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# Surgery plus TKIs therapy for gastrointestinal stromal tumors

Review

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**Abstract**

**Introduction.** In this era of tyrosine kinase inhibitors (TKIs), the clinical benefit of surgery for patients with metastatic or recurrent gastrointestinal mesenchymal tumor (GIST) is not well defined. The aim of our study was to demonstrate the survival advantage of adding surgery in patients with recurrent or metastatic GIST.
**Methods.** A systematic search of PubMed, Web of Knowledge, Ovid's database was conducted. Relevant studies published by 31 July 2022 on the role of surgery in recurrent or metastatic GIST were identified. Research quality was assessed using the Newcastle-Ottawa Quality Assessment Scale.
**Results.** Eight studies involving 842 patients were included. The four included studies covered 3-year survival and included 441 patients, of whom 302 received TKIs, and 139 received TKIs plus surgery. 3-year overall survival was significantly higher in the TKIs plus surgery group than in the TKIs group (OR=2.37, 95% CI 1.45–3.88, P = 0.001). The 5-year overall survival was 69.0% in the TKIs plus surgery group compared with 49.1% in the TKIs only group. Survival was significantly higher in TKIs plus surgery group (OR = 2.69, 95%CI 1.49-4.86, P=0.001). Four studies, including 453 patients, indicated 3-year progression-free survival (PFS). The pooled analysis revealed the TKIs plus surgery group did have a better PFS than the TKIs only group (OR = 4.02, 95% CI: 1.45–11.16, P=0.008). Three included studies focused on gastrointestinal stromal tumor liver metastasis (GLM). The role of surgery plus TKIs had statistically significant better 5-year overall survival as compared with TKI treatment alone (OR = 2.34, 95%CI 1.30-4.22, P=0.005).
**Conclusions.** Treatment with surgical resection and TKIs could significantly improve the prognosis of patients with recurrent or metastatic GIST.

**Keywords**

*gastrointestinal stromal tumor • tyrosine kinase inhibitors • surgery • meta-analysis*

## 1. Introduction

Gastrointestinal stromal tumors (GISTs) arising from the interstitial cells of Cajal are the most frequent type of mesenchymal tumors in the gastrointestinal tract [1]. While the mainstay of treatment for primary resectable GIST is complete surgical resection, significant advances have been made in the treatment of recurrent or metastatic GIST with the development of tyrosine kinase inhibitors (TKIs) such as imatinib [2-5].

A number of reviewed studies suggest that surgical resection of GISTs in combination with TKIs may be of benefit to patients with recurrent or metastatic GIST [6-9], possibly due to the assumption that operation lessens the tumor burden and slows the development of secondary resistance to TKIs therapy, and helps improve prognosis [10,11]. Nevertheless, conflicting data have been reported [12], as it has a limited prolongation of survival and is accompanied by a high likelihood of surgical complications. Therefore, there is a necessity to re-evaluate the effect of surgery in combination with TKIs in patients with recurrent or metastatic GISTs.

This study conducted a meta-analysis to explore survival rates between TKIs plus surgery and TKIs treatment alone in patients with recurrent or metastatic GISTs.

## 2. Methods

### 2.1. Search strategy

The following keyword combinations and their variants were searched in PubMed, Web of Knowledge, and Ovid databases by July 31, 2022: "gastrointestinal stromal tumors," "recurrence," "metastasis," "surgery," and "TKIs." The reference lists of relevant studies were manually checked for missing studies.

### 2.2. Study selection

The eligibility of the identified studies for inclusion in the review was assessed by carefully examining the title, abstract, and keywords of each record retrieved. Studies were limited to studies published in English and Chinese. Clinical studies on any aspect of the comparison between surgery plus TKIs and TKIs alone for the treatment of recurrent or metastatic GISTs were also included. In accordance with the PICOS model [13], the following inclusion criteria were applied: (a) Participants: patients with GISTs; (b) Interventions: patients received surgery plus TKIs therapy; (c) Comparison: patients received TKIs; (d) Outcome: progression-free survival, overall survival; and (e) Study design: retrospective study.

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### 2.3. Data extraction

Three co-authors (ZK, GB, and YT) separately evaluated the methodological quality of every study on the basis of the Methodological Index Criteria for Non-Randomized Studies (MINORS) [14]. Variables such as the following were recorded: authors, publication journal and year, number of patients, sex, age, tumor size, use of TKIs, surgical management, overall survival (OS), and progression-free survival (PFS). In case of necessity, we contacted the corresponding authors of the study for more information.

