

Efficacy and Safety of Laparoscopic Endoscopic Cooperative Surgery in Upper Gastrointestinal Lesions: A Systematic Review and Meta-Analysis

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Keywords

Laparoscopic endoscopic cooperative surgery · Endoscopic submucosal dissection · Laparoscopic resection · Subepithelial lesions · Meta-analysis

Abstract

Background and Aims: Laparoscopic and endoscopic cooperative surgery (LECS) combines advantages of endoscopy and laparoscopy in order to resect upper gastrointestinal lesions. Our aim was to evaluate the efficacy and safety of LECS in patients with EGJ (esophagogastric junction), gastric and duodenal lesions, as well as to compare LECS with pure endoscopic and pure laparoscopic procedures. **Methods:** PubMed, Scopus, and ISI Web of Knowledge were searched. Efficacy (R0, recurrence) and safety (conversion rate, procedure and hospitalization time, adverse events, mortality) outcomes were extracted and pooled (odds ratio or mean difference) using a random-effects model. Study quality was assessed with Newcastle-Ottawa Scale and heterogeneity by Cochran's Q test and I². Subgroup analysis according to location was performed. **Results:** This meta-analysis included 24

studies/1,336 patients (all retrospective cohorts). No significant differences were found between LECS and preexisting techniques (endoscopic submucosal dissection (ESD)/laparoscopy) regarding any outcomes. However, there was a trend to shorter hospitalization time, longer procedure duration, and fewer adverse events in LECS versus Laparoscopy and ESD. R0 tended to be higher in the LECS group. Hospitalization time was significantly shorter in gastric versus EGJ lesions (mean 7.3 vs. 13.7 days, 95% CI: 6.6–7.9 vs. 8.9–19.3). There were no significant differences in conversion rate, adverse events, or mean procedural time according to location. There was a trend to higher conversion rate and longer procedure durations in EGJ and higher rate of adverse events in duodenal lesions. **Conclusion:** LECS is a valid, safe, and effective treatment option in patients with EGJ, gastric, and duodenal lesions, although existing studies are retrospective and prone to selection bias. Prospective studies are needed to assess if LECS is superior to established techniques. **Key Messages:** LECS is safe and effective in the treatment of upper gastrointestinal lesions, but there is no evidence of superiority over established techniques.

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Eficácia e segurança da Cirurgia Laparoscópica e Endoscópica Cooperativa em lesões gastrointestinais superiores: revisão sistemática e meta-análise

Palavras Chave

Cirurgia cooperativa Laparoscópica e endoscópica · disseção endoscópica da submucosa · ressecção laparoscópica · Lesões subepiteliais · Meta-análise

Resumo

Introdução e objetivos: A Cirurgia cooperativa laparoscópica e endoscópica (LECS) combina vantagens da endoscopia e laparoscopia na ressecção de lesões gastrointestinais superiores. O nosso objetivo é avaliar a eficácia e segurança da LECS em pacientes com lesões na junção esofagástrica (EGJ), estômago e duodeno, e comparar a LECS com procedimentos puramente endoscópicos e laparoscópicos. **Métodos:** PubMed, Scopus, ISI Web of Knowledge foram pesquisadas. Dados sobre eficácia (R0, recorrência) e segurança (taxa de conversão, duração do procedimento e hospitalização, recorrência, eventos adversos, mortalidade) foram colhidos e agrupados (odds ratio ou média das diferenças), usando modelo de efeitos randomizados. Qualidade dos estudos foi avaliada pela Escala Newcastle-Ottawa e heterogeneidade pelos testes Q da Cochran e I^2 . Foi realizada análise de subgrupos, consoante a localização. **Resultados:** Esta meta-análise incluiu 24 estudos/1336 pacientes (todos coortes retrospectivos). Não encontramos diferenças significativas entre LECS e as técnicas pré-existentes (Disseção endoscópica da submucosa (ESD)/Laparoscopia) em nenhum aspeto. Porém, encontramos uma tendência para hospitalização mais curta, procedimentos mais longos e menos efeitos adversos na LECS versus Laparoscopia e ESD. R0 tende a ser maior no grupo LECS. Hospitalização foi significativamente menor em lesões gástricas versus EGJ (média 7.3 vs. 13.7 dias, 95% CI: 6.6–7.9 vs. 8.9–19.3). Não encontramos diferenças significativas na taxa de conversão, eventos adversos nem tempo médio de procedimento. Porém encontramos uma tendência para taxas de conversão maiores e procedimentos mais longos na EGJ e maior taxa de eventos adversos no duodeno. **Conclusão:** LECS é um tratamento válido, seguro e eficaz em pacientes com lesões na EGJ, estômago e duodeno, apesar dos estudos retrospectivos existentes estarem propensos a viés de seleção. São necessários estudos prospectivos para avaliar a superioridade da LECS face às técnicas existentes. **Mensagens-chave:** LECS é um trata-

mento seguro e eficaz para lesões gastrointestinais superiores, mas sem evidência de superioridade face às técnicas existentes.

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Introduction

Laparoscopic and endoscopic cooperative surgery (LECS) is a procedure, which combines the advantages of endoscopy and laparoscopy. It was proposed by Hiki et al. [1] in 2008 as a technique to resect gastric subepithelial lesions (SELs). Before LECS was developed, SELs were generally treated by laparoscopic wedge resection (LWR). However, gastric SELs may not be recognized from outside of the stomach wall, making it difficult to accurately determine resection lines through LWR [2–4]. This can lead to incomplete or excessive resection, which may lead to increased recurrence or postoperative alterations of the stomach with gastric stasis [2, 4].

The first proposed technique was classical LECS that consists of endoscopic confirmation of the incision lines, followed by an endoscopic mucosal incision, while the seromuscular layer is incised laparoscopically. At the end, the incision line is sutured laparoscopically and the specimen is removed transabdominally [5, 6]. Classical LECS was proposed for SELs without ulceration, regardless of location. Its main benefits are allowing complete resection with minimal margins, preserving gastric motility and postoperative quality of life. Specially in esophago-gastric junction SELs, LECS could avoid total or proximal gastrectomy [4]. However, classical LECS also has some limitations: possible peritoneal contamination with tumor cells or gastric juice (due to opening of the gastric wall) and requirement of advanced endoscopic and laparoscopic skills [7, 8].

To overcome these disadvantages and expand LECS for treatment of SELs with ulceration and gastric epithelial neoplasms, some modifications were developed, such as inverted LECS, combination of laparoscopic and endoscopic approaches to neoplasia with nonexposure technique (CLEAN-NET), nonexposed endoscopic wall-inversion surgery (NEWS), and closed-LECS [4, 6, 7, 9].

Inverted LECS decreases the risk of intraperitoneal seeding by inverting the mass into the gastric lumen. Although this risk is not null, there is also intentional perforation. In addition to classical LECS, it allows the resection of masses with less than 5 cm regardless of the location [6, 7, 10].

CLEAN-NET, NEWS, and closed-LECS are only suitable for SELs lesser than 3 cm. CLEAN-NET includes eversion of the mass and nonexposed full-thickness resection after seromuscular incision, preserving the continuity of the mucosa, that works as a barrier. The risk of mucosal laceration in lesions superior to 3 cm justifies the size limitation [9, 11]. NEWS stands on a “suture first and then cut” rule, including a full-thickness resection technique without intentional perforation [8, 12, 13]. The previous 2 types of modified LECS are not indicated for lesions located at the EGJ or pyloric ring. On closed-LECS and NEWS, lesions are retrieved by the transoral route [3, 4, 7, 9, 14, 15].

Endoscopic submucosal dissection (ESD) is the first-line treatment for gastric epithelial lesions without deep submucosal invasion, allowing en bloc resection, independently of size. Despite this, in SELs the risk of perforation is higher since the resection plan is deeper and is associated with long operation times and long learning curves [6, 7, 16]. Modified LECS procedures can also have a role in SELs located in the deep submucosa/muscle layer and in some early gastric cancers that would be technically difficult to treat with ESD. Specifically in the duodenum, where ESD is associated with a high perforation risk (20–30%), LECS is an attractive option since it might be safer than ESD and conventional surgery [4–6].

