Comparison of Prognosis Between Microscopically Positive and Negative Surgical Margins for Primary Gastrointestinal Stromal Tumors: A Systematic Review and Meta-Analysis

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Background: This meta-analysis aimed to determine the prognostic impact of microscopically positive margins (R1) on primary gastrointestinal stromal tumors.

Methods: A literature search was performed using PubMed, Embase, Web of Science, and Cochrane Library for studies up to 23 November 2020. The pooled disease-free survival (DFS) and overall survival (OS) between R1 and negative margins (R0) were estimated using a random-effects model.

Results: Twenty studies with 6,465 patients were included. Compared with R0 resection, R1 was associated with poor DFS in patients who did not receive adjuvant Imatinib (HR: 1.62, 95% CI: 1.26–2.09; P = 0.48, I² = 0%; reference: R0). This negative impact of R1 disappeared with the use of adjuvant Imatinib (HR: 1.23, 95% CI: 0.95–1.60; P = 0.38, I² = 6%; reference: R0). R1 was related to poor DFS in gastric GISTs (HR: 2.15, 95% CI: 1.15–5.02, I² = 0%; reference: R0), which was attenuated in the subgroup of adjuvant Imatinib (HR: 2.24, 95% CI: 0.32–15.60; P = 0.84, I² = 0%; reference: R0). Rectal GIST with R1 margin who even received adjuvant Imatinib still had poor DFS (HR: 3.79, 95% CI: 1.27–11.31; P = 0.54, I² = 0%; reference: R0). Patients who underwent R1 resection had similar OS compared with those who underwent R0 resection regardless of the use of adjuvant Imatinib.

Conclusion: R1 was associated with poor DFS for primary GISTs, which was attenuated by adjuvant therapy with Imatinib. Similar result was observed in the gastric GISTs.
INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are one of the most common mesenchymal tumors, accounting for 80% of tumors that arise from the gastrointestinal tract (1). The rare invasion to lymph nodes or adjacent organs that occurs with these tumors makes it possible to perform a local resection as a radical curative treatment, which requires a negative resection margin (R0) and avoidance of tumor rupture to achieve a satisfactory oncological outcome (2, 3). However, incomplete resection might occur in cases with tumors located in unfavorable anatomical sites, which results in microscopically or grossly positive resection margins (R1). With the advent of minimally invasive procedures, such as laparoscopy and endoscopy, whether the status of resection margin impacts oncological outcomes of GISTs remains a core concern for surgeons.

Several studies (4–7) have evaluated the prognostic value of R1 margin for GIST, through which controversial results were drawn out partially because of the retrospective nature or the relatively small sample size of these studies. The only previous meta-analysis (8) revealed that adjuvant Imatinib could attenuate the negative influence of R1 resection on disease-free survival (DFS) of GISTs. However, a recent post hoc study based on the EORTC 62024 randomized trial suggested that tumor rupture rather than R1 margin significantly influenced the overall survival (OS) of GIST regardless of the acceptance of adjuvant Imatinib (9). To date, high-quality evidence focusing on this issue is still lacking, which is why a decisive conclusion remains unclear. Therefore, the current meta-analysis aimed to review the current literature and provide a comprehensive perspective on the influence of the R1 margin on the prognosis of GIST.

MATERIALS AND METHODS

Search Strategy

A systematic search of literature using keywords such as “gastrointestinal stromal tumor,” “GIST,” “margin,” and “R1” was carried out by two investigators (ZL and YZ) through PubMed, Embase, Web of Science, and Cochrane Library to identify studies that reported the relationship between the status of surgical margins and prognosis of gastrointestinal stromal tumor. The search included studies up to 23 November 2020. Attempts have been made to obtain additional eligible studies by searching the references of relevant studies. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (10).

Selection Criteria

Eligible studies were identified by two investigators (ZL and HY) according to the following criteria: (1) Participants (P): The patients were diagnosed pathologically and immunohistochemically as primary GISTs without metastasis or other cancers; (2) Interventions (I) and comparisons (C): All the patients underwent surgery and outcomes between R1 and R0 resection margin were compared; (4) Outcomes (O): DFS and/or OS were available or able to be calculated by sufficient data in the studies. When duplicate studies based on similar populations were identified, only the newest or largest study was included. Any discrepancies were resolved by discussion with a third investigator (XG).

