Table 3 Factor structures in the 23 symptom items of PGSAS-45

Factor and item	Mean	SD	Factor loading						
			I	II	III	IV	V	VI	VII
I. Esophageal reflux subscale									
Acid regurgitation	1.81	1.12	**0.968**	−0.031	−0.059	−0.005	0.013	−0.020	−0.065
Bile regurgitation	1.77	1.07	**0.932**	−0.094	−0.127	0.048	−0.001	0.018	0.020
Heartburn	1.75	1.01	**0.638**	0.236	0.091	0.004	−0.048	−0.025	−0.067
Nausea and vomiting	1.49	0.93	**0.617**	−0.039	0.222	−0.144	0.049	0.029	0.091
II. Abdominal pain subscale									
Sucking sensations in the epigastrium	1.49	0.82	0.231	**0.782**	−0.309	−0.006	0.000	0.047	0.042
Abdominal pains	1.74	0.96	0.049	**0.781**	0.176	−0.052	0.001	−0.042	−0.024
Lower abdominal pains	1.87	1.11	−0.258	**0.547**	0.322	0.025	0.117	0.108	0.070
III. Meal-related distress subscale									
Postprandial fullness	2.39	1.21	0.051	0.004	**0.786**	0.019	−0.030	0.021	0.081
Early satiation	2.41	1.21	0.019	−0.002	**0.738**	0.006	−0.009	0.073	0.089
Sense of foods sticking	1.79	1.07	0.388	−0.259	**0.550**	−0.026	0.000	−0.019	0.160
IV. Indigestion subscale									
Increased flatus	2.72	1.43	−0.098	−0.245	−0.118	**0.880**	0.110	0.108	0.080
Borborygmus	1.87	1.06	0.056	0.107	−0.065	**0.723**	0.050	−0.135	0.084
Abdominal distension	1.99	1.12	0.008	0.138	0.174	**0.675**	−0.049	0.034	−0.067
Eructation	1.70	0.97	0.211	0.141	0.197	**0.546**	−0.121	−0.001	−0.210
V. Diarrhea subscale									
Increased passage of stools	2.13	1.29	−0.004	0.035	−0.072	0.003	**0.957**	−0.045	−0.030
Loose stools	2.10	1.18	0.009	0.032	−0.034	−0.018	**0.940**	−0.027	−0.054
Urgent need for defecation	2.19	1.30	0.039	−0.064	−0.030	−0.040	**0.895**	0.008	0.019
VI. Constipation subscale									
Decreased passage of stools	2.12	1.25	−0.001	0.029	−0.043	−0.029	−0.068	**0.956**	−0.016
Hard stools	1.96	1.12	0.017	0.027	−0.012	−0.058	−0.113	**0.942**	−0.021
Feeling of incomplete evacuation	2.42	1.16	−0.037	−0.125	0.099	0.099	0.301	**0.667**	−0.039
VII. Dumping subscale									
Late dumping symptoms	1.81	1.17	0.005	0.020	0.001	0.048	−0.053	0.006	**0.837**
Early dumping general symptoms	1.99	1.21	−0.001	−0.031	0.289	−0.057	0.047	−0.053	**0.778**
Early dumping abdominal symptoms	2.32	1.31	−0.124	0.112	0.369	0.067	0.248	0.004	**0.391**

Extraction method: principal factor method with Promax rotation

Maximum value of factor loading for each item was expressed as bold fonts

almost equivalent to R^2 values evaluated by multivariate analysis (Table 4). These facts indicate that the symptoms asked in the JPGSWP items were significantly more associated with the well-being of the patients than the GSRS items.

Internal consistency of items in each subscale of the PGSAS-45

In addition to the seven symptom-related subscales, two additional subscales have been proposed: a subscale showing quality of food intake and a subscale showing dissatisfaction in daily life. Internal consistency of the items in each of the nine subscales was acceptable, as shown by the Cronbach's α, ranging from 0.65 to 0.88 (Table 5).

Interrelationship between symptom subscales

Correlations between the scores for each symptom subscale are summarized in Table 6. Significant interrelationship ($r > 0.5$) was observed between five subscales—esophageal reflux, abdominal pain, meal-related distress, indigestion, and dumping—whereas the interrelationship between these and two remaining subscales, diarrhea and constipation, were relatively weak ($r > 0.3$).

Table 4 Significance of added 8 symptoms to 15 symptoms of GSRS for evaluating living status and QOL in the gastrectomized patients

	Simple linear regression analysis						Multiple linear regression analysis					
	Sum of GSRS Sx (15)			Sum of added Sx (8)			Sum of GSRS Sx (15)		Sum of added Sx (8)			
	b	*p* value	R^2	*b*	*p* value	R^2	β	*p* value	β	*p* value	R^2	*p* value
Change in body weight (%)*	−0.117	<0.0001	(0.014)	−0.181	<0.0001	0.033	(0.074)	0.0851	−0.240	<0.0001	0.035	<0.0001
Ingested amount of food per meal*	−0.277	<0.0001	0.077	*−0.340*	<0.0001	0.116	(−0.020)	≥0.1	*−0.324*	<0.0001	0.116	<0.0001
Necessity for additional meals	0.288	<0.0001	0.083	*0.365*	<0.0001	*0.133*	(−0.004)	≥0.1	*0.368*	<0.0001	*0.133*	<0.0001
Ability for working	*0.369*	<0.0001	*0.137*	*0.424*	<0.0001	*0.180*	(0.091)	0.0196	*0.353*	<0.0001	*0.183*	<0.0001
Dissatisfaction with symptoms	**0.533**	<0.0001	**0.284**	**0.613**	<0.0001	**0.375**	0.127	0.0002	**0.512**	<0.0001	**0.381**	<0.0001
Dissatisfaction at the meal	*0.480*	<0.0001	*0.230*	**0.580**	<0.0001	**0.336**	(0.054)	≥0.1	**0.537**	<0.0001	**0.338**	<0.0001
Dissatisfaction at working	*0.475*	<0.0001	*0.226*	**0.553**	<0.0001	**0.306**	(0.098)	0.0058	*0.476*	<0.0001	**0.310**	<0.0001
Dissatisfaction for daily life subscale	**0.579**	<0.0001	**0.335**	**0.682**	<0.0001	**0.464**	0.105	0.0007	**0.598**	<0.0001	**0.469**	<0.0001
Physical component summary*	*−0.443*	<0.0001	*0.196*	*−0.481*	<0.0001	*0.231*	−0.166	<0.0001	*−0.349*	<0.0001	*0.241*	<0.0001
Mental component summary*	*−0.458*	<0.0001	*0.210*	*−0.461*	<0.0001	*0.212*	−0.249	<0.0001	−0.269	<0.0001	*0.235*	<0.0001
Interpretation of effect size	*b*, β	R^2										
None–very small	<(0.100)	<(0.020)										
Small	≥0.100	≥0.020										
Medium	*≥0.300*	*≥0.130*										
Large	**≥0.500**	**≥0.260**										

In items or subscales with *, higher score indicating better condition. In items or subscales without *, higher score indicating worse condition

The fonts of values of *b*, β or R^2 were varied according to their effect size; 'None-very small' as parenthetic, 'Small' as normal fonts, 'Medium' as italic fonts and 'Large' as bold fonts

Table 5 Internal consistency of each subscale of the PGSAS-45

Subscales	Cronbach's α
Esophageal reflux	0.83
Abdominal pain	0.71
Meal-related distress	0.76
Indigestion	0.74
Diarrhea	0.88
Constipation	0.81
Dumping	0.80
Quality of ingestion	0.65
Dissatisfaction for daily life	0.81
Interpretation of Cronbach's α	
Excellent	$0.9 \leq \alpha$
Good	$0.7 \leq \alpha < 0.9$
Acceptable	$0.6 \leq \alpha < 0.7$
Poor	$0.5 \leq \alpha < 0.6$
Unacceptable	$\alpha < 0.5$

Main outcome measures and other outcome measures in the PGSAS study (Table 2)

After the validation process, data obtained by the PGSAS study will undergo subsequent analyses, mainly comparisons between different surgical procedures, and the results will be published in due time. For use in these analyses, main outcome measures were determined.

Seven symptoms subscales, total symptom score, a subscale showing quality of feeding, a subscale showing dissatisfaction in life, PCS, and MCS were selected as main outcome measures in the future analyses. In addition, the amount of food per meal occasion (item 34) and necessity of an additional meal (item 41) were added as single items because they correlated well with the ability to work (item 42) and various QOL measures such as PCS, MCS, and dissatisfaction for daily life subscale (data not shown). Dissatisfaction with the symptoms, dissatisfaction at the meal, and dissatisfaction during work (items 43–45) were also added as single items to see how these affected QOL of the postgastrectomy patients. Apart from the scores derived from PGSAS-45, body weight loss (percentage of body weight loss in relationship to preoperative weight) as obtained from the medical record was added as the main outcome measures.