### 2.4. Quality assessment

The quality of retrospective studies was estimated in accordance with the Newcastle–Ottawa Scale (NOS) [15]. Study quality assessment evaluated each case-control study based on three elements, including selection, comparability, and exposure outcome conditions. The maximum score for the scale is a total of 9. "Good" is defined as a total score of 7–9, "fair" a total score of 4–6, and "poor" a total score of <4.

### 2.5. Statistical analysis

A formal meta-analysis of all included studies was performed to compare the survival rates between the surgery plus TKIs group and the TKIs only group. Heterogeneity was analyzed using Q statistics and $I^2$ statistics, which measures the extent to which differences between studies can be attributed to inter-study variation rather than chance. P<0.05 for the Q statistic and $I^2$>50% were considered to indicate strong heterogeneity. A fixed effects model was used to calculate pooled estimates for OS and PFS. However, with $P < 0.05$ and $I^2 > 50\%$ for heterogeneity, a random effects model was used. Survival outcomes such as 3- and 5-year OS rate data were analyzed by dichotomous variables with an estimation of odds ratio (OR) together with a 95% confidence interval (CI). In all the tests, a P value smaller than 0.05 was considered statistically significant. Begg's and Egger's tests [16, 17] were used to estimate the publication bias. The statistical analyses in this review were conducted using the Cochrane Collaboration's Review Manager software (version 5.0) and STATA software (version 14.0).

## 3. Results

### 3.1. Study characteristics

After a thorough examination, 8 studies [8, 9, 18-23] were included in our meta-analysis (Figure 1). The initial search yielded 83 publications. Excluding the duplicates, irrelevant topics, non-original studies, studies without a control group or TKIs alone group or surgery alone group, 54 full-text articles were assessed for qualification. Finally, 8 studies [8, 9, 18-23] with therapies—TKIs plus surgery and TKIs alone in patients with recurrent or metastatic GISTs—were eligible and included in our meta-analysis (Fig. 1).

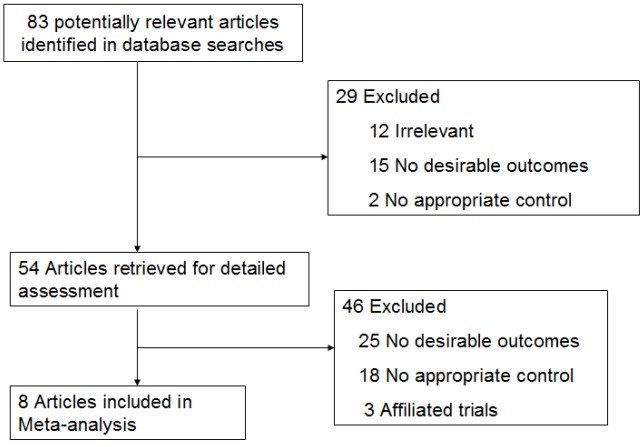


*Figure 1. Flow chart of literature selection process*

A total of 842 patients were recruited for these eight studies, 326 of whom underwent surgery after treatment with TKIs and 516 of whom received TKIs alone. 304 GIST patients included in seven studies were reported surgical margins, and the surgical management was illustrated in Table 1. R0 resection rates were demonstrated to be as low as 60.5%. The patients in 5 studies received TKIs preoperatively and postoperatively, the other 3 studies received TKIs postoperatively. The year of publication ranged from 2005 to 2022. The recruitment period ranged from 2001 to 2018. The characteristics of the included studies are presented in Table 1 and Table 2.

### 3.2. Survival outcomes

The four studies [8, 18, 21, 23], including 453 patients, reported 3-year PFS. The pooled analysis indicated the TKIs plus surgery group did have better PFS than the TKIs only group (OR = 4.02; 95% CI: 1.45 to 11.16; P=0.008, Fig. 2A). The publication bias confirmed by the Begg's and Egger's tests did not appear significant ($Pr > |z| = 0.734$, $P > t = 0.306$, Fig. 2B and Fig. 2C).

The four enrolled studies [8, 18, 20, 22] comprised 441 patients, of whom 302 received TKIs and 139 proceeded with TKIs plus surgery. The 3-year OS was significantly higher in the TKIs plus surgery group than in the TKIs group (OR 2.37, 95% CI 1.45–3.88; p = 0.001, Fig. 3). No significant publication bias appeared ($Pr > |z| = 0.734$, $P > t = 0.207$).

