISTs.

**Methods**

**Search strategy and selection criteria.** We conducted comprehensive literature searches in the PubMed, EMBASE and Web of Science databases in September 2014 with no low limit set for date of publication, using the following keywords: c-KIT or KIT and GIST or gastrointestinal stromal tumor. The language was limited to English and Chinese. A total of 1206 articles were identified with the initial search. Inclusion criteria for study selection were: 1) The articles in which the association between c-KIT mutation and the clinicopathological significance of GIST was evaluated; 2) The articles in that the association between c-KIT mutations and prognosis in patients with GIST was evaluated. Exclusion criteria were: 1) The studies which used the same population or overlapping database; 2) The studies of in vitro cell culture models; 3) The studies which showed insufficient data to calculate Odds Ratio or Hazard Ratio (Fig. 2). The search identified 18 articles of which were eligible for quantitative analysis in this meta-analysis. The detailed information of 18 relevant citations is listed in Table 1.

**Data extraction and study assessment.** Two investigators (LY and LZ) independently extracted data and reviewed the contents of the articles to determine whether or not they met the criteria for inclusion. Any discontent was discussed and resolved by a consensus including other two investigators (WZ and YW). A data extract form was developed accordingly. One review author (KL) extracted the following data from the included studies: first author’s name, year of publication, number of patients, mitosis number per 50 HPFs in GISTs, size of GISTs, and c-KIT mutation status. The second author (LX) checked the extracted data, and disagreement was resolved by the discussion with other two authors (BL and HY) for all issues.

**Statistics analysis.** All analysis was performed with Review Manager 5.2. Heterogeneity between studies was assessed using the Q-test and I² index. Odds Ratio (OR) with 95% confidence intervals were calculated by using a fixed or random effect model depending on heterogeneity (a fixed effect model for
I^2 \leq 50\%, a random effect model for I^2 > 50\%). Meta-analysis was performed to compare 5 year relapse free survival (RFS) in c-KIT exon 11 deletion and other type of c-KIT mutations in patients with GIST. C-KIT mutation frequency was compared in different size and different MI of tumors. The multivariate HRs were collected, and the log HRs and its standard errors were calculated for individual study. Pooled hazard ratio (HR) with a 95% confidence interval was calculated for the association between the risk of GISTs and c-KIT mutation status. All p values were two sided. Funnel plots were used for detection of publication bias. A sensitivity analysis, in which one study was removed at a time, was conducted to assess the result stability.

Figure 2. Schematic flow diagram for selection of included studies.

| Author          | Year | Country | Sample size | Follow-up (Median) | Treatment |
|-----------------|------|---------|-------------|--------------------|-----------|
| Ma et al. \(^{26}\) | 2014 | China   | 68          | 91.3 mo            |           |
| Origone et al. \(^{26}\) | 2013 | Italy   | 80          |                    |           |
| Lv et al. \(^{23}\) | 2013 | China   | 114         | 50 mo              | Surgery   |
| Kunstlinger et al. \(^{14}\) | 2013 | Germany | 1366        |                    |           |
| Gao et al. \(^{26}\) | 2013 | China   | 50          | 36 mo              | Imatinib  |
| Soreide et al. \(^{26}\) | 2012 | Norway  | 38          | 8 year             | Imatinib  |
| Wozniak et al. \(^{5}\) | 2012 | Belgium | 427         | 3.8 year           | Surgery   |
| Kang et al. \(^{37}\) | 2012 | Korea   | 370         | 43.3               | Imatinib  |
| Daniels et al. \(^{36}\) | 2011 | Germany | 87          |                    |           |
| Garces-Albit et al. \(^{28}\) | 2012 | Spain   | 36          | 64.8 mo            | Surgery   |
| Kontogianni-Katsarou et al. \(^{29}\) | 2008 | Greece  | 30          |                    |           |
| Tzen et al. \(^{40}\) | 2008 | China   | 134         | 47 mo              |           |
| DeMatteo et al. \(^{14}\) | 2008 | USA     | 127         | 5.2 year           | Surgery   |
| Imamura et al. \(^{31}\) | 2007 | Japan   | 95          | 160 mo             |           |
| Debiec-Rychter et al. \(^{42}\) | 2006 | Belgium | 476         | 25.3 mo            | Imatinib  |
| Yeh et al. \(^{43}\) | 2006 | China   | 64          | 16.1 mo            | Imatinib  |
| Cho et al. \(^{44}\) | 2006 | Japan   | 56          | 56.3 mo            | Imatinib  |
| Martin et al. \(^{45}\) | 2005 | Spain   | 162         | 42 mo              |           |

Table 1. Main characteristics of included studies. Abbreviations: mo, month.
Results

Flow chart for study selection is reported in Fig. 2. There were 18 relevant articles available for meta-analysis, which included 3938 patients. The following items were collected from each study: first author’s name, year of publication, number of patients, countries, the number of mitosis per 50 HPFs in GIST, tumor size, c-KIT mutation, treatment and the time of follow-up (Table 1).