According to previous studies, LECS is a safe and feasible procedure, with a complication rate lesser than 5%, but there are no studies demonstrating if LECS is in fact better than ESD or conventional surgery, neither showing which is the better LECS procedure, among the classical and the modified ones [2, 4, 6, 17–19].

The aim of this systematic review and meta-analysis was to evaluate efficacy and safety outcomes of LECS for gastric, EGJ, and duodenal lesions and to compare LECS with competing techniques (ESD and conventional surgery) whenever possible.

Methods

This systematic review and meta-analysis followed the principles set in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement [20].

Study Search and Selection

Studies were identified through scanning of 3 electronic databases (MEDLINE through PubMed, Scopus, and ISI Web of Knowledge), with the last search performed on March 8, 2021. The search query for PubMed was (gastric OR stomach OR duodenal OR duodenum OR “esophagogastric junction”) AND (“laparoscopic and endoscopic cooperative surgery” OR “Laparoscopic-

endoscopic cooperative surgery” OR LECS OR D-LECS OR “non-exposed endoscopic wall-inversion surgery” OR “non-exposed endoscopic wall-inversion surgery” OR “Nonexposed wall-inversion surgery” OR “non-exposed wall-inversion surgery” OR CLEAN-NET OR “combination of laparoscopic and endoscopic approaches for neoplasia with non-exposure technique” OR “Closed-LECS” OR “closed laparoscopic and endoscopic cooperative surgery” OR “non-exposure endoscopic-laparoscopic cooperative surgery” OR “inverted LECS”). Queries for other databases were adapted from this query. No time or language restrictions were made in this phase.

After removal of duplicates, two authors (J.T., S.B.) independently screened all titles and abstracts to exclude irrelevant studies. The full text of selected and relevant studies was then evaluated independently by the same two researchers according to the inclusion criteria described below. This phase was performed with Rayyan online platform [21]. Disagreements were solved by consensus between the authors or with the intervention of a third reviewer (D.L.) when required.

Inclusion criteria were: (1) retrospective or prospective, case-control, or cohort studies and clinical trials; (2) including patients submitted to laparoscopic and endoscopic cooperative surgery due to esophagogastric, gastric and/or duodenal lesions (single-arm studies as well as comparative studies with competing techniques were included); (3) evaluating at least one of the following efficacy or safety outcomes: R0/complete resection; need for conversion; procedure time; hospitalization time; recurrence; adverse events; and mortality. Exclusion criteria were: (1) case reports, reviews, letters to editor, surveys, and animal studies; (2) language other than English/Portuguese/Spanish/Italian/French; (3) studies published only in abstract form; (4) studies including less than 10 patients; and (5) studies with patient overlap with other included studies (in this case, the most informative reference was used).

Data Extraction and Quality Evaluation

Data extraction was performed by S.B. and D.L. Data extraction forms included (1) author, publication year, country, study period, study design, setting (2) population characteristics: numbers of participants, tumor location, histological subtypes; (3) type of resection techniques: LECS (NEWS, CLEAN-NET; closed-LECS), LWR, ESD, laparoscopic resection; and (4) outcomes: R0, need for conversion, procedure time (minutes), hospitalization time (days), recurrence, adverse events, and mortality. Data regarding costs and quality of life were also extracted whenever possible.

Quality evaluation was performed using the Newcastle-Ottawa Assessment Scale adapted, for cohort studies, by S.B. and D.L. [22]. Newcastle-Ottawa Scale ranges from 0 to 9 points in double-arm studies and from 0 to 6 points in single-arm studies. No specific value is assigned to high or low quality, although higher scores indicate higher quality and greater methodological aspects.

Data Synthesis and Statistical Analysis

Raw data regarding each outcome (number of events and total) were collected in order to calculate outcome prevalence and standard error. Effect measures included odds ratio (OR) for categorical variables and mean difference (MD) for continuous variables. For continuous outcomes, in some studies, median and range were transformed into mean and standard deviation through the methods proposed by the Cochrane collaboration and Hozo et al. [23, 24]. Meta-analysis was performed with Review Manager 5.4 soft-

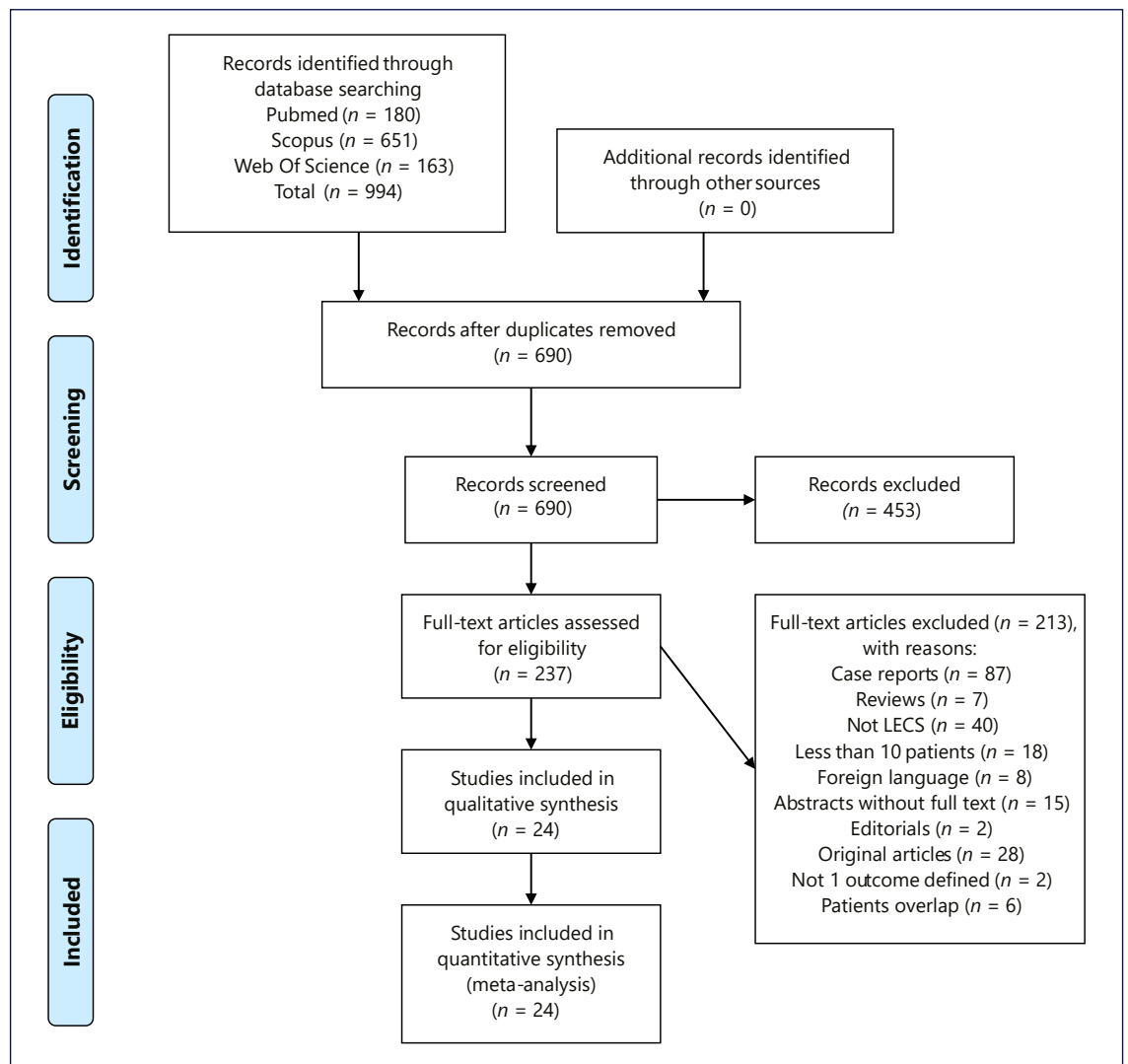


Fig. 1. Flowchart of included studies. LECS, laparoscopic and endoscopic cooperative surgery.

ware [25], using a random-effect model (when at least 3 studies were available for each outcome) [26]. Heterogeneity was evaluated with Cochran Q test and I^2 , being significant heterogeneity defined as $p < 0.05$ or $I^2 > 40\%$, respectively. Subgroup analysis according to lesion was performed for 4 outcomes (need for conversion, procedure time, hospitalization time, and adverse events). Pooled mean for continuous variables and prevalence for categorical variables were calculated with OpenMetaAnalyst and Meta-XL, using a random-effect model [26, 27]. Publication bias was planned if ≥ 10 studies were included in comparative analysis for the primary outcomes (procedure time and adverse events).