Discussion

After gastrectomy, patients suffer from various illnesses and functional problems comprehensively referred to as

Table 6 Inter-factor correlations among symptom subscales of the PGSAS-45

Subscale	I	II	III	IV	V	VI	VII
I. Esophageal reflux	1.000						
II. Abdominal pain	**0.590**	1.000					
III. Meal-related distress	**0.598**	**0.608**	1.000				
IV. Indigestion	**0.545**	**0.549**	**0.584**	1.000			
V. Diarrhea	0.276	*0.374*	*0.364*	*0.450*	1.000		
VI. Constipation	*0.391*	*0.445*	*0.447*	*0.454*	0.274	1.000	
VII. Dumping	**0.514**	**0.607**	**0.640**	**0.575**	*0.467*	*0.391*	1.000
Interpretation of effect size	*r*						
Small	≥0.100						
Medium	*≥0.300*						
Large	**≥0.500**						

The fonts of values of *r* were varied according to their effect size; 'Small' as normal fonts, 'Medium' as italic fonts and 'Large' as bold fonts

PGS [1–6]. Although the primary objective of gastrectomy is to cure cancer, the second most important goal is to minimize PGS-related adverse events and to preserve the patients' QOL. This goal is particularly important in the Far East where gastric cancer is often found at early clinical stages so that more patients manage to survive their cancer and consequently need to face the PGS in the long term [9]. It is known that the type of gastrectomy affects the incidence and severity of PGS [10–21], and various procedures to preserve or reconstruct gastric function have been proposed to confront these problems [7, 8]. To gain deeper understanding of the PGS, a group of iatrogenic disorders, and treat them appropriately, it is important to grasp the impact of various symptoms, along with feeding problems and body weight loss, to the living status and QOL of the patients. In addition, identifying the problems and their correlations with various types of surgical procedures may lead to evolution of a novel surgical technique as well as more adequate selection of conventional technique to circumvent the problems. However, instruments designed to focus on the evaluation of PGS have not been established to date.

Patient-reported outcome directly reflects the symptoms and complaints of patients. This type of report is particularly valuable as an endpoint when evaluating QOL after surgery because PGS often is detected only through complaints from the patients [22]. Several studies made comparisons between different surgical procedures to find which procedure is beneficial for the patients from the point of view of PGS, but these comparisons often looked only at specific outcomes that particularly aroused the interest of the investigators [17, 19] and were not necessarily comprehensive and convincing. Moreover, using arbitrary endpoints renders comparisons between different studies impossible. More recently, investigators turned to the established and authorized questionnaires for comparisons between gastric surgery procedures [10–15, 18, 20], because there are several combinations of core questionnaires and disease-specific modules that are considered appropriate and have been approved for evaluation of QOL [23, 24]. A combination of SF-36, a core questionnaire, and GSRS, a symptom-specific QOL, has been one of the examples [11, 14], but the GSRS may have a tendency to overlook some of the symptoms that are peculiar to the patients who have undergone gastrectomy and are unusual for other disorders of the gastrointestinal tract. EORTC QLQ-C30 [25], a cancer-specific core questionnaire, and STO-22 [26] is another combination that has been used to evaluate postgastrectomy patients [12, 13]. However, these questionnaires have been developed to evaluate QOL of the patients who are burdened with cancer and are receiving treatments rather than those who became cancer free through surgery but are suffering from PGS.

The investigators who wish to evaluate PGS had thus been obliged to turn to modules designed for other purposes because of the lack of an optimally constructed questionnaire. Therefore, there are possibilities that a large proportion of these studies have overlooked several important postgastrectomy symptoms that actually affect the living status of the patients but cannot be evaluated by conventional scales. More recently, Nakamura et al. reported on DAUGS, a questionnaire designed to measure symptoms after upper gastrointestinal surgery, and the actual attempt to use this in the clinical setting [16, 21]. However, items concerning living status or QOL of the patients rather than the symptoms were lacking in the DAUGS.

PGSAS-45 was constructed through contribution of several expert surgeons with abundant experience coping with postgastrectomy patients as the only comprehensive questionnaire that is suitable for evaluating patients who have undergone various types of gastrectomy and reconstruction. PGSAS-45 is a package with complex structures

and includes items from multiple dimensions. Its core stems from internationally acclaimed questionnaires in that it contains items from SF-8 [27] and GSRS under the permission of each copyright owner for this study. GSRS has five subscales that are in common with the PGSAS-45 and has been extensively used to evaluate patients with various disorders of the gastrointestinal tract [28, 29]. However, it does not cover some symptoms that are peculiar to postgastrectomy patients such as postprandial satiation and symptoms related to the dumping syndrome. PGSAS-45 was constructed through contributions of several expert surgeons during the comprehensive item generation phase. Inclusion of the 8 additional symptom-related items that were proposed and selected by the surgeons to evaluate postgastrectomy patients is expected to increase sensitivity to more meticulously detect and evaluate the PGS. Multivariate regression analysis has shown through larger β coefficients that the 8 items actually correlated more significantly with most of the subscales looking at the living status and QOL of the patients when compared with the 15 items derived from GSRS. Moreover, the R^2 values of the JPGSWP items as calculated by the bivariate regression analysis were almost equivalent to R^2 values of all symptom items calculated by the multivariate analysis, indicating that the 8 items had a decisive role in evaluating the effect of surgery on the living status and QOL of the patients. The relatively large effect size of the total symptoms in the R^2 value, which was calculated by multivariate analysis, indicates that the symptom has a certain impact on living status and QOL in the postgastrectomy patients (Table 4).

Factor analysis resulted in construction of five subscales that are in common with the GSRS. Two of these subscales actually contained items that are different from the GSRS. In addition, two novel subscales, meal-related distress and dumping, were generated that would apparently result in extra sensitivity to detect symptoms. Two further subscales showing dissatisfaction for daily life and quality of ingestion were added to augment QOL and living status domains. Cronbach's α is a coefficient of internal consistency and is commonly used as an estimate of the reliability. The interpretation of Cronbach's α is shown in Table 5. Acceptable internal consistency was observed in all nine subscales, including the four new subscales.

Conclusions

In conclusion, we have developed a useful multidimensional integrated quality of life measure, PGSAS-45. This questionnaire benefited from addition of the eight symptom-related items derived from comprehensive item generation process contributed by expert surgeons, and led to generation of two additional subscales: meal-related distress subscale and dumping subscale. It is expected to serve as a gold standard in the evaluation of PGS and provide a meticulous profile of symptoms in postgastrectomy patients. Furthermore, the PGSAS study generated a prospective multi-institutional database of HRQOL assessed by PGSAS-45 among patients who were treated by the six most frequent types of gastrectomy. Several comparative analyses using these data and main outcome measures as defined in the current study are ongoing, and results are awaited.

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REVIEW ARTICLE

Totally laparoscopic total gastrectomy for gastric cancer: Literature review and comparison of the procedure of esophagojejunostomy

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KEYWORDS
circular stapler;
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totally laparoscopic total gastrectomy

Summary There has been a recent increase in the use of totally laparoscopic total gastrectomy (TLTG) for gastric cancer. However, there is no scientific evidence to determine which esophagojejunostomy (EJS) technique is the best. In addition, both short- and long-term oncological results of TLTG are inconsistent. We reviewed 25 articles about TLTG for gastric cancer in which at least 10 cases were included. We analyzed the short-term results, relationships between EJS techniques and complications, long-term oncological results, and comparative study results of TLTG. TLTG was performed in a total of 1170 patients. The mortality rate was 0.7%, and the short-term results were satisfactory. Regarding EJS techniques and complications, circular staplers (CSs) methods were significantly associated with leakage (4.7% vs. 1.1%, $p < 0.001$) and stenosis (8.3% vs. 1.8%, $p < 0.001$) of the EJS as compared with the linear stapler method. The long-term oncological prognosis was acceptable in patients with early gastric cancers and without metastases to lymph nodes. Although TLTG tended to increase surgical time compared with open total gastrectomy and laparoscopy-assisted total gastrectomy, it reduced intraoperative blood loss and was expected to shorten postoperative hospital stay. TLTG is found to be safer and more feasible than open total gastrectomy and laparoscopy-assisted total gastrectomy. At present, there is no evidence to encourage performing TLTG for patients with advanced gastric cancer from the viewpoint of long-term oncological prognosis. Although the current major EJS techniques

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are CS and linear stapler methods, in this review, CS methods are significantly associated with leakage and stenosis of the EJS.