The quality of each study was assessed with the Newcastle Ottawa Quality Assessment Scale (NOQAS). These scales were utilized to allocate a maximum of nine points for the quality of selection, comparability, exposure, and outcomes for study participants. Of the studies, one scored 8 points, ten scored 7 points, six scored 6 points, and one scored 5 points. Hence, the studies were of a relatively high quality (data not shown). The funnel plots were largely symmetric (Fig. 3) suggesting there were no publication biases in the meta-analysis of c-KIT mutation and clinicopathological features. We conducted a sensitivity analysis by removing a single study at one time. The pooled HR was not significantly changed, indicating the stability of our analyses.

Progression-free survival (PFS) of GIST patients was significantly worse in patients with KIT exon 9 mutations than in those with KIT exon 11 mutations, OR was 3.60, 95% CI 2.17–5.98, \(z = 4.96\), \(p < 0.00001\), heterogeneity \(I^2 = 0\%\) (Fig. 4). 5-year RFS rate was significantly lower in patients with KIT...
exon 11 deletion than in those with other type of KIT exon 11 mutations, OR was 0.36, 95% CI 0.24–0.56, z = 4.68, p < 0.00001, heterogeneity $F = 0\%$ (Fig. 5). Moreover, RFS for 5 year was significantly worse in patients with GISTs bearing deletions involving KIT codon 557–558 than in those bearing other deletions of KIT exon 11 (Fig. 6). The rate of KIT mutation was not significantly changed between GISTs in stomachs and those in small intestines, OR was 1.00, 95% CI 0.51–1.95, z = 0.01, p = 0.99, heterogeneity $I^2 = 84\%$, p < 0.00001 (Fig. 7).

KIT mutations were significantly more frequently observed in the patients with larger size (≥5 cm) of GISTs than those with smaller size (≤5 cm) of tumors, OR was 1.51, 95% CI 1.05–2.17, z = 2.22, p = 0.03, heterogeneity $F = 84\%$, p < 0.00001 (Fig. 7). KIT mutations were significantly increased in the patients with higher mitosis index (MI) (≥5/50 HPFs) of GISTs compared to the patients with lower MI (≤5/50 HPFs) of tumors. OR was 1.76, 95% CI 1.05–2.95, z = 2.15, p = 0.03, heterogeneity $F = 57\%$, p = 0.03 (Fig. 9). KIT mutations were not significantly associated with the risk of mortality of patients with GIST. Hazard Ratio (HR) was 0.35 with a 95% confidence interval (CI) 0.09–1.30, z = 1.57, p = 0.12, heterogeneity $F = 51\%$ (Fig. 10).
GISTs are the tumors with KIT expression, located in the gastrointestinal tract. Gain of function mutations in either KIT or platelet-derived growth factor receptor alpha (PDGFRA) were found in about 80%–85% of cases. Many types of KIT mutations involved in exon 9, 11, 13 and 17 have been described in GISTs, including point mutation, insertion, deletion and duplication. Treatment with tyrosine kinase inhibitor (TKIs) is effective in reducing disease recurrence after primary surgery and controlling unresectable disease. Therefore, it is essential to identify mutation status to predict its response to TKIs and prognosis. Our analysis showed that KIT mutation was not associated with the risk of mortality of patients with GISTs. In the future, the stratified analysis by tumor size and mitosis index should be carried out to identify the prognosis power of KIT mutation, because tumor size and mitosis index are the most important confounding factors. In addition, the overall survival of patients with GISTs may depend on the specific type of KIT mutation. We performed a detailed subgroup analysis of relationship between different types of KIT mutations and prognosis of patients with GISTs. The result indicated that PFS of GIST patients was significantly worse in KIT exon 9 mutations than in KIT exon 11 mutations. Previous studies indicated the response to imatinib treatment was worse in patients whose tumors harbored KIT exon 9 mutations than in those with KIT exon 11 mutations. Patients with GIST treated with imatinib in all three studies were included in present meta-analysis (Fig. 2). There was no bias created from different treatments. Thus, GIST patients with KIT exon 9 mutations have higher risk of progression than those with exon 11 mutations.