Results

Study Selection

A total of 994 studies were identified through data base search. After removing the duplicates, 690 studies were screened regarding title and abstract and 453 were considered irrelevant. Therefore, the full text of 237 studies was assessed for eligibility by applying inclusion and exclusion criteria. Of those, 24 were included in this systematic review and all were included in meta-analysis. Study flowchart is shown in Figure 1, according to the PRISMA statement [20].

Table 1. General characteristics of included studies

Study and year	Country	Type of study	N	Technique	Histological type	Newcastle
<i>Esophagogastric junction</i>						
Aoyama et al. [42], 2020	Japan	Retrospective Single-center	21	LECS (N = 13); NEWS (N = 4); CLEAN-NET (N = 4)	18 Leiomyomas, 2 GISTs, 1 Ectopic pancreas	6*
Hoteya et al. [19], 2014	Japan	Retrospective Single-center	5	LECS	4 Leiomyoma, 1 GIST	6
Ri et al. [48], 2020	Japan	Retrospective Single-center	20	LECS	Not available (all SEL)	7
<i>Stomach</i>						
Hajer et al. [39], 2019	Czech Republic and Austria	Retrospective Two-center	23	NEWS (N = 11); LWR (N = 12)	NEWS: 6 GISTs; 1 Submucosal lipoma, 1 Leiomyoma, 1 Endocrine tumor, 1 Vaneč's tumor, and 1 Ectopic pancreatic; LWR: 7 GISTs; 1 Leiomyoma, 2 Ectopic pancreatic tissue, 1 Endometriosis, 1 Hyperplasiogenic polyp	6
Kanehira et al. [44], 2020	Japan	Retrospective Single-center	69	CLEAN-NET (N = 50); LWR (N = 19)	CLEAN-NET: 25 GIST; 10 Schwannoma; 6 Leiomyoma; 3 Ectopic pancreas; 3 Granuloma; 1 Carcinoid tumor; 1 Glomus tumor; 1 Cyst; LWR: 11 GIST; 7 Leiomyoma; 1 Schwannoma	6
Mahawongkajit and Chansawangphuvana [45], 2020	Thailand	Retrospective Single-center	15	LECS (N = 10); NEWS (N = 5)	LECS: 9 GIST; 1 Leiomyoma NEWS: 3 GIST; 1 Schwannoma; 1 Ectopic pancreas	5*
Mitsui et al. [34], 2018	Japan	Retrospective Single-center	28	NEWS	28 GIST	3*
Okubo et al. [47], 2020	Japan	Retrospective Single-center	69	CLEAN-NET (N = 25); Laparoscopic distal gastrectomy (N = 44)	Not available	7
Aoyama et al. [41], 2020	Japan	Retrospective Single-center	42	NEWS	24 GIST; 6 Ectopic pancreas; 5 Leiomyoma; 3 Neurinoma; 2 Granuloma; 1 Hemangioma; 1 Gastritis cystica profunda; 1 Desmoid fibromatosis	6*
Shoji et al. [37], 2018	Japan	Retrospective Single-center	71	LECS (N = 14); NEWS (N = 26); LWR (N = 31)	LECS: 6 GIST; 7 Leiomyoma; 1 other; NEWS: 16 GIST; 2 Leiomyoma; 8 others; LWR: 27 GIST; 1 Leiomyoma; 3 others	7
Balde et al. [30], 2016	China	Retrospective Single-center	60	LECS (N = 30); ESD (N = 30);	60 GIST	9
Cao et al. [38], 2019	China	Retrospective Single-center	45	LECS (N = 25) ESD (N = 20)	45 GIST	5
Hoteya et al. [19], 2014	Japan	Retrospective Single-center	20	LECS	15 GIST; 1 Leiomyoma; 1 Schwannoma; 1 Cavernous hemangioma; 2 Aberrant pancreas	6
Komatsu et al. [32], 2016	Japan	Retrospective Single-center	48	LECS (N = 33) LWR (N = 15)	Not available	7
Kang et al. [28], 2013	China	Retrospective Single-center	101	LECS	78 GIST; 13 Leiomyoma; 3 Ectopic pancreas; 3 NET; 2 Lipoma; 1 Glomus tumor; 1 Inflammatory pseudotumor	6*
Kikuchi et al. [14], 2017	Japan	Retrospective Single-center	10	Closed-LECS	Not available	5*
Ri et al. [48], 2020	Japan	Retrospective Single-center	194	LECS	Not available (all SEL)	7
Waseda et al. [29], 2014	Japan	Retrospective Single-center	22	LECS	10 GIST; 1 NET; 3 Aberrant pancreas; 3 Leiomyoma; 2 Glomus tumor; 2 Schwannoma; 1 Granuloma	6*

Table 1 (continued)

Study and year	Country	Type of study	N	Technique	Histological type	Newcastle
Ojima et al. [36], 2018	Japan	Retrospective Single-center	46	LECS (N = 21); EIGS (N = 25)	46 GIST	7
Tsujimoto et al. [17], 2012	Japan	Retrospective Single-center	20	LECS	16 GIST, 1 Inflammation for parasite; 1 Leiomyoma; 1 Glomus tumor; 1 Aberrant pancreas	5*
Yin et al. [33], 2017	China	Retrospective Single-center	91	LECS (N = 15); Laparoscopic resection (N = 30); ESD (N = 46)	91 GIST	9
<i>Duodenum</i>						
Kanaji et al. [43], 2020	Japan	Retrospective Single-center	20	D-LECS	16 Adenocarcinoma; 2 NET; 1 Adenoma; 1 Ectopic pancreas	5*
Ichikawa et al. [31], 2016	Japan	Retrospective Single-center	12 (13 lesions)	D-LECS	10 Adenocarcinoma; 2 NET; 1 Adenoma	5*
Numobe et al. [46], 2020	Japan	Retrospective Multicenter	206	D-LECS	79 Adenoma; 70 Adenocarcinoma; 36 NET; 7 GIST; 6 Hyperplasia of Brunner's gland; 5 Hyperplastic polyp; 1 Ectopic pancreas; 1 Schwannoma; 1 Ulcer formation and malformation of vessels	5*
Ojima et al. [35], 2018	Japan	Retrospective Single-center	68	D-LECS (N = 18) D-ESD (N = 50)	D-LECS: 7 Intramucosal adenocarcinoma; 1 Adenoma; 6 NET; 4 GIST D-ESD: 14 Intramucosal adenocarcinoma; 27 Adenoma; 6 NET; 1 Hyperplastic polyp; 2 Lipoma	5
Yanagimoto et al. [40], 2019	Japan	Retrospective Single-center	10	D-LECS	6 Adenocarcinoma; 3 Adenoma; 1 Neuroendocrine tumor	6*
Mahawongkajit and Chanswangphuvana [45], 2020	Thailand	Retrospective Single-center	1	NEWS	1 Neuroendocrine tumor	5*

N, total number of cases; M-A, meta-analysis; LECS, laparoscopic and endoscopic cooperative surgery; NEWS, non-exposed endoscopic wall-inversion surgery; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique; GIST, gastrointestinal stromal tumor; SEL, subepithelial lesions; LWR, laparoscopic wedge resection; ESD, endoscopic submucosal dissection; closed-LECS, closed laparoscopic and endoscopic cooperative surgery; D-LECS, laparoscopic and endoscopic cooperative surgery for duodenal neoplasm. *These are single-arm studies. Therefore, the score potential using Newcastle-Ottawa Quality Assessment Form for Cohort Studies ranges from 0 to 6 points.