Data Extraction

The name of the first author, year of publication, country, sample size, tumor site, recurrence events, adjuvant therapy, follow-up, DFS, disease-specific survival, and OS were extracted independently by two investigators (SL and JZ). If the hazard ratio (HR) and 95% confidence interval (CI) were not provided in the studies, we calculated these data from available data or from the Kaplan–Meier survival curves using the methods reported by Tierney et al. (11). A third observer (ZZ) engaged in discussions to resolve any controversial issues.

Quality Assessment

Two authors (ZL and ZZ) independently assessed the quality of all included studies using the Newcastle–Ottawa Quality Assessment Scale (NOS) with the highest score of nine (12), and any discrepancies in the scores were resolved by discussion with a third reviewer (YZ).

Statistical Analysis

The pooled survival data were measured using the HR and 95% CI. Some HRs and 95% CIs were extracted from Kaplan–Meier curves using Engauge Digitizer (version 4.1). Statistical heterogeneity was evaluated using the chi-square test and I² statistics. Subgroup analysis was conducted to identify the source of heterogeneity. The random-effects model was used by default because of the nature of the included studies. The estimated results of the fixed-effects model are also provided for reference. Sensitivity analysis was performed to validate the stability of the model by sequentially omitting each study. Potential publication bias was assessed using the Begg’s and Egger’s tests. Statistical analyses were performed using R software 3.6.1 (R Project for Statistical Computing) with the meta package (4.13-0) (13).

Abbreviations: GIST, gastrointestinal stromal tumor; R1, microscopically positive resection margin; R0, microscopically negative resection margin; DFS, disease-free survival; OS, overall survival; ESMO, European Society for Medical Oncology; NOS, Newcastle–Ottawa Quality Assessment Scale; RCT, Randomized Controlled Trial.
two-sided $P < 0.05$ was considered significant. The GRADE profiler software (version 3.6) was used to estimate the level of evidence (14).

**RESULTS**

**Eligible Studies and Characteristics**

As shown in Figure 1A, 960 relevant publications were identified in the literature search. After screening and assessment, a total of 20 eligible studies (6, 7, 9, 12, 15–30) with 6,465 patients were included in this meta-analysis (Table 1). In their studies, McCarter and Cavnar analyzed two sub-series of patients with GIST with or without adjuvant Imatinib. Therefore, the final analysis involved 22 series from 20 studies. There were 5,662 patients who underwent R0 resection, and 803 patients who underwent R1 resection. A total of 915 patients experienced recurrence after R0 resection, while 159 patients who underwent R1 resection experienced recurrence. Adjuvant Imatinib was prescribed to patients in 13 studies. The NOS scores of the studies ranged from seven to eight, indicating their relatively high quality of methodology. The DFS and OS of GIST between R1 and R0 resection were compared, and the subgroup analyses, according to study type, use of adjuvant Imatinib, and tumor site (Figure 1B).

**Disease-Free Survival**

As shown in Figure 2, DFS data between R1 and R0 resection were available in 17 studies (19 series). R1 resection was associated with poor DFS compared with R0 resection (HR: 1.40, 95% CI: 1.16–1.70; reference: R0), which was consistent with the estimated results of the fixed-effects model (HR: 1.41, 95% CI: 1.18–1.67; reference: R0), indicating a lack of heterogeneity among studies ($P = 0.35$, $I^2 = 8$%). Sensitivity

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**FIGURE 1** | Flow chart of (A) search strategy and (B) study design.
Two of the 17 studies (three series) analyzed data from randomized controlled trials (RCT) and the remaining 15 were observational studies. Thus, subgroup analysis according to the type of study (observational study vs. RCT, Figure 2A) was performed. The results showed that R1 resection was related to poor DFS in the subgroup of observational studies (HR: 1.47, 95% CI: 1.26–2.09; P = 0.48, I² = 0%; reference: R0) but not in subgroup of RCT (HR: 1.29, 95% CI: 0.97–1.93; I² = 0%; reference: R0). However, patients of two series of the three in the subgroup analyzing data from RCTs received adjuvant Imatinib.

Thus, another subgroup analysis was performed according to the use of adjuvant Imatinib (Figure 2B). R1 resection was correlated with poor DFS compared with R0 resection (HR: 1.62, 95% CI: 1.26–2.09; P = 0.48, I² = 0%; reference: R0) in the subgroup without adjuvant Imatinib, while the status of resection margin had no significant impact on DFS in the adjuvant Imatinib subgroup (HR: 1.23, 95% CI: 0.95–1.60; P = 0.38, I² = 6%; reference: R0).