1. Introduction

Laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer was first performed by Kitano et al[1] in 1994 and showed satisfying short-term results.[2] The long-term results of LADG for early gastric cancer were also favorable,[3] and LADG was reported to be surgically less invasive and lead to an earlier recovery than open surgery.[4,5]

The number of reports on laparoscopy-assisted total gastrectomy (LATG) for gastric cancer has increased with the advancement of techniques for lymphadenectomy and reconstructive procedures for the upper stomach.[6–10] However, esophagojejunostomy (EJS) via minilaparotomy in LATG is relatively difficult because of the limited angle of the direct view, depending on the patient's somatotype and obesity index, and totally laparoscopic total gastrectomy (TLTG) has become more commonly used for intracorporeal anastomosis performed under pneumoperitoneum. As surgical techniques progressed from LATG to TLTG, new EJS techniques have been devised for TLTG.[11–15] TLTG has been widely performed in Japan and Korea and has shown favorable short-term performance results.[16–19]

EJS in TLTG is a very important surgical procedure because it is associated with the risk of anastomotic leakage, bleeding, and stenosis.[20,21] No scientific conclusion can be drawn at present regarding which procedure reduces the postoperative complications of EJS in TLTG because no clear evidence is available based on well-designed randomized controlled trials (RCTs). We retrospectively reviewed reports on various techniques for EJS in TLTG, compared various EJS techniques and complications, and investigated short- and long-term oncological results and comparative study results of TLTG.

2. Methods

2.1. Definition and surgical techniques

This review included TLTG or totally laparoscopic degastrectomy for gastric or remnant gastric cancer, using Roux-en Y reconstruction. As with surgical procedures via minilaparotomy, the removal of resected specimens and performing jejunojejunostomy were permitted. EJS had to be performed intracorporeally under pneumoperitoneum to satisfy the determination of TLTG. Regarding EJS techniques, this review targeted the so-called single stapling technique (SST), double stapling technique (DST), and hemidouble stapling technique (HDST) using circular staplers (CSs), as well as the functional end-to-end anastomosis (FETEA) and overlap methods using linear staplers (LSs), and the hand-sewn (HS) method, and classified procedures into these six types. Reports that did not meet the above criteria or those using several or unknown EJS techniques were excluded from the analyses of EJS techniques.

We analyzed short-term results, relationships between EJS techniques and complications, as well as long-term oncological results and comparative study results of TLTG.

2.2. Search strategy

This review included only English articles identified by the term "totally laparoscopic" or a combination of "laparoscopic" and "total gastrectomy" in the PubMed online database. On July 15, 2013, a final search of PubMed was performed, and we selected and reviewed original articles describing the clinical results of TLTG performed in at least 10 cases. Reports using animal data or those including robotic surgeries were excluded.

2.3. Statistical analyses

Data were collected and analyzed using StatMate IV for Windows (ATMS Co., Ltd., Tokyo, Japan). The Student t test was used to compare the continuous variable, and the Chi-square test was used to compare the categorical variable. A p value < 0.05 was considered significant.

3. Results

3.1. Literature overview

In 2005, Dulucq et al[22] reported the first case series of TLTG for gastric cancer ($n = 8$), which was a prospective single-center study of TLTG and other surgical procedures. Since then, TLTG has become a more commonly used surgical procedure for gastric cancer, and many reports focusing on reconstruction techniques in EJS and short-term results have been published in recent years. Our initial literature search found 629 articles; however, only 25 of them satisfied the conditions described above.[11–19,23–38]

Table 1[11–19,23–36] summarizes the reports cited in this review. Of the 25 articles cited in this review, only two were prospective studies and the remaining 23 were retrospective studies. Three articles described comparative studies of TLTG and open total gastrectomy (OTG),[16,17,19] including one comparing TLTG versus LATG.[18] Sixteen articles focused on surgical and short-term results only, and nine articles described long-term oncological results.[13,17,23,25,27,29,35–37]

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Table 1 Outline of the cited articles.

Author	Publication year	Study design	Comparative study	Total number	EJS method
Huscher et al[23]	2007	Retrospective	No	11	FETEA
Topal et al[16]	2008	Prospective	TLTG vs. OTG	38	SST/DST
Usui et al[11]	2008	Retrospective	TLTG vs. TLTG with J pouch	23	SST
Ziqiang et al[24]	2008	Retrospective	No	14	FETEA
Okabe et al[12]	2009	Retrospective	No	16	FETEA
Jeong and Park[13]	2009	Retrospective	No	16	DST
Shinohara et al[25]	2009	Retrospective	No	55	FETEA
Kinoshita et al[14]	2010	Retrospective	No	10	SST
Bracale et al[26]	2010	Retrospective	No	67	FETEA
Inaba et al[15]	2010	Retrospective	No	53	Overlap
Marangoni et al[27]	2012	Retrospective	No	53	DST
Moisan et al[17]	2012	Prospective	TLTG vs. OTG	31	HS
Nunobe et al[28]	2011	Retrospective	No	41	DST
Tsujimoto et al[29]	2012	Retrospective	TLTG vs. LPG	15	Overlap
Jeong et al[30]	2012	Retrospective	TLTG vs. LDG	118	SST/DST
Lee et al[31]	2012	Retrospective	No	27	FETEA
Shim et al[32]	2013	Retrospective	SST vs. DST vs. HDST vs. Overlap	48	SST/DST/HDST/Overlap
Kim et al[33]	2012	Retrospective	No	124	FETEA
Yoshikawa et al[34]	2013	Retrospective	No	20	SST
Kim et al[18]	2013	Retrospective	TLTG vs. LATG	90	FETEA
Kim et al[19]	2013	Retrospective	TLTG vs. OTG	139	FETEA
Ebihara et al[35]	2013	Retrospective	No	65	FETEA
Lafemina et al[36]	2013	Retrospective	No	17	DST
Kim et al[37]	2013	Retrospective	No	36	SST
Nagai et al[38]	2013	Retrospective	Early group vs. recent group	94	Overlap

DST = double stapling technique; EJS = esophagojejunostomy; FETEA = functional end-to-end anastomosis; HDST = hemidouble stapling technique; HS = hand-sewn; LATG = laparoscopy assisted total gastrectomy; LDG = laparoscopic distal gastrectomy; LPG = laparoscopic proximal gastrectomy; OTG = open total gastrectomy; SST = single stapling technique; TLTG = totally laparoscopic total gastrectomy.

As for EJS techniques, SST, DST, HDST, FETEA, overlap, and HS methods were used in seven, seven, one, 10, four, and one articles, respectively.

3.2. Patient demographics

Table 2[1–19,23–38] summarizes the backgrounds of patients reported in the articles cited in this review. TLTG was performed in a total of 1170 patients, and of the 1094 with data on sex ratios, TLTG was more often performed on men (760 men vs. 334 women). Some studies reported mean values, and the others used median values for age and body mass index; when mean values were used, the mean age and mean body mass index were calculated to be 62.2 years and 23.2 kg/m^2, respectively. A history of open abdominal surgery was described in seven articles, and 92 patients (92/559, 16.5%) had a history of open abdominal surgery. In 462 patients with data on clinical stage, the numbers of patients in each of the TNM classification (7th edition) by the Union for International Cancer Control were 1/317/65/54/25 in the order of clinical stages 0/I/II/III/IV, respectively.

Table 2 also presents data containing clear surgical indication of TLTG. Thirteen reports had no limitations on the indication of TLTG for advanced gastric cancer, and the others limited indication to cases of T3 or less and N1 or less gastric cancer.

3.3. Surgical data

Table 3[11–19,23–38] provides the surgical results of TLTG. Some studies used median values, and others used mean values to report the surgical results. The mean surgical time and mean blood loss calculated from reported mean values were 254.2 minutes and 114.0 mL, respectively. For lymphadenectomy, the numbers of patients classified as D0/D1/D1+/D2 in the 14th edition of the Japanese Classification of Gastric Carcinoma by the Japan Gastric Cancer Association were 0/13/238/270, respectively, and some of the patients with advanced gastric cancer concomitantly underwent pancreatosplenectomy or splenectomy. Twenty-three patients were converted to OTG, mostly owing to intraoperative accidental symptoms as well as uncontrollable bleeding and difficulties in EJS techniques. The mean number of dissected lymph nodes calculated from the reported mean values was 39.5.

3.4. Postoperative data

Table 4[11–19,23–38] provides the postoperative results of TLTG. Postoperative complications included leakage of the EJS (n = 33), leakage of the duodenal stump (n = 19), anastomotic bleeding (n = 33), postoperative pancreatic fistula (n = 16), and stenosis of the EJS (n = 38). The

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Table 2 Patients demographics.

