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Efficiency of bursectomy in patients with resectable gastric cancer: An updated meta-analysis

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ABSTRACT

Aims: A meta-analysis was performed to evaluate the safety and efficiency of bursectomy for patients with gastric cancer.
Method: A literature search was performed in PubMed, EMBASE, and the Cochrane Library databases,-China National Knowledge Infrastructure databases, China Science and Technology Journal(CSTJ) database and ASCO proceedings for clinical research that compared bursectomy with non-bursectomy published before July 2017. Operative time, blood loss, the number of dissected lymph nodes, complications, mortality, length of hospital stay, recurrence rate, overall survival and recurrence-free survival were compared using weighted mean differences(WMD) and relative risks(RR). RevMan 5.3. software was used for statistical analysis.
Results: Fifteen studies including 4858 patients were included for the analysis (2687 in the bursectomy group(BT), 2171 in the non-bursectomy group(NB)). The bursectomy group was associated with longer operative time ($P < 0.00001$)and more blood loss ($P = 0.003$)compared with NB. No statistically significant difference was observed in the number of dissected lymph nodes ($P = 0$ 0.08), the length of hospital stay ($P = 0$ 0.30), rate of complications($P = 0.07$), mortality ($P = 0.15$), recurrence rate ($P = 0.44$)between the bursectomy group and the non-bursectomy group. Bursectomy did not have a significant effect on overall survival and recurrence-free survival.
Conclusions: Gastrectomy with bursectomy is not superior to non-bursectomy in terms of survival,bursectomy is not recommended as a standard surgery for resectable cT3 or cT4 gastric cancer.

Introduction

Gastric cancer(GC) is the second most common cause of cancer-related death due to its malignant potential [1–3]. Radical gastrectomy and regional lymph node dissection were the mainstream of the treatment for advanced (beyond the submucosa) gastric adenocarcinomas. Bursectomy has been developed as a part of radical gastrectomy with the aim of removing the potential microscopic tumor seeding since the 1960s in Japan. Bursectomy is mainly defined as a complete dissection of the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon and with an omentectomy during gastrectomy [4,5]. The clinical value of bursectomy in the treatment of GC is still under debate. Some people think bursectomy may eliminate the majority of cancer cells seeded within the peritoneum. However, other studies found bursectomy cannot eliminate all disseminated free cancer cells, omentum-preserving gastrectomy for advanced gastric cancer(AGC) may not increase the risk of peritoneal relapse. This surgical technique is usually preferred by Far East surgeons [6]

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but is not accepted in the rest of the world. The treatment guideline of Japanese Gastric Cancer Association (JGCA) only recommended that bursectomy can be selectively used for tumors with invasion of the serosa, and should be avoided in T1/T2 tumors [7].

However, the therapeutic effect of bursectomy is controversial because the survival benefit is uncertain. Few studies found that bursectomy could improve survival and should not be abandoned as a futile procedure. Some studies indicated that there were no survival benefits for bursectomy when compared with non-bursectomy for GC patients. A previous meta-analysis [8] in 2014 revealed that bursectomy did not have a significant effect on overall survival, and it was not a significant factor for recurrence-free survival. It only included four studies with language restrictions, unpublished studies and conference abstracts were not included in the meta-analysis. In the recent years, some new studies were presented, and some trials updated the long-term outcomes, the results of large-scale multi-institutional randomized trial (JCOG 1001) was revealed in 2017 ASCO meeting. Therefore, it is necessary to reevaluate the efficiency of bursectomy in the treatment of patients with resectable GC.

Materials and methods

Literature search strategy

A PubMed, Embase, Cochrane Library search, American Society of Clinical Oncology (ASCO) meetings, China National Knowledge Infrastructure(CNKI) databases and China Science and Technology Journal(CSTJ) Database for relevant trials was performed on all studies between 1990 and 2017 to compare bursectomy group(a D2 gastrectomy with bursectomy) and the non-bursectomy group (a D2 gastrectomy without bursectomy) for GC. The following text words were searched as text: “bursectomy ”, “gastric cancer OR stomach cancer”. The “related articles” function was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. No language restrictions were made. All of the abstracts, studies and citations scanned were reviewed. The latest date for this search was July 2017.