Tumor site is another key prognostic factor for GISTs. The eligible studies were categorized into three subgroups: stomach, rectum, and mixed sites. The mixed sites included studies that analyzed more than one tumor site. The results of this subgroup analysis (Figure 3A) showed that R1 was associated with poor DFS in all three subgroups (stomach: HR: 2.35, 95% CI: 1.15–5.02, I² = 0%; reference: R0; rectum: HR: 3.79, 95% CI: 1.27–11.31; I² = 0%; reference: R0; mixed sites: HR: 1.32, 95% CI: 1.10–1.58; I² = 0%; reference: R0). The results differed when tumor site and Imatinib use were both taken into consideration (Figure 3B). For gastric GIST patients, margin status had no significant influence on DFS regardless of the use of adjuvant Imatinib (without Imatinib: HR: 1.14, 95% CI: 0.76–1.72; I² = 0%; reference: R0; with Imatinib: HR: 1.23, 95% CI: 0.86–1.77; I² = 0%; reference: R0). However, a relatively high heterogeneity was observed in the gastric subgroup without adjuvant Imatinib (P =
FIGURE 2 | Forest plots illustrating disease-free survival between R1 and R0 margins. Subgroup analysis according to (A) study type and (B) use of imatinib.

| A | Study or Subgroup | TE | SE | Fixed (random) | Hazard Ratio | 95% CI Fixed (random) | Hazard Ratio 95% CI Fixed (random) | X2 (p value) |
|---|-----------------|----|----|----------------|-------------|-----------------------|-----------------------------------|------------|
| Subgroup | Type of observational study | | | | | | | |
| Pros 2001 | 0.36 0.0330 | 1.1 | 1.4 | 1.40 (0.92, 2.10) | | | |
| Rulkowski 2007 | 0.48 0.1911 | 21.0 | 18.7 | 1.63 (0.81, 3.26) | | | |
| Halkin 2008 | 1.11 0.0303 | 2.2 | 2.0 | 3.03 (0.86, 10.63) | | | |
| Maciejewski 2008 | 0.21 0.0706 | 4.4 | 3.6 | 2.40 (1.21, 4.75) | | | |
| Cartier 2012 | 0.58 0.2468 | 0.4 | 0.3 | 0.31 (0.12, 0.87) | | | |
| Total (random, 95% CI) | — | 5.2 | 4.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |
| Total (random, 95% CI) | — | 4.1 | 3.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |
| Subgroup | Use of adjuvant Imatinib | | | | | | | |
| Pros 2001 | 0.36 0.0330 | 1.1 | 1.4 | 1.40 (0.92, 2.10) | | | |
| Rulkowski 2007 | 0.48 0.1911 | 21.0 | 18.7 | 1.63 (0.81, 3.26) | | | |
| Halkin 2008 | 1.11 0.0303 | 2.2 | 2.0 | 3.03 (0.86, 10.63) | | | |
| Maciejewski 2008 | 0.21 0.0706 | 4.4 | 3.6 | 2.40 (1.21, 4.75) | | | |
| Cartier 2012 | 0.58 0.2468 | 0.4 | 0.3 | 0.31 (0.12, 0.87) | | | |
| Total (random, 95% CI) | — | 5.2 | 4.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |
| Total (random, 95% CI) | — | 4.1 | 3.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |

FIGURE 3 | Forest plots illustrating disease-free survival between R1 and R0 margins. Subgroup analysis according to (A) tumor site and (B) combination of tumor site and use of imatinib.

