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Systematic review and meta-analysis of safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors of the stomach

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Abstract
Objective To evaluate the safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors (GISTs) of the stomach with systematic review and meta-analysis.
Methods The literature database before March, 2014 was extensively searched to retrieve the comparative studies of laparoscopic (LAP) and open resection (OPEN) for GISTs with a relevance of study goal. The inclusion and exclusion criteria were formulated. After a quality evaluation, the data were extracted. The Cochrane collaboration RevMan5.1 version software was used for meta-analysis.
Results There are nineteen studies meeting the inclusion criteria for meta-analysis. The total sample size of these studies was 1,060 cases. The operation time was similar between the two groups [weighted mean difference (WMD) −7.20 min, 95 % confidence interval (CI) −25.65 to 11.25, $P = 0.44$)]. Compared to OPEN, however, LAP experienced less blood loss (WMD −54.21 ml, 95 % CI −82.65 to −25.77, $P < 0.01$), earlier time to flatus (WMD −1.34 days, 95 % CI −1.62 to −1.06, $P < 0.01$) and oral diet (WMD −1.80 days, 95 % CI −2.18 to −1.42, $P < 0.01$), shorter hospital stay (WMD −3.68 days, 95 % CI −4.52 to −2.85, $P < 0.01$) and decrease in overall complications [relative risk (RR) 0.51, 95 % CI 0.32–0.80, $P < 0.01$)]. In addition, the long-term follow-up result shows that there is no significant difference in the two groups of patients.
Conclusion Laparoscopic resection for gastric GISTs is a safe and feasible procedure with less blood loss, less overall complications and quicker recovery. The long-term survival situation of patients mainly depends on the tumor itself risk, and laparoscopic surgery will not increase the risks of tumor relapse and metastasis.

Keywords Gastrointestinal stromal tumor · Gastrectomy · Laparoscopy · Complications · Meta-analysis

Gastrointestinal stromal tumors (GISTs), which are often characterized by high expression of KIT [1, 2], are the most common mesenchymal tumor in the gastrointestinal tract. GISTs most frequently occurs in the stomach (60 %) in the form of submucosal tumors, followed by jejunum or ileum (30 %), duodenum (5 %), colon and rectum (<5 %), esophagus (<1 %) and appendix (<1 %) [2]. GISTs have malignant potential, and it is reported that recurrence of GISTs often occurs at the peritoneal surface or liver [3]. Because gastric gastrointestinal stromal tumor is not completely distinguished from other submucosal tumors, a surgical excisional biopsy is recommended for tumors >2 cm. The surgical principles of gastrointestinal stromal tumor are composed of an R0 resection with a normal mucosa margin, no systemic lymph node dissection and avoidance of rupture, which results in peritoneal seeding even in cases with otherwise low risk profiles.

Since the development of minimally invasive surgical approaches, laparoscopic surgery (LAP) for gastrointestinal tumors has evolved rapidly over the past decade. Various types of laparoscopic approaches for GISTs have been described, including wedge resection of the stomach,

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intragastric tumor resection and combined endoscopic-laparoscopic resection [4–7]. Several case series have proved the safety and feasibility of LAP for gastric GISTs; however, the oncologic benefits of LAP for GISTs have not been widely reported and the sample size of those researches were relatively small. Furthermore, there is no randomized controlled trials (RCTs) yet, which compares outcomes between LAP and the open approach (OPEN). Lack of RCTs may be because of the difficulty encountered in conducting a large RCT in clinical practice. Therefore, we present a systematic review of the literature and a comparative effectiveness analysis of LAP versus OPEN. Using meta-analytic techniques, we set out to evaluate the surgical and oncologic outcomes of patients undergoing either procedure as reported in the published literature.

Methods

Search strategy

Systematic searches of PubMed, Embase, Cochrane Library, and Web of Science were performed to identify articles published up to March 2014 that compared LAP and OPEN. The search terms "gastrointestinal stromal tumor", "GIST", "laparoscopic", "laparoscopy", "gastrectomy" and "gastric resection" were utilized. The links of every search result and all references in the original articles identified were reviewed to identify the additional literature that was not indexed. The language of the articles was limited to English and Chinese according to the reviewers' language competence.

Eligibility criteria

Studies meeting the following criteria were included: Comparative, peer-reviewed studies of LAP versus OPEN for patients with GISTs for which the full text of the article was available. If two studies from the same group were identified, the most recent study or that including more subjects was selected unless the reports were from different time periods. The papers containing any of the following were excluded: (1) tumors out of the stomach such as jejunum or ileum; (2) studies in which <2 interested indexes were reported, or it was difficult to calculate these from the results.

Data extraction and quality assessment

Two authors independently extracted the data using a unified datasheet, and decided upon the controversial issues through discussion. Extracted data included the following: author, study period, geographical region, number of patients, operation time, blood loss, time to flatus, time to oral intake, length of hospital stay, morbidity, mortality and long-term outcomes. Postoperative complications were classified as medical (cardiovascular, respiratory, or metabolic events; nonsurgical infections; deep venous thrombosis; and pulmonary embolism) or surgical (any anastomotic leakage or fistula, any complication that required reoperation, intra-abdominal collections, wound complications, bleeding events, pancreatitis, ileus, delayed gastric emptying, and anastomotic stricture). This classification system is based on the Memorial Sloan–Kettering Cancer Center complication reporting system [8]. If the study provided medians and ranges instead of means and standard deviations (SDs), we estimated the means and SDs as described by Hozo et al. [9]. The qualities of the included studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). This scale varies from zero to nine stars: Studies with a score equal to or higher than six were considered methodologically sound.

Statistical analysis

Continuous variables were assessed using weighted mean difference (WMD), and dichotomous variables were analyzed using the risk ratio (RR). Statistical heterogeneity, which indicated between-study variance, was evaluated according to the Higgins I^2 statistic [10]. To account for clinical heterogeneity, which refers to diversity in a sense that is relevant for clinical situations, we used the random-effects model based on DerSimonian and Laird's method. We hypothesized the outcomes of the comparison may be affected by the uneven distribution of the surgical types between the LAP and OPEN groups, especially by the relatively larger proportion of extended surgeries performed in the OPEN group. Thus, we performed a subgroup analysis of patients who underwent wedge resection in the two groups to eliminate the bias from the surgical type selection. We also conducted a subgroup analysis of studies which had comparable tumor size or risk index because the learning curve may have an impact on the operative outcomes. Potential publication bias was determined by conducting informal visual inspection of funnel plots based on the complications. Data analyses were performed using Review Manage version 5.1 (RevMan 5.1) software downloaded from Cochrane Library. $P < 0.05$ was considered statistically significant.

