Meta-analysis of Laparoscopic and Open Surgery for Gastric Gastrointestinal Stromal Tumor

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Abstract. *Aim: A meta-analysis was conducted to evaluate and compare the short- and long-term outcomes of laparoscopic and conventional open surgery for gastric gastrointestinal stromal tumors (GISTs). Materials and Methods: We searched MEDLINE, EMBASE, Science Citation Index, and the Cochrane Controlled Trial Register for relevant articles published between 2000 and July 2013 by using the search terms "laparoscopic", "laparoscopy-assisted", "surgery", "gastrointestinal tumor", "GIST" and "gastric". Results: We identified 12 articles reporting results that compared laparoscopic surgery with open surgery for gastric GISTs. Our meta-analysis included 644 patients with GISTs; 312 had undergone laparoscopic surgery, and 332 had undergone open surgery. In the short-term period, 14 outcome variables were examined. In the long-term period, six oncological variables were analyzed. Laparoscopic surgery for gastric GIST was associated with a reduction in intraoperative blood loss, shorter period to flatus, earlier resumption of oral intake, and shorter duration of hospital stay over the short-term, and with a significantly lower rate of overall recurrence, metastatic recurrence and local recurrence in the long-term compared to open surgery. Conclusion: Laparoscopic surgery may be an acceptable surgical treatment option compared to open surgery for gastric GIST.*

Gastrointestinal stromal tumors (GISTs) originate from the interstitial cell of Cajal, an intestinal pacemaker cell in the gut (1, 2). GISTs are rare tumors and represent approximately 0.3-3% of all gastrointestinal tumors (3), while they are the most common mesenchymal tumors in the gastrointestinal tract (4). The incidence of GISTs ranges between 11 and 14.6/million/year based on national epidemiological studies (5, 6) and is slightly higher in men than in women (7). Although GISTs can occur anywhere along the length of the GI tract, they are located mainly in the stomach (60-70%), followed by the small intestine (20-30%), the colon and rectum (5%), and the esophagus (5%) (8). Occasionally, GISTs arise in the omentum, the mesentery, or the retroperitoneum (2). Most GISTs metastasize to the liver hematogenously and disseminate throughout the peritoneal cavity, and rarely, they metastasize to the lymph nodes (9). Activating mutations in receptor tyrosine kinase (*KIT*) or platelet-derived growth factor receptor alpha (*PDGFRA*) have been identified in up to 80% and 10% of GISTs, respectively (10). Surgery is potentially curative and currently is main treatment for patients with operable GIST (11, 12). The aim of surgery for resectable GIST is complete resection with macroscopically-negative margins of at least 1-2 cm, avoiding tumor rupture (13, 14). Prognosis of patients with a primary GIST is related to tumor size and its mitotic index (15, 16). Partial resection is recommended to preserve organ function, and no report has so far defended that systematic lymph node dissection improves the prognosis of patients with GIST. Partial resection for gastric GISTs was traditionally performed by conventional open surgery (Open). Recently, the feasibility and safety of laparoscopic surgery (Lap) for gastric GISTs has been reported (17, 18). While tumor size and location are limiting factors, several studies have indicated that Lap for GISTs of 5 cm or smaller can be safely performed (17, 18). The value of Lap for gastric GISTs has remained controversial because the short- and long-term outcomes have not been clarified. To accurately evaluate the efficacy of Lap for gastric GISTs, the short- and long-term outcomes of Lap must be compared to those of Open. However, no randomized controlled trials comparing Lap with Open for gastric GISTs have been reported, largely because of the low occurrence rate of gastric GISTs. The

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Key Words: Gastric gastrointestinal stromal tumor, gastric, GIST, meta-analysis, laparoscopy-assisted surgery.

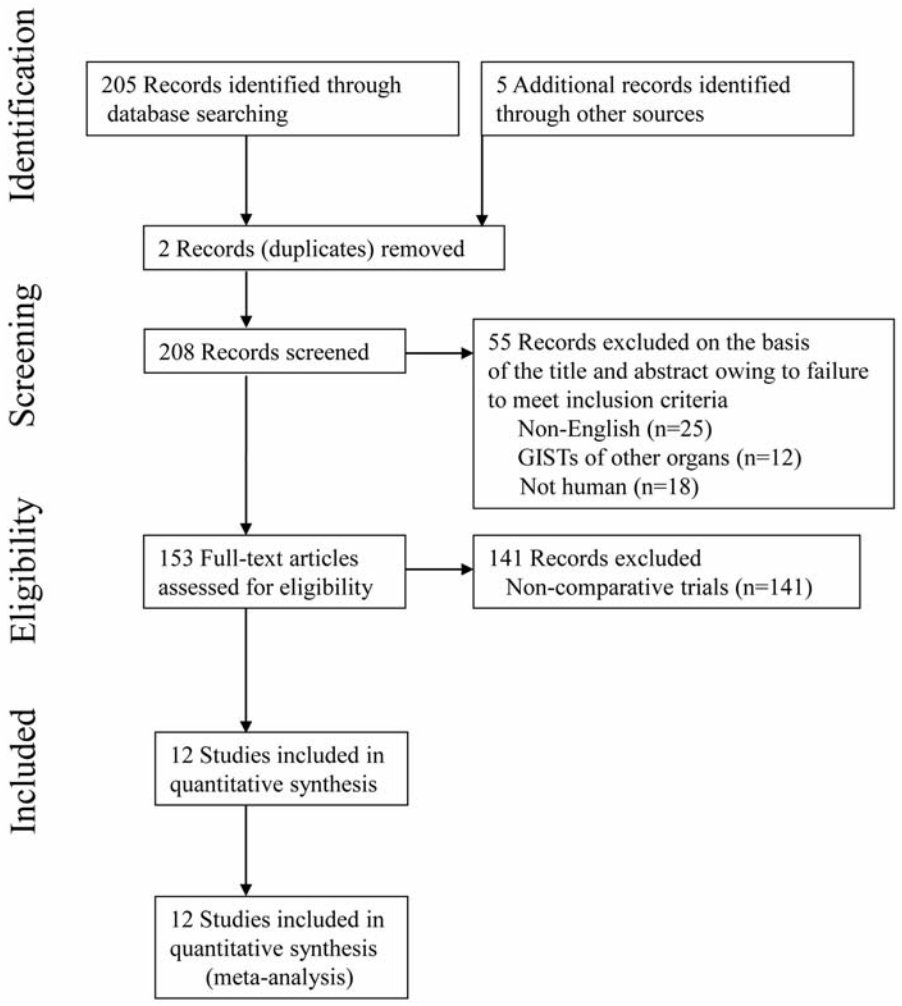


Figure 1. *Flow diagram of this meta-analysis in accordance with the PRISMA Statement.*

methodological index for non-randomized studies (MINORS) is a valid instrument for assessing the methodological quality of non-randomized studies, especially for purposes of meta-analysis (19, 20). Here, we conducted a meta-analysis of previously conducted non-randomized controlled trials (21-32). The outcomes of each of the surgical procedures were analyzed for short- and long-term periods.