Author	Publication year	Total number	Sex M/F	Age (y) Mean ± SD or median (range)	BMI (kg/m^2) Mean ± SD or median (range)	Previous abdominal surgery	TNM classification UICC, 7th edition (0/I/II/III/IV)	Surgical indication
Huscher et al[23]	2007	11	ND	ND	ND	ND	0/4/1/2/4	Advanced included
Topal et al[16]	2008	38	23/15	68.0 (37–85)	24.0 (17–30)	ND	0/17/7/10/4	Advanced included
Usui et al[11]	2008	23	18/5	67.7 ± 11.5	23.7 ± 11.5	ND	ND	Under T2 and N1
Ziqiang et al[24]	2008	14	9/5	57.4 ± ND	ND	ND	ND	Advanced included
Okabe et al[12]	2009	16	11/5	70.0 (39–81)	20.8 (16.7–27.6)	ND	ND	Any T and N0
Jeong and Park[13]	2009	16	10/6	59.0 ± ND	23.0 ± ND	0	ND	Under T2 and N0
Shinohara et al[25]	2009	55	41/14	59.0 (29–80)	ND	ND	0/17/12/16/10	Advanced included
Kinoshita et al[14]	2010	10	9/1	63.7 (45–80)	22.4 (18.0–26.0)	ND	ND	Any T and N0
Bracale et al[26]	2010	67	45/22	66.9 ± ND	ND	ND	0/35/15/12/5	Advanced included
Inaba et al[15]	2010	53	40/13	59.4 (30–82)	22.0 (15.0–32.4)	ND	ND	Advanced included
Marangoni et al[27]	2012	13	ND	ND	ND	ND	1/3/4/5/0	Advanced included
Moisan et al[17]	2012	22	ND	67.0 (29–83)[a]	26.0 (19–30)[a]	10[a]	ND	Advanced included
Nunobe et al[28]	2011	41	31/10	65.8 ± 1.6	23.8 ± 0.6	9	0/41/0/0/0	Under T1 and N0
Tsujimoto et al[29]	2012	15	10/5	65.8 ± 14.3	20.8 ± 3.8	ND	0/10/2/1/2	Under T3 and N1
Jeong et al[30]	2012	118	77/41	63.7 ± 11.0	23.2 ± 3.6	2	ND	Under T2 and N0
Lee et al[31]	2012	27	16/11	59.1 ± ND	24.6 ± ND	ND	0/23/4/0/0	ND
Shim et al[32]	2013	48	33/15	56.7 ± ND	24.3 ± ND	ND	ND	ND
Kim et al[33]	2012	124	77/47	57.4 ± ND	23.6 ± ND	27	ND	Advanced included
Yoshikawa et al[34]	2013	20	ND	ND	ND	ND	ND	ND
Kim et al[18]	2013	90	61/29	58.0 ± 10.8	23.2 ± 2.9	21	ND	Advanced included
Kim et al[19]	2013	139	86/53	58.0 (30–84)	23.6 (13.6–32.4)	23	ND	Advanced included
Ebihara et al[35]	2013	65	45/20	65.9 ± 10.2	23.5 ± 4.0	ND	0/65/0/0/0	Stage I
Lafemina et al[36]	2013	17	40/8	64.0 (55–70)[b]	27.1 (24.0–30.5)[b]	ND	ND	Advanced included
Nagai et al[38]	2013	94	64/30	66.0 ± ND	21.6 ± ND	ND	0/71/19/4/0	Advanced included
Kim et al[37]	2013	36	24/12	60.9 ± 11.4	23.4 ± 3.4	ND	0/31/1/4/0	Under T1 and N0
Total or mean		1170	760/334	62.2 [c]	23.2 [d]	92	1/317/65/54/25	

BMI = body mass index; ND = not described in the article; OTG = open total gastrectomy; SD = standard deviation; TLTG = totally laparoscopic total gastrectomy; UICC = Union for International Cancer Control.

[a] Nine laparoscopic subtotal gastrectomy cases were included in these data.[17]

[b] Thirty-one OTG cases were included in these data.[36]

[c] Mean age of the TLTG cases was calculated using every data of the articles, except for median value.

[d] Mean BMI of the TLTG cases was also calculated using every data of the articles, except for median value.

Table 3 Surgical data.

Author	Publication year	Surgical time (min) Mean ± SD or median (range)	Blood loss (mL) Mean ± SD or median (range)	Lymphadenectomy (D0/D1/D1+/D2)	Conversion to OTG	Harvested lymph nodes Mean ± SD or median (range)
Huscher et al[23]	2007	304.0 ± 83.0	ND	0/2/0/9	3 [a]	35.0 ± 18.0 [a]
Topal et al[16]	2008	187.0 (120–360)	10.0 (5–400)	0/0/0/38	0	17.0 (0–90)
Usui et al[11]	2008	305.9 ± 57.6	77.5 ± 71.7	0/0/22/1	0	ND
Ziqiang et al[24]	2008	255.1 ± ND	107.5 ± ND	0/0/0/14	0	ND
Okabe et al[12]	2009	325.0 ± 68.0	195.0 ± 197.0	ND	0	47.0 ± 13.0
Jeong and Park[13]	2009	194.0 ± ND	170.0 ± ND	0/0/16/0	0	33.0 ± ND
Shinohara et al[25]	2009	406.0 (200–865)	102.0 (20–694)	0/0/0/55	0	46 (17–106)
Kinoshita et al[14]	2010	257.0 ± ND	69.0 ± ND	ND	0	43.3 ± ND
Bracale et al[26]	2010	249.0 ± ND	ND	0/5/0/62	7	ND
Inaba et al[15]	2010	373.4 ± 105.0	146.5 ± 325.3	ND	0	ND
Marangoni et al[27]	2012	260.0 ± ND	125.0 ± ND	ND	1	26.0 ± ND
Moisan et al[17]	2012	250.0 (160–240) [b]	100.0 (50–500) [b]	0/3/5/23 [b]	1 [b]	35 (9–68) [b]
Nunobe et al[28]	2011	298.6 ± 10.1	85.9 ± 15.2	0/0/0/41	0	42.8 ± 2.3
Tsujimoto et al[29]	2012	236.4 ± 43.4	51.2 ± 58.0	0/3/7/5	0	38.6 ± 15.4
Jeong et al[30]	2012	292.0 ± 88.0	256.0 ± 207.0	0/0/99/19	1	41.0 ± 16.0
Lee et al[31]	2012	126.2 ± 21.3	ND	0/0/27/0	0	33.7 ± 16.2
Shim et al[32]	2013	A : 229.1 ± 45.7 [c] B : 226.5 ± 51.4 [c] C : 209.0 ± 39.4 [c] D : 205.5 ± 33.1 [c]	ND	ND	0	ND
Kim et al[33]	2012	F : 189.0 ± 46.3 [d] S : 148.3 ± 51.9 [d]	ND	ND	0	42.6 ± 15.5 [d] 37.4 ± 15.7 [d]
Yoshikawa et al[34]	2013	297.1 ± ND	ND	ND	0	ND
Kim et al[18]	2013	166.4 ± 47.5	ND	ND	0	43.1 ± 17.2
Kim et al[19]	2013	144.0 (72–345)	ND	ND	0	37 (2–94)
Ebihara et al[35]	2013	271.5 ± 64.7	85.2 ± 143.2	0/0/62/3	1	30.2 ± 12.4
Lafemina et al[36]	2013	230 (190–277)	250 (150–450)	ND	9	22 (17–28)
Nagai et al[38]	2013	E : 341.4 ± 75.7[e] R : 368.0 ± 94.6[e]	70.2 ± 77.3[e] 80.4 ± 115.0[e]	ND	0	53.4 ± 21.0[e] 47.0 ± 18.8[e]
Kim et al[37]	2013	227.1 ± 57.6	77.1 ± 71.7	ND	0	37.9 ± 10.9
Total or mean		254.2 [f]	114.0 [g]	0/13/238/270	23	39.5 [h]

DST = double stapling technique; HDST = hemidouble stapling technique; ND = not described in the article; OTG = open total gastrectomy; SD = standard deviation; SST = single stapling technique; TLTG = totally laparoscopic gastrectomy.

[a] Eighty-nine laparoscopic subtotal gastrectomy cases were included in these data.[23]

[b] Nine laparoscopic subtotal gastrectomy cases were included in these data.[17]

[c] Shim et al[32] reported four types of EJS techniques: types A, B, C, and D denote SST, DST, HDST, and overlap methods, respectively.

[d] Kim et al[33] reported the comparison of TLTG cases between first 70 cases (F) and subsequent 54 cases (S).

[e] Nagai et al[38] reported the comparison of TLTG cases between early period (E) and recent period (R).

[f] Mean surgical time was calculated using every data of the articles, except for median value.

[g] Mean blood loss was calculated using every data of the articles, except for median value.

[h] Average of harvested lymph nodes was also calculated using every data of the articles, except for median value.

mortality rate was only 0.7% (8/1170). Based on articles with mean values, the time to the first flatus and time to restart oral intake were 3.3 days and 5.0 days, respectively, and the mean postoperative hospital stay was 12.0 days.