| A | Study or Subgroup | TE | SE | Fixed (random) | Hazard Ratio | 95% CI Fixed (random) | Hazard Ratio 95% CI Fixed (random) | X2 (p value) |
|---|-----------------|----|----|----------------|-------------|-----------------------|-----------------------------------|------------|
| Subgroup | Site of diagnosis | | | | | | | |
| Pros 2001 | 0.36 0.0330 | 1.1 | 1.4 | 1.40 (0.92, 2.10) | | | |
| Rulkowski 2007 | 0.48 0.1911 | 21.0 | 18.7 | 1.63 (0.81, 3.26) | | | |
| Halkin 2008 | 1.11 0.0303 | 2.2 | 2.0 | 3.03 (0.86, 10.63) | | | |
| Maciejewski 2008 | 0.21 0.0706 | 4.4 | 3.6 | 2.40 (1.21, 4.75) | | | |
| Cartier 2012 | 0.58 0.2468 | 0.4 | 0.3 | 0.31 (0.12, 0.87) | | | |
| Total (random, 95% CI) | — | 5.2 | 4.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |
| Total (random, 95% CI) | — | 4.1 | 3.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |
| Subgroup | Combination of tumor site and use of imatinib | | | | | | | |
| Pros 2001 | 0.36 0.0330 | 1.1 | 1.4 | 1.40 (0.92, 2.10) | | | |
| Rulkowski 2007 | 0.48 0.1911 | 21.0 | 18.7 | 1.63 (0.81, 3.26) | | | |
| Halkin 2008 | 1.11 0.0303 | 2.2 | 2.0 | 3.03 (0.86, 10.63) | | | |
| Maciejewski 2008 | 0.21 0.0706 | 4.4 | 3.6 | 2.40 (1.21, 4.75) | | | |
| Cartier 2012 | 0.58 0.2468 | 0.4 | 0.3 | 0.31 (0.12, 0.87) | | | |
| Total (random, 95% CI) | — | 5.2 | 4.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |
| Total (random, 95% CI) | — | 4.1 | 3.8 | 3.96 (1.45, 10.33) | | | | 0.10 (0.76, 0.90) |
0.16, $I^2 = 50\%$), which made the result of this subgroup less reliable. Notably, rectal GIST patients with R1 resection had poor DFS even when they received adjuvant Imatinib (HR: 3.79, 95% CI: 1.27–11.31; $P = 0.54, I^2 = 0\%$; reference: R0). In the mixed sites group, R1 resection was correlated with poor DFS compared with R0 resection (HR: 1.55, 95% CI: 1.18–2.03; $P = 0.58, I^2 = 0\%$; reference: R0) for patients without adjuvant Imatinib, while the status of resection margin did not impact DFS for patients receiving adjuvant Imatinib (HR: 1.15, 95% CI: 0.90–1.48; $P = 0.47, I^2 = 0\%$; reference: R0).

**Overall Survival**

Six studies that analyzed the OS were included. Patients who underwent R1 resection had similar OS compared with R0 resection (HR: 1.24, 95% CI: 0.82–1.86; $P = 0.61, I^2 = 0\%$), regardless of whether they received adjuvant Imatinib (HR: 1.09, 95% CI: 0.69–1.70; $P = 0.50, I^2 = 0\%$) or not (HR: 2.25, 95% CI: 0.86–5.89; $P = 0.80, I^2 = 0\%$) (Figure 4). The estimated results did not significantly differ after omitting each study sequentially, indicating the stability of the model (Supplementary Figure 1B).

**Publication Bias and GRADE Quality of Evidence**

As shown in Figure 5, the funnel plot and Egger’s test ($P = 0.84$) indicated that no potential publication bias was detected in the DFS data. No asymmetry was observed in the funnel plot of OS. Egger’s test was not performed for OS because of the relatively small number of studies ($n = 6$). The GRADE evidence profiles of the two indicators (DFS and OS) are presented in Table 2.

**DISCUSSION**

The present study found that R1 resection was associated with poor DFS for primary GISTs. Subgroup analysis was performed according to study type, use of adjuvant Imatinib, and tumor site. DFS did not worsen for patients who underwent R1 resection in the subgroup of RCT. However, patients of two of the three series in the RCT subgroup received adjuvant Imatinib. To illustrate this point, in the subgroup analysis of the use of adjuvant Imatinib, the negative influence of R1 resection on DFS was attenuated by adjuvant Imatinib. Similar effect of adjuvant Imatinib in DFS was observed in the subgroup of gastric GISTs. Rectal GIST patients who underwent R1 resection had poor DFS even when they received adjuvant Imatinib. Patients who underwent R1 resection had similar OS compared with those underwent R0 resection regardless of the use of adjuvant Imatinib.

Although surgical margin was removed from the 2014 edition of the European Society for Medical Oncology (ESMO) guidelines (31) as a prognostic factor for GIST, debates around this point have not diminished. Consistent with this, a recent study evaluating 371 cases...
of GIST that were all endoscopically resected and the majority of which were very low or low risk, showed that the R1 margin was not associated with a higher rate of recurrence of GIST. The only previous meta-analysis (8) focusing on resection margins found that the difference in DFS between R1 and R0 margins disappeared in a subgroup of studies in which parts of patients received adjuvant Imatinib, which is recommended for moderate or high-risk patients according to guidelines. The current meta-analysis also found that R1 resection was associated with poor DFS of GISTs, but this negative effect disappeared with use of adjuvant Imatinib. That is to say, in the presence of adjuvant Imatinib, R1 did not negatively impact the DFS of GISTs.