Materials and Methods

Study designs. There were no randomized controlled trials comparing Lap *vs*. Open for gastric GIST. Non-randomized studies that compared the short- and long-term outcomes of Lap *versus* Open for gastric GIST were considered for this meta-analysis.

Literature search. To identify articles relevant to our study, we searched the major medical databases–MEDLINE, EMBASE, Science Citation Index, and the Cochrane Controlled Trial Register–for studies published between 2000 and July 2013. The following search terms were used: "laparoscopic", "laparoscopy-assisted", "surgery", "gastrointestinal stromal tumor", "GIST" and "gastric". Appropriate data from the studies were used for this meta-analysis. This meta-analysis was prepared in accordance with the Preferred Reporting Items for Systemic reviews and Meta-Analysis (PRISMA) statement (33) (Figure 1).

Inclusion criteria. To enter this meta-analysis, studies had to: be written in English; compare Lap with Open for gastric GISTs; and report on at least one of the outcome measures mentioned below.

Exclusion criteria. Studies were excluded from this analysis if the outcomes of interest were not reported for the two surgical techniques.

Study quality. The MINORS was used to evaluate the methodological quality of the non-randomized studies (19, 20). Two reviewers independently evaluated the studies. Disagreements were resolved by discussion and consensus.

Data extraction. Three researchers (HO, HN, and KM) extracted data from each article by using a structured sheet and entered the data into a database. We conducted meta-analyses for the short- and long-term. For the short-term analysis, we collected data on operation time, estimated blood loss, time-to-first flatus, time-to-oral diet, hospital stay, overall complications, anastomotic leakage, pneumonitis, ileus, deep venous thrombosis (DVT), perioperative mortality, positive resection margin, conversion rate, and tumor size. For the long-term analysis, we used data on the rate of overall recurrence, local recurrence, metastatic recurrence, wound-site recurrence, overall mortality, and GIST-related mortality.

Statistical analysis. Weighted mean differences (WMDs) and odds ratios were used for the analysis of continuous and dichotomous variables, respectively. Random effects models were used to identify heterogeneity between the studies (34), and the degree of heterogeneity was assessed using the χ^2 test. For the analysis of the conversion rate, the χ^2 test was used. The confidence interval (CI) was established at 95%, and *p*-values of less than 0.05 were considered to indicate statistical significance. For the computation of the CI, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo *et al*. (35). Statistical analyses were performed using Review Manager (RevMan) software, version 5.2.6 (Cochrane Collaboration, Copenhagen, Denmark).

Results

Search results. The present meta-analysis met the PRISMA statement. Overall, 205 citations were retrieved from the search strategy. Five additional articles were identified by contacting clinical experts and searching bibliographies. Two studies were excluded because of duplicate reporting. Fifty-five studies were removed from the 208 because they were not written in English, and reported GISTs of the other organs and no human studies. One hundred and forty-one studies were excluded on account of non-comparative trials. We identified 12 trials that suitably compared Lap with Open for gastric GISTs for this meta-analysis. The characteristics of each trial are presented in Table I. Our meta-analysis included 644 patients with gastric GIST; of these, 312 had undergone Lap, and 332 had undergone Open. Short- and long-term results are shown in Figures 2 and 3, respectively. Only two articles reported neoajuvant or adjuvant therapy for GIST. The study quality by using the MINORS is shown in Table II.

Short-term Outcomes

No significant difference was found in the operative time between Lap and Open from the analysis of 581 resections (290 Lap and 291 Open). Intraoperative estimated blood loss in the Lap group was significantly lower (by 34.47 ml) than in the Open group. The time-to-flatus, the time-to-oral diet, and the duration of hospital stay were significantly shorter in Lap than in Open. The occurrence rate of overall postoperative complications, anastomotic leakage, ileus, pneumonia and DVT did not differ significantly between the two procedures. Examining 201 resections (105 Lap and 96 Open), there was none and one perioperative mortality among patients who underwent Lap and Open, respectively.

Resection margins. Examining 310 resections (165 Lap and 145 Open), there were no cases with positive resection margins in either Lap or Open. The resection margin of one case was less than 0.1 cm and the extent of that of the one other case is unclear in the Lap group.

Conversion rate. The conversion rate from Lap to Open ranged from 0 to 25% (Table I). The overall conversion rate was 7.0%. The conversion rate for studies whose number of Lap-treated patients was fewer than 30 was 7.8%, whereas that for studies with 30 or more Lap-treated patients was 5.9%. The difference was not statistically significant.

Tumor size. The tumor size for Lap was significantly smaller (by 1.15 cm) than that for Open from the analysis of 644 resections (312 Lap and 332 Open).

Long-term Outcomes

Tumor recurrence. The rate of overall recurrence, metastatic recurrence, and local recurrence were significantly lower in Lap than in Open, from the analysis of 524 resections (252 Lap and 272 Open), 379 resections (200 Lap and 179 Open) and 379 resections (200 Lap and 179 Open), respectively. No cases of wound-site recurrence were observed in either of the two surgical groups from 256 resections examined (128 Lap and 128 Open).

Mortality. In the analysis of 275 resections (141 Lap and 134 Open), we found no significant difference in overall mortality between patients who underwent Lap and those who underwent Open. No significant difference was observed in GIST-related mortality between the two groups, examining 279 resections (158 Lap and 121 Open).

Heterogeneity

In the short-term period, significant heterogeneity was found between studies with respect to operative time, estimated blood loss, time-to-first flatus, time-to-oral intake, duration of hospital stay, and tumor size. There was no significant heterogeneity in overall complications, anastomotic leakage, ileus, pneumonia and DVT. In the long-term period, we found no significant heterogeneity in the recurrence and mortality rates between studies.