3.5. EJS techniques: Overview

Table 5 summarizes the EJS techniques used in the cited articles. For methods of anvil insertion and purse-string suture placement, only representative methods are listed in Table 5. With EJS techniques using LSs, disruption of the esophageal hiatus and slippage of the EJS site into the lower mediastinum are possible. The HS method is highly feasible to use for intracorporeal anastomosis, providing a sufficient view under pneumoperitoneum, and has the advantage of not requiring an entry hole closure. EJS techniques used in 101 patients, 139 patients, 14 patients, 553 patients, 176 patients, 31 patients, and 156 patients were SST, DST, HDST, FETEA, overlap, HS, and unknown methods, respectively.

For the time required to perform EJS, Kinoshita et al[14] reported 6 minutes on average from purse-string suture placement using the HS method to the insertion of the anvil using the SST method. Kim et al[37] also reported that the mean times for purse-string suture and for anvil placement in the SST method were 8.9 minutes and 6.4 minutes,

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Table 4 Postoperative data.

Author	Publication year	EJS leakage	Stump leakage	Bleeding	Pancreatic fistula	EJS stenosis	Mortality	Time to flatus (d) Mean ± SD or median (range)	Time to intake (d) Mean ± SD or median (range)	Hospital stay (d) Mean ± SD or median (range)
Huscher et al[23]	2007	0	2	2	0	0	2	3.4 ± 1.0 [a]	5.9 ± 4.5[a]	11.4 ± 4.5[a]
Topal et al[16]	2008	2	0	0	0	0	1	ND	ND	11.0 (6–73)
Usui et al[11]	2008	0	0	0	0	0	0	ND	ND	11.2 ± 5.3
Ziqiang et al[24]	2008	0	0	0	1	0	0	3.9 ± ND	4.9 ± 1.0	ND
Okabe et al[12]	2009	0	0	0	0	1	0	ND	3.0 (ND)	11.0 (ND)
Jeong and Park[13]	2009	0	0	0	0	0	0	ND	ND (3–5)	11.0 (8–14)
Shinohara et al[25]	2009	2	0	0	7	0	0	ND	3.0 (3–6)	14.0 (9–25)
Kinoshita et al[14]	2010	0	0	0	0	0	0	ND	4.0 (2–10)	13.0 (8–24)
Bracale et al[26]	2010	4	3	5	0	2	1	4.7 ± ND	ND	12.4 (8–45)
Inaba et al[15]	2010	2	1	0	3	1	0	ND	ND	14.4 ± ND
Marangoni et al[27]	2012	0	0	0	0	0	1	ND	ND	11.0 (ND)
Moisan et al[17]	2012	2	2	1	0	0	0	ND	4.0 (2–13)	7.0 (4–59)
Nunobe et al[28]	2011	2	0	0	3	3	0	ND	2.7 ± 0.5	16.9 ± 1.5
Tsujimoto et al[29]	2012	0	0	0	0	0	0	3.0 ± 1.3	4.1 ± 2.2	13.5 ± 9.1
Jeong et al[30]	2012	9	1	11	0	4	2	2.9 ± 0.8	3.5 ± 4.5	11.9 ± 11.9
Lee et al[31]	2012	0	0	3	0	0	0	ND	ND	8.1 ± ND
Shim et al[32]	2013	A : 2 [b]	1 [b]	0 [b]	0 [b]	5 [b]	0 [b]	ND	ND	10.3 ± ND [b]
		B : 2 [b]	0 [b]	0 [b]	0 [b]	4 [b]	0 [b]			8.4 ± ND [b]
		C : 1 [b]	1 [b]	1 [b]	0 [b]	1 [b]	0 [b]			9.3 ± ND [b]
		D : 0 [b]	0 [b]	0 [b]	0 [b]	0 [b]	0 [b]			8.8 ± ND [b]
Kim et al[33]	2012	F : 2 [c]	1 [c]	1 [c]	0 [c]	5 [c]	0 [c]	3.2 ± 0.9 [c]	8.6 ± 9.6 [c]	12.7 ± 11.5 [c]
		S : 0 [c]	0 [c]	3 [c]	0 [c]	1 [c]	0 [c]	3.3 ± 0.9 [c]	5.6 ± 4.6 [c]	8.8 ± 5.8 [c]
Yoshikawa et al[34]	2013	0	0	0	0	0	0	ND	ND	ND
Kim et al[18]	2013	0	1	2	0	4	0	3.4 ± 1.0	4.5 ± 1.8	7.9 ± 4.3
Kim et al[19]	2013	0	1	3	0	2	0	3.0 (2–6)	3.0 (3–46)	7.0 (5–72)
Ebihara et al[35]	2013	0	1	0	1	3	1	1.9 ± 0.7	4.6 ± 1.8	21.4 ± 13.5
Lafemina et al[36]	2013	1	2	1	0	1	0	ND	ND	8.0 (6–9)
Nagai et al[38]	2013	E : 2 [d]	0 [d]	0 [d]	0 [d]	0 [d]	0 [d]	ND	5.5 ± 2.5 [d]	16.7 ± 9.5 [d]
		R : 0 [d]	1 [d]	0 [d]	1 [d]	0 [d]	0 [d]		4.9 ± 4.7 [d]	14.2 ± 12.1 [d]
Kim et al[37]	2013	0	1	0	0	0	0	3.1 ± 0.7	ND	9.2 ± 8.7
Total or Mean		33	19	33	16	38	8	3.3 [e]	5.0 [f]	12.0 [g]

DST = double stapling technique; EJS = esophagojejunostomy; HDST = hemidouble stapling technique; ND = not described in the article; SD = standard deviation; SST = single stapling technique; TLTG = totally laparoscopic gastrectomy.

[a] Eighty-nine laparoscopic subtotal gastrectomy cases were included in these data.[23]

[b] Shim et al[32] reported four types of EJS techniques: types A, B, C, and D denote SST, DST, HDST, and overlap methods, respectively.

[c] Kim et al[33] reported the comparison of TLTG cases between first 70 cases (F) and subsequent 54 cases (S).

[d] Nagai et al[38] reported the comparison of TLTG cases between early period (E) and recent period (R).

[e] Mean time to first flatus was calculated using every data of the articles, except for median value.

[f] Mean time to oral intake was calculated using every data of the articles, except for median value.

[g] Average of postoperative hospital stay was also calculated using every data of the articles, except for median value.

Table 5 EJS techniques overview and comparison of postoperative complications.

	SST	DST	HDST	FETEA	Overlap	HS	*p*
Anvil insertion	Endo PSI EndoStitch Hand-sewn, etc.	Orvil EST, etc.	Orvil, etc.	–	–	–	
Double stapling	–	+	+	–	–	–	
Hiatus destroy	–	–	–	+	+	–	
Anastomosis in mediastinum	–	–	–	+	+	–	
Necessity of entry hole closure	+	+	+	+	+	–	
Diameter of anastomosis (mm)	< 30	< 30 mm	< 30	> 30	> 30	20–30	
Number (*n*) [a]	101	139	14	553	176	31	
Duration of anastomosis Mean ± SD or median (range)	6.0 ± ND [d] 43.2 ± 11.5 [f] P: 8.9 ± 5.1 [g] A: 6.4 ± 3.6 [g]	54.0 ± ND [c] 42.8 ± 11.3 [f]	37.0 ± 7.1 [f]	42.5 ± ND [b] 44.0 ± ND [e]	34.3 ± 6.4 [f]		0.041[f]
Complications (*n*, %)							
EJS leakage	6, 5.9	5, 3.6	1, 7.1	6, 1.1	2, 2.3	2, 6.5	0.009
Bleeding	4, 4.0	1, 0.7	1, 7.1	15, 2.7	0, 0	1, 3.2	0.110
EJS stenosis	12, 11.9	8, 5.8	1, 7.1	12, 2.2	1, 0.6	0, 0	< 0.001
Stump leakage	3, 3.0	2, 1.4	1, 7.1	8, 1.4	2, 1.1	2, 6.5	0.198
Pancreatic fistula	0, 0	3, 2.2	0, 0	9, 1.6	4, 2.3	0, 0	0.680
Mortality (*n*, %)	0, 0	1, 0.7	0, 0	4, 0.7	0, 0	0, 0	0.803

DST = double stapling technique; EJS = esophagojejunostomy; EST = efficient purse-string stapling technique; FETEA = functional end-to-end anastomosis; HDST = hemidouble stapling technique; HS = hand-sewn; ND = not described in the article; SD = standard deviation; SST = single stapling technique.

[a] A total of 156 cases were excluded from these series, because descriptions of EJS techniques and breakdown of methods were unclear.

[b] Ziqiang et al[24] reported these data; the range was 32–66 minutes.

[c] Jeong and Park[13] reported these data; the range was 38–75 minutes.

[d] Kinoshita et al[14] reported these data, but this was the mean time for purse-string by hand-sewn suturing. Its range was 5–7 minutes.

[e] Bracale et al[26] reported these data; the range was 38–54 minutes.