Data extraction

Two reviewers(XBH,ML) independently extracted the following from each study: authors, year of publication, country of investigators, sample size (total, eligible, and per arm), study population characteristics, study design, follow-up period, operative time, blood loss, length of hospital stay, the number of harvested lymph node, complications, mortality, recurrence rate, curative effect including overall survival (OS)rate, and the recurrence-free survival (RFS) rate of each eligible trial .

Inclusion and exclusion criteria

All published RCTs and NRCTs in journals or published as meeting abstracts with essential data comparing bursectomy group(BT,a D2 gastrectomy with bursectomy) *vs* the non-bursectomy group (NB,a D2 gastrectomy without bursectomy) for GC were included in our analysis. The inclusion criteria were patients with histologically proven primary adenocarcinoma of the stomach (according to the Japanese classification of gastric carcinoma, second English edition or the Union Internationale contre le Cancer (UICC) tumor-node -metastasis(TNM) system, 7th edition), no prior chemotherapy or radiation therapy; no history of gastrectomy or other malignancy during the previous 5 years.

If necessary, we contacted the authors of the original studies to receive further information. Non-controlled trials, case reports, reviews and comments were excluded.

Assessment of methodological quality

The quality of the RCTs was assessed using modified Jadad's scoring system [9]and Cochrane reviewers' handbook 5.0 RCT criteria [10]. The assessment was based on the randomization methods, the report of dropout rates, allocation concealment, the use of intention-to-treat (ITT) analysis, and losses to follow-up, the extent to which valid results were depicted. Based on these criteria, the studies were divided into high quality group (score ≥ 4) and low quality group (score < 4). The quality of the NRCTs was assessed using a checklist based on a modified version of the Methodological Index for Non-randomized Studies(MINORS) [11].Two reviewers (XBH, ML) independently assessed the eligibility of each trial. Disagreement between authors was resolved by discussion and consensus.

Statistical analysis

The meta-analysis was performed using the Review Manager (RevMan) software, version 5.3, provided by the Cochrane Collaboration. Dichotomous variables were analyzed with relative ratios (RR) and continuous variables with weighted mean difference (WMD). A fixed effect model was adopted unless there was evidence of significant unexplained heterogeneity, in which case, a random effects model was used. Heterogeneity was evaluated by χ^2 and I^2. According to the Higgins' I^2 statistic, heterogeneities<25, 25–50, and>50% were defined as low, moderate, and high, respectively. Publishing bias was tested using the funnel plot. Sensitivity analysis was performed to investigate the possible influence of the study quality on the results. This meta-analysis was performed in accordance with the recommendations of the preferred reporting items for systematic reviews (PRISMA) statements [12]. The confidence interval (CI) was established at 95% and p values of less than 0.05 were considered to indicate statistical significance.

Results

Included trials

The initial search strategy identified 73 articles; screening of their titles and abstracts removed 58 articles, fifteen studies [13–27]published between 1990 and 2017 that met our inclusion criteria and compared BT with NB for GC were therefore included in this meta-analysis. The three studies [15–17] came from the same institution, they shared the same study number, as the separately published data was complementary. Therefore, 13 studies were eligible for the meta-analysis (Fig. 1). The selection process of the studies identified, included and excluded included was shown in Fig. 1. These included a combined total of 4858 subjects, of which 2687(55.31%) was in BT group and 2171 (44.69%) in NB group. The characteristics of these 13 studies are summarized in Table 1. On review of the data extraction, there was 100% agreement among the two reviewers. Quality assessment of studies included in the meta-analysis are listed in Table 1.

Effect of the intervention

Operative outcomes

Eleven studies [14,15,18–21,23–27]reported that operative time. Analysis of the pooled data revealed that operative time was significantly longer in the BT group than in NB group. (WMD: 33.95, 95% CI: [23.21, 44.69], $P < 0.00001$) (Table 2, Fig. 2A). Test for overall effect: $Z = 6.20$ ($P < 0.00001$).