Discussion

Lap is increasingly performed for surgical treatment of gastric GISTs. While there have been no randomized trials comparing Lap to Open for gastric GIST, several non-randomized trials have been reported (21-32). The short- and

Table I. *Characteristics of all trials.*

	Year	Reference number	Style of study	Number of patients		Conversion rate (%)	Reasons for conversion	Operation method		Limit of tumor size for Lap	Follow-up period		
				Lap	Open			Lap	Open		Entire	Lap	Open
Catena *et al.*	2008	21	Retrospective	21	25	0	-	Wedge resection (n=21)	Wedge resection (n=25)	U	35 M (mean)	35 M	91 M
Goh *et al.*	2010	22	Retrospective	14	39	7	U	Wedge resection (n=14)	Wedge resection (n=39)	7 cm	15 M (median)	21 M (median)	8 M (median)
Karakousis *et al.*	2011	23	Prospective	40	40	25	Tumor location Tumor size	Wedge resection (n=40)	Wedge resection (n=38) Distal gastrectomy (n=2)	U	34 M (median)	28 M (median)	43 M (median)
Lee *et al.*	2010	24	Prospective	50	50	2	Occult tumor location	Wedge resection (n=50)	Wedge resection (n=50)	U	U	21 M (mean)	22 M (mean)
Matthews *et al.*	2002	25	Retrospective	21	12	U	U	Wedge resection (n=15) Partial gastrectomy (n=3) Enucleation (n=3)	Wedge resection (n=6) Antrectomy (n=4) Partial proximal gastrectomy (n=2)	U	1.6 Y (mean)	20 M (mean)	18 M (mean)
Pitsinis *et al.*	2007	26	Prospective	6	7	U	U	U	U	U	9 M (median)	U	U
Nishimura *et al.*	2007	27	Retrospective	39	28	2.6	Obesity	Partial gastrectomy (n=29) Intragastric surgery (n=10)	Partial gastrectomy (n=19) Formal gastrectomy (n=9) (proximal n=5, total n=3, distal n=1)	5 cm	U	18.9 M	31.2 M
Silberhumer *et al.*	2009	28	Cohort	22	41	18.2	Tumor location Tumor size	Tumorectomy (n=19) Wedge resection (n=3)	Tumorectomy (n=30) Distal resection (n=5) Gastrectomy (n=4) Debulking (n=2)	U	37±27.9 M (mean) 30.1 M (median)	41±31 M	30±20 M
Wu *et al.*	2010	29	Retrospective	15	13	U	U	Wedge resection (n=15)	Wedge resection (n=13)	U	U	U	U
Melstrom *et al.*	2011	30	Retrospective	17	29	6	Tumor location Adhesion	Wedge resection (n=17)	Wedge resection (n=24) Distal gastrectomy (n=2) Subtotal gastrectomy (n=2) Total gastrectomy (n=1)	U	U	32 M (median)	59 M (median)
Vogelaere *et al.*	2012	31	Prospective	37	16	0	-	Wedge resection (n=37)	Wedge resection (n=U) Partial gastrectomy (n=U) Polar gastrectomy (n=U) Total or subtotal gastrectomy (n=U)	U	83.9±49.6 M (mean)	80±44.8 M	91±60.0 M
Lee *et al.*	2013	32	Retrospective	30	32	0	-	Wide excision (n=30)	Wide excision (n=32)	U	U	U	U

U: Unknown, M: months, Y: years.

Table II. *Scoring for the studies by the revised and validated version of MINORS (19).*

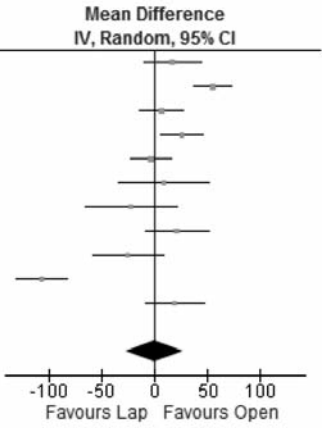
Study (Ref.)	Methodological items for non-randomized studies								Additional criteria in the case of comparative study				
	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	End-points appropriate to the aim of the study	Unbiased assessment of the study end-point	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospectve calculation of the study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Global score
Catena *et al*. (21)	2	2	0	2	0	2	2	0	2	2	2	2	18
Goh *et al*. (22)	2	2	0	2	0	1	2	0	2	2	2	2	17
Karakousis *et al*. (23)	2	2	1	2	0	2	2	0	2	2	2	2	19
Lee *et al*. (24)	2	2	1	2	0	2	2	0	2	2	2	2	19
Matthews *et al*. (25)	2	2	0	2	0	2	2	0	2	2	2	2	18
Pitsinis *et al*. (26)	2	2	2	2	0	1	2	0	2	2	2	2	19
Nishimura *et al*. (27)	2	2	0	2	0	1	2	0	2	2	2	2	17
Silberhumer *et al*. (28)	2	2	2	2	0	2	2	0	2	2	2	2	20
Wu *et al*. (29)	2	2	0	2	0	0	0	0	2	2	2	2	14
Melstrom *et al*. (30)	2	2	0	2	0	2	2	0	2	2	2	2	18
Vogelaere *et al*. (31)	2	2	2	2	0	2	2	0	2	2	2	2	20
Lee *et al*. (32)	2	2	0	2	0	0	0	0	2	2	2	2	14

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The ideal global score being 16 for non-comparative studies, and 24 for comparative studies.

Operative time (minutes)

Study or Subgroup	Lap Mean	Lap SD	Lap Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Catena et al. (21)	151	56	21	134	33	25	9.2%	17.00 [-10.22, 44.22]
Goh et al. (22)	150	22.5	14	95	42.5	39	9.7%	55.00 [37.20, 72.80]
Karakousis et al. (23)	96	38	40	89	54.75	40	9.6%	7.00 [-13.65, 27.65]
Lee et al. (24)	152.9	58.2	50	127	40.6	50	9.6%	25.90 [6.23, 45.57]
Lee et al. (32)	116.6	26.1	30	119.6	48.5	32	9.6%	-3.00 [-22.23, 16.23]
Matthews et al. (25)	169	83.75	21	160	41.25	12	8.1%	9.00 [-33.75, 51.75]
Melstrom et al. (30)	135	67.5	17	157	78.5	29	8.0%	-22.00 [-64.96, 20.96]
Nishimura et al. (27)	136	68	39	115	57.5	28	9.0%	21.00 [-9.15, 51.15]
Pitsinis et al. (26)	110	7.5	6	135	45	7	8.7%	-25.00 [-58.87, 8.87]
Vogelaere et al. (31)	48.5	16	37	155	48.1	16	9.4%	-106.50 [-130.63, -82.37]
Wu et al. (29)	129.6	36.1	15	110.8	38.1	13	9.2%	18.80 [-8.82, 46.42]
Total (95% CI)			**290**			**291**	**100.0%**	**0.17 [-26.68, 27.02]**