Interestingly, deletions in the KIT exon 11 most frequently involve the 5′ portion between codons 550 and 560, and less frequently involve codons 562–579. There is no significant difference in the response rate of imatinib or median progression-free survival among the patients with exon 11 deletion, point mutations and mixed-type mutations. Our result showed 5-year RFS was significantly worse in...
patients with KIT exon 11 deletion than in those with other type of KIT exon 11 mutations. Moreover, RFS for 5 year was significantly worse in codon 557–558 deletion of KIT exon 11 than other deletion of KIT exon 11. Recently, a few studies reported controversial results of RFS for five year in patients of GIST with codon 557–558 deletion and other deletion of KIT exon 11 due to the small size of patient samples. For the first time, we pooled four studies in this meta-analysis with a total of 127 patients and more precisely assessed RFS for five year in patients of GIST with different parts of KIT exon 11 deletion.

KIT is a member of type III receptor tyrosine kinase family that contains platelet-derived growth factor receptors-α and -β (PDGFRα and PDGFRβ), as well as the macrophage colony stimulating factor receptor (CSF1R) and the IL cytokine receptor (FLT3) Mutations of the KIT gene in GISTs occur most frequently in KIT exon 11, the juxtamembrane domain that disrupts the normal juxtamembrane secondary structure and activate downstream signaling pathways, including the MAP kinase pathway (RAF, MEK, and ERK), the PI3 kinase/AKT pathway, and STAT3 The MAP and PI3 kinase pathway upregulate important transcriptional factors and lead to cell proliferation, and they downregulate the cell cycle inhibitor p27KIP as well as anti-apoptotic signaling. Therefore, KIT mutation is a potential predictive factor for prognostic implication. We compared the frequency of KIT mutations in different size of tumors and different MI. Our result indicated that KIT mutation was significantly more frequent in the patients with larger size (≥5 cm) and higher MI (≥5/50 HPFs) of GIST than in patients with smaller size (<5 cm) and lower MI (<5/50 HPFs) of GIST respectively. Taniguchi et al. have reported that there is a direct relationship between the presence of mutation in tumor size and mitotic count, which is in agreement with our result. Previous studies revealed that tumors larger than 5 cm and the presence of more than 5 mitoses/50 HPF were clearly associated with worse outcome. Tumor size and mitotic counts traditionally have been the two factors for estimation of prognosis. Zhao et al. conducted a meta-analysis and found that incidence of MI (≥5/50 HPFs) was significantly higher in patients with mutated KIT than in the patients with wild type KIT. This discrepancy could be due to relatively small sample size (1751 patients). Present meta-analysis included 3890 patients and the result is more accurate. Taken together, our study indicated that KIT mutation status is another evaluable factor to estimate prognosis in GISTs in addition to tumor size and mitotic counts.

In conclusion, KIT mutational status has prognostic significance for patients with GISTs. GIST patients with KIT exon 9 mutations have higher risk of progression than those with exon 11 mutations. The deletion of KIT exon 11, particularly codon 557–558 deletion of KIT exon 11, was a valuable predictor of prognosis for patients with GISTs. The frequency of KIT mutation was significantly increased in the GIST patients with higher mitosis (≥5/50 HPFs) and larger size (≥5 cm) of tumors.

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Acknowledgements

We thank Dr. Christopher L. Corless for the diagram (Fig. 1) which we used in present study.

Author Contributions

L.Y., L.Z., W.Z. and H.Y. contributed substantially to the study and design, collection of data, and analysis and interpretation of data. L.Y., L.Z. and Y.W. contributed substantially to the acquisition, analysis, interpretation of data and performed the statistical analysis. Y.W., B.L. and H.Y. have been involved in the drafting and critical revision of the article for important intellectual content. The corresponding authors have full access to all data and the final responsibility for the decision to submit the article for publication. All authors read and approved the final manuscript.

Additional Information

Competing financial interests: The authors declare no competing financial interests.
How to cite this article: Yan, L. et al. Clinicopathological significance of c-KIT mutation in gastrointestinal stromal tumors: a systematic review and meta-analysis. Sci. Rep. 5, 13718; doi: 10.1038/srep13718 (2015).

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