5-year OS was reported in six included articles [9, 18-21, 23]. The 5-year OS was 69.0% in the TKIs plus surgery group compared with 49.1% in the TKIs group, and the 5-year OS was significantly higher in TKIs plus surgery group than in the TKIs group (OR = 2.69, 95% CI 1.49-4.86, P=0.001, Fig. 4). Publication bias was not significant ($Pr > |z| = 0.133$, $P > t = 0.156$).

*Table 1. Characteristics of studies included in meta-analysis of role of surgery for patients with recurrent or metastatic gastrointestinal stromal tumors*

| Author, Year | Country | No. of patients | Sex(male/female) | Mean age(year) | Mean Tumor size (cm) | Classification of recurrent or metastatic GISTs | Type of TKIs | Timing of TKIs | Surgical management | Follow-up (median, range) | Study design |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chang SC 2015[18] | China | 182 | S:44/32 | S:55.89 | ---- | metastatic or recurrent GISTs | imatinib | Preop + Postop | R0 30<br>R1 9<br>R2 37 | ---- | Retrospective |
| | | | NS:66/40 | NS:58.42 | | | | | | | |
| Zaydfudim V 2015[9] | USA | 87 | S:31/23 | S:61 | S:9 | metastatic or recurrent GISTs | Imatinib or sunitinib | Preop + Postop | R0 32<br>R1 3 | ---- | Retrospective |
| | | | NS:17/16 | NS:60 | NS:9 | | | | R2 19 | | |
| Sato S 2016 [19] | Japan | 93 | S:28/22 | S:60 | S:7.5 | metastatic or recurrent GISTs | Imatinib | Postop only | R0 29<br>R1 5<br>R2 13 | 75.2 | Retrospective |
| | | | NS:28/15 | NS:69.7 | NS:8 | | | | | | |
| Shi YN 2017 [20] | China | 130 | 90/54 | 56 | ---- | metastatic GISTs | Imatinib then sunitinib | Postop only | R0 23<br>R1/R2 9 | 48.2 | Retrospective |
| Xiao B 2018 [21] | China | 102 | S:11/10 | 52 | 4.4 | metastatic GISTs | Imatinib then sunitinib | Postop only | R0 15<br>R1/R2 6 | ---- | Retrospective |
| | | | NS:60/21 | | | | | | | | |
| Xia L 2010 [22] | China | 39 | S:10/9 | 53 | S: 8.9 | metastatic GISTs | Imatinib | Preop + Postop | ---- | 36 | Retrospective |
| | | | NS:11/9 | 55 | N:9.3 | | | | | | |
| Bauer S 2005[8] | USA | 90 | S:6/6 | S:57 | ----- | MetastaticGISTs | Imatinib | Preop + Postop | R0 11<br>R1/R2 1 | ---- | Retrospective |
| | | | NS:45/33 | NS:62 | | | | | | | |
| Xue A 2022 [23] | China | 119 | S:34/28 | 56 | 4 | metastatic GISTs | imatinib | Preop + Postop | R0 44<br>R1 16<br>R2 2 | 56 | Retrospective |
| | | | NS:37/20 | | | | | | | | |

*Table 2. Newcastle-Ottawa Scale Assessment of enrolled studies*

| Author, Year | Selection (0-4) | Comparability (0-2) | Outcome (0-3) | Quality score |
|---|---|---|---|---|
| Chang SC 2015[18] | 4 | 1 | 3 | 8 |
| Zaydfudim V 2015[9] | 4 | 1 | 2 | 7 |
| Sato S 2016 [19] | 4 | 1 | 2 | 7 |
| Shi YN 2017 [20] | 4 | 1 | 2 | 7 |
| Xiao B 2018 [21] | 4 | 1 | 3 | 8 |
| Xia L 2010 [22] | 4 | 1 | 2 | 7 |
| Bauer S 2005[8] | 4 | 1 | 3 | 8 |
| Xue A 2022 [23] | 4 | 1 | 3 | 8 |