[f] Shim et al[32] reported four types of EJS techniques: types A, B, C, and D denote SST, DST, HDST, and overlap methods, respectively.

[g] Kim et al[37] reported time for purse-string suture (P) and time for anvil placement (A).

respectively. Jeong and Park[13] reported that EJS using the DST method took 54 minutes on average. Ziqiang et al[24] reported that EJS using the FETEA method took 42.5 minutes on average, and Bracale et al[26] also reported that it took 44.0 minutes on average, accounting for 17.7% of the entire surgical time. Shim et al[32] compared four EJS techniques (SST, DST, HDST, and overlap methods) and showed that EJS took 43.2 ± 11.5 minutes, 42.8 ± 11.3 minutes, 37.0 ± 7.1 minutes, and 34.3 ± 6.4 minutes, respectively, with a significantly shorter time required for the overlap method ($p = 0.041$).

Regarding the major postoperative complications associated with each method, the incidence rates of leakage of the EJS were 5.9% (6/101), 3.6% (5/139), 7.1% (1/14), 1.1% (6/553), 2.3% (2/176), and 6.5% (2/31) using the SST, DST, HDST, FETEA, overlap, and HS methods, respectively, showing high rates with HDST, HS, and SST methods ($p = 0.009$). The incidence rates of anastomotic bleeding were also 4.0% (4/101), 0.7% (1/139), 7.1% (1/14), 2.7% (15/553), 0%, and 3.2% (1/31) using the SST, DST, HDST, FETEA, overlap, and HS methods, respectively, with no significant difference between the six methods ($p = 0.110$). The incidence rates of stenosis of the EJS were 11.9% (12/101), 5.8% (8/139), 7.1% (1/14), 2.2% (12/553), 0.6% (1/176), and 0%, using SST, DST, HDST, FETEA, overlap, and HS methods, respectively, showing the highest rate with the SST method ($p < 0.001$). No significant difference was detected for the incidences of leakage of the duodenal stump, postoperative pancreatic fistula, and mortality.

Table 6 Comparison of postoperative complications between CS methods and LS methods.

	CS methods SST DST HDST	LS methods FETEA Overlap	*p*
Number (*n*)	254	729	
Complication (*n*, %)			
EJS leakage	12, 4.7	8, 1.1	< 0.001
Bleeding	6, 2.4	15, 2.1	0.777
Stenosis of EJS	21, 8.3	13, 1.8	< 0.001

CS = circular stapler; DST = double stapling technique; EJS = esophagojejunostomy; FETEA = functional end-to-end anastomosis; HDST = hemidouble stapling technique; LS = linear stapler; SST = single stapling technique.

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In the analysis using the stapling device (Table 6), the incidence of leakage of the EJS was significantly higher in the CS methods than in the LS methods (4.7% vs. 1.1%, $p < 0.001$). The incidence of stenosis of the EJS was also significantly higher in the CS methods than in the LS methods (8.3% vs. 1.8%, $p < 0.001$). No significant difference was detected for the incidence of anastomotic bleeding.

3.6. Long-term outcome

Table 7[13,17,23,25,27,29,35–37] summarizes nine articles that followed the long-term oncological prognosis of patients who underwent TLTG. The use of various prognostic indexes in these articles made it difficult for us to appropriately evaluate the results. The observation periods varied widely (1–160 months) among reports, and several reports included many cases of advanced gastric cancer. For case series including advanced gastric cancer patients, the incidences of recurrence were 11 patients (20.0%) in the report by Shinohara et al,[25] 11 patients (22.0%) in the report by Marangoni et al,[27] five patients (16.1%) in the report by Moisan et al,[17] and 14 patients (29.2%) in the report by Lafemina et al.[36] In the reports of Tsujimoto et al[29] and Ebihara et al,[35] in which strict conditions were established for the indication of TLTG, no recurrence was reported during the observation period.

Regarding survival time, Moisan et al[17] reported 3-year disease-free survival (DFS) and 3-year overall survival (OS) rates of 79.4% and 82.3%, respectively. When the analysis was limited to patients with early gastric cancer, the 3-year DFS and 3-year OS rates were pegged at 81.7% and 93.3%, respectively. Huscher et al[23] reported 5-year DFS and 5-year OS rates of 57.0% and 59.0%, respectively.

3.7. Comparative studies between TLTG and OTG or LATG

Table 8[16–19] provides the overview and conclusions of three TLTG versus OTG comparative studies and one TLTG versus LATG comparative study. The surgical time of TLTG was significantly longer than that of OTG in two articles (Topal et al[16]: 187.0 minutes vs. 150.0 minutes, $p = 0.0003$; Moisan et al[17]: 250.0 minutes vs. 210.0 minutes, $p = 0.007$, mean). However, TLTG was associated with significantly less blood loss in two articles (Topal et al[16]: 10.0 mL vs. 175.0 mL, $p = 0.0001$; Moisan et al[17]: 100.0 mL vs. 300.0 mL, $p = 0.001$, median) and a significantly shorter postoperative hospital stay in two articles (Moisan et al[17]: 7.0 days vs. 10.5 days, $p = 0.001$; Kim et al[19]: 7.0 days vs. 8.0 days, $p < 0.001$, median), with no difference in postoperative complications compared to OTG. All articles concluded that TLTG was safe and feasible compared with OTG and LATG.[16–19]

4. Discussion

At present, low invasive treatments for gastric cancer include endoscopic procedures (such as endoscopic mucosal resection and endoscopic submucosal dissection) and laparoscopic gastrectomy (LG).[39] As is the trend for laparoscopic surgery for various organs,[40,41] laparoscopic-assisted surgery has been switched to totally laparoscopic surgery in LG to allow greater magnification, a wider view, and practical use of more refined surgical techniques. As the noninferiority of LATG to OTG has been demonstrated,[42–44] many reports about TLTG, as cited in this review, have been published. The critical point in TLTG is intracorporeal EJS techniques, if special techniques such as combined resection of adjacent organs[45] and extended lymphadenectomy[25,46] are not taken into consideration.[47] In this review, EJS techniques using CSs were significantly more associated with leakage and stenosis of the EJS, as compared with those using LSs. When SST and DST methods were used for esophageal cancer and colorectal cancer surgery, anastomotic stenosis was considered a relatively frequent complication and occurred in 2.4–10.0% of patients.[48–50] As EJS is performed using longitudinally long devices in LS methods, a wider diameter of anastomosis can be secured, although there are concerns about the possible onset of gastroesophageal reflux disease owing to the disruption of the esophageal hiatus, slippage of the EJS site into the mediastinum, and severe consequences of leakage

Table 7 Long-term outcome.

Author	Publication year	Surgical indication	Follow-up period Mean ± SD or median (range)	Recurrence, *n* (%)	Survival rates (%)
Huscher et al[23]	2007	Advanced included	57.6 ± 44.5[a]	31,[a] 31.0[a]	OS = 59%,[b] DFS = 57%[b]
Jeong and Park[13]	2009	Under T2 and N0	6.4 ± ND	ND	ND
Shinohara et al[25]	2009	Advanced included	16.0 (7–130)	11, 20.0	ND
Marangoni et al[27]	2012	Advanced included	10.0 (3–26)	11, 22.0	ND
Moisan et al[17]	2012	Advanced included	28.0 (ND)	5, 16.1	OS = 82.3,[c] DFS = 79.4[c]
Tsujimoto et al[29]	2012	Under T3 and N1	18.9 ± ND	0, 0	ND
Ebihara et al[35]	2013	Stage I	37.0 (11–68)	0, 0	ND
Lafemina et al[36]	2013	Advanced included	18.0 (11–34)	14, 29.2	ND
Kim et al[37]	2013	Under T1 and N1	13.2 (ND)	ND	ND

DFS = disease-free survival; ND = not described in the article; OS = overall survival; SD = standard deviation.
[a] Eighty-nine laparoscopic subtotal gastrectomy cases were included in these data.[23]
[b] These were the 5-year OS and DFS rates.[23]
[c] These were the 3-year OS and DFS rates.[17]

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Table 8 Comparative studies between TLTG and OTG or LATG.