Fig. 2. a–g Forest plots of several outcomes according to surgical technique. **a** Forest plot of procedure time according to surgical technique (Laparoscopic Techniques vs. LECS). **b** Forest plot of hospitalization time according to surgical technique (Laparoscopic Techniques vs. LECS). **c** Forest plot of adverse event according to the surgical technique (Laparoscopic Techniques vs. LECS). **d** Forest plot of R0 according to the surgical technique (ESD vs. LECS). **e** Forest plot of procedure time according to the surgical technique (ESD vs. LECS). **f** Forest plot of hospitalization time according to the surgical technique (ESD vs. LECS). **g** Forest plot of adverse event according to the surgical technique (ESD vs. LECS). LECS, laparoscopic and endoscopic cooperative surgery; ESD, endoscopic submucosal dissection; SD, standard deviation.

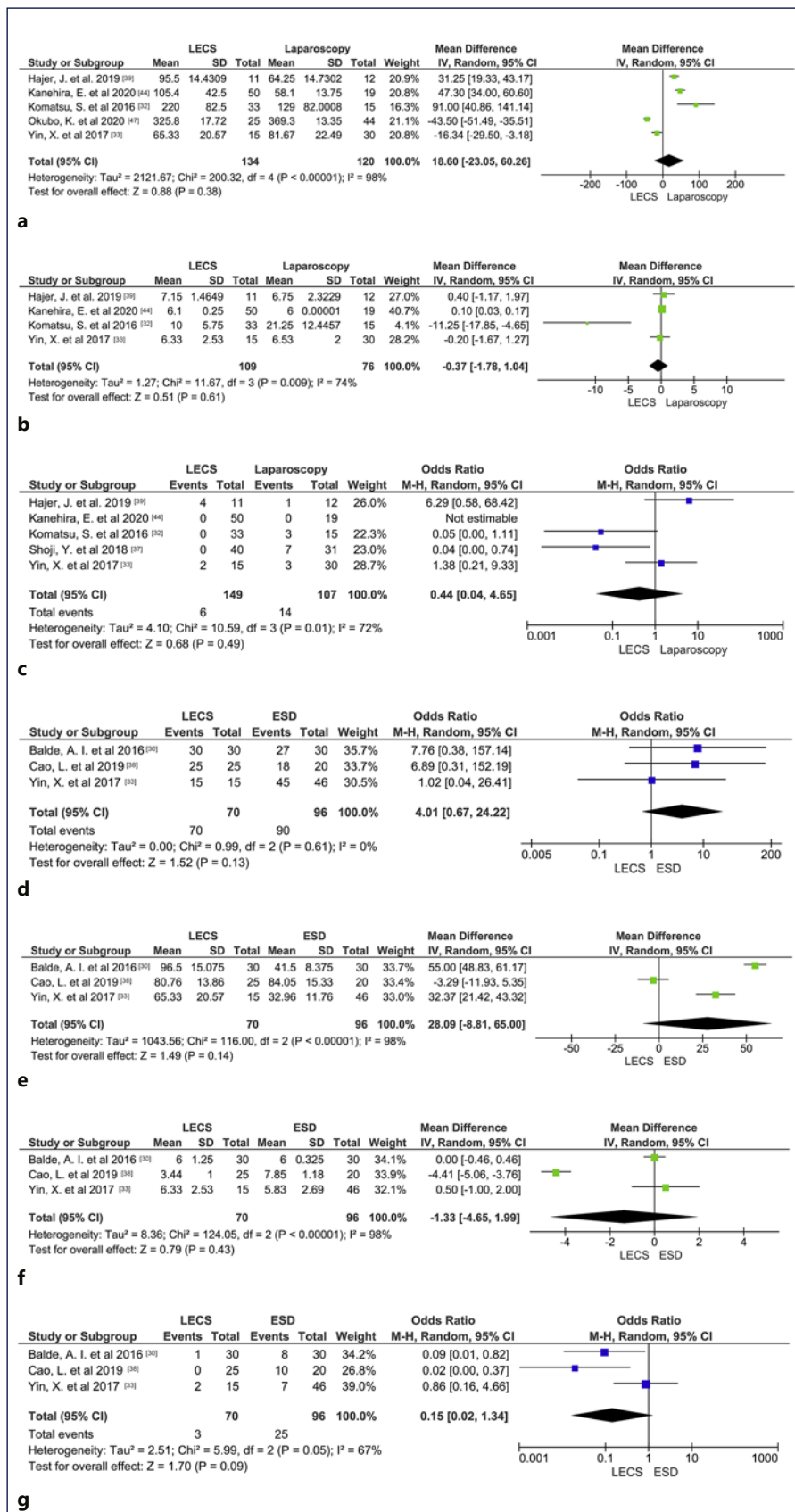


Table 2. Comparative studies

Study	Location	N	Histology SEL versus EL (%)	Ro	Need for conversion	Procedure time, min	Hospitalization time, days	Recurrence	Adverse events	Mortality
<i>EGJ versus Non-EGJ</i>										
Hoteya et al. [19], 2014	EGJ	5	100% versus 0%	5	0	196±48.6	13.2±3.7	0	0	NR
	Non-EGJ	20	100% versus 0%	20	0	145.9±36.5	9.9±1.4	0	0	NR
Ri et al. [48], 2020	EGJ	20	100% versus 0%	20	8	320.25±102.25	20.5±12.5	NR	4	NR
	Non EGJ	194	100% versus 0%	194	2	195.25±86.321	31.75±30.3442	NR	8	NR
<i>LECS versus Laparoscopic Techniques</i>										
Hajer et al. [39], 2019	NEWS	11	100% versus 0%	11	NR	95.5±14.4309	7.15±1.4649	0	4	0
	LWR	12	92% versus 8%	11	NR	64.25±14.7302	6.75±2.3229	0	1	2
Kanehira et al. [44], 2020	CLEAN-NET	50	100% versus 0%	50	0	105.4±42.5	6.1±0.25	0	0	0
	LWR	19	100% versus 0%	19	0	58.1±13.75	6±0.00001	0	0	0
Shoji et al. [37], 2018	LECS (LECS and NEWS)	40	100% versus 0%	40	NR	NR	NR	0	0	NR
	LWR	31	100% versus 0%	31	NR	NR	NR	0	7	NR
Komatsu et al. [32], 2016	LECS	33	NR	33	NR	220±82.5	10±5.75	0	0	NR
	LWR	15	NR	15	NR	129±82.0008	21.25±12.4457	2	3	NR
Okubo et al. [47], 2020	CLEAN-NET	25	NR	NR	NR	325.8±17.72	NR	NR	NR	NR
	Laparoscopic distal gastrectomy	44	NR	NR	NR	369.3±13.35	NR	NR	NR	NR
Yin et al. [33], 2017	LECS	15	100% versus 0%	15	0	65.33±20.57	6.33±2.53	0	2	0
	Laparoscopic resection*	30	100% versus 0%	30	0	81.67±22.49	6.53±2	1	3	0
<i>LECS versus ESD</i>										
Balde et al. [30], 2016	LECS	30	100% versus 0%	30	0	96.5±15.075	6±1.25	0	1	NR
	ESD	30	100% versus 0%	27	0	41.5±8.375	6±0.325	2	8	NR
Cao et al. [38], 2019	LECS	25	100% versus 0%	25	0	80.76±13.86	3.44±1	0	0	0
	ESD	20	100% versus 0%	18	0	84.05±15.33	7.85±1.18	0	10	0
Yin et al. [33], 2017	LECS	15	100% versus 0%	15	0	65.33±20.57	6.33±2.53	0	2	0
	ESD	46	100% versus 0%	45	0	32.96±11.76	5.83±2.69	0	7	0
<i>Duodenal LECS versus ESD</i>										
Ojima et al. [35], 2018	LECS	18	56% versus 44%	18	0	132.75±57.5	7±1.5	NR	0	0
	ESD	50	16% versus 84%	26	0	41±28	3±12	NR	14	0

N, total number of cases; SEL, subepithelial lesions; EL, epithelial lesions; EGJ, esophagogastric junction; NR, data not reported on the study; LECS, laparoscopic and endoscopic cooperative surgery; NEWS, nonexposed endoscopic wall-inversion surgery; LWR, laparoscopic wedge resection; CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia with nonexposure technique; ESD, endoscopic submucosal dissection. *This includes LWR, proximal, and distal gastrectomy.