Results

Studies selected

A total of 628 citations were obtained from searches of the various electronic bibliographies. After the titles and abstracts were reviewed, papers without comparison of LAP and OPEN were excluded, which left 24 comparative

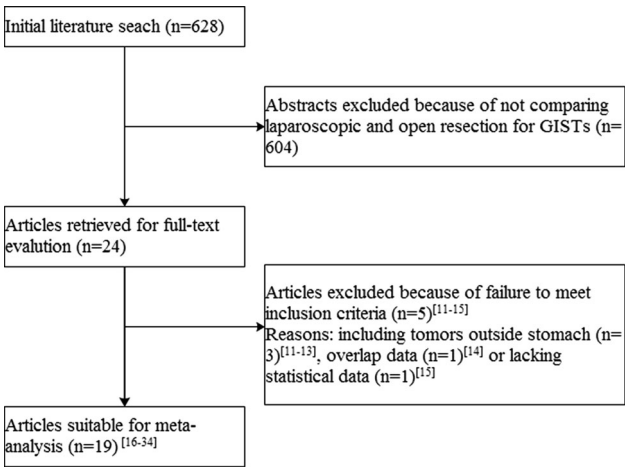


Fig. 1 Flow chart of the literature search strategies

studies, five [11–15] of which did not meet the inclusion criteria and were excluded. This left a total of nineteen observational studies [16–34], all of which were accessible in full-text format. Eighteen studies were published in English and one in Chinese. A flow chart of the search strategies, which contains reasons of excluded studies, is illustrated in Fig. 1.

Study characteristics and quality

A total of 1,060 patients were included in the analysis with 516 undergoing LAP (48.7 %) and 544 undergoing OPEN (51.3 %). They represented an international experience including data from 10 different countries or regions (4 Japan, 4 United States, 3 China, 2 Korea, 1 United Kingdom, 1 Italy, 1 Belgium, 1 Austria, 1 Singapore and 1 Taiwan). Table 1 presents the characteristics of the included studies, whereas Table 2 presents the quality assessment based on the NOS. In general, the quality of the included studies was satisfactory. According to the NOS, three out of the nineteen observational studies got 6 stars, eight articles got 7 stars, three articles got 8 stars and the remaining five got 9 stars.

Evidence from primary outcomes

Eighteen studies reported operation time [16–22, 24–34]. The present analysis showed no statistically significant difference

Table 1 Summary of studies included in the meta-analysis

Author	Region	Study design	Year	Study period	Sample size		Conversion (%)	Follow-up (month)		Recurrence	
					LAP	OPEN		LAP	OPEN	LAP	OPEN
Shimizu [16]	Japan	OCS (R)	2002	1986–2000	11	8	0	NR	NR	NR	NR
Matthews [17]	USA	OCS (R)	2002	1994–2000	21	12	NR	20	18	1	1
Ishikawa [18]	Japan	OCS (R)	2006	1993–2004	14	7	NR	60 (5–119)	61 (3–130)	2	1
Mochizuki [19]	Japan	OCS (R)	2006	2000–2004	12	10	NR	26 (6–53)	NR	0	0
Nishimura [20]	Japan	OCS (R)	2007	1993–2004	39	28	2.6	18.9 (2.6–96.4)	31.2 (4.4–121.9)	1	4
Pitsinis [21]	UK	OCS (P)	2007	2004–2006	6	7	NR	9	9	0	0
Catena [22]	Italy	OCS (P)	2008	1995–2006	21	25	NR	35 (5–58)	91 (80–136)	0	1
Silberhumer [23]	Austria	OCS (R)	2009	1998–2006	22	41	18.2	30 ± 20	41 ± 31	0	4
Goh [24]	Singapore	OCS (R)	2010	2001–2009	14	39	7.1	8 (3–60)	21 (2–72)	0	2
Karakousis [25]	USA	OCS (P)	2011	1998–2009	40	40	22.5	28 (0.3–70)	43 (0.1–139)	1	1
Dai [26]	China	OCS (R)	2011	2000–2009	18	30	NR	78	64	2	3
De Vogelaere [27]	Belgium	OCS (P)	2012	1997–2011	37	16	NR	83 (2–163)	71 (0.3–199)	0	6
Melstrom [28]	USA	OCS (P)	2012	1999–2008	17	29	5.9	32	59	0	4
Lee [29]	Korea	OCS (R)	2011	2001–2008	50	50	2	21.1 (0–64)	22.3 (0–93)	0	0
Wan [30]	China	OCS (R)	2012	2004–2011	68	88	NR	29 (4–89)	36 (4–90)	3	4
Pucci [31]	USA	OCS (P)	2012	2002–2012	57	47	1.8	NR	NR	NR	NR
Kim [32]	Korea	OCS (R)	2012	1998–2011	24	14	NR	62.6 (8.9–164.4)	58.3 (18.8–123.2)	1	3
Shu [33]	China	OCS (R)	2013	2010–2012	15	21	NR	NR	NR	NR	NR
Lee [34]	Taiwan	OCS (R)	2013	2007–2009	30	32	NR	NR	NR	NR	NR

OCS observational clinical study, *P* prospectively collected data, *R* retrospectively collected data, *NR* not reported