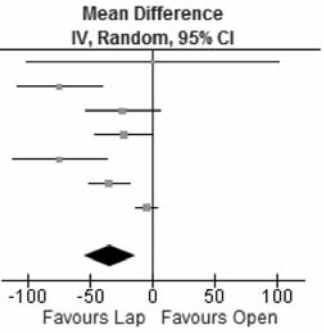
Heterogeneity: Tau² = 1852.44; Chi² = 124.69, df = 10 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.01 (P = 0.99)



Estimated intraoperative blood loss (ml)

Study or Subgroup	Lap Mean	Lap SD	Lap Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Goh et al. (22)	0	75	14	0	300	39	3.6%	0.00 [-102.02, 102.02]
Karakousis et al. (23)	25	48.75	40	100	98.75	40	13.6%	-75.00 [-109.13, -40.87]
Lee et al. (32)	58.5	30.1	30	82.7	80.4	32	14.8%	-24.20 [-54.07, 5.67]
Matthews et al. (25)	106	45	21	129	23.75	12	16.7%	-23.00 [-46.47, 0.47]
Melstrom et al. (30)	94	47	17	169	84.5	29	12.5%	-75.00 [-113.01, -36.99]
Nishimura et al. (27)	45	22.5	39	80	40	28	18.6%	-35.00 [-51.41, -18.59]
Wu et al. (29)	35.5	11.7	15	40.3	12.1	13	20.2%	-4.80 [-13.65, 4.05]
Total (95% CI)			**176**			**193**	**100.0%**	**-34.47 [-55.64, -13.31]**

Heterogeneity: Tau² = 556.11; Chi² = 32.48, df = 6 (P < 0.0001); I² = 82%
Test for overall effect: Z = 3.19 (P = 0.001)



Time to first flatus (days)

Study or Subgroup	Lap Mean	Lap SD	Lap Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Goh et al. (22)	2	1	14	4	1.75	39	21.3%	-2.00 [-2.76, -1.24]
Lee et al. (24)	2.3	0.6	50	3.6	0.9	50	31.2%	-1.30 [-1.60, -1.00]
Lee et al. (32)	2.5	1.25	30	4	2	32	20.0%	-1.50 [-2.32, -0.68]
Wu et al. (29)	2.7	0.7	15	3.2	0.6	13	27.5%	-0.50 [-0.98, -0.02]
Total (95% CI)			**109**			**134**	**100.0%**	**-1.27 [-1.84, -0.70]**

Heterogeneity: Tau² = 0.25; Chi² = 13.32, df = 3 (P = 0.004); I² = 77%
Test for overall effect: Z = 4.34 (P < 0.0001)

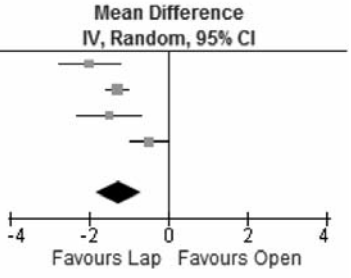


Figure 2. *Continued*

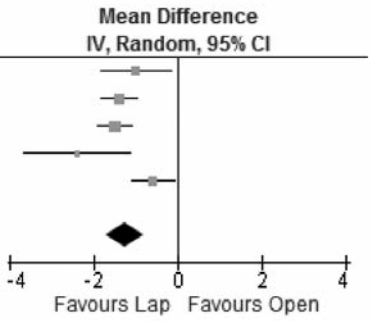
long-term outcomes of laparoscopic and open gastric GIST resection were compared in this meta-analysis.

In the short-term period, analysis of pooled data revealed that there was no significant difference in the operative time between the Lap and Open group. Significant reduction in intraoperative blood loss in Lap may be accomplished by meticulous resection using instruments for laparoscopic surgery and videoscopic magnification. Patients who underwent Lap experienced flatulence significantly earlier, resumed oral intake significantly earlier, and had significantly shorter hospital stays than did patients who underwent Open; this finding suggests that Lap leads to faster recovery. This observation is in agreement with the studies comparing Lap and Open for other conditions,

Time to oral intake (days)

Study or Subgroup	Lap Mean	Lap SD	Lap Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Goh et al. (22)	2	1	14	3	2	39	15.9%	-1.00 [-1.82, -0.18]
Lee et al. (24)	3.4	0.9	50	4.8	1.3	50	25.2%	-1.40 [-1.84, -0.96]
Lee et al. (32)	2.5	0.7	30	4	0.9	32	26.2%	-1.50 [-1.90, -1.10]
Vogelaere et al. (31)	4	0.8	37	6.4	2.5	16	9.4%	-2.40 [-3.65, -1.15]
Wu et al. (29)	3.1	0.5	15	3.7	0.8	13	23.4%	-0.60 [-1.10, -0.10]
Total (95% CI)			**146**			**150**	**100.0%**	**-1.27 [-1.72, -0.82]**

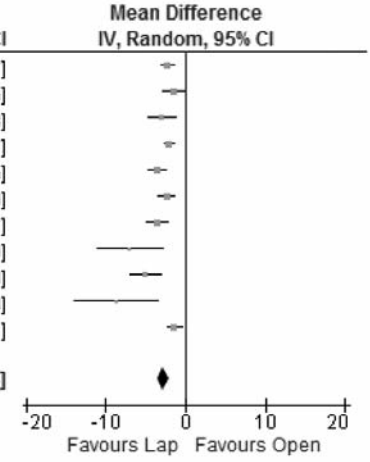
Heterogeneity: Tau² = 0.16; Chi² = 11.96, df = 4 (P = 0.02); I² = 67%
Test for overall effect: Z = 5.49 (P < 0.00001)



Hospital stay (days)

Study or Subgroup	Lap Mean	Lap SD	Lap Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Catena et al. (21)	4.8	1.6	21	7.1	1.2	25	12.7%	-2.30 [-3.13, -1.47]
Goh et al. (22)	4.5	1.5	14	6	3.5	39	9.7%	-1.50 [-2.85, -0.15]
Karakousis et al. (23)	4	1.25	40	7	5.25	40	8.1%	-3.00 [-4.67, -1.33]
Lee et al. (24)	5.7	1.6	50	7.8	1.6	50	13.8%	-2.10 [-2.73, -1.47]
Lee et al. (32)	7.1	1.9	30	10.7	2.3	32	11.4%	-3.60 [-4.65, -2.55]
Matthews et al. (25)	3.8	1.25	21	6.2	1.5	12	11.7%	-2.40 [-3.40, -1.40]
Melstrom et al. (30)	2.68	1.34	17	6.25	3.125	29	9.9%	-3.57 [-4.87, -2.27]
Pitsinis et al. (26)	4	1.25	6	11	5.5	7	2.3%	-7.00 [-11.20, -2.80]
Silberhumer et al. (28)	7.8	3.1	22	12.8	5	41	6.6%	-5.00 [-7.01, -2.99]
Vogelaere et al. (31)	8.2	3.3	37	16.9	10.6	16	1.5%	-8.70 [-14.00, -3.40]
Wu et al. (29)	5.8	1.2	15	7.2	1.2	13	12.3%	-1.40 [-2.29, -0.51]
Total (95% CI)			**273**			**304**	**100.0%**	**-2.81 [-3.49, -2.13]**