Study Characteristics and Quality Evaluation

The main study characteristics are shown in Table 1 [14, 17, 19, 28–48]. Most of the studies (23) were from Asia (96%) and 22 studies (92%) were single-center. All studies were retrospective. The median Newcastle-Ottawa Scale score of included studies was 6 (7 in double-arm studies and 5 in single-arm studies). A total of 1,337 lesions, from 1,336 patients, were included in the analysis, of which 46 (3.4%) were located in the EGJ, 974 (72.9%) in the stomach, and 317 (23.7%) in the duodenum. Half of the studies (12) were single-arm (of which 1 study was about lesions on the EGJ, 6 on the stomach, 4 on the duodenum, and 1 had lesions on both the stomach and the duodenum [45]). The other 12 studies were comparative. One study reported data regarding costs [37] and another one regarding quality of life [47].

Comparative Studies

LECS versus Laparoscopic Techniques

Six studies compared the outcomes of LECS and laparoscopic techniques (4 LECS vs. LWR [32, 37, 39, 44]; 1 LECS vs. laparoscopic gastrectomy [47]; 1 LECS vs. LWR and gastrectomy [33]) in gastric lesions. In meta-analysis, procedure time, hospitalization time, and adverse events were not significantly different between the two groups (shown in Fig. 2a–c), although there was a trend to longer procedure time in LECS' group (MD 18.3 min, 95% CI: –23.1 to 60.3, $I^2 = 98\%$), shorter hospitalization time in LECS' group (MD –0.37, 95% CI: –1.8 to 1.0, $I^2 = 74\%$), and lower adverse events rate in LECS' group (4.0% vs. 13.1%, OR: 0.44, 95% CI: 0.04–4.65, $I^2 = 72\%$). Despite the tendency to longer procedure time in LECS' group, in the 2 studies that compared LECS with Laparoscopic gastrectomy [33, 47], procedure time was higher in laparoscopic techniques' group (shown in Table 2). R0 was 100% in LECS group and 99.6% (1/256) in LWR/laparoscopy's group. R0 was not achieved in 1 case using LWR [39]. The conversion rate was 0% in both groups. Recurrence occurred in 3 of 107 cases (2.8%) in laparoscopic techniques' group [32, 33] and in 0 of 149 cases (0%) in LECS' group. Two deaths were reported among the 61 cases of the laparoscopic group [39], and 0 among the 76 cases of the LECS' group (shown in Table 2). Both reported deaths were not related to the oncological disease neither its treatment. Meta-analysis was not possible in these last outcomes.

LECS versus ESD

Three studies compared the outcomes of LECS and ESD in gastric lesions [30, 33, 38]. In meta-analysis, R0,

procedure time, hospitalization time, and adverse events were not significantly different between the two groups (shown in Fig. 2d–g), although there was a trend to higher complete resection rate in LECS's group (100% vs. 94%, OR: 4.01, 95% CI: 0.67–24.22, $I^2 = 0\%$), longer procedure time in LECS' group (MD 28.1, 95% CI: –8.81 to 65.00, $I^2 = 98\%$), shorter hospitalization time in LECS' group (MD –1.33, 95% CI: –4.65 to 1.99, $I^2 = 98\%$), and lower adverse events rate in LECS' group (4.3% vs. 26%, OR: 0.15, 95% CI: 0.02–1.34, $I^2 = 67\%$). The conversion rate was 0% in both groups. Recurrence was noticed in 2 of the 96 cases (2.08%) using ESD [30] and in 0 of the 70 cases using LECS. No deaths were reported in 106 cases (shown in Table 2).

Duodenal LECS versus ESD

One study compared the outcomes of LECS and ESD in duodenal lesions [35]. R0 was 100% in LECS' group, but only 52% in ESD group, corresponding to 26 among the 50 cases. There was no need for conversion in any studies. Procedure duration and hospitalization time were higher in LECS' group. Recurrence was not reported. ESD's group accounted for a total of 14 adverse events (28%), whereas LECS had 0 adverse events among its 18 cases (0%). No deaths were reported (shown in Table 2). Meta-analysis was not performed due to a low number of studies.

Single-Arm Studies regarding LECS

Half of all included studies were noncomparative LECS studies. Twenty-four studies provided data for the calculation of pooled efficacy and safety outcomes. This is shown in Table 3.

EGJ

Three studies provided data on 46 EGJ lesions [19, 42, 48]. R0 resection rate was 100% and pooled conversion rate was 11.3% (95% CI: 0–47.1%, $I^2 = 87\%$). The 8 conversion cases occurred in the same study [48]. Pooled mean procedural time was 246 min (95% CI: 185–307, $I^2 = 89\%$), and pooled mean hospitalization time was 13.7 days (95% CI: 8.0–19.3, $I^2 = 91\%$). Two studies reported recurrence rates [19, 42] and it was 0% (0 in 26 cases). Pooled adverse events' rate was 7.1% (95% CI: 0–24.7%, $I^2 = 67\%$), with all 4 adverse events occurring in the same study [48]. Mortality was 0% (0 in 21 cases).

Gastric

Eighteen studies provided data on 702 gastric lesions [14, 17, 19, 28–30, 32–34, 36–39, 41, 44, 45, 47, 48]. R0

Table 3. Single-arm studies

Study	N	Histology SEL/EL (%)	Ro	Need for conversion	Procedure time, min	Hospitalization time, days	Recurrence	Adverse events	Mortality
<i>EGJ</i>									
Aoyama et al. [42], 2020	21	100% versus 0%	21	0	225±48	9.0±1.9	0	0	0
Hoteya et al. [19], 2014	5	100% versus 0%	5	0	196.0±48.6	13.2±3.7	0	0	NR
Ri et al. [48], 2020	20	100% versus 0%	20	8	320.25±102.25	20,5±12,5	NR	4	NR
<i>Stomach</i>									
Hajer et al. [39], 2019	11	100% versus 0%	11	NR	95.5±14.4309	7.15±1.4649	0	4	0
Kanehira et al. [44], 2020	50	100% versus 0%	50	0	105.4±42.5	6,1±0.25	0	0	0
Mitsui et al. [34], 2018	28	100% versus 0%	NR	2	193.107±59.726	NR	NR	1	NR
Okubo et al. [47], 2020	25	NR	NR	NR	325.80±17.72	NR	NR	NR	NR
Mahawongkajit and Chanswangphuvana [45], 2020	15	100% versus 0%	15	NR	NR	NR	0	0	0
Aoyama et al. [41], 2020	42	100% versus 0%	42	NR	198±14.25	7.0±0.425	0	1	0
Shoji et al. [37], 2018	40	100% versus 0%	40	NR	NR	NR	0	0	NR
Balde et al. [30], 2016	30	100% versus 0%	30	0	96.5±15.075	6.0±1.25	0	1	NR
Cao et al. [38], 2019	25	100% versus 0%	25	0	80.76±13.86	3.44±1.00	0	0	0
Hoteya et al. [19], 2014	20	100% versus 0%	20	0	145.9±36.5	9.9±1.4	0	0	NR
Komatsu et al. [32], 2016	33	NR	33	NR	220±82.5	10±5.75	0	0	NR
Kang et al. [28], 2013	101	100% versus 0%	101	0	113±36	NR	0	2	0
Kikuchi et al. [14], 2017	10	NR	NR	1	253±45	9.2±1.5	0	2	NR
Ri et al. [48], 2020	194	100% versus 0%	194	2	181±49.8333	7±17.5	NR	8	NR
Waseda et al. [29], 2014	22	100% versus 0%	22	0	NR	NR	0	2	NR
Ojima et al. [36], 2018	21	100% versus 0%	21	NR	151±53.5	8.5±2.5	1	1	0
Tsujimoto et al. [17], 2012	20	100% versus 0%	20	0	157.5±68.4	11.6±9.5	0	0	0
Yin et al. [33], 2017	15	100% versus 0%	15	0	65.33±20.57	6.33±2.53	0	2	0
<i>Duodenum</i>									
Mahawongkajit and Chanswangphuvana [45], 2020	1	100% versus 0%	1	0	261	NR	0	0	0
Kanaji et al. [43], 2020	20	15% versus 85%	19	0	236.25±56.75	12.5±2.5	0	2	0
Ichikawa et al. [31], 2016	12	15% versus 85%	NR	0	358.5±101.0511	18.5±12.1552	0	4	NR
Nunobe et al. [46], 2020	206	25% versus 75%	196	11	180±90.1667	9±12	0	38	NR
Ojima et al. [35], 2018	18	56% versus 44%	18	0	132.75±57.5	7±1.5	NR	0	0
Yanagimoto et al. [40], 2019	10	10% versus 90%	10	0	256.35±60.6412	8.75±2.0052	0	2	NR