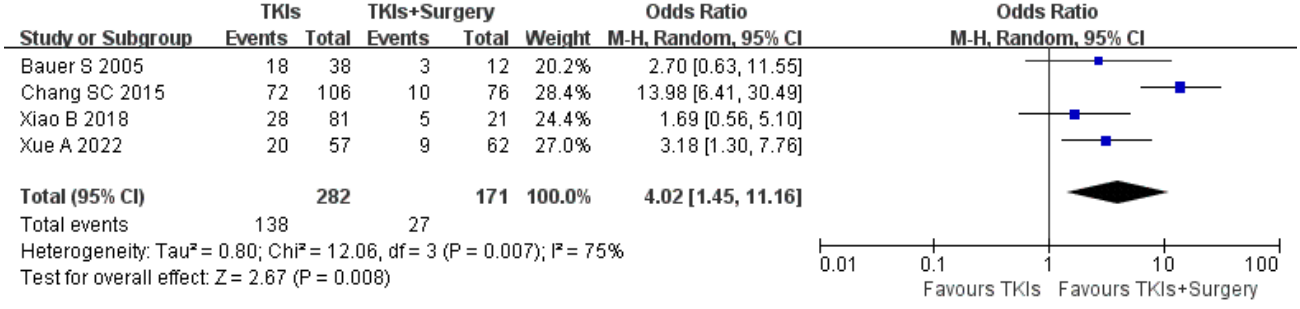


*Figure 2A. Meta-analysis of 3-year PFS between surgery plus TKIs group and TKIs alone group. A forest plot displays individual study results (squares) along with their confidence intervals (horizontal lines). The size of the square represents the weight of the study. The pooled odds ratio is represented by a diamond, with the diamond's width indicating the 95% confidence interval for the pooled odds ratio*

The three included studies [20, 21, 23] focused on gastrointestinal stromal tumor liver metastasis (GLM). The role of surgery combined with TKIs had a statistically better 5-year OS compared to treatment with TKIs alone (OR = 2.34, 95% CI 1.30-4.22, P=0.005, Fig. 5). No significant publication bias appeared (Pr > |z| = 0.296, P > t = 0.103).

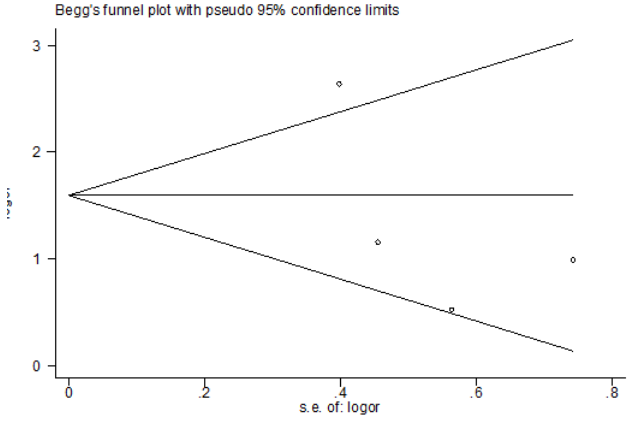


*Figure 2B. Begg's funnel plot for visual assessment of no publication bias for 3-year PFS*

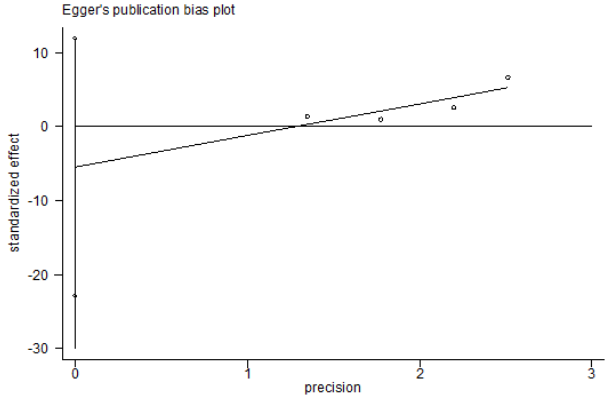


*Figure 2C. Egger's publication bias plot showed no publication bias for 3-year PFS*

## 4. Discussion

A previous prospective randomized trial [24] pointed out that the PFS was not statistically significantly different between surgery plus imatinib and imatinib alone for patients with recurrent/metastatic GISTs. Meanwhile, this trial noted that median OS was prolonged significantly in patients with surgery plus imatinib. Moreover, another report demonstrated that surgery improved the prognosis of patients with TKIs-resistant focally progressive GISTs [25]. Therefore, surgical resection of recurrent or metastatic GISTs was considered as an additional treatment option to remove residual tumors or drug-resistant clones, thereby palliating or curing the disease. However, some studies found limited benefit in patients who underwent surgery for focal progressive disease [6, 26]. In our study, surgery plus TKIs was strongly associated with improvement of the 3-year PFS and the 3- and 5-year OS in patients. This finding can be explained by the fact that surgery can reduce the tumor burden, in order to reduce secondary resistance and improve survival.