Table 2 Quality assessment based on the NOS for observational studies

Author	Selection (Out of 4)				Comparability (Out of 2)	Outcomes (Out of 3)			Total (Out of 9)
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at the start of the study		Assessment of outcomes	Length of follow-up	Adequacy of follow-up	
Shimizu [16]	*	*	*	*	*	*			6
Matthews [17]	*	*	*	*	**	*			7
Ishikawa [18]	*	*	*	*	*	*	*	*	8
Mochizuki [19]	*	*	*	*	**	*			7
Nishimura [20]	*	*	*	*	**	*			7
Pitsinis [21]	*	*	*	*	*	*			6
Catena [22]	*	*	*	*	**	*	*	*	9
Silberhumer [23]	*	*	*	*	*	*	*	*	8
Goh [24]	*	*	*	*	*	*			7
Karakousis [25]	*	*	*	*	**	*	*	*	9
Dai [26]	*	*	*	*	*	*	*	*	9
De Vogelaere [27]	*	*	*	*	*	*	*	*	9
Melstrom [28]	*	*	*	*	*	*	*		7
Lee [29]	*	*	*	*	**	*			7
Wan [30]	*	*	*	*	**	*	*	*	9
Pucci [31]	*	*	*	*	*	*			6
Kim [32]	*	*	*	*	*	*	*	*	8
Shu [33]	*	*	*	*	**	*			7
Lee [34]	*	*	*	*	**	*			7

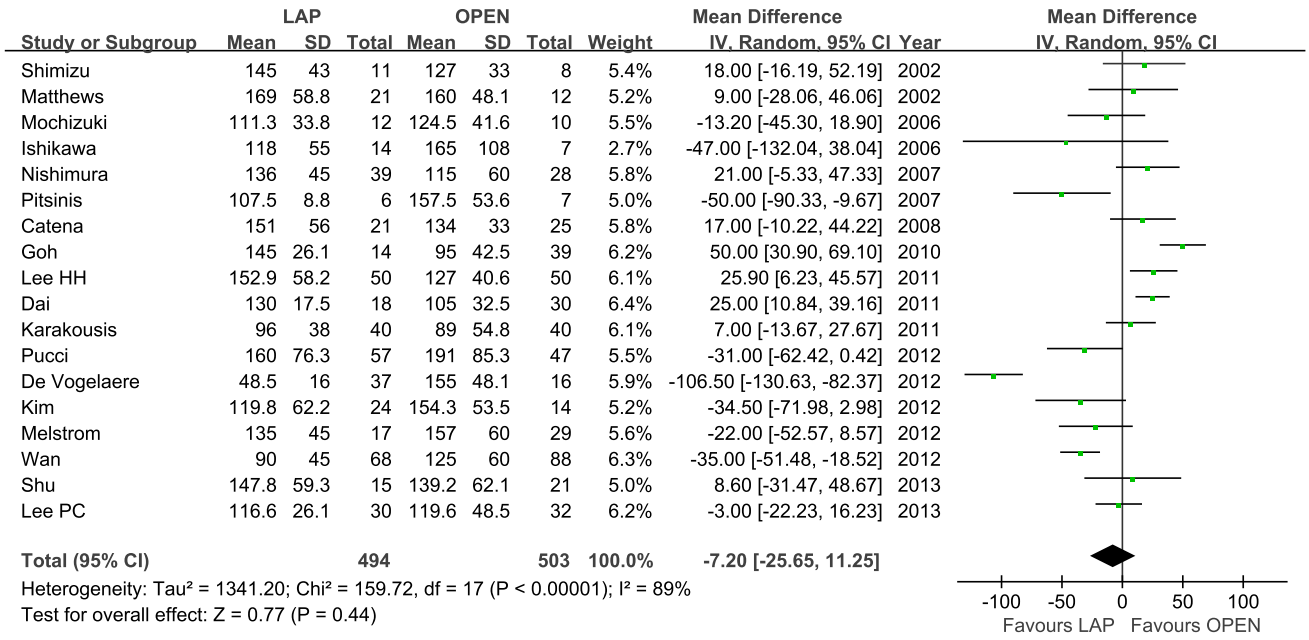


Fig. 2 Meta-analysis of the pooled data: operation time

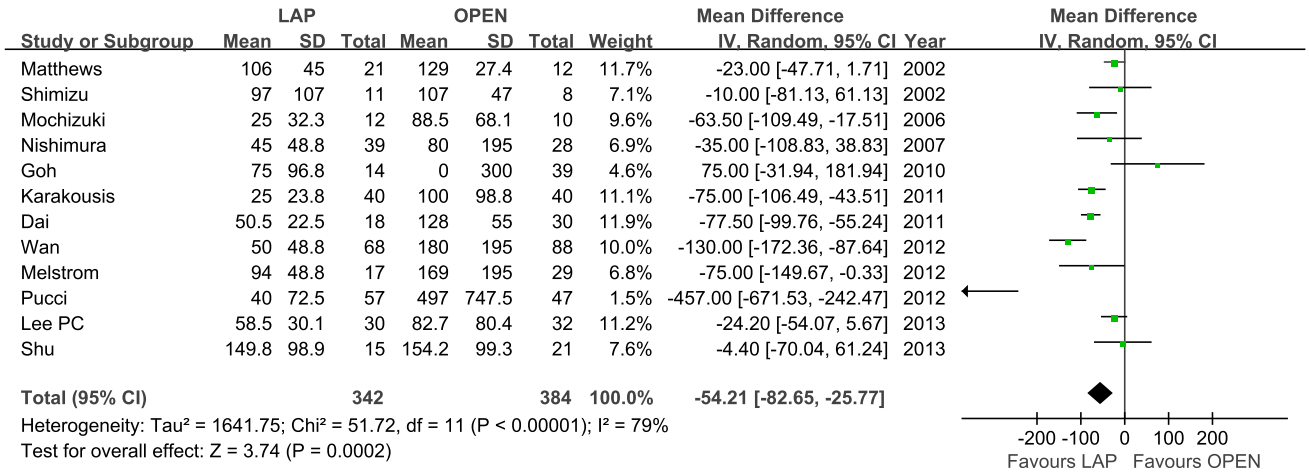


Fig. 3 Meta-analysis of the pooled data: intraoperative blood loss

in the operation time of the two groups (WMD −7.20 min; 95 % CI −25.65 to 11.25; $P = 0.44$) (Fig. 2). Twelve studies reported blood loss [16, 17, 19, 20, 24–26, 28, 30, 31, 33, 34]. Intraoperative blood loss was significantly lower in the LAP compared with the OPEN group (WMD −54.21 ml; 95 % CI −82.65 to −25.77 ml; $P < 0.01$) (Fig. 3). The outcomes also favored LAP in first flatus day (WMD −1.34 days; 95 % CI −1.62 to −1.06, $P < 0.01$) (Fig. 4) and first oral intake (WMD −1.80 days; 95 % CI −2.18 to −1.42, $P < 0.01$) (Fig. 5), which indicated a quicker recovery of the bowl function. Three studies reported shorter duration or the lower dosage of analgesic application after LAP [18, 24, 26]. Moreover, postoperative hospital day was 3.68 days shorter for LAP patients (WMD −3.68 days; 95 % CI −4.52 to −2.85, $P < 0.01$) (Fig. 6).