N, total number of patients; SEL, subepithelial lesions; EL, epithelial lesions; EGJ, esophagogastric junction; NR, data not reported on the study.

resection rate was 100%. Pooled conversion rate was 1.0% (95% CI: 0.4–2.2%, $I^2 = 0\%$). The 5 conversion cases occurred in 3 different studies [14, 34, 48]. Pooled mean procedural time was 158 min (95% CI: 118–199, $I^2 = 100\%$), and pooled mean hospitalization time was 7.3 days (95% CI: 6.6–8.0, $I^2 = 98\%$). Fifteen studies reported recurrence rates and it was 0.22% (1 in 455 cases). This case was reported by Ojima et al. [36], in an 85-year-old patient with a 90-mm lesion. Pooled adverse events' rate was 3.5% (95% CI: 1.8–6.0; $I^2 = 44\%$), with a total of 24

adverse events reported in 677 cases. Mortality was reported only in 9 studies and it was 0% (0 in 300 cases).

Duodenal

Six studies provided data on 267 duodenal lesions [31, 35, 40, 43, 45, 46]. R0 resection rate was 95.7%. Incomplete resection was reported in 11 of 255 cases (4.3%), which included 2 studies: Kanaji et al. [43] and Nunobe et al. [46]. Pooled conversion rate was 4.3% (95% CI: 2.2–7.1; $I^2 = 0\%$). Need for conversion was reported in 11

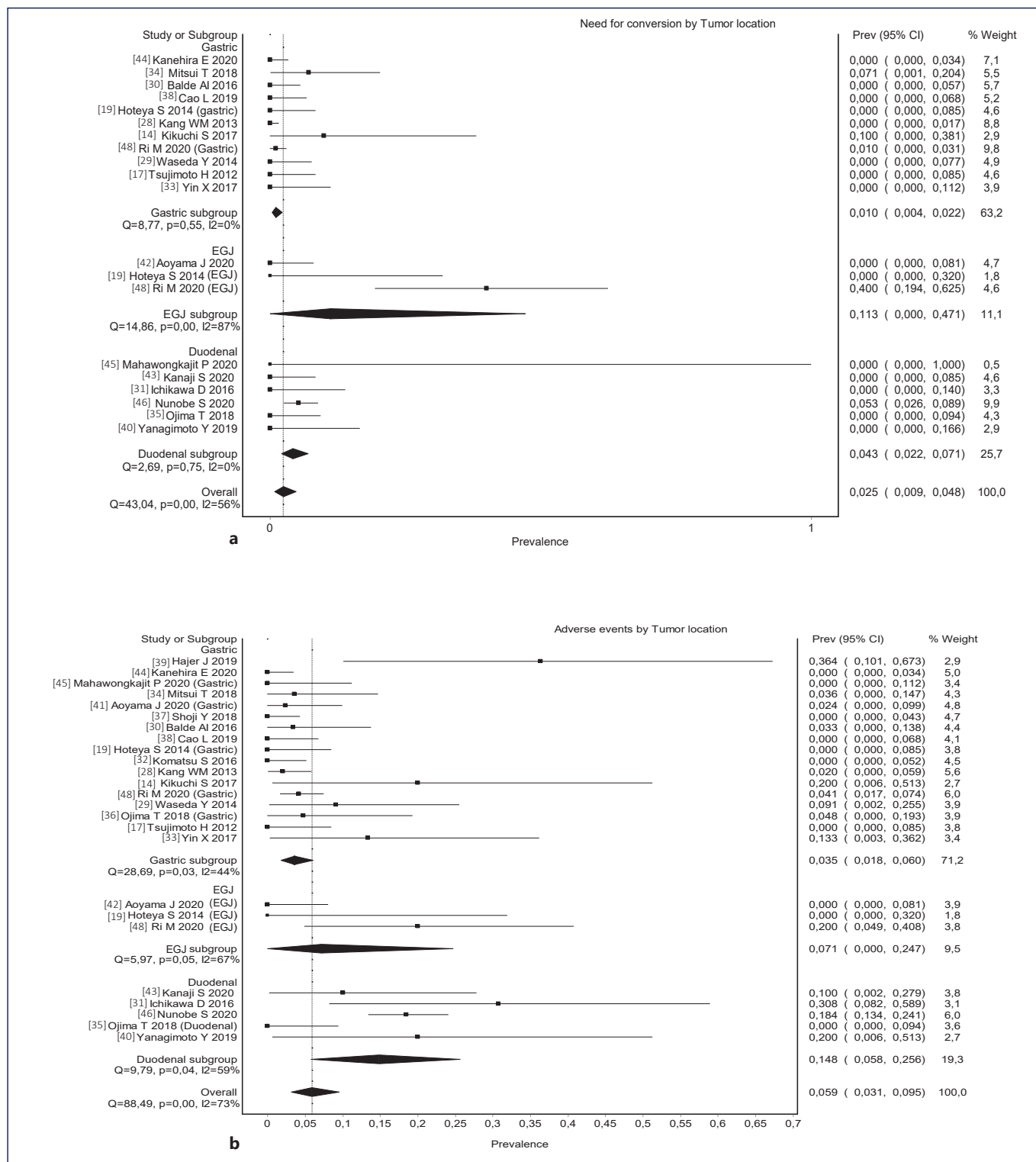
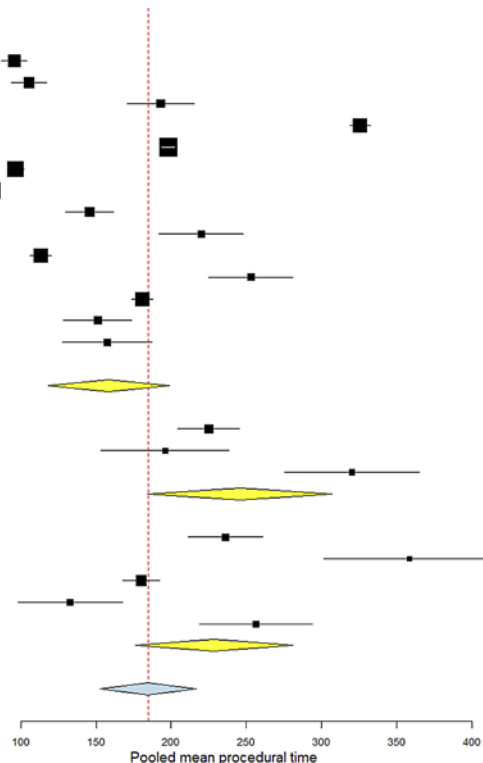


Fig. 3. a–d Rates of conversion and adverse events according to location (gastric, EGJ, and duodenal). Forest plots of mean hospitalization time and mean procedure time according to the location (gastric, EGJ and duodenal). **a** Rates of conversion according to the location (gastric, EGJ, and duodenal). **b** Rates of adverse events

according to the location. **c** Forest plots of mean hospitalization time according to the location (gastric, EGJ, and duodenal). **d** Forest plots of mean procedure time according to the location (gastric, EGJ, and duodenal). EGJ, esophagogastric junction.