The four included analyses suggested that being responsive, partially responsive, or stable to preoperative imatinib was associated with prolonged survival in patients with recurrent or metastatic GIST [8, 9, 22, 23]. One possible explanation was that patients with recurrent or metastatic GIST were more likely to achieve R0 resection after tumor reduction with TKIs. Response to TKIs is associated with exon mutations in KIT. Clinical benefit rates of 74% to 80% have been reported for imatinib in patients with KIT exon 9 mutations and 92% in patients with KIT exon 11 mutations [27-29]. Our studies included eight studies with 842 GIST patients of which 304 were surgically treated. Only 60.5% patients achieved R0 resection in seven enrolled studies. Maybe it was hard to achieve R0 resection in metastatic lesions. The benefits of surgery for focally progressive GIST during imatinib therapy were still in discussion. Gao X [25] noted that surgery could significantly improve the survival of patients with local progression. Hasegawa [30] indicated that surgical intervention was effective after complete resection in patients with imatinib treatment-resistant GIST. The three included studies suggested

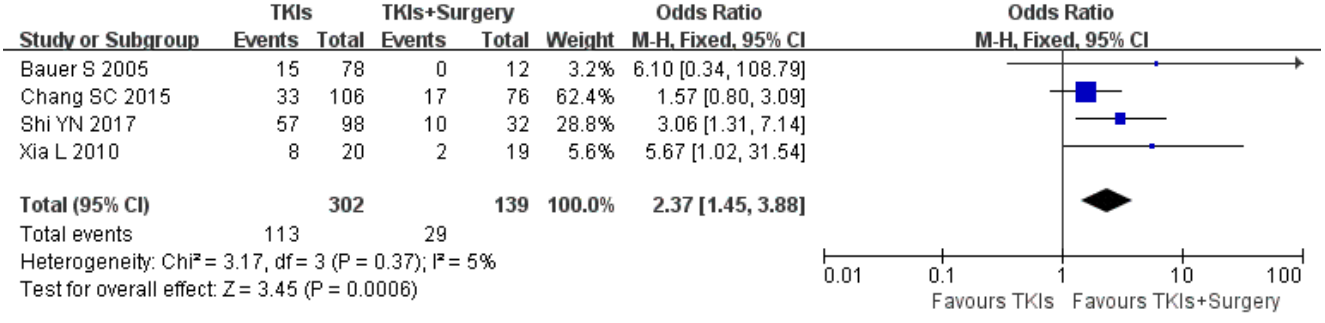


*Figure 3. Meta-analysis of 3-year OS between surgery plus TKIs group and TKIs alone group. A forest plot displays individual study results (squares) along with their confidence intervals (horizontal lines). The size of the square represents the weight of the study. The pooled odds ratio is represented by a diamond, with the diamond's width indicating the 95% confidence interval for the pooled odds ratio*

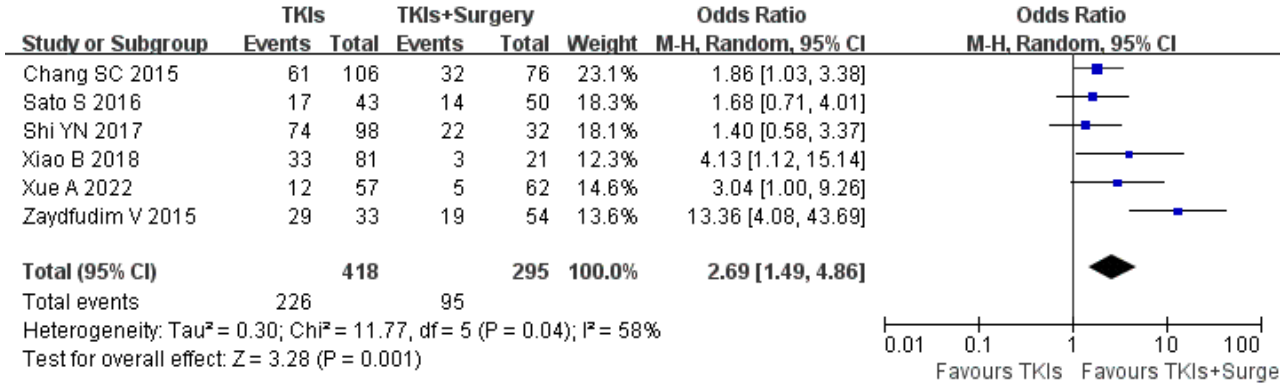


*Figure 4. Meta-analysis of 5-year OS between surgery plus TKIs group and TKIs alone group. A forest plot displays individual study results (squares) along with their confidence intervals (horizontal lines). The size of the square represents the weight of the study. The pooled odds ratio is represented by a diamond, with the diamond's width indicating the 95% confidence interval for the pooled odds ratio*