The rate of overall postoperative complications was significantly lower for LAP (RR 0.51, 95 % CI 0.32–0.80, $P < 0.01$) (Fig. 7). Visual inspection of the funnel plot revealed symmetry, indicating no serious publication bias (Fig. 8). After further analysis, surgical complications were similar between the two groups (RR 0.71, 95 % CI 0.36–1.39, $P = 0.31$). However, LAP was associated with a marginal reduction in medical complications (RR 0.53, 95 % CI 0.28–1.02, $P = 0.06$). The specific postoperative complications included in the studies are summarized in Table 3.

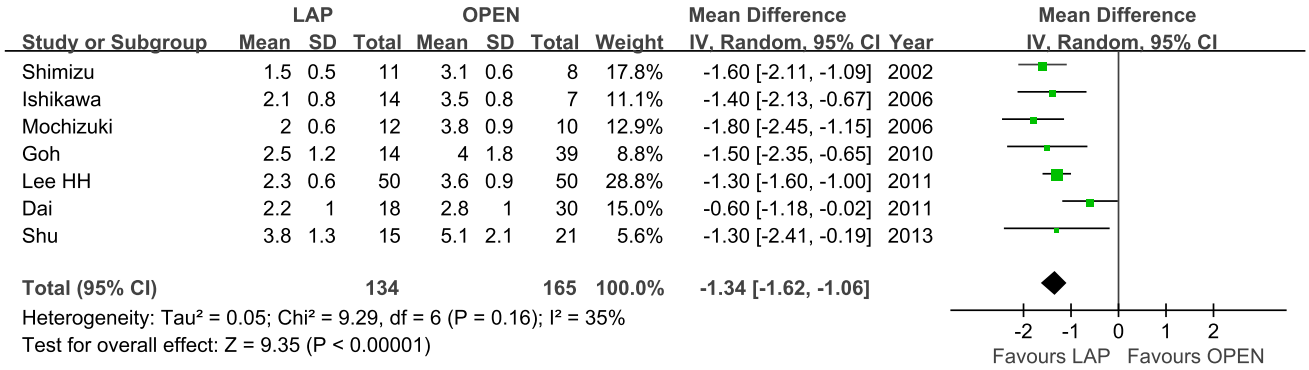


Fig. 4 Meta-analysis of the pooled data: time to first flatus

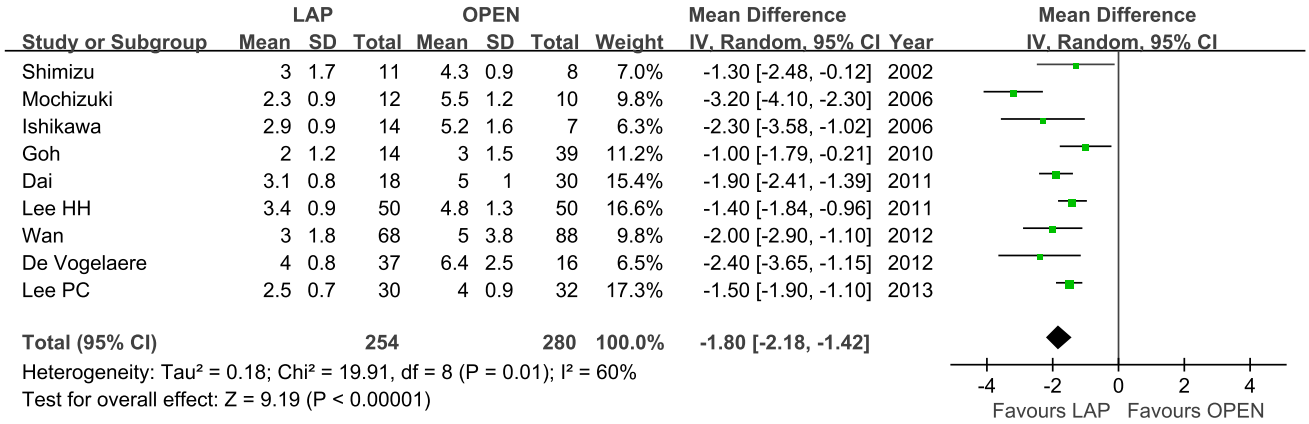
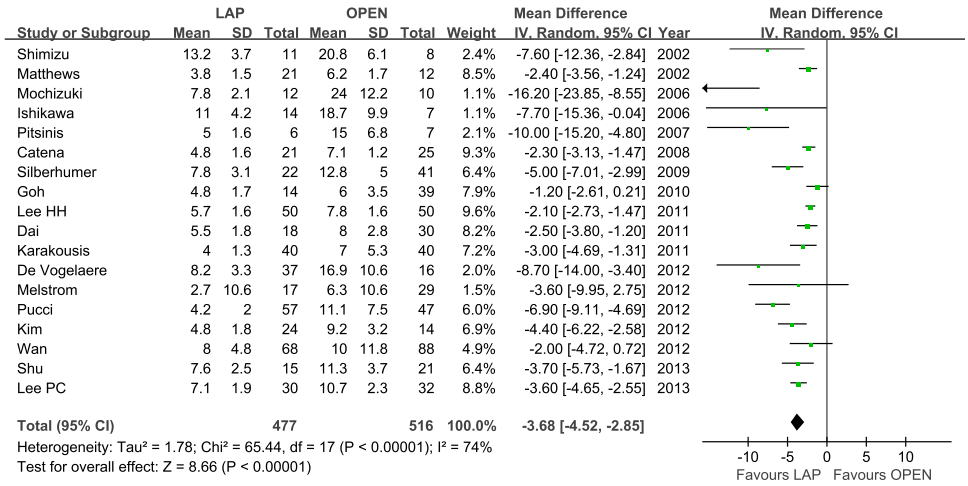


Fig. 5 Meta-analysis of the pooled data: time to oral intake

Fig. 6 Meta-analysis of the pooled data: hospital stay



Seventeen studies reported tumor size [16–20, 22–27, 29–34]. The tumor size for LAP was significantly smaller than that for OPEN from the analysis of 1,001 resections (WMD −0.93 cm; 95 % CI −1.33 to −0.53, $P < 0.01$) (Fig. 9).