Heterogeneity: Tau² = 0.77; Chi² = 32.51, df = 10 (P = 0.0003); I² = 69%
Test for overall effect: Z = 8.07 (P < 0.00001)



Tumor size (cm)

Study or Subgroup	Lap Mean	Lap SD	Lap Total	Open Mean	Open SD	Open Total	Weight	Mean Difference IV, Random, 95% CI
Catena et al. (21)	4.5	2	21	6.2	1.9	25	8.7%	-1.70 [-2.83, -0.57]
Goh et al. (22)	3.1	1.45	14	4.5	1.25	39	10.4%	-1.40 [-2.25, -0.55]
Karakousis et al. (23)	3.6	1.775	40	4.3	1.75	40	10.9%	-0.70 [-1.47, 0.07]
Lee et al. (24)	2.9	1.3	50	3.3	1.5	50	12.1%	-0.40 [-0.95, 0.15]
Lee et al. (32)	5.84	1.92	30	7	2.3	32	9.2%	-1.16 [-2.21, -0.11]
Matthews et al. (25)	4.5	1.625	21	4.9	1.375	12	9.3%	-0.40 [-1.44, 0.64]
Melstrom et al. (30)	4.27	1.9	17	6.39	3.95	29	6.0%	-2.12 [-3.82, -0.42]
Nishimura et al. (27)	3.8	1.625	39	4.2	1.25	28	11.4%	-0.40 [-1.09, 0.29]
Pitsinis et al. (26)	5	1.25	6	11.5	3.375	7	3.2%	-6.50 [-9.19, -3.81]
Silberhumer et al. (28)	3.5	1.4	22	5.8	4	41	7.5%	-2.30 [-3.66, -0.94]
Vogelaere et al. (31)	5.6	2.8	37	7.5	7	16	2.1%	-1.90 [-5.45, 1.65]
Wu et al. (29)	2.6	1.8	15	2.5	1	13	9.2%	0.10 [-0.96, 1.16]
Total (95% CI)			**312**			**332**	**100.0%**	**-1.15 [-1.70, -0.60]**

Heterogeneity: Tau² = 0.58; Chi² = 36.01, df = 11 (P = 0.0002); I² = 69%
Test for overall effect: Z = 4.07 (P < 0.0001)

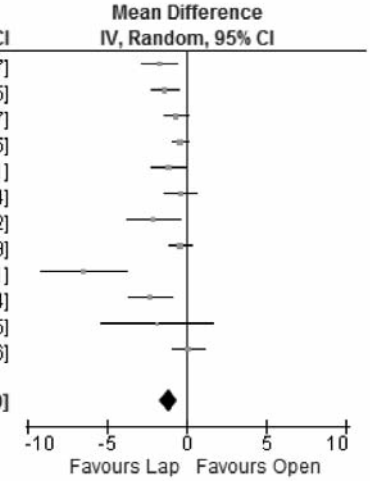
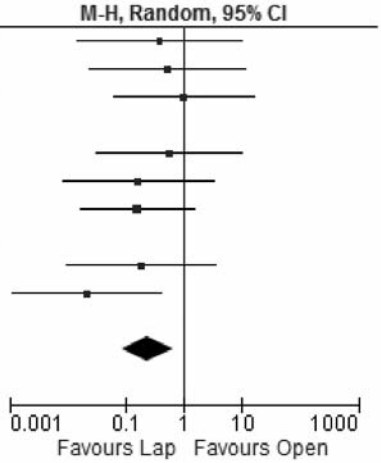


Figure 2. *Meta-analysis of the short-term outcomes for gastric gastrointestinal stromal tumors (GISTs).*

Overall recurrence

Study or Subgroup	Lap Events	Lap Total	Open Events	Open Total	Weight	Odds Ratio M-H, Random, 95% CI
Catena et al. (21)	0	21	1	25	9.6%	0.38 [0.01, 9.82]
Goh et al. (22)	0	14	2	39	10.6%	0.52 [0.02, 11.44]
Karakousis et al. (23)	1	40	1	40	12.9%	1.00 [0.06, 16.56]
Lee et al. (24)	0	35	0	35		Not estimable
Matthews et al. (25)	1	21	1	12	12.3%	0.55 [0.03, 9.68]
Melstrom et al. (30)	0	17	4	29	11.4%	0.16 [0.01, 3.20]
Nishimura et al. (27)	1	39	4	28	20.1%	0.16 [0.02, 1.50]
Pitsinis et al. (26)	0	6	0	7		Not estimable
Silberhumer et al. (28)	0	22	4	41	11.5%	0.19 [0.01, 3.60]
Vogelaere et al. (31)	0	37	6	16	11.6%	0.02 [0.00, 0.41]
Total (95% CI)		**252**		**272**	**100.0%**	**0.23 [0.09, 0.64]**
Total events	3		23			

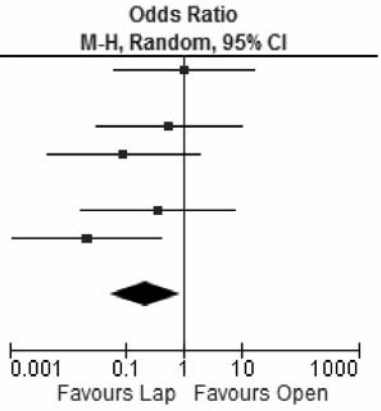
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.52$, df = 7 (P = 0.72); $I^2 = 0\%$
Test for overall effect: Z = 2.83 (P = 0.005)



