Type: Original Research

Title: Feasibility of Laparoscopic Surgery for Large Gastric Gastrointestinal Stromal Tumors: Systematic Review and Meta-analysis

Running title: Feasibility of Laparoscopic Surgery for Large Gastric Gastrointestinal Stromal Tumors

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Abstract

**Background:** Surgical resection of gastric gastrointestinal stromal tumors (GISTs) via laparoscopy is the gold standard of treatment, but an open laparotomy is the preferred mode of treatment if the patient is unstable. This study aims at comparing the feasibility and safety of laparoscopic versus open resection for gastric gastrointestinal stromal tumors (GISTs) larger than 5 cm.

**Methods:** A systematic search was performed over different medical databases to identify general surgery studies, which studied the outcome of the Laparoscopic group versus the open surgery group of large GIST patients. Further, a meta-analysis was performed on blood loss and length of hospital stay (LOS) as primary efficacy outcomes and overall complications and recurrence rates as secondary safety outcomes.

**Results:** Nine studies were identified involving 564 patients, 274 patients in the Laparoscopic group, and 290 patients in the open surgery group. Our meta-analysis analysis showed a highly significant decrease in mean blood loss, LOS and complications rate in the laparoscopic group compared to the open surgery group (p < 0.05), respectively. However, we also found a non-significant difference in the overall recurrence rate (p > 0.05).

**Conclusion:** To conclude, the laparoscopic approach was associated with decreased length of stay, a trend to less blood loss, and common complications compared with the open surgical approach, but there was no significant difference between both groups according to tumor recurrence.

**Keywords:** Laparoscopic surgery, large, gist.
Introduction

GISTs (gastrointestinal stromal tumors) are uncommon gastrointestinal neoplasms with a high rate of malignant transformation [1]. GISTs were thought to originate in the gastrointestinal tract's mesenchymal cells (GIT) [2]. As a result of tumor rupture and intraperitoneal bleeding, GISTs can induce various symptoms ranging from vague abdominal pain to peritonitis. Other modes of presentation include abdominal fullness, early satiety, weakness, and fatigue secondary to anemia from occult gastrointestinal bleeding [3]. The diagnosis of GIST necessitates a high index of suspicion due to the wide variety of symptoms and rarity of the condition. Therefore, a contrast-enhanced CT scan of the abdomen and pelvis is the most common way to diagnose and assess the degree of disease [3]. Although GISTs are considered rare tumors, the actual prevalence is unknown because most GISTs are identified by chance. Because traditional chemotherapy and radiation are ineffective against GISTs, surgical excision has traditionally been the treatment of choice [4]. Surgical resection of GISTs via laparoscopy is the gold standard of treatment, but if the patient is unstable, an open laparotomy is the preferred mode of treatment [5]. The therapy of malignant cancers has changed dramatically since discovering mutations linked to them. Imatinib mesylate, a selective tyrosine kinase receptor inhibitor (TKI), is used as an adjuvant or neoadjuvant treatment for GISTs to reduce morbidity and mortality. Sunitinib and regorafenib are effective second-line TKIs due to rising resistance [6]. This work aims at comparing the safety and feasibility of laparoscopic versus open resection for gastric gastrointestinal stromal tumors (GISTs) larger than 5 cm.
Subjects and methods:

The present study followed (PRISMA) statement guidelines [7]. Basic searching was done using PubMed, Cochrane library, and Google scholar using the following keywords: Laparoscopic Surgery, Large, and GIST. Outcome measures for the study included blood loss and length of hospital stay (LOS) as primary efficacy outcomes and overall complications and recurrence rates as secondary safety outcomes. Inclusion criteria comprised English studies animal or non-English studies or articles describing small GIST patients (< 5 cm) were excluded. At last, a total of 230 records were obtained of which 165 were excluded because of the title; 65 articles are searched for eligibility by full-text review; 21 articles could not be accessed; 19 studies were reviews and case reports; the desired procedure was not used in 16 studies. The studies, which met all inclusion criteria, were nine studies. Pooled odds ratios (OR), Standard Mean Differences (SMDs), Proportions (%), with 95% confidence intervals (CI) were assessed, using statistical package (MedCalc, Belgium). According to the Q test for heterogeneity, the meta-analysis process was established via $I^2$-statistics (either the fixed-effects model or the random-effects model).