However, the Imatinib in these studies was not specifically given to those who had R1 margins, and the mechanism by which Imatinib attenuated the negative survival impact of R1 requires further exploration. Interestingly, Shannon et al. (27) in their study found that the R1 resection margin was correlated with larger tumor size, which means more aggressive tumor biology that leads to poor prognosis. These results raise the question of whether the prognostic difference is actually caused by the difference in risk factors collinear with the R1 margin rather than the margin status itself. To confirm this point of view, Gronchi et al. (9) analyzed 908 GIST patients from a randomized trial and compared survival between R1 and R0 margins stratified by treatment arm (with or without adjuvant Imatinib). The results showed that when tumor rupture was excluded, the R1 margin was not related to worse relapse-free survival and OS in either arm. The current estimated effect of the R1 margin on the OS of GIST was consistent with this result. However, it could not be simply concluded that margin status did not need to be considered in the decision-making for postoperative treatment of GIST.

Further subgroup analysis of this meta-analysis according to tumor site and use of adjuvant Imatinib showed that gastric GISTs with R1 margin had poor DFS which was attenuated in the subgroup of adjuvant Imatinib. Notably, R1 margin was associated with poor DFS of rectal GISTs that even received adjuvant Imatinib. The relatively lower malignancy of GISTs in the stomach (1, 32) and higher aggressiveness in the rectum (33, 34) might contribute to these results, which require further investigation focusing on the impact of R1 on the survival of GISTs at different sites. It is clear that the resection margin should not be sacrificed to preserve the organ for at least rectal GISTs. Neo-Imatinib treatment has been reported to reduce the rate of positive margins and is associated with a higher rate of anal preservation for rectal GISTs (35). However, a study by Cavnar_Neo-IM 2020, in which patients all received neo-Imatinib, showed that reduction of tumor size after neo-Imatinib occurred in only 40% of patients and was not associated with better oncologic outcomes. The sensitivity analysis

### TABLE 2 | GRADE profile evidence.

| Indicators | Quality assessment | N. of patients | Effect | Quality | Importance |
|------------|--------------------|----------------|--------|---------|------------|
|            | N. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | R1 | R0 | Relative (95% CI) |         |            |
| DFS        | 17 | observational studies* | not serious | not serious | not serious | not serious | Tumor site might influence the effect of R1 | none | 719 | 3,506 | HR 1.40 (1.16–1.70) | ◊◊◊◊ | moderate |
| OS         | 6 | observational studies** | not serious | not serious | not serious | not serious | none | 185 | 3,038 | HR 1.24 (0.82–1.86) | ◊◊ | low |

*Including two observational studies that analyzed data from two RCTs. **Including one observational study that analyzed data from an RCT.
confirmed that omitting this study did not differ from the estimated OS results in the current study. Nevertheless, neo-Imatinib is still recommended for patients with a high potential risk of incomplete resection evaluated preoperatively. Additional attention and treatment are warranted for rectal GISTs when R1 margin occurs.

The current study has some limitations. First, the majority of the included studies were retrospectively designed such that bias was inevitable in the process of this meta-analysis. Second, adjuvant Imatinib was not given specifically to those who experienced R1 margin, so the mechanism of Imatinib attenuating the negative survival impact of R1 needs further exploration. Third, a relatively high heterogeneity was observed in the gastric subgroup without adjuvant Imatinib ($P = 0.16, I^2 = 50\%$), which makes the result of this subgroup less reliable and requires further exploration. Fourth, risk factors that are collinear with the R1 margin were not analyzed in the current study. In summary, further high-quality case-controlled observational trials with a balanced baseline are needed.

Conclusions
In comparison with R0 resection, R1 was associated with poor DFS for primary GISTs, which was attenuated by adjuvant therapy with Imatinib. A similar effect of adjuvant Imatinib was observed in the gastric GISTs subgroup. However, rectal GIST patients with R1 resection had poor DFS even when they received adjuvant Imatinib, which suggests that these patients require further investigation. Patients who underwent R1 resection had similar OS compared with those undergone R0 resection regardless of the use of adjuvant Imatinib.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

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AUTHOR CONTRIBUTIONS
Concept and design: WK and FF. Literature search and extracting of data: ZL, YZ, HY, XG and JZ. Analyzing and interpretation of data: ZL, SL and ZZ. Drafting of the manuscript: ZL. Critical revision of the manuscript: XY and JY. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.679115/full#supplementary-material

Supplementary Figure 1 | Sensitivity analysis of (A) disease-free survival and (B) overall survival.