Metastatic recurrence

Study or Subgroup	Lap Events	Lap Total	Open Events	Open Total	Weight	Odds Ratio M-H, Random, 95% CI
Karakousis et al. (23)	1	40	1	40	21.7%	1.00 [0.06, 16.56]
Lee et al. (24)	0	35	0	35		Not estimable
Matthews et al. (25)	1	21	1	12	20.9%	0.55 [0.03, 9.68]
Nishimura et al. (27)	0	39	3	28	19.2%	0.09 [0.00, 1.86]
Pitsinis et al. (26)	0	6	0	7		Not estimable
Silberhumer et al. (28)	0	22	2	41	18.4%	0.35 [0.02, 7.64]
Vogelaere et al. (31)	0	37	6	16	19.8%	0.02 [0.00, 0.41]
Total (95% CI)		**200**		**179**	**100.0%**	**0.22 [0.05, 0.86]**
Total events	2		13			

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 4.44$, df = 4 (P = 0.35); $I^2 = 10\%$
Test for overall effect: Z = 2.17 (P = 0.03)



Local recurrence

Study or Subgroup	Lap Events	Lap Total	Open Events	Open Total	Weight	Odds Ratio M-H, Random, 95% CI
Karakousis et al. (23)	0	40	0	40		Not estimable
Lee et al. (24)	0	35	0	35		Not estimable
Matthews et al. (25)	0	21	0	12		Not estimable
Nishimura et al. (27)	1	39	2	28	43.4%	0.34 [0.03, 3.97]
Pitsinis et al. (26)	0	6	0	7		Not estimable
Silberhumer et al. (28)	0	22	2	41	27.5%	0.35 [0.02, 7.64]
Vogelaere et al. (31)	0	37	4	16	29.1%	0.04 [0.00, 0.74]
Total (95% CI)		**200**		**179**	**100.0%**	**0.18 [0.04, 0.91]**
Total events	1		8			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.54$, df = 2 (P = 0.46); $I^2 = 0\%$
Test for overall effect: Z = 2.08 (P = 0.04)

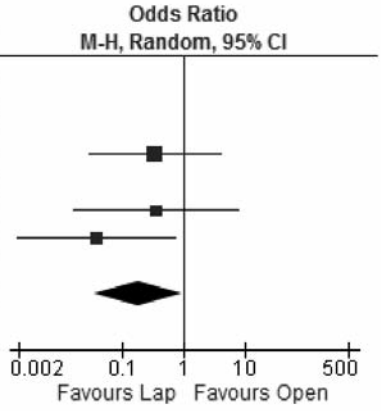


Figure 3. *Continued*

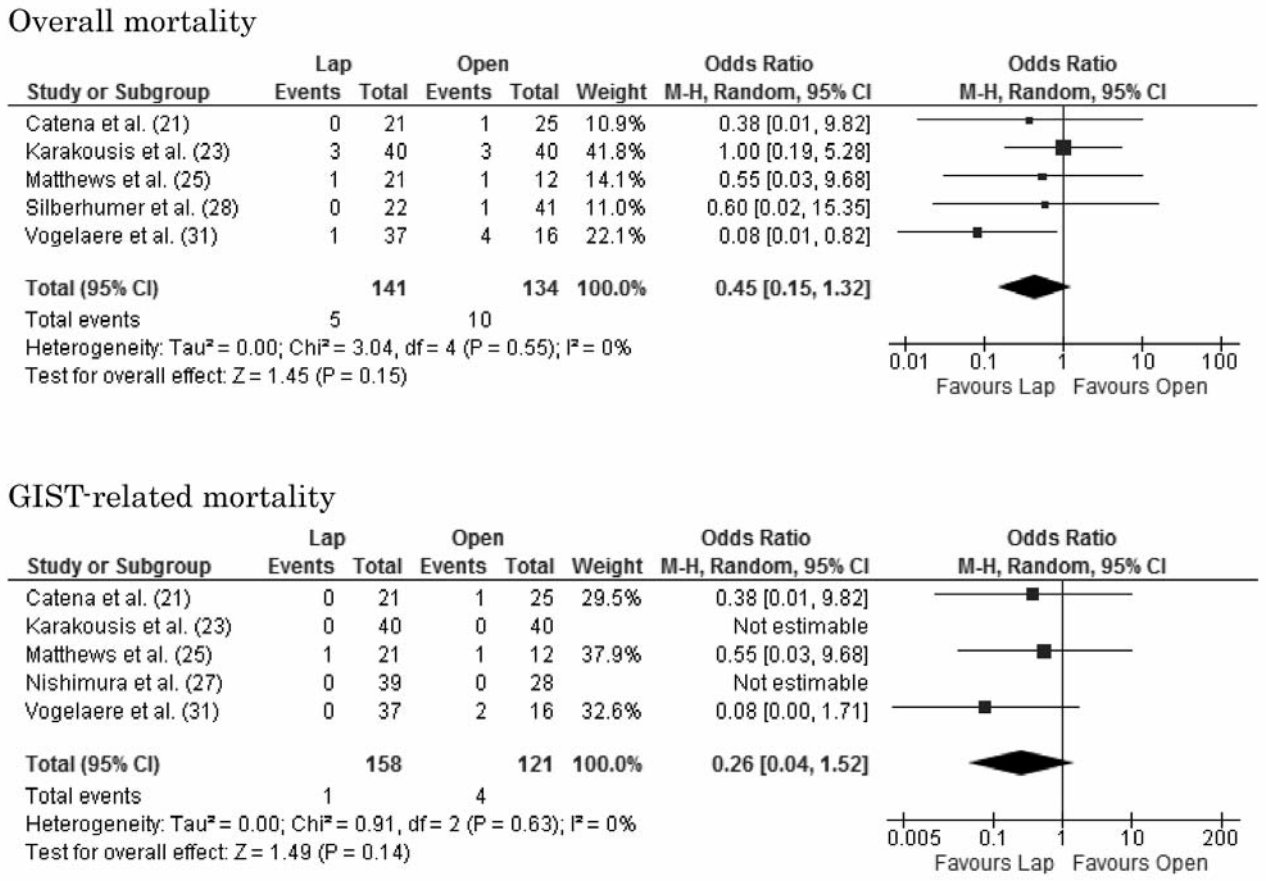


Figure 3. *Meta-analysis of long-term outcomes for gastric gastrointestinal stromal tumors (GISTs).*

including gastric cancer (36) and colorectal cancer (37, 38). There was no significant difference in overall postoperative complications or in specific complications, such as anastomotic leakage, ileus, pneumonia or DVT between Lap and Open. Only one case out of 282 in the Lap group had anastomotic leakage, which was managed conservatively. One patient out of 300 in the Open group who had anastomotic leakage died due to multiple organ failure. No cases in the Lap group had ileus after surgery. There were no cases and one case of perioperative mortality in Lap and in Open, respectively. All of these observations suggest that the safety and feasibility of Lap for gastric GIST is not inferior to that of Open. Moreover, the quality of Lap may be practically similar to that of Open, as shown by the absence of cases with positive surgical margins in both groups. Two cases out of 165 in Lap had similar resection margins (23, 31). It may be necessary to resect the margin more carefully in Lap.