Author	Publication year	Comparison	Surgical time (min) Mean ± SD or median (range)	Blood loss (ml) Mean ± SD or median (range)	Postoperative complications *n* (%)	Hospital stay Mean ± SD or median (range)	Conclusion for TLTG
Topal et al[16]	2008	Prospective TLTG vs. OTG (38 vs. 22)	187.0 (120–360) 150.0 (120–360) $p = 0.0003$	10.0 (5–400) 175.0 (50–1400) $p < 0.0001$	15, 39.4 9, 40.9 $p = 0.913$	11.0 (6–73) ND $p = 0.847$	Safe and feasible
Moisan et al[17]	2012	Prospective TLTG vs. OTG (31 vs. 31)	250.0 (160–420) 210.0 (135–390) $p = 0.007$	100.0 (50–500) 300.0 (200–1400) $p < 0.001$	7, 22.5 4, 12.9 $p = 0.506$	7.0 (4–59) 10.5 (6–37) $p = 0.001$	Safe and feasible
Kim et al[19]	2009	Retrospective TLTG vs. OTG (139 vs. 207)	144.0 (72–345) 137.0 (65–355) $p = 0.381$	ND ND ND	14, 10.0 45, 21.7 $p = 0.005$	7.0 (5–72) 8.0 (2–34) $p < 0.001$	Safe and feasible
Kim et al[18]	2011	Retrospective TLTG vs. LATG (90 vs. 23)	166.4 ± 47.5 158.5 ± 45.5 $p = 0.461$	ND ND ND	10, 11.1 4, 16.0 $p = 0.500$	7.9 ± 4.3 9.5 ± 7.5 $p = 0.198$	Safe and feasible

LATG = laparoscopy-assisted total gastrectomy; ND = not described in the article; OTG = open total gastrectomy; SD = standard deviation; TLTG = totally laparoscopic total gastrectomy.

of the EJS.[14,34,51] By contrast, the HS method is a simple and low-cost surgical technique, although currently not mainstream.[17,52] According to the time for anastomosis, it may not be a good comparative item in this study, as the devices used and the surgeons' experience and surgical technique cannot be at the same level. The current major EJS techniques of TLTG are obviously CS and LS methods, and which one is superior to the other remains to be determined. To correctly answer the question, analysis of clinical results from well-planned RCTs of EJS techniques in TLTG between CS and LS methods is warranted.

Based on the short-term results of comparative studies of TLTG versus OTG or LATG, it has been concluded that TLTG is, at present, safe and feasible.[16–19] The short-term results of TLTG from the 25 articles cited in the present review are substantially favorable and almost equivalent to the short-term results of OTG.[30–38] Topal et al[16] have suggested that the concomitance of splenectomy ($p = 0.006$) and the number of dissected lymph nodes ($p = 0.042$) are surgical factors related to the onset of postoperative complications of TLTG. Surgeons with only recent experience in performing TLTG more often encounter complications ($p = 0.032$),[16] and so even surgeons who are well experienced in LG should not readily switch to TLTG for advanced gastric cancer.

Regarding the long-term oncological prognosis investigated in this review, TLTG produced extremely satisfying results in patients with early gastric cancer and without metastases to lymph nodes.[29,35] However, the global effectiveness of LADG has been demonstrated only for early gastric cancer,[3,5] and therefore close attention should be paid to the long-term oncological results of LATG and TLTG in Japan. Most of the articles on TLTG were relatively new, and only a few articles included long-term results.[17,23] In addition, the disease stages of cases included in the survey varied widely, and variable prognostic factors specific to advanced gastric cancer, such as peritoneal dissemination, were not taken into consideration at all, and thus the data used in this review were insufficient for accurate analysis of the long-term oncological prognosis.[36] In the future, long-term oncological effectiveness or noninferiority of TLTG for early gastric cancer should be demonstrated based on RCTs using the same method as that used for LADG.

5. Conclusion

We investigated various EJS techniques in TLTG, as well as short-term results, long-term oncological results, and comparative study results of TLTG. At present, TLTG is believed to be a safe and feasible surgical technique for surgeons with a steep learning curve, comparable to OTG and LATG.[52–54] However, because of the difficulty of TLTG when applied to advanced gastric cancer requiring combined resection of adjacent organs and extended lymphadenectomy and its association with an increased risk of serious perioperative complications,[25] the risks and benefits should be weighed prior to performing TLTG. The potential effects of TLTG on the long-term oncological prognosis have not been determined and warrant further investigation.[55] For EJS techniques, leakage and stenosis of the EJS may occur more frequently in CS methods than in LS methods. Although CS and LS methods for EJS are the major techniques used in TLTG at present, further research is necessary to establish which reconstruction techniques are suitable for EJS.

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ORIGINAL ARTICLE

Long-term quality of life after laparoscopic distal gastrectomy for early gastric cancer: results of a prospective multi-institutional comparative trial

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Abstract
Background The aim of this study was to compare the postoperative health-related quality of life (HRQOL) between open and laparoscopic distal gastrectomy.
Methods A multi-institutional nonrandomized study was conducted. Patients with clinical T1 gastric cancer were prospectively enrolled and underwent distal gastrectomy by either the open or laparoscopic approach. HRQOL was measured using the European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 and the site-specific module for gastric cancer. Questionnaires were completed at baseline and at 1, 3, 6, and 12 months postoperatively. Clinicopathological characteristics and short-term outcome including postoperative morbidity and HRQOL were compared between the approaches.
Results A total of 145 patients (open, $n = 72$; laparoscopic, $n = 73$) were enrolled between September 2008 and January 2011 and analyzed. The laparoscopic approach was associated with longer operating time, less blood loss, and a similar incidence of postoperative complications. At each time point, the questionnaires were retrieved from more than 90 % of the patients. The worst scores for most of the scales were observed at 1 month postoperatively and improved thereafter. No statistically significant differences were observed regarding physical functioning, the primary endpoint. On the other hand, role, emotional, cognitive, and social functioning scores were superior in the laparoscopic group at 6 and 12 months postoperatively. Symptom scales including fatigue, pain, eating restriction, taste problems, and anxiety were better in the laparoscopic group before 6 months but not at 12 months.

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Conclusions The study was considered to be negative because no benefit of the laparoscopic approach was observed in terms of physical functioning. However, more favorable scores for some of the symptom scales during the first 6 months and several functioning scales at 12 months after surgery suggest a potential benefit of the laparoscopic approach.

Keywords Quality of life · Questionnaire · Laparoscopic surgery · Gastrectomy · Gastric cancer

Introduction

The laparoscopic approach has been keenly pursued by surgeons who opt to provide patients with minimally invasive surgery, and the indication has been expanded to include oncological surgery. Several prospective randomized trials conducted for colon cancer have shown that the long-term outcome is not inferior when the laparoscopic approach was used [1, 2]. Whether the same is true for gastric cancer surgery remains uncertain because of the greater propensity of gastric cancer cells to scatter into the peritoneal cavity and form deposits, the process being reportedly facilitated by abdominal inflation at the time of laparoscopic surgery. Given the paucity of resectable gastric cancers and expert laparoscopic surgeons devoted to gastric surgery in Western countries, randomized trials of sufficient sample size to make comparisons between the approaches have been conducted exclusively in the Far East. Despite such circumstances, the proportion of laparoscopic approach in gastric cancer surgery in general has increased exponentially during the past decade. In particular, clinically T1 stage gastric cancer tends to be an optimal target for this approach if it is considered to be ineligible for endoscopic submucosal dissection [3].

Regarding short-term outcome, the laparoscopic approach for distal gastric cancer is known for reduced blood loss, prolonged operating time, and lymph node retrieval and morbidity that are equivalent to the open approach [4–7]. Health-related quality of life (HRQOL) as evaluated by established instruments is another important outcome to be compared between the two approaches. In the current study, patient-reported outcome was evaluated and compared between the approaches using the Japanese language version of the European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire Core 30 (QLQ-C30) and QLQ-STO22, a module for evaluating gastric cancer patients [8–11]. The comparison was made among patients with early-stage gastric cancer who underwent distal gastrectomy with the Japanese guideline-oriented lymph node dissection [12]. The study was conducted by a group of hospitals that are affiliated to the Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine.

Patients and methods

This is a prospective nonrandomized phase II study of the difference in the patient-reported outcome between open and laparoscopic gastrectomy for early-stage gastric cancer. The primary endpoint was the longitudinal score of physical functioning as measured by the QLQ-C30 up to 12 months after surgery, and the secondary endpoints were the operating time, amount of blood loss, morbidity, and other subscales in QLQ-C30 and QLQ-ST22.

Patients who were eligible for the following criteria were registered: gastric adenocarcinoma confirmed by endoscopic biopsy; diagnosed as T1 through endoscopy, endoscopic ultrasonography, and computerized tomography; considered as resectable by either distal gastrectomy or pylorus-preserving gastrectomy (PPG); considered as sufficiently medically fit to undergo gastrectomy under general anesthesia; considered to have sufficient ability to fill in the EORTC questionnaires; and having given written consent after the nature of the study had been explained. Patients with secondary malignancy, those with body mass index (BMI) exceeding 28 kg/m^2, and those who needed co-resection of organs other than the gallbladder were deemed ineligible.

The patients were given a set of questionnaires and were asked to fill them in and send them by mail to the Chubu Clinical Oncology Group data center (Nagoya, Japan), which is independent from any of the hospitals. The clinical research coordinator at the data center checked patient eligibility with the registration form sent from the surgeon in charge of the patient and communicated with the patient thereafter regarding retrieval of the additional questionnaires at 1, 3, 6, and 12 months following surgery. The surgeon reported on the surgical data including operating time, blood loss, lymph node retrieval, and morbidity, and pathological findings as soon as all the data were available, and the personnel at the data center decided whether to send further questionnaires based on the exclusion criteria.