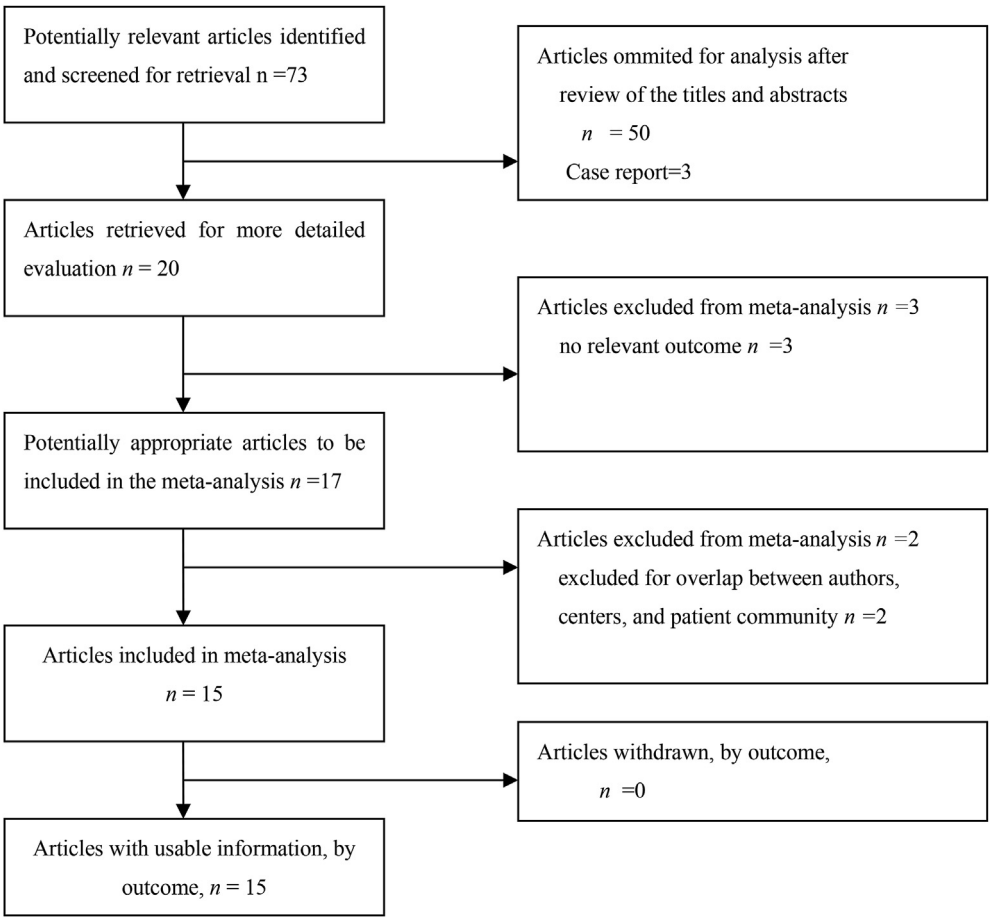


Fig. 1. Flow chart of studies identified, included and excluded.

Seven studies [15,19,21]· [24–27]reported the data regarding the estimated blood loss (EBL).Meta-analysis of all studies revealed BT group was associated with more EBL compared with NB group(WMD: 67.18, 95% CI: [22.42, 111.94], P = 0.003) (Fig. 2B).

Six studies [14,15,18,20,21,25]reported the number of dissected lymph nodes. There was no significant difference in the number of dissected lymph nodes between the two groups (WMD = 5.55; 95% CI: [-0.68, 11.78]; P = 0 0.08) (Fig. 2C).

Hospital stay (d)

Six studies [14,20,21,23–25] mentioned the length of hospital stay (d). The length of hospital stay was similar between the two groups (WMD = 0.31; 95% CI: [-0.27, 0.89]; P = 0 0.30) (Fig. 2D).