During the follow-up period, tumor recurrence was observed in twelve studies [17, 18, 20, 22–28, 30, 32]. The recurrence risk in LAP was 3.3 % (11/330) and 9.3 % (32/345) in OPEN, and patients who underwent LAP were less likely than the OPEN to have recurrence (RR 0.47, 95 % CI 0.24–0.93, $P = 0.03$) (Fig. 10). The available data about recurrence patterns, specific recurrent sites and survival outcomes are summarized in Table 4.

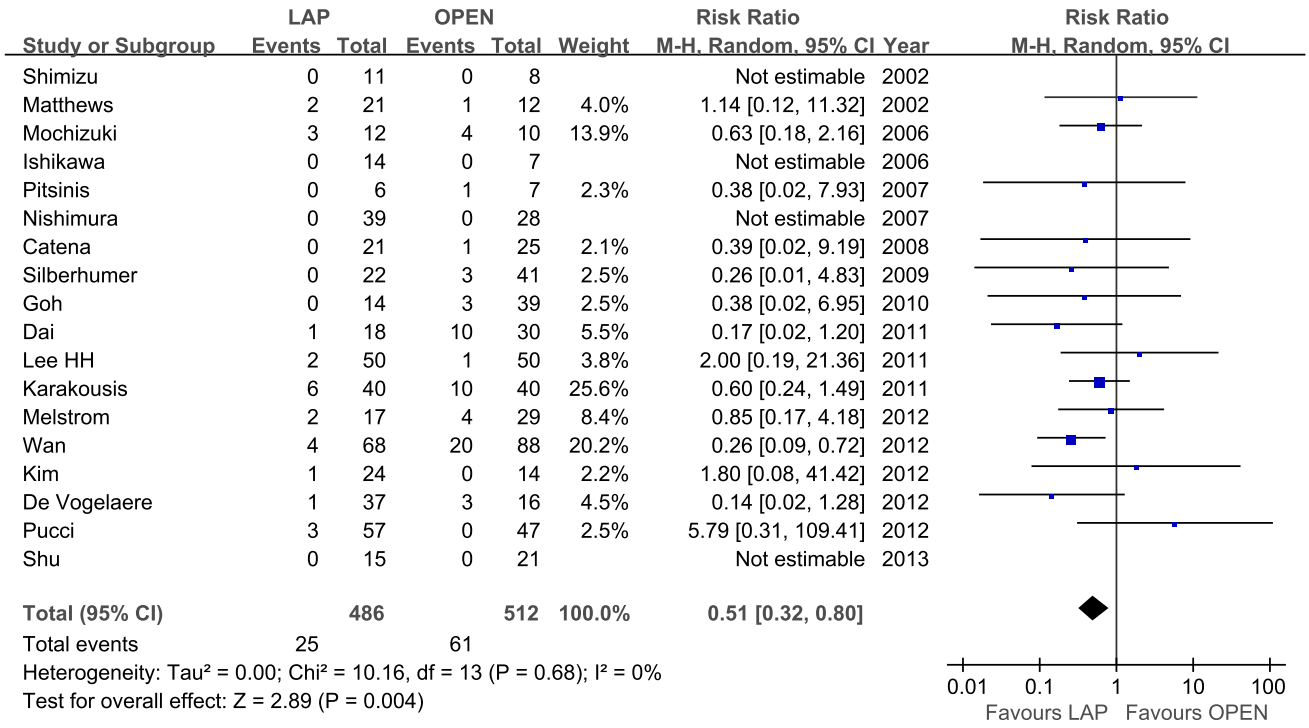


Fig. 7 Meta-analysis of the pooled data: overall complications

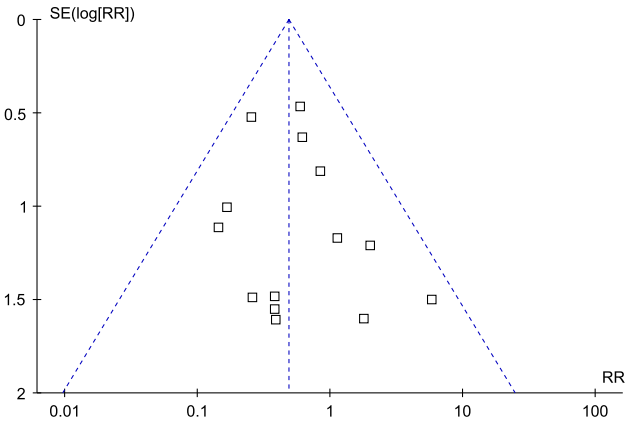


Fig. 8 Funnel plot of the overall postoperative complications

Subgroup analysis for studies of wedge resection

Seven studies used only wedge resection in both LAP and OPEN group [16, 18, 19, 22, 24, 26, 29]. Another one study provided a subgroup analysis of wedge resection with adequate data [30]. We also used it for pooled analysis. The overall effects such as operation time, blood loss, time to flatus or oral intake, hospital stay, complications and tumor size remained unchanged in subgroups. However, in this subgroup analysis, the recurrence risk in LAP was 5.4 % (7/130) and 5.5 % (9/165) in OPEN, and the difference was not significant (RR 1.01, 95 % CI 0.39–2.63, $P = 0.99$). The outcomes of subgroup analysis for studies of wedge resection are summarized in Table 5.

Subgroup analysis for studies with comparable tumor size or risk index

Eleven studies were qualified for this subgroup analysis [16, 17, 19, 20, 22, 25, 26, 29, 30, 33, 34]. Like the subgroup analysis for wedge resection, outcomes other than tumor recurrence remained unchanged. And the recurrence risk was similar between LAP and OPEN (RR 0.69, 95 % CI 0.30–1.60, $P = 0.39$). The outcomes of subgroup analysis for studies with comparable tumor size or risk index are summarized in Table 6.