In this analysis, the conversion rate was not significantly related to the number of cases in each of the studies, *i.e.* studies whose number of patients was fewer than 30, or 30 or more, who underwent Lap. Karakousis *et al*. reported that tumor location and size, as well as technical factors, were the most common reasons for conversion (23).

The follow-up period in the Lap group was 18.9-80 months. In the long-term period, we found that the rates of overall recurrence, metastatic recurrence and local recurrence were significantly lower in patients who underwent Lap than in those who underwent Open. This finding is a positive outcome for Lap though there is a limitation that tumor size in Lap is significantly smaller than in Open. There were no cases of wound-site recurrence in the two groups. Kim *et al*. reported a case of a port-site metastasis following laparoscopic surgery for a malignant GIST (39). On the other hand, it is recommended in the 2010 National Cancer Care Network guidelines that GISTs are safely retrieved by using a specimen bag (40). We found no significant difference in overall mortality and GIST-related mortality. These findings suggest that Lap is comparable to Open with respect to long-term oncological results and, therefore, may be an optional surgical treatment for gastric GIST. Since the most important prognostic features for GIST are tumor size and mitotic

index, it is fundamentally necessary to take these factors into account for accurately evaluating the long-term oncological outcomes of Lap *versus* Open. If possible, prospective randomized trials comparing Lap to Open should be performed in the near future.

There are several limitations of this study. Firstly, it is difficult to match the tumor size between the Lap group and the Open group. All of the 12 articles reported data on the tumor size. Nine out of the 12 reported that there was no significant difference in tumor size between the two groups. However, in an analysis of pooled data, we found that the tumor size for Lap was significantly smaller (by 1.16 cm) than that for Open. The difference may result from the principle that Lap can be safely performed for GISTs of 5 cm or smaller (14). Secondly, there is a problem regarding the variation of tumor location within the stomach. Nine out of the 12 articles reported data on tumor location in the stomach. Eight out of the nine reported that there was no significant difference in the tumor location between the two groups. Yet most procedures were wedge resection of the stomach, the type of operation, *e.g.* gastrectomy or laparoscopic intragastric surgery, varied depending on tumor size or location. Thirdly, the mitotic index for GIST was variable. Eight out of the 12 articles reported data on the mitotic index in the two groups; all of them reported that there was no significant difference in the mitotic index between the two groups. Fourthly, only two out of the 12 articles reported neoajuvant or adjuvant therapy for GIST. The influence of neoajuvant or adjuvant therapy on prognosis can therefore not be discussed. Considering the period tthat hese studies were carried out, neoajuvant or adjuvant therapy for GIST may not have been performed in some studies.

Significant heterogeneity between studies was observed only for short-term outcomes, including operative time, estimated blood loss, time-to-flatus, time-to-oral intake, duration of hospital stay, and tumor size. In the long-term period, we found no significant heterogeneity between studies. The reason for the observed heterogeneity in operative time and estimated blood loss may be variations in the skills of the surgeon, tumor size, location, and vascularity. The heterogeneity in time-to-flatus may result from differences in operative time and estimated blood loss. Differences in the clinical approach at different institutions may have caused the heterogeneity in time-to-oral intake and the duration of hospital stay. Heterogeneity in tumor size may have resulted from the principle that Lap for GIST should be considered for tumors smaller than 5 cm on preoperative imaging studies.

In conclusion, although there are several limitations, the present meta-analysis shows that Lap for GIST is associated with a reduction in intraoperative blood loss, shorter period to flatus, earlier resumption of oral intake, and shorter duration of hospital stay over the short-term, and is not inferior in long-term oncological outcomes compared to Open. Therefore, Lap may be an acceptable optional treatment to Open for gastric GISTs.

References

1 Katz SC and DeMatteo RP: Gastrointestinal stromal tumors and leiomyosarcomas. J Surg Oncol *97*: 350-359, 2008.

2 Kindblom LG, Remotti HE, Aldenborg F and Meis-Kindblom JM: Gastrointestinal pacemaker cell tumor (GIPACT): Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol *152*: 1259-1269, 1998.

3 Rossi CR, Mocellin S, Mencarelli R, Foletto M, Pilati P, Nitti D and Lise M: Gastrointestinal stromal tumors: From a surgical to a molecular approach. Int J Cancer *107*: 171-176, 2003.

4 von Mehren M: The role of adjuvant and neoadjuvant therapy in gastrointestinal stromal tumors. Curr Opin Oncol *20*: 428-432, 2008.

5 Rubió J, Marcos-Gragera R, Ortiz MR, Miró J, Vilardell L, Gironès J, Hernandez-Yagüe X, Codina-Cazador A, Bernadó L, Izquierdo A and Colomer R: Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. Eur J Cancer *43*: 144-148, 2007.

6 Mucciarini C, Rossi G, Bertolini F, Valli R, Cirilli C, Rashid I, Marcheselli L, Luppi G and Federico M: Incidence and clinicopathologic features of gastrointestinal stromal tumors. A population-based study. BMC Cancer *7*: 230, 2007.

7 DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM and Brennan MF: Two hundred gastrointestinal stromal tumors: Recurrence patterns and prognostic factors for survival. Ann Surg *231*: 51-58, 2000.

8 Essat M and Cooper K: Imatinib as adjuvant therapy for gastrointestinal stromal tumors: a systematic review. Int J Cancer *128*: 2202-2214, 2011.

9 Nishida T, Takahashi T and Miyazaki Y: Gastrointestinal stromal tumor: A bridge between bench and bedside. Gastric Cancer *12*: 175-188, 2009.

10 Downs-Kelly E and Rubin BP: Gastrointestinal stromal tumors: Molecular mechanisms and targeted therapies. Patholog Res Int *2011*: 708596, 2011.

11 Benjamin RS, Blanke CD, Blay JY, Bonvalot S and Eisenberg B: Management of gastrointestinal stromal tumors in the imatinib era: Selected case studies. Oncologist *11*: 9-20, 2006.

12 Eisenberg BL and Judson I: Surgery and imatinib in the management of GIST: Emerging approaches to adjuvant and neoadjuvant therapy. Ann Surg Oncol *11*: 465-475, 2004.