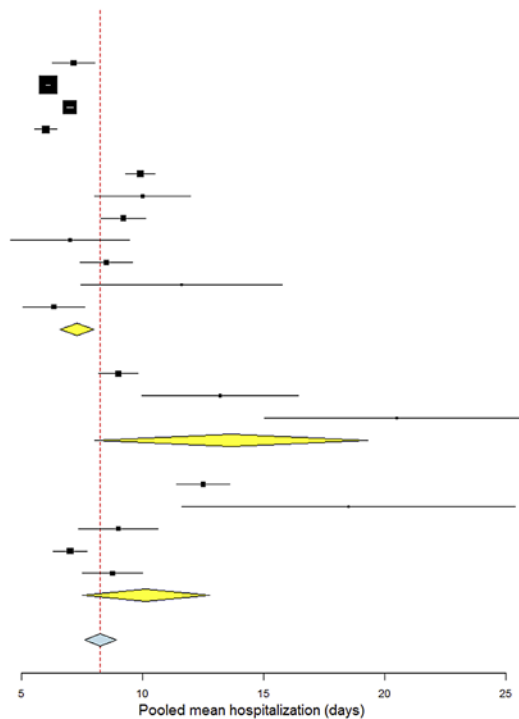
(Figure continued on next page.)

Studies	Estimate (95% C.I.)
Hajer T [39]	95.500 (86.972, 104.028)
Kanehira E [44]	105.400 (93.620, 117.180)
Mitsui T [34]	193.107 (170.985, 215.229)
Okubo K [47]	325.800 (318.854, 332.746)
Aoyama J (Gastric) [41]	198.000 (193.690, 202.310)
Balde AI [30]	96.500 (91.106, 101.894)
Cao L [38]	80.760 (75.327, 86.193)
Hoteya S (Gastric) [19]	145.900 (129.903, 161.897)
Komatsu S [32]	220.000 (191.852, 248.148)
Kang WM [28]	113.000 (105.979, 120.021)
Kikuchi S [14]	253.000 (225.109, 280.891)
Ri M (Gastric) [48]	181.000 (173.988, 188.012)
Ojima T (Gastric) [36]	151.000 (128.118, 173.882)
Tsujimoto H [17]	157.500 (127.523, 187.477)
Yin X [33]	65.330 (54.920, 75.740)
Subgroup Gastric (I²=100% , P=0.000)	158.484 (118.305, 198.662)
Aoyama J (EGJ) [42]	225.000 (204.470, 245.530)
Hoteya S (EGJ) [19]	196.000 (153.401, 238.599)
Ri M (EGJ) [48]	320.250 (275.438, 365.062)
Subgroup EGJ (I²=89% , P=0.000)	245.749 (184.403, 307.095)
Kanaji S [43]	236.250 (211.379, 261.121)
Ichikawa D [31]	358.500 (301.326, 415.674)
Nunobe S [46]	180.000 (167.687, 192.313)
Ojima T (Duodenal) [35]	132.750 (97.871, 167.629)
Yanagimoto Y [40]	256.350 (218.765, 293.935)
Subgroup Duodenal (I²=94% , P=0.000)	228.534 (176.274, 280.793)
Overall (I²=100% , P=0.000)	184.808 (152.510, 217.105)



c

Studies	Estimate (95% C.I.)
Hajer T [39]	7.150 (6.284, 8.016)
Kanehira E [44]	6.100 (6.031, 6.169)
Aoyama J (Gastric) [41]	7.000 (6.871, 7.129)
Balde AI [30]	6.000 (5.553, 6.447)
Cao L [38]	3.440 (3.048, 3.832)
Hoteya S (Gastric) [19]	9.900 (9.286, 10.514)
Komatsu S [32]	10.000 (8.038, 11.962)
Kikuchi S [14]	9.200 (8.270, 10.130)
Ri M (Gastric) [48]	7.000 (4.537, 9.463)
Ojima T (Gastric) [36]	8.500 (7.431, 9.569)
Tsujimoto H [17]	11.600 (7.437, 15.763)
Yin X [33]	6.330 (5.050, 7.610)
Subgroup Gastric (I²=98% , P=0.000)	7.282 (6.587, 7.978)
Aoyama J (EGJ) [42]	9.000 (8.187, 9.813)
Hoteya S (EGJ) [19]	13.200 (9.957, 16.443)
Ri M (EGJ) [48]	20.500 (15.022, 25.978)
Subgroup EGJ (I²=91% , P=0.000)	13.656 (8.025, 19.287)
Kanaji S [43]	12.500 (11.404, 13.596)
Ichikawa D [31]	18.500 (11.623, 25.377)
Nunobe S [46]	9.000 (7.361, 10.639)
Ojima T (Duodenal) [35]	7.000 (6.307, 7.693)
Yanagimoto Y [40]	8.750 (7.510, 9.990)
Subgroup Duodenal (I²=95% , P=0.000)	10.134 (7.513, 12.756)
Overall (I²=98% , P=0.000)	8.257 (7.613, 8.902)



d

3

cases, in Nunobe et al. [46]. Pooled mean procedural time was 229 min (95% CI: 176–281, $I^2 = 94\%$), and pooled mean hospitalization time was 10.1 days (95% CI: 7.5–12.7, $I^2 = 95\%$). Recurrence rate was 0% (0 in 249 cases). Pooled adverse events' rate was 14.8% (95% CI: 5.8–25.6, $I^2 = 59\%$), with a total of 46 adverse events reported in 267 cases. Mortality was reported only in 3 studies [35, 43, 45] and it was 0% (0 in 39 cases).

Overall, pooled conversion rate was 2.5% (95% CI: 0.9–4.8%, $I^2 = 56\%$). Although there were no statistically significant differences in the conversion rate according to the location, there was a trend to higher conversion in EGJ lesions (11.3%, 95% CI: 0–47.1%, $I^2 = 87\%$), followed by duodenal lesions (4.3%, 95% CI: 2.2–7.1%, $I^2 = 0\%$) and gastric lesions (1.0%, 95% CI: 0.4–2.2%, $I^2 = 0\%$). This is shown in Figure 3. Pooled adverse events' rate was 5.9% (95% CI: 3.1–9.5, $I^2 = 73\%$). Although there were no statistically significant differences in adverse events' rate according to the location, there was a trend to higher rate of adverse events in duodenal lesions (14.8%, 95% CI: 5.8–25.6, $I^2 = 59\%$), followed by EGJ lesions (7.1%, 95% CI: 0–24.7, $I^2 = 67\%$) and gastric lesions (3.5%, 95% CI: 1.8–6, $I^2 = 67\%$). This is shown in Figure 3b. Pooled mean procedural time was 185 min (95% CI: 153–217, $I^2 = 100\%$). Mean procedural time was also not significantly different according to the location. However, the same trend was verified: higher procedural time in EGJ lesions (246 min, 95% CI: 184–307, $I^2 = 100\%$), followed by duodenal lesions (229 min, 95% CI: 176–281, $I^2 = 94\%$) and gastric lesions (158 min, 95% CI: 118–199, $I^2 = 100\%$). This is shown in Figure 3c. Pooled mean hospitalization time was 8.3 days (95% CI: 7.6–8.9, $I^2 = 98\%$). Hospitalization time was significantly shorter in gastric lesions versus EGJ lesions (mean 7.3 vs. 13.7 days, 95% CIs of 6.6–7.9 and 8.9–19.3, respectively). There was higher hospitalization time in EGJ lesions (13.7 days, 95% CI: 8–19.3, $I^2 = 91\%$), followed by duodenal lesions (10.1 days, 95% CI: 7.5–12.8, $I^2 = 95\%$) and gastric lesions (7.3 days, 95% CI: 6.6–8, $I^2 = 98\%$). This is shown in Figure 3d.