Morbidity and mortality

Twelve studies [14,15,18–27] reported postoperative complication rate was similar between the two groups. Meta-analysis of 12 studies revealed that there was no difference between the two groups(RR: 1.14, 95% CI: [0.99, 1.31], *P* = 0.07) (Fig. 2E). There was no significant difference in pancreatic fistula(RR:1.17, 95% CI: [0.56, 2.44], P = 0.67), anastomotic leakage(RR:1.27, 95% CI: [0.47, 3.46], P = 0.64), ileus(RR: 0.96, 95% CI: [0.59, 1.55], P = 0.86), wound infection(RR: 0.93, 95% CI: [0.45, 1.95], P = 0.86), bleeding (RR: 2.67, 95% CI: [0.73, 9.77], P = 0.14), anastomotic stenosis(RR: 0.98, 95% CI: [0.14, 6.94], P = 0.99), abdominal abscess(RR: 0.81, 95% CI: [0.27, 2.48,P = 0.71], pneumonia (RR: 1.19, 95% CI: [0.67, 2.11], P = 0.55) between the two groups(Table 2).

Six studies [15,20,21]· [25–27]mentioned the mortality. Meta-analysis of pooled analysis revealed mortality was similar in the two groups. (RR: 0.42, 95% CI: [0.13, 1.38],*P* = 0.15) (Fig. 2F).

Recurrence rate

Nine studies [13,16,18–22,25,26]reported the data about the recurrence rate. Li [13], Fujita [16], Hasegawa [19], Eom [20], Zhang [25], Yang [26] expatiated and compared the recurrence rate and recurrence type between the two groups. Recurrence patterns were classified as locoregional,peritoneal, hematogenous, or combined metastasis .Meta-analysis of pooled analysis showed that there was no significant difference in the recurrence rate between BT and NB (20.85% *vs.* 19.33%, RR: 1.12, 95% CI: [0.87, 1.44], P = 0.38) (Fig. 3A).

OS and RFS

Nine studies [13,16,18,19]· [21–23,25,27]reported the data about 3-year OS. Meta-analysis of pooled analysis showed that there was no significant difference in 3 −year OS rate between BT and NB(RR: 1.09, 95% CI: [0.95, 1.24], P = 0.21) (Fig. 3B)·In the serosa-positive (pT3–T4) patients, 3-year OS was similar between the two groups. (RR: 1.33, 95% CI: [0.92, 1.91], P = 0.13).

Four studies [17,19,21,24]reported the data about 5-year OS. Meta-analysis of pooled analysis showed that there was no significant difference in 5 −year OS rate between BT and NB (RR: 1.06,95% CI: [0.90, 1.26], P = 0.49) (Fig. 3C). In the serosa-positive (pT3–T4) patients, 5-year OS was similar between the two groups. (RR: 1.53, 95% CI: [0.92, 2.56], P = 0.10).

Three studies reported the data about 3 −year RFS [16,19,21] and 5-year RFS [17,19,21]. Meta-analysis of pooled analysis showed that

Table 1
Characteristics of the 15 selected studies included in the meta-analysis.