Results

The included studies were published between 2012 and 2021. All studies were retrospective in nature (Table 1). Regarding patients’ characteristics, the total number of patients comprising all included studies was 564 patients (274 patients in the Laparoscopic group, and 290 patients in the open surgery group). At the same time, their average follow-up time was (45.5 months) (Table 1). The mean tumor size was 7 cm (Table 1). The meta-analysis included nine studies comparing two different groups of patients, with a total number of patients (N= 564) (Table 1). Each outcome was measured by Standard Mean Difference (SMD, for blood loss; Length of hospital stay (LOS) odds Ratio (OR), for overall complications rate and for overall recurrence rates. Concerning the primary efficacy outcome measures, we found seven studies that reported blood loss: $I^2$ (inconsistency) was 74.8%, Q test for heterogeneity (p = 0.0006), so random-effects model was carried out; with overall SMD = -0.74 (95% CI = -1.2 to -0.28). The random-effects model of the meta-analysis process revealed a highly significant decrease in mean blood loss in the Laparoscopic group compared to the open surgery group (p = 0.002) (Figure 1). We found seven studies that reported LOS: $I^2$ (inconsistency) was 72.4%, Q test for heterogeneity (p = 0.0014), so random-effects model was carried out with overall SMD = -0.68 (95% CI = -1.1 to -0.25). The random-effects model of the meta-analysis process revealed a highly significant decrease in mean LOS in the Laparoscopic group compared to the open surgery group (p = 0.002) (Figure 2). Concerning the secondary safety outcome measures, we found five studies that reported an overall complications rate: $I^2$ (inconsistency) was 19.7%, Q test for heterogeneity (p > 0.05), so fixed-effects model was carried out; with overall OR = 0.33 (95% CI = 0.15 to 0.73). The fixed-effects model of the meta-analysis process revealed a highly significant decrease in overall complications rate in the Laparoscopic group compared to the open surgery group (p = 0.006) (Figure 3). We found six studies that reported an overall recurrence rate: $I^2$ (inconsistency) was 0%, Q test for
heterogeneity (p > 0.05), so fixed-effects model was carried out; with overall OR = 0.44 (95% CI = 0.18 to 1.09). The fixed-effects model of the meta-analysis process revealed a non-significant difference in overall recurrence rate in the Laparoscopic group compared to the open surgery group (p > 0.05) (Figure 4).

### Table 1: Patients and study characteristics:

<table>
<thead>
<tr>
<th>N</th>
<th>Author</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Tumor size (average cm)</th>
<th>Follow-up time (average months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Laparoscopic group</td>
<td>Open surgery group</td>
</tr>
<tr>
<td>1</td>
<td>Kim et al., 2012 [8]</td>
<td>Retrospective</td>
<td>38</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Lin et al., 2014 [9]</td>
<td>Retrospective</td>
<td>46</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Hsiao et al., 2015 [10]</td>
<td>Retrospective</td>
<td>36</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Piessen et al., 2015 [11]</td>
<td>Retrospective</td>
<td>183</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Takahashi et al., 2015 [12]</td>
<td>Retrospective</td>
<td>27</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Khoo et al., 2017 [13]</td>
<td>Retrospective</td>
<td>59</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>Qiu et al., 2017 [14]</td>
<td>Retrospective</td>
<td>48</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>Xiong et al., 2021 [16]</td>
<td>Retrospective</td>
<td>102</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>

*Studies arranged via publication year.

### Table 2: Summary of outcome measures in all studies:

<table>
<thead>
<tr>
<th>N</th>
<th>Author</th>
<th>Primary efficacy outcomes</th>
<th>Secondary safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood loss (ml)</td>
<td>LOS (days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laparoscopic group</td>
<td>Open surgery group</td>
</tr>
<tr>
<td>1</td>
<td>Kim et al., 2012</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>Lin et al., 2014</td>
<td>35.6</td>
<td>127.8</td>
</tr>
<tr>
<td>3</td>
<td>Hsiao et al., 2015</td>
<td>42.2</td>
<td>51.4</td>
</tr>
<tr>
<td>4</td>
<td>Piessen et al., 2015</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>Takahashi et al., 2015</td>
<td>202.5</td>
<td>255</td>
</tr>
<tr>
<td>6</td>
<td>Khoo et al., 2017</td>
<td>78.3</td>
<td>128.5</td>
</tr>
<tr>
<td>7</td>
<td>Qiu et al., 2017</td>
<td>73</td>
<td>105</td>
</tr>
<tr>
<td>8</td>
<td>Florin et al., 2020</td>
<td>50</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>Xiong et al., 2021</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>
**Figure 1:** Forest plot (blood loss).

**Figure 2:** Forest plot (LOS).
Figure 3: Forest plot (overall complications rate).

Fixed-effects model (p = 0.006)
OR (overall complications) = 0.33
Significant decreased OR in Laparoscopic group
Figure 4: Forest plot (overall recurrence rate).