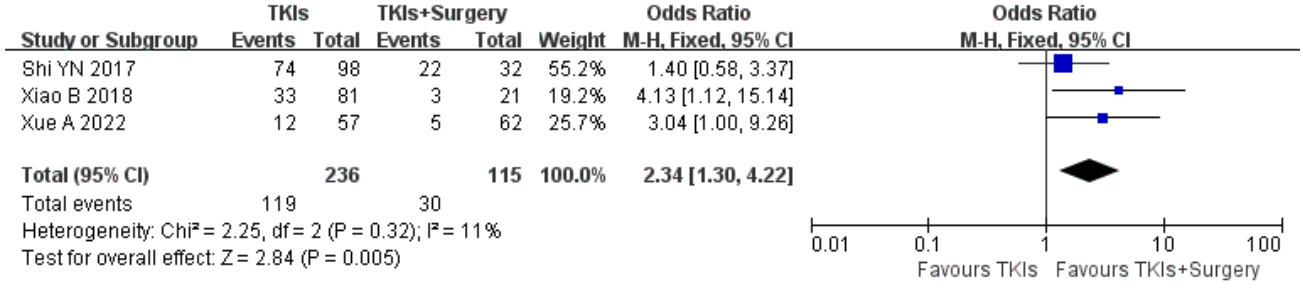


*Figure 5. Meta-analysis of 5-year OS between surgery plus TKIs group and TKIs alone group for GLM. A forest plot displays individual study results (squares) along with their confidence intervals (horizontal lines). The size of the square represents the weight of the study. The pooled odds ratio is represented by a diamond, with the diamond's width indicating the 95% confidence interval for the pooled odds ratio*

that [8, 9, 19] the OS of R0 group was better than that of R2 group, which was consistent with the previous article [31].

In terms of the GLM patients, several previous studies [32-34] illustrated hepatectomy in combination with TKIs was more favorable for improving prognosis than TKIs alone. Also, in a retrospective analysis, R0 resection was the only independent prognostic factor for PFS and OS in patients with GLM [35]. As with previous studies, our meta-analysis confirmed that patients with GLM who received surgery plus TKIs had improved 5-year OS.

Therefore, we recommend that patients with metastatic or recurrent GISTs should receive a combination of surgical resection and TKIs, with the final decision being made judiciously by an experienced multidisciplinary team (MDT), taking into account the potential risks and benefits, in order to personalize the treatment approach and ensure that the patient receives the maximum benefit.

Several limitations of our meta-analysis should be carefully considered. First, the total sample sizes were not large, and some studies did not provide enough time for long-term follow-up. Second, RCTs were not included in our meta-analysis, which may influence the outcome of treatment. Third, as tumors respond differently to TKIs, it was difficult to calculate patient survival data into subgroups. Fourth, patients in six of the eight included studies [18-23] were treated with TKIs postoperatively, and patients in the other two studies [7, 8] received TKIs preoperatively, which can lead to bias.

## 5. Conclusions

Surgery plus TKIs was more effective than TKIs alone in prolonging OS and PFS. Surgery plus TKIs may be considered an appropriate approach for the treatment of advanced GIST. However, the findings of this study should be tested by long-term follow-up of these patients, and further randomized controlled trials are required to ascertain the clinical efficacy of these two treatments.

## Author's contribution

**K.Z.**: research concept and design, analysis and interpretation of data, designing the figures, drafting the article or revising it critically for important intellectual content, writing the manuscript, literature review, final proofreading and approval of the version for publication; **G.B.**: evaluated the methodological

quality of every study, final proofreading and approval of the version for publication**. T.Y.**: analysis and interpretation of data, acquisition of data, designing the figures, drafting the article or revising it critically for important intellectual content, literature review, final proofreading and approval of the version for publication.

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