Study	Year	Country	Study size			Age		Sex(M/F)		Study type	T stage (T1+2/T3+4)		LND	AC	Follow time		Score[a]
			BT	NB	Total	BT	NB	BT	NB		BT	NB			BT	NB	
Li XM(13)	2007	China	35	21	56	46-71(56.3)		37/19		RCNT		NA	D2	NA	3 Y		15/24
Ha(14)	2008	Korea	992	124	1216	57 ± 11.3	56.3 ± 11.3	681/311	87/37	RCNT	992/0	124/0	D2	NA	20.5 ± 8.6M		19/24
Imamura(15)	2011	Japan	104	106	210	65 (31–79)	63 (34–78)	73/31	77/29	RCT	79/25	83/23	D2	NO	NA		3/7
Fujita(16)	2012	Japan	104	106	210	65 (31–79)	63 (34–78)	73/31	77/29	RCT	79/25	83/23	D2	NO	46M		3/7
Hirao(17)	2015	Japan	104	106	210	65 (31–80)	64 (34–79)	73/31	77/29	RCT	79/25	83/23	D2	NO	80M		3/7
Li HL (18)	2012	China	52	54	106	60.3 ± 7.6	59.6 ± 8.5	30/22	34/20	RCT	20/32	NA	D2	NA	3Y		2/7
Hasegawa(19)	2013	Japan	98	98	196	69.0 (40–91)	68.7 (45–91)	72/26	72/26	RCNT	30/68	34/64	D2	DI	5.1Y	3.3Y	17/24
Eom(20)	2013	Korea	107	363	470	56.1 ± 12.2	57.1 ± 12.3	65/42	241/122	RCNT	10/97	79/284	D2	NS	5Y		13/24
Kochi(21)	2014	Japan	121	133	254	67 (30–82)	66 (40–81)	82/39	97/36	RCNT		NA	D2	NO	5Y		15/24
Chen(22)	2014	China	50	50	100	56.7 ± 3.8		65/35		RCNT		NA	D2	NA	3Y		13/24
Hu(23)	2014	China	43	57	100	59.7 ± 11.	58.8 ± 10.9	28/15	37/20	RCNT	6/37	8/49	D2	NA	3Y		17/24
Shchepotin (24)	2014	Ukraine	278	276	554	NA		NA		RCT	NA		NA	NA	5Y		1/7
Zhang(25)	2015	China	159	247	406	57.3 ± 11.5	58.3 ± 12.2	108/51	160/87	RCNT	20/139	48/199	D2	NA	20(2–35)M		17/24
Yang(26)	2016	China	46	40	86	62.35 ± 9.34	60.95 ± 6.84	62/24		RCT	46/0	40/0	D2	NA	1Y		3/7
Terashima(27)	2017	Japan	602	602	1204	NA		NA		RCT	0/602	0/602	D2	NA	3Y		1/7

[a] Jadad score for RCTs, MINORS score for NRCTs. Fujita,Imamura, Hirao's reports(15–17) were published by the same institute, were included as one study and share the same study number (the separately published data was complementary). BT bursectomy group, NB non-bursectomy group, M/F male/female, CC case–control study, RCT randomized comparative trials, RCNT retrospective comparative nonrandomized trial, NRCT: Non-randomized comparative studies, NA not available. LND lymph node dissection, AC adjuvant chemotherapy, DI differ, NS no significance,M month, Y year.

3 −year RFS and 5-year RFS was similar between BT and NB(RR: 1.00, 95% CI: [0.89, 1.12], P = 0.99; RR: 1.05, 95% CI: [0.97, 1.15], P = 0.25,respectively) (Fig. 3D,E).

Sensitivity analysis and sub-group analysis

Sensitivity analysis

When the study(Yang 2016[26]) in which the number of cases was least was excluded, sensitivity analysis showed that operation time was longer in RG than in LG(WMD: 35.31,95%CI: [23.76, 46.86], P < 0.00001), which was consistent with the raw data. When the RCT (Terashima 2017[27]) in which the number of cases was maximum was excluded, sensitivity analysis showed the same result (WMD: 34.69,95%CI: [22.17, 47.21], P < 0.00001), which was also consistent with the raw data. When the studies 14,15,21,26in which the patients with T1+2 stage were much than those with T3+4 was excluded, sensitivity analysis showed the same result (WMD: 47.06,95%CI: [32.99, 61.13], P < 0.00001).(Table 3).The same results was also observed in sensitivity analysis of EBL and 3 −year OS. Therefore, the sample size, study quality, and tumor stage had no effect on the results of the meta-analysis .