Costs

Shoji et al. [37] analyzed the operative costs of 3 techniques: LWR, LECS, and NEWS. NEWS was associated with a significantly lower mean total cost, followed by LECS, and being LWR the most expensive technique. The major cause pointed by the authors for these differences was the cost of suturing devices, such as laparoscopic linear staplers, which were less used in the NEWS' group ($p < 0.001$). Authors also referred that, although a hand-sewn technique used on LECS and NEWS was cheaper, it

increased the operative time, resulting in higher personnel and anesthetic expenses.

Quality of Life

Okubo et al. [47] evaluated postoperative quality of life after local resection (CLEAN-NET) and distal gastrectomy, using the Postgastrectomy Syndrome Assessment Scale (PGSAS-45) questionnaire and endoscopic evaluation at 1, 6, and 12 months after surgery. Authors reported significantly endoscopic differences 12 months after gastrectomy, with less esophageal reflux and residual gastritis in the group submitted to CLEAN-NET. CLEAN-NET subgroup also presented better clinical symptoms 12 months after procedure, reporting less indigestion, less dissatisfaction during meals, less dissatisfaction for daily life, and more amount of food ingested per meal, resulting in better nutritional status and body weight ratio.

Histology

Three studies reported histological evaluation of the surgical specimens in the EGJ [19, 42, 48]. All lesions were subepithelial (total of 46 lesions). Regarding gastric lesions, 15 studies reported histological evaluation of 847 surgical specimens [17, 19, 28–30, 33, 34, 36–39, 41, 44, 45, 48]. One lesion (0.1%) was epithelial [39] and the other 846 lesions (99.9%) were subepithelial. Six studies reported histological evaluation of retrieved lesions in the duodenum, making a total of 318 lesions [31, 35, 40, 43, 45, 46]. Seventy-six lesions (24%) were subepithelial and 242 (76%) were epithelial lesions. The location with higher number of epithelial retrieved lesions was the duodenum. This is shown in Tables 2 and 3.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis comparing LECS with laparoscopic techniques (LWR and laparoscopic gastrectomy) and endoscopic techniques (ESD). We found that LECS is an effective and safe therapy for upper GI SELs, with high rates of R0 and low adverse events rates, shorter hospitalization time, and longer procedure time. Additionally, we found that, to date, there is no clear evidence of the benefit of LECS over ESD or LWR/laparoscopy namely in procedural/hospitalization time nor in R0/adverse events, in gastric lesions.

Regarding gastric lesions, no significant differences were found between LECS and preexisting techniques (ESD or LWR/laparoscopy) regarding any outcomes.

This might be explained by the high heterogeneity and low number of comparative studies. However, we could observe some trends in our results: LECS was associated with higher R0, shorter hospitalization time, and longer procedure duration, comparing to ESD. Comparing to laparoscopic techniques, hospitalization time was lower and procedure duration was higher when LECS was the chosen procedure. Although analyzing separately LWR and laparoscopic gastrectomy's procedure duration, we noticed that LECS was shorter than those procedures using laparoscopic gastrectomies and longer than those using LWR. LECS was associated with fewer adverse events comparing with both laparoscopic and endoscopic procedures. Hajer et al. [39] stood out from the other 4 studies [32, 33, 37, 44], which compared adverse events between LECS and LWR/laparoscopy, having a marked deviation to the direction that favors LWR/laparoscopy. It is important to mention that it is a two-center study in which the two compared subgroups were from different hospitals and from different countries. Given that, we cannot assure that both groups have the same characteristics [39].

Regarding duodenal lesions, ESD was associated with nonsignificantly higher rates of incomplete local resection and adverse events, while LECS was associated with nonsignificantly longer procedure duration and hospital stay.

Hospitalization time was significantly shorter in gastric lesions compared to EGJ lesions. There were no statistically significant differences in conversion rate, mean procedural time, or adverse events' rate according to the location. However, there was a trend to higher conversion rate and longer procedure duration in EGJ lesions and higher rate of adverse events in duodenal lesions.

The conversion rate tended to be higher in the EGJ subgroup because Ri et al. [48] reported 8 cases who needed conversion due to esophageal invasion and large defects after lesion resection (more than half of the circumference of the EGJ). This might explain the higher need for conversion presented by this study.

Two studies that reported the need for conversion in gastric lesions [14, 34] used 2 modified procedures: NEWS and closed-LECS, which include transoral removal of the lesion. Several lesions with more than 30 mm were reported, which require conversion to achieve adequate specimen retrieval. Therefore, this may partially explain the higher rates of conversion in these studies.

R0 was nonsignificantly lower in duodenal procedures (95.7% vs. 100%). This can be explained by several technical difficulties such as maintaining an adequate vision

field, accessing the narrow duodenal lumen, holding the endoscope on position, and maneuvering it in such limited space [31, 43, 49, 50]. These difficulties can also explain the higher adverse events' rates in the duodenum, comparing with other gastrointestinal locations.

Both procedure and hospitalization durations tended to be longer in the EGJ group, followed by the duodenum. This can be explained by the higher rate of conversion in these locations, as it will inevitably prolong the duration of the procedure and may lead to more complex techniques, such as proximal gastrectomies. EGJ lesions may be difficult to completely resect without excessive removal of surrounding tissues, increasing the conversion rate. Additionally, it also requires hand-suturing, which contributes to longer duration of the procedure [51].

Some other characteristics were approached. LWR was associated with higher operative costs than LECS and its modified procedures [37]. CLEAN-NET was associated with better postoperative quality of life than distal gastrectomy [47].

In another meta-analysis on this topic, Cai et al. [52] compared LECS with ESD and included Ojima et al. [36] in their meta-analysis. The procedure used by Ojima et al. [36] in the ESD arm (EIGS) did not fit in our definition of ESD, as it required the opening of the abdominal and gastric walls in order to deliver the endoscope and surgical instruments. Despite these differences, Cai et al. [52] reported higher incidence of complications and lower procedure time in ESD. Our results tended to the same conclusions.

This is the first systematic review and meta-analysis comparing LECS with laparoscopic and endoscopic techniques. We evaluated the safety and efficacy of LECS on three different locations: EGJ, stomach, and duodenum.

This systematic review and meta-analysis has some limitations. First, all studies were observational and retrospective reports (mainly single-center), as no randomized controlled trials exist on this subject, making them prone to selection bias. Although median quality of existing studies is good (6), the risk of bias is not null. Second, high heterogeneity was found in some outcomes, probably due to large variations among techniques. Despite being inspired by the same technique, modified LECS procedures have some differences. Moreover, our sample size was relatively small: we analyzed 1,337 lesions in this systematic review and most studies had a small number of cases, which can decrease their precision. Lastly, the number of relevant studies comparing LECS on EGJ and other locations as well as comparing duodenal LECS with ESD was insufficient to perform meta-analysis.

Conclusion

LECS can be a valid, safe, and effective treatment option in patients with EGJ, gastric, and duodenal lesions. However, we consider that treatment choice must be individualized, taking in account the experience of the center and the clinical expertise of the medical team involved. Prospective studies are needed to confirm if LECS is superior to other established techniques.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on the published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Sara Oliveira de Brito and Diogo Libânio conceived and designed the study. Sara Oliveira de Brito and João Pedro Pinho Osório de Araújo Teixeira undertook the bibliographic research and, independently, screened the articles. Sara Brito, Diogo Libânio, and João Pedro Pinho Osório de Araújo Teixeira selected for eligibility, determined inclusion, and reviewed the articles included. Sara Oliveira de Brito drafted the manuscript. Diogo Libânio, Cláudia Martins Marques Pinto, and João Paulo Meireles de Araújo Teixeira revised the draft and approved the final manuscript.

Data Availability Statement

All data generated and analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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