The following patients were excluded from the study: those who were intraoperatively converted to open surgery because of unexpected findings of advanced gastric cancer, those who were converted to total gastrectomy for oncological reasons that were not predictable preoperatively (such as multiple cancer undetected preoperatively and positive surgical margin from unexpected cancerous infiltration). Those who were found at pathological examination of the resected specimens to have disease ≥stage II were also excluded because the influence of adjuvant chemotherapy or disease recurrence was likely to interfere

with detection of a difference in postoperative HRQOL. However, patients who were converted to total gastrectomy for technical reasons such as iatrogenic splenic injury were not excluded. In addition, those who were converted to open surgery because of any technical mishaps during surgery were to remain in the laparoscopic surgery group at analyses.

Pylorus-preserving gastrectomy (PPG) was performed when cancer occupied the middle third of the stomach and nodal metastasis seemed unlikely by preoperative imaging studies. D1+ dissection as defined in the Japanese Gastric Cancer Treatment Guidelines [12] was performed in clinically N0 cases and D2 dissection in clinically N1 cases. Cholecystectomy was indicated for those with cholelithiasis at the time of surgery. As a principle, the hepatic branch of the vagal nerve was preserved, but whether to preserve the celiac branch was left to the discretion of the surgeons. Billroth type I anastomosis was generally selected as a node of reconstruction, but Roux-en-Y anastomosis was conducted for patients with small gastric remnants.

The study was performed by ten participating hospitals affiliated to Nagoya University Graduate School of Medicine. Well-trained laparoscopic surgeons approved by the Japan Society for Endoscopic Surgery had been employed in four of the ten hospitals. In these hospitals, a majority of surgery for early-stage cancer is performed by the laparoscopic approach, and patients undergoing open approach were registered only when the patient wished to avoid laparoscopic surgery. In the other six hospitals, all surgery for early-stage cancer was performed by the open approach. Other affiliated hospitals that are in the process of introducing laparoscopic gastrectomy were discouraged from participating in the study because only lean patients with favorable characteristics are likely to undergo surgery by the laparoscopic approach. Surgeons are well accustomed to the technique needed to perform D2 dissection by open approach in all hospitals: the number of gastric cancer patients operated in the year 2009 were 199, 91, 79, and 66 in the four hospitals that performed laparoscopic surgery and 196, 90, 82, 81, 39, and 32 in the other six hospitals. The study was approved by the institutional review board in all hospitals.

Statistical considerations

The study was designed to have a power of 0.8 at a significance level of 5 % to detect the difference in a physical functioning score of 5 points at 1 month postoperatively. Although the calculated sample size was 64 per group, accrual of 70 patients per group was planned to adjust for missing data.

Responses to the questionnaires were scored and missing data treated according to the EORTC scoring manual [13]. Chi-squared analysis was used to compare categorical data, and Student's t test was used for comparison of continuous variables. Linear mixed models were used for comparison of longitudinal scores for QLQ-C30 and QLQ-STO22. For estimating the change in QOL scores from baseline, these models included surgical approach, baseline QOL score, time since the surgery, and the interaction term between surgical approach and time as covariates. A value of $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Between September 2008 and January 2011, 159 patients were registered prospectively and preoperative score sheets were retrieved. Of these, 14 patients were deemed ineligible: 12 patients because of the final histopathological diagnosis of stage II disease, 1 patient because of subsequent total gastrectomy upon confirmation of cancer at the resection margin, and 1 patient because of body weight increase after registration that exceeded BMI of 28 kg/m^2. The remaining 145 patients underwent analyses; 72 underwent open surgery and 73 the laparoscopic approach. One patient who underwent laparoscopic distal gastrectomy was later treated by completion gastrectomy by open approach as a consequence of severe pancreatic fistula and related perforation of the remnant stomach but remained in the laparoscopic approach group for analysis. Six patients in the open surgery group and 10 patients in the laparoscopic surgery group underwent PPG. D2 lymph node dissection was performed in 12 patients among the open surgery group and 7 patients among the laparoscopic surgery group. Nine patients of the open group and 2 of the laparoscopic group underwent preservation of the celiac branch of the vagal nerve.

There were no significant differences between the groups regarding patient demographics and histopathological findings (Table 1). Reflecting the characteristics of gastric cancer patients in Japan, the mean age of the patients was relatively young (62.5 years for the laparoscopic group and 62.8 years for the open surgery group), with favorable BMI (22.3 ± 3.1 kg/m^2 for the laparoscopic group and 22.4 ± 2.7 kg/m^2 for the open surgery group). The laparoscopic approach required longer operating time (230 ± 52 min vs. 214 ± 54 min, $p = 0.07$) but the amount of blood loss was significantly less (98.8 ± 154.1 g vs. 222.8 ± 145.9 g, $p < 0.0001$) (Table 2). The number of lymph nodes retrieved was similar for both groups (33.5 for laparoscopic surgery and 31.0 for open surgery). Postoperative complications were observed in 7 patients treated by the laparoscopic approach

(2 cases of pancreatic fistula, 1 case each of anastomotic leakage, cholangitis, anastomotic stenosis, splenic infarction, and voiding disturbance) and 8 patients treated by open surgery (1 case of delayed gastric emptying and deep vein thrombosis and 1 case each of intraabdominal abscess, anastomotic stenosis, anastomotic bleeding, wound infection, pseudomembranous colitis, delayed gastric emptying, and paralytic ileus), with no in-hospital mortality in either group.

No patient received postoperative adjuvant chemotherapy. One case in the open surgery group had metachronous cancer in the gastric remnant 17 months after surgery but it was removed by endoscopic submucosal dissection. Another case treated by open surgery committed suicide 19 months after surgery, and 1 case treated by laparoscopic surgery died of lung cancer 15 months after surgery. These patients were not excluded from the study.

The questionnaires were retrieved from 97.9 %, 97.9 %, 97.9 %, 93.8 %, and 95.9 % of the patients at baseline, 1 month postoperatively, 3 months postoperatively, 6 months postoperatively, and 12 months postoperatively, respectively. The worst scores in most components of the questionnaire were observed at 1 month postoperatively and improved thereafter. Scores in the functioning scales recovered or surpassed the preoperative value by 12 months postoperatively, but several symptom scores remained inferior to the preoperative value (Fig. 1).

Analyses using the linear mixed model were conducted to detect differences between the two approaches throughout the 12 months of postoperative follow-up. No statistically significant differences were observed regarding physical functioning ($p = 0.17$), the primary endpoint, and global health status/QOL ($p = 0.09$). On the other hand, statistically significant differences in favor of the

Table 1 Comparison of patient characteristics between open gastrectomy (OG) group and laparoscopic gastrectomy (LAG) group

	OG group ($n = 72$)	LAG group ($n = 73$)	p value
Gender (M/F)	47/25	51/22	0.56
Mean age (range) (years)	62.8 (36–81)	62.5 (36–77)	0.70
Mean body mass index ± SD (kg/m^2)	22.4 ± 2.7	22.3 ± 3.1	0.83
Macroscopic type			
Type 0	71	72	0.99
Type 2	1	1	
Depth of invasion			
T1	70	72	0.62
T2	2	1	
Lymph node metastasis			
N0	67	68	0.29
N1	3	5	
N2	2	0	
Pathological stage			
I A	65	67	0.78
I B	7	6	
Pathological type			
Differentiated	32	41	0.34
Undifferentiated	38	31	
Others	2	1	

Table 2 Comparison of surgical procedures and short-term outcomes between open gastrectomy (OG) group and laparoscopic gastrectomy (LAG) group

	OG group ($n = 72$)	LAG group ($n = 73$)	p value
Procedure for gastrectomy			
Distal gastrectomy (DG)	66	63	0.42
Pylorus-preserving gastrectomy (PPG)	6	10	
Lymph node dissection			
D1 and D1+[a]	60	66	0.31
D2	12	7	
Combined resection			
Gallbladder	6	3	0.33
Vagal nerve preservation			
Abdominal branch	9	2	0.031
Reconstruction procedure			
B-I	61	54	0.31
B-II	1	0	
Roux-en-Y	5	9	
Gastro-gastro for PPG	6	10	
No. of retrieval lymph nodes	31.0 ± 15.6	33.5 ± 13.5	0.32
Operating time (min)	213.8 ± 53.8	229.5 ± 51.6	0.07
Bleeding (g)	222.8 ± 145.9	98.8 ± 154.1	<0.0001
Operative morbidity	8 (11.1 %)	7 (9.6 %)	0.79

[a] D1+ is D1 with additional resection of some second-tier lymph nodes (nodes around the left gastric artery, common hepatic artery, and celiac axis)