Discussion

GISTs are uncommon mesenchymal tumors that arise in the wall of the gastrointestinal tract. The advent of imatinib mesylate significantly reduces the recurrence rate of GISTs, but surgery remains the mainstay of therapy for primary GISTs with no evidence of metastasis. Laparoscopic surgery is increasingly performed for surgical treatment of gastric GISTs. Although RCTs are the most ideal tool for meta-analysis, there have been no RCTs comparing laparoscopic surgery with open surgery for gastric GISTs. This may be due to the difficulties to conduct a high-quality

Table 3 Systematic review of postoperative complications

Author	Group	*n*	Total event	Specified complications
Matthews [17]	LAP	21	2	Reoperations × 2
	OPEN	12	1	Antral stenosis and stricture of gastroesophageal junction × 1
Mochizuki [19]	LAP	12	3	Pneumothrax × 1, Pneumonia × 1, Bowel injury × 1
	OPEN	10	4	(did not specified)
Pitsinis [21]	LAP	6	0	
	OPEN	7	1	Respiratory failure × 1
Catena [22]	LAP	21	0	
	OPEN	25	1	Wound infection × 1
Silberhumer [23]	LAP	22	0	
	OPEN	41	3	Catheter sepsis × 1, ileus × 1, gastrocutaneous fistula × 1
Karakousis [25]	LAP	40	6	GI bleeding × 1, leakage lead to abdominal collection × 1 (some complications did not specified)
	OPEN	40	10	Pneumonia × 1, deep venous thrombus × 1 (some complications did not specified)
Dai [26]	LAP	18	1	GI bleeding × 1
	OPEN	30	10	Leakage × 1, wound infection × 4, gastric motility dysfunction × 2, GI bleeding × 3
De Vogelaere [27]	LAP	37	1	Lung embolism × 1
	OPEN	16	3	Pneumonia × 1, pneumonia × 1, ulcer × 1
Melstrom [28]	LAP	17	2	pneumonia × 1, atrial fibrillation × 1
	OPEN	29	4	wound infection × 2, deep venous thrombus × 1, bleeding × 1
Wan [30]	LAP	68	4	wound infection × 1, gastrointestinal obstruction × 2, anastomosis site bleeding × 1
	OPEN	88	20	wound infection × 1, wound dehiscence × 1, gastrointestinal obstruction × 1, gastric motility dysfunction × 3, pulmonary infection × 4, sour regurgitation × 2, pyrexia of unknown origin × 7, cerebrovascular accident × 1

RCT to evaluate a new surgical intervention because of obstacles such as learning curve effects, ethical and cultural resistance, urgent or unexpected conditions during the operation and the relatively low incidence. Therefore, due to the unavailability of RCTs, inclusion of non-RCTs is an appropriate strategy to extend the source of evidence. In order to assess the efficacy and safety of laparoscopic surgery for gastric GISTs, we extracted relative data as much as possible and we pooled the outcome whenever possible.

The operative time in the LAP group was not longer than OPEN which is different from many other types of gastrointestinal surgery [35–37]. Because of the low frequency of lymph node metastasis, local resection of the tumor with a disease-free margin is recommended and lymphadenectomy, which is time-consuming under laparoscopy, is not generally required. As time spent on the establishment of pneumoperitoneum and the closure of the trocar incision and mini-laparotomy is likely to be shorter than the opening and closure of laparotomy, it might explain the possible fact that the LAP to be shorter than OPEN with the development of the surgical techniques and laparoscopic instruments. Operative blood loss was shown in the pooled analysis to be lower in LAP cases. The reduced length of incision wound and the application of energy-dividing devices, such as the Harmonic Scalpel and LigaSure, contribute to the reduction in blood loss. Another reason is that laparoscopy allows for the magnified view of small vessels. However, this result should be interpreted prudently for the variation in blood loss between studies was high, with heterogeneity as a result of different methods of estimating blood loss. Besides, some included studies selected patients with smaller tumors in LAP group [16, 18, 21, 23, 27, 28, 31, 32, 34] or more extensive gastrectomy or higher additional resection rate in OG group [17, 23, 27–32]. Lack of adequate matching in such results makes comparison of operative blood loss inherently flawed and at a high risk for confounding.

The postoperative morbidity is usually used to estimate the feasibility and safety of a procedure. The meta-analysis demonstrated a reduced number of complications in the LAP versus OPEN group, which may have resulted from a reduction in medical complications. It was conceivable that surgical complications were similar between groups because LAP results in the same resection extent as OPEN. And the marginally decreased medical complications could be explained by the reduced invasiveness of the laparoscopic technique and less postoperative pain. Pain after surgery was less serious in LAP than in OPEN surgery due to the shorter duration or the lower dosage of analgesic application [18, 24, 26]. The pain caused by large incision as well as the use of tension sutures and abdominal bandages after laparotomy can make it difficult for patients to cough, expectorate and perform breathing exercise effectively, thus leading to complications such as