Discussion
The included studies were published between 2012 and 2021. Regarding the type of included studies, all studies are retrospective. Regarding patients' characteristics, the total number of patients in all the included studies was 564 patients, 274 patients in the Laparoscopic group, and 290 patients in the open surgery group. At the same time, their average follow-up time was (45.5 months). The mean tumor size was 7 cm. Our meta-analysis included nine studies comparing two different groups of patients; with a total number of patients (N=564). We found seven studies that reported blood loss concerning the primary efficacy outcome measures. Using the Random-effects model of the meta-analysis process revealed a highly significant decrease in mean blood loss in the Laparoscopic group compared to the open surgery group (p = 0.002), which came in agreement with Q.-L. Chen et al., 2014 [17], Chi et al., 2017 [18], Z. Xiong et al., 2020 [19], Koh et al., 2013 [20], H. Xiong et al., 2017 [21] and Zheng et al., 2014 [22]. Q.-L. Chen et al., 2014 reported that Laparoscopic resection was related to decreased blood loss, an earlier time to flatus and oral food, and shorter hospital stays when compared to open surgery [17]. Chi et al., 2017 reported that the laparoscopic group had a shorter/faster operation time, intraoperative blood loss, return of bowel function and oral intake, nasogastric tube retention time, and postoperative stay than the open group [18]. Z. Xiong et al., 2020 reported that the LAP group exceeded the OPEN group significantly in blood loss, GI function recovery, and hospital stay [19]. Koh et al. 2013 reported that there was even less blood loss and a lower frequency of complications [20]. H. Xiong et al., 2017 reported that reduced surgical time, reduced blood loss, and fewer overall problems are all advantages of laparoscopic GIST excision [21]. Zheng et al., 2014 reported that The combined results revealed that in LRG, intraoperative blood loss was reduced by roughly 55 mL, and laparoscopic resection leads to a faster recovery and return to everyday life [22]. We found seven studies that reported LOS concerning the primary efficacy outcome measures. Using Random-effects model of the meta-analysis process revealed a highly significant decrease in mean LOS in the Laparoscopic group compared to the open surgery group (p = 0.002), which came in the agreement of Melstrom et al., 2012 [23], Ye et al., 2017 [24], De Vogelaere et al., 2013 [25] and Hu et al., 2016 [26]. Melstrom et al., 2012 reported that the length of stay after surgery in the laparoscopic group was dramatically reduced. There were two (11.8 percent) laparoscopic postoperative complications, including pneumonia in one patient and atrial fibrillation in another. There were four (13.8 percent) problems in the open group, with two patients having wound infections, one with a deep venous thrombus, and one with transfusion-dependent bleeding [23]. Ye et al., 2017 reported that Short-term surgical results in the LAP group were improved, including postoperative time to oral intake (P < 0.001) and postoperative time to first flatus (P < 0.001). Furthermore, the LAP group had fewer surgical problems (P0.01) and shorter hospital stays (P < 0.001). The advantage of LAP is that it has a smaller incision, which means less pain and bed rest, which speeds up recovery [24]. De Vogelaere et al., 2013 reported that the 30-day morbidity rate was reduced (2.7 percent vs. 18.9 percent; p = 0.077). The duration of stay was significantly shorter (median seven vs. 14 days; p = 0.007) after LAP resection. After OPEN resection, the operational mortality was 12.5%, but there was no operative mortality after LAP (p = 0.087) [25]. Hu et al., 2016 reported that Another advantage of laparoscopy is that, according to our findings, laparoscopic resection is linked to a 24–36 percent reduction in LOS, even after controlling for patient and tumor characteristics [26]. We found five studies that reported an overall complication rate concerning the secondary safety outcome measures. Using Fixed-effects model of the meta-
analysis process revealed a non-significant difference in overall recurrence rate in the Laparoscopic group compared to the open surgery group (p > 0.05), which came in the agreement of Ye et al., 2017 [24], Kasetsermwiriya et al., 2014 [27], Lian et al., 2017 [28] and Q.-F. Chen et al., 2016 [29]. Ye et al., 2017 reported that When the tumor was more extensive than 5 cm, no significant differences in recurrence rates or long-term disease-free survival were identified between the two groups [24]. Kasetsermwiriya et al., 2014 reported that Most cases of Recurrence or metastasis had higher-risk profiles, and no port metastasis was seen, implying that tumor recurrence is not associated with the surgical method [27]. Lian et al., 2017 reported that laparoscopy is a safe and viable option for stomach GISTs greater than 5 cm. In addition, the meta-analysis demonstrated that patients who had a laparoscopic resection had a decreased recurrence rate, but there was no statistically significant difference between the two groups [28]. Q.-F. Chen et al., 2016 reported that Recurrence occurred in 9 (6.8%) and 11 (13.6%) cases in the LAP and OPEN groups, respectively, before propensity-score matching (PSM). The LAP and OPEN groups experienced Recurrence in 6 (8.5%) and 5 (7.0%) cases, respectively, after PSM. These rates were not significantly different [29]. On the other hand, our result came in disagreement with Pelletier et al., 2015 who reported that Patients who received LAP had a lower rate of Recurrence. The authors speculated that this was related to the shorter follow-up duration in this group [30].

**Conclusion**

To conclude, the laparoscopic approach was associated with decreased length of stay, a trend to less blood loss, and common complications compared with the open surgical approach. Still, there was no significant difference between both groups according to tumor recurrence.

**List of abbreviations**

CI Confidence interval.

OR Odds ratio

PRISMA Preferred reporting items for systematic reviews and meta-analyses.

RCT Randomized controlled trial

SMD Standard mean difference.

**Conflict of Interests:**

The authors declare that there is no conflict of interest regarding the publication of this article.

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Not applicable

Ethical Approval

Not applicable

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