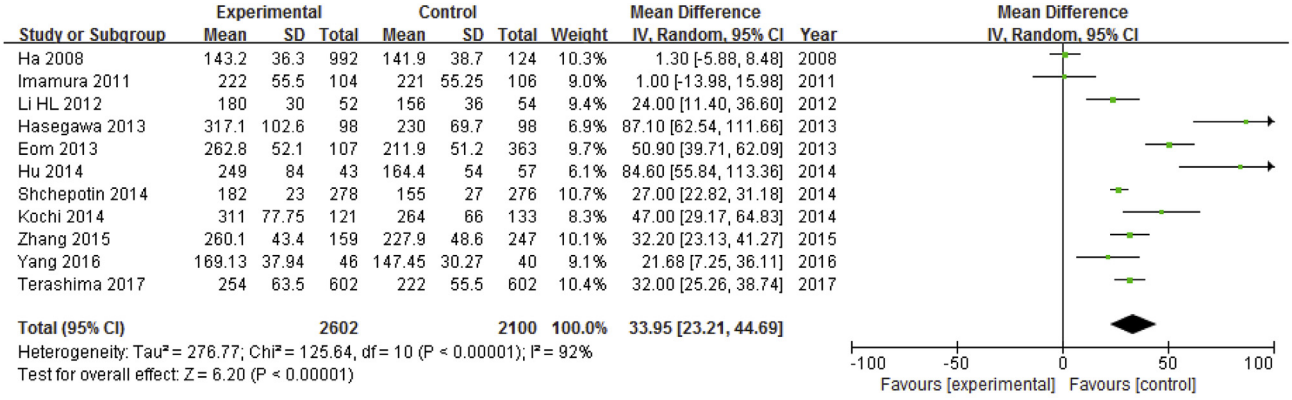
Sub-group analysis

Sub-group analysis could help us discover potential information of what the clinicians are interested in. Therefore, we studied some factors which might be related with operation time, EBL and the 3 −year OS between the two groups (Table 4). In the Japan subgroup, operation time was longer in BT group than in NB group (WMD: 40.09,95%CI: [14.15, 66.03], P = 0.002).In the other area subgroup, operation time was also longer in BT group than in NB group (WMD: 31.45,95%CI: [18.27, 44.64], P < 0.00001). In the RCT subgroup, operation time was longer in BT group than in NB group (WMD: 23.24,95%CI: [15.53, 30.94], P < 0.00001).In the NRCT subgroup, operation time was also longer in BT group than in NB group (WMD: 48.50,95%CI: [24.02, 72.99], P = 0.0001). In theT1+2 > T3+4(the number of patients with stage T1+2 was more than it with T3+4) subgroup, operation time was longer in BT group than in NB group (WMD: 16.80,95%CI: [-2.22, 35.81], P = 0.08), but it didn't reach the significant difference . In the T1+2 < T3+4(the number of patients with stage T1+2 was less than it with T3+4) subgroup, operation time was longer in BT group than in NB group (WMD: 47.06,95%CI: [32.99, 61.13], P < 0.00001).

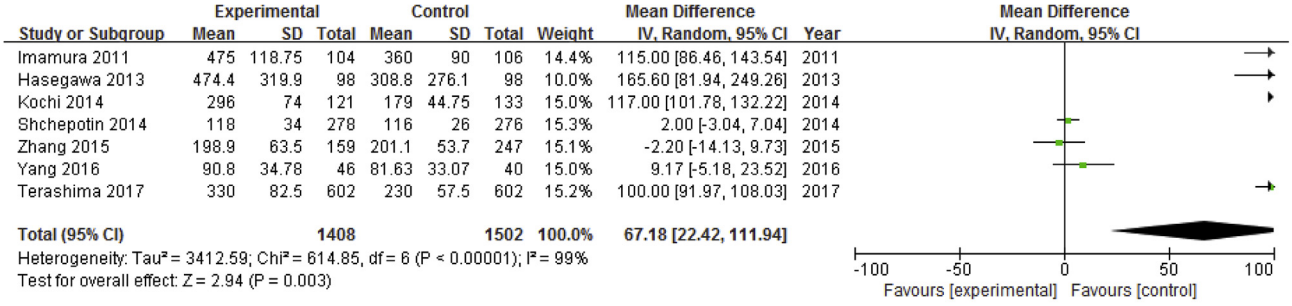
As to the EBL, In the Japan subgroup, EBL was greater in in BT than in NB group (WMD: 110.12,95%CI: [95.80, 124.44], P < 0.00001); In the other area subgroup, EBL was similar between the two groups (WMD: 2.10,95%CI: [-2.31, 6.52], P = 0.35). In the RCT subgroup, EBL was greater in in BT than in NB group, but it did not reach the statistical significance (WMD: 55.89,95%CI: [-4.71, 116.50], P = 0.07). In the NRCT subgroup, EBL was greater in in