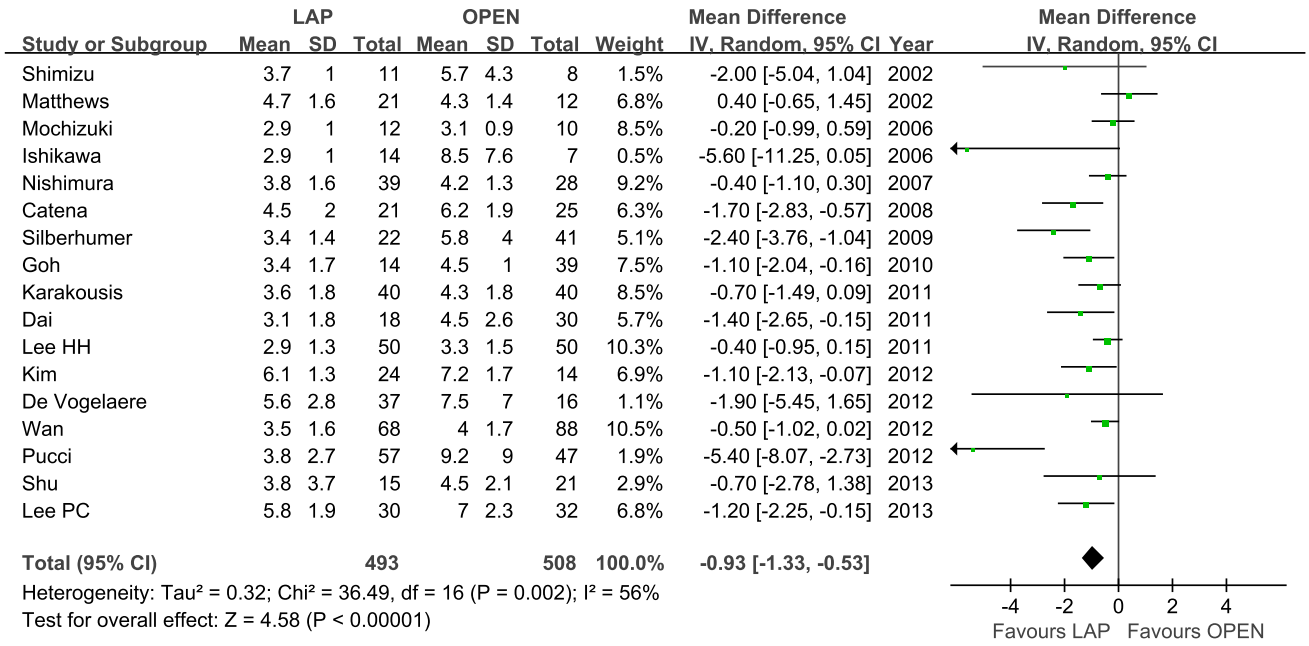


Fig. 9 Meta-analysis of the pooled data: tumor size

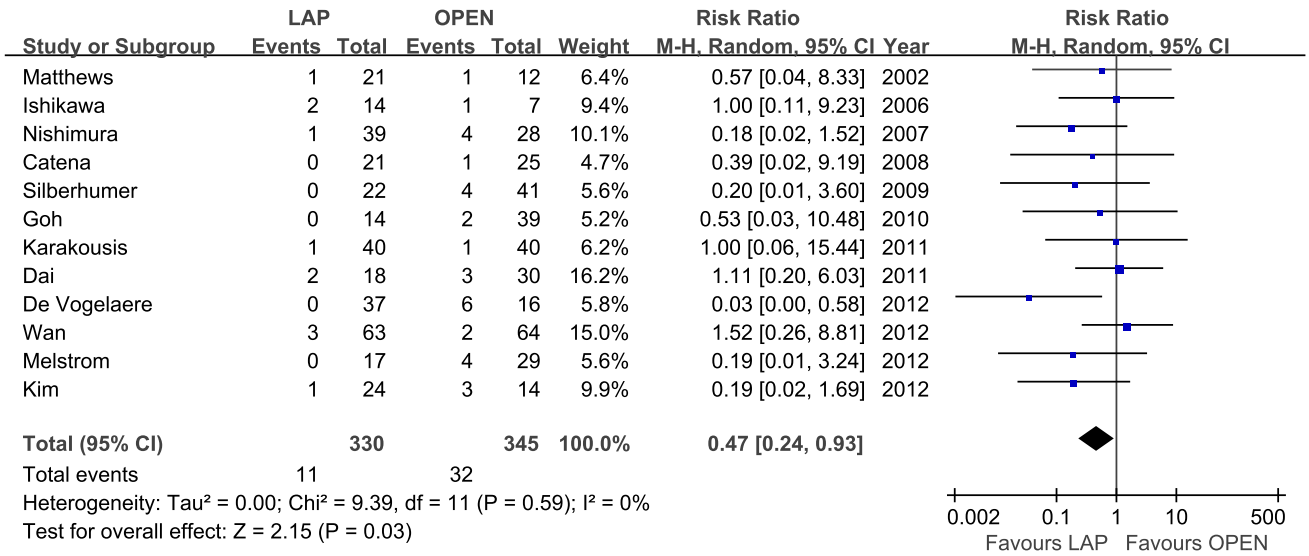


Fig. 10 Meta-analysis of the pooled data: recurrences

pulmonary infection [38]. Our pooled analysis demonstrated the postoperative hospital day was 3.68 days shorter for LAP patients. Reduced use of analgesic drugs, shortened time of abdominal cavity exposure, less bowel manipulation, alleviated inflammatory reactions and earlier postoperative activities are considered to be the main reasons for earlier gastrointestinal recovery from laparoscopic surgery.

Long-term survival remains critical for all patients with GISTs regardless of a benign or malignant designation since these tumors have an uncertain biologic behavior. Our pooled analysis of primary data demonstrated that postoperative recurrence in LAP group was less than that of OPEN group, and the difference was statistically significant. However, in part of the included literatures, the diameter of tumor in OPEN group was larger than that in LAP group, or the risk classification was higher than LAP group. It is widely accepted that the tumor size and mitotic index are two key factors on GISTs long-term outcomes. Thus, the literatures with the same surgical approach (wedge resection) [16, 18, 19, 22, 24, 26, 29] as well as the literatures with comparable tumor size or risk

Table 4 Summary of the available data about recurrence patterns and survival outcomes

Case	Group	Risk	Recurrence	Survival	Case	Group	Risk	Recurrence	Survival	Case	Group	Risk	Recurrence	Survival
1 [17]	LAP	High	NR	Dead	11 [22]	OPEN	NR	NR	Dead	21 [27]	OPEN	High	6 m Liver	52 m Alive*
2 [17]	OPEN	High	NR	14 m Dead	12 [23]	OPEN	High	Local	Dead[a]	22 [27]	OPEN	High	9 m Liver	75 m Alive*
3 [18]	LAP	High	Liver	32 m Dead	13 [23]	OPEN	High	Local	Alive*	23 [27]	OPEN	High	21 m Liver	16y Dead*
4 [18]	OPEN	High	Liver	9 m Dead	14 [23]	OPEN	High	Liver	Alive*	24 [32]	OPEN	High	52 m Peritoneal	Dead*
5 [18]	LAP	Low	Local	Alive	15 [23]	OPEN	High	Multiple	Alive*	25 [32]	OPEN	High	60 m Liver	Alive
6 [20]	LAP	Low	33 m Local	Alive	16 [25]	LAP	High	Peritoneal	4y Alive	26 [32]	OPEN	High	6 m Colon	Dead*
7 [20]	OPEN	High	7 m Peritoneal	Alive	17 [25]	OPEN	Moderate	Liver	10y Alive	27 [32]	LAP	High	31 m Stomach	Alive
8 [20]	OPEN	High	53 m Local	Alive	18 [27]	OPEN	High	4 m Liver	28 m Dead*	28 [32]	OPEN	High	15 Peritoneal	Dead*
9 [20]	OPEN	High	37 m Liver	Alive	19 [27]	OPEN	High	10 m Liver	Alive*					
10 [20]	OPEN	High	15 m Multiple[c]	Alive	20 [27]	OPEN	High	42 m Liver	46 m Dead*[b]					