13 Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, Corless CL, Debiec-Rychter M, DeMatteo RP, Ettinger DS, Fisher GA, Fletcher CD, Gronchi A, Hohenberger P, Hughes M, Joensuu H, Judson I, Le Cesne A, Maki RG, Morse M, Pappo AS, Pisters PW, Raut CP, Reichardt P, Tyler DS, Van den Abbeele AD, von Mehren M, Wayne JD and Zalcberg J; NCCN Task Force: NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)-update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw *5*: 1-29, 2007.

14 Nishida T, Hirota S, Yanagisawa A, Sugino Y, Minami M, Yamamura Y, Otani Y, Shimada Y, Takahashi F and Kubota T; GIST Guideline Subcommittee: Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. Int J Clin Oncol *13*: 416-430, 2008.

15 Caterino S, Lorenzon L, Petrucciani N, Iannicelli E, Pilozzi E, Romiti A, Cavallini M and Ziparo V: Gastrointestinal stromal tumors: correlation between symptoms at presentation, tumor location and prognostic factors in 47 consecutive patients. World J Surg Oncol *9*: 13, 2011.
16 Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH and Weiss SW: Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol *33*: 459-465, 2002.
17 Nguyen SQ, Divino CM, Wang JL and Dikman SH: Laparoscopic management of gastrointestinal stromal tumors. Surg Endosc *20*: 713-716, 2006.
18 Otani Y, Furukawa T, Yoshida M, Saikawa Y, Wada N, Ueda M, Kubota T, Mukai M, Kameyama K, Sugino Y, Kumai K and Kitajima M: Operative indications for relatively small (2-5 cm) gastrointestinal stromal tumor of the stomach based on analysis of 60 operated cases. Surgery *139*: 484-492, 2006.
19 Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y and Chipponi J: Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg *73*: 712-716, 2003.
20 Abraham NS, Byrne CM, Young JM and Solomon MJ: Meta-analysis of non-randomized comparative studies of the short-term outcomes of laparoscopic resection for colorectal cancer. ANZ J Surg *77*: 508-516, 2007.
21 Catena F, Di Battista M, Fusaroli P, Ansaloni L, Di Scioscio V, Santini D, Pantaleo M, Biasco G, Caletti G and Pinna A: Laparoscopic treatment of gastric GIST: Report of 21 cases and literature review. J Gastrointest Surg *12*: 561-568, 2008.
22 Goh BK, Chow PK, Chok AY, Chan WH, Chung YF, Ong HS and Wong WK: Impact of the introduction of laparoscopic wedge resection as a surgical option for suspected small/medium-sized gastrointestinal stromal tumors of the stomach on perioperative and oncologic outcomes. World J Surg *34*: 1847-1852, 2010.
23 Karakousis GC, Singer S, Zheng J, Gonen M, Coit D, DeMatteo RP and Strong VE: Laparoscopic *versus* open gastric resections for primary gastrointestinal stromal tumors (GISTs): A size-matched comparison. Ann Surg Oncol *18*: 1599-1605, 2011.
24 Lee HH, Hur H, Jung H, Park CH, Jeon HM and Song KY: Laparoscopic wedge resection for gastric submucosal tumors: A size-location matched case-control study. J Am Coll Surg *212*: 195-199, 2011.
25 Matthews BD, Walsh RM, Kercher KW, Sing RF, Pratt BL, Answini GA and Heniford BT: Laparoscopic *vs*. open resection of gastric stromal tumors. Surg Endosc *16*: 803-807, 2002.
26 Pitsinis V, Khan AZ, Cranshaw I and Allum WH: Single center experience of laparoscopic *vs*. open resection for gastrointestinal stromal tumors of the stomach. Hepatogastroenterology *54*: 606-608, 2007.
27 Nishimura J, Nakajima K, Omori T, Takahashi T, Nishitani A, Ito T and Nishida T: Surgical strategy for gastric gastrointestinal stromal tumors: Laparoscopic *vs*. open resection. Surg Endosc *21*: 875-878, 2007.
28 Silberhumer GR, Hufschmid M, Wrba F, Gyoeri G, Schoppmann S, Tribl B, Wenzl E, Prager G, Laengle F and Zacherl J: Surgery for gastrointestinal stromal tumors of the stomach. J Gastrointest Surg *13*: 1213-1219, 2009.
29 Wu JM, Yang CY, Wang MY, Wu MH and Lin MT: Gasless laparoscopy-assisted *versus* open resection for gastrointestinal stromal tumors of the upper stomach: Preliminary results. J Laparoendosc Adv Surg Tech A *20*: 725-729, 2010.
30 Melstrom LG, Phillips JD, Bentrem DJ and Wayne JD: Laparoscopic *versus* open resection of gastric gastrointestinal stromal tumors. Am J Clin Oncol *35*: 451-454, 2012.
31 De Vogelaere K, Hoorens A, Haentjens P and Delvaux G: Laparoscopic *versus* open resection of gastrointestinal stromal tumors of the stomach. Surg Endosc *27*: 1546-1554, 2013.
32 Lee PC, Lai PS, Yang CY, Chen CN, Lai IR and Lin MT: A gasless laparoscopic technique of wide excision for gastric gastrointestinal stromal tumor *versus* open method. World J Surg Oncol *11*: 44, 2013.
33 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol 62: e1-34, 2009.
34 DerSimonian R and Laird N: Meta-analysis in clinical trials. Control Clin Trials *7*: 177-188, 1986.
35 Hozo SP, Djulbegovic B and Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol *5*: 13, 2005.
36 Ohtani H, Tamamori Y, Noguchi K, Azuma T, Fujimoto S, Oba H, Aoki T, Minami M and Hirakawa K: A meta-analysis of randomized controlled trials that compared laparoscopy-assisted and open distal gastrectomy for early gastric cancer. J Gastrointest Surg *14*: 958-964, 2010.
37 Ohtani H, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K and Hirakawa K: A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and conventional open surgery for colorectal cancer. J Cancer *2*: 425-434, 2011.
38 Ohtani H, Tamamori Y, Azuma T, Mori Y, Nishiguchi Y, Maeda K and Hirakawa K: A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and conventional open surgery for rectal cancer. J Gastrointest Surg *15*: 1375-1385, 2011.
39 Kim MD, Kang DH, Park JH, Lee JH, Choi CW, Kim do H, Kim HW and Kim GH: Abdominal wound metastasis after laparoscopic surgery of gastrointestinal stromal tumor. Gut Liver *4*: 283-286, 2010.
40 Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetze S, Sundar HM, Trent JC and Wayne JD: NCCN Task Force report: Update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw *8*: 1-44, 2010.

Received August 20, 2013
Revised September 17, 2013
Accepted September 18, 2013