NR not reported, *m* month, *y* year

*Treated with imatinib; [a] due to cardiac insufficiency; [b] due to lung cancer; [c] included liver and local recurrence

classification were given subgroup analysis [16, 17, 19, 20, 22, 25, 26, 29, 30, 33, 34]. However, the results of two subgroup analysis still showed that the risk of postoperative recurrence in LAP group was not higher than OPEN group. In addition, it can be seen from Table 4 that the common sites of postoperative recurrence of GISTs included liver metastasis, peritoneal metastasis and local recurrence. It was not hard to find that the vast majority of cases of recurrence or metastasis were patients with high-risk classification, which was not clearly related to the operative grouping [17, 18, 20, 22, 23, 25, 27, 32]. Therefore, it was believed that with the continuous advances in the technology, as long as the surgeon strictly select the proper case, strictly follow the radical principles of tumor surgery for complete resection and avoid tumor ruptures, LAP could achieve a long-term effect almost the same with laparotomy in addition to its advantage of minimally invasive.

There are several limitations to our studies. First, all of the studies included in this meta-analysis are non-RCTs, such as clinical controlled trial, prospective or retrospective cohort and as a result of study design limitations, and these studies were more likely to suffer from various kinds of bias. Furthermore, confounding factors which were balanced by randomization in RCTs often disturbed the observation of effect of the intervention in NRTs. The allocation concealment was not described in the included studies, which played an equally important role to randomization in preventing bias, so that the absence of allocation concealment could overstate the intervention effect by 30–41 % [39]. In this study, since the funnel plot was not completely symmetrical, the bias would be overcome only with collection of more literatures. Thus, the clinicians must be aware of possible publication bias in the use of evidences to guide clinical practice, which might have a greater impact on the final conclusion. The majority of the studies analyzed focussed only on GISTs. However, some included studies had cases of other type gastric submucosal tumors (SMTs) such as neurilemmomas and leiomyoma. SMTs display a wide spectrum, ranging from benign to highly malignant, with GISTs being the most common [16, 40], and preoperative histologic diagnosis remains difficult. Because the sample size of remaining studies is still small for definitive conclusions on the safety and effectiveness of LAP and the larger the number of patients in a meta-analysis, the greater its power to detect a possible treatment effect. Therefore, we did not exclude the study. Although, such a low number does not imply a significant bias, it still can lead to clinical heterogeneity. Also, the majority of cases in our study are in the past 3 years, which is short for the low risk GISTs to develop recurrence, and the follow-up will continue.

Table 5 Pooled outcomes of subgroup analysis for studies of wedge resection

Outcomes	No. of studies	Sample size		Heterogeneity (P, I^2) %	Overall effect size	95 % CI of overall effect	P value
		LAP	OPEN				
Operation time (min)	8	203	233	<0.001, 82	WMD = 12.03	−8.03 to 32.09	0.24
Blood loss (ml)	5	118	151	0.03, 64	WMD = −48.29	−78.23 to −18.36	<0.01
Time to first flatus (d)	6	119	144	0.10, 46	WMD = −1.35	−1.66 to −1.03	<0.01
Time to oral intake (d)	7	182	208	0.001, 73	WMD = −1.67	−2.19 to −1.15	<0.01
Hospital stay (d)	8	203	233	0.002, 68	WMD = −2.53	−3.50 to −1.57	<0.01
Overall complications	8	203	233	0.70, 0	RR = 0.47	0.22 to 1.01	0.05
Surgical complications	4	157	193	0.37, 4	RR = 0.64	0.25 to 1.64	0.35
Medical complications	3	94	137	0.12, 53	RR = 0.28	0.04 to 1.83	0.18
Tumor size (cm)	8	203	233	0.10, 42	WMD = −0.77	−1.23 to −0.31	<0.01
Recurrence	5	130	165	0.95, 0	RR = 1.01	0.39 to 2.63	0.99

WMD weighted mean difference, *RR* risk ratio

Table 6 Pooled outcomes of subgroup analysis for studies with comparable tumor size or risk index

Outcomes	No. of studies	Sample size		Heterogeneity (P, I^2) %	Overall effect size	95 % CI of overall effect	P value
		LAP	OPEN				
Operation time (min)	11	325	344	<0.001, 75	WMD = 6.95	−7.11 to 21.01	0.33
Blood loss (ml)	9	254	269	<0.001, 75	WMD = −52.99	−78.59 to −27.40	<0.01
Time to first flatus (d)	5	106	119	0.06, 56	WMD = −1.32	−1.69 to −0.94	<0.01
Time to oral intake (d)	6	189	218	0.01, 66	WMD = −1.83	−2.27 to −1.38	<0.01
Hospital stay (d)	10	286	316	0.004, 63	WMD = −2.90	−3.64 to −2.15	<0.01
Overall complications	10	295	312	0.54, 0	RR = 0.48	0.28 to 0.81	<0.01
Surgical complications	7	255	261	0.63, 0	RR = 0.67	0.25 to 1.43	0.30
Medical complications	5	157	154	0.12, 53	RR = 0.37	0.14 to 0.98	0.05
Tumor size (cm)	11	351	352	0.26, 19	WMD = −0.57	−0.87 to −0.28	<0.01
Recurrence	6	207	223	0.81, 0	RR = 0.69	0.30 to 1.60	0.39

WMD weighted mean difference, *RR* risk ratio

Conclusions

Laparoscopic resection for gastric GISTs is a safe and feasible procedure, which will not increase the risks of tumor relapse and metastasis. However, the lack of randomized trials or high-quality, nonrandomized prospective studies does not allow for firm conclusions to be drawn. Randomized controlled trials or prospective cohort studies, which avoid selection and experimenter bias and control for confounding factors are necessary to adequately evaluate the status of laparoscopic resection for gastric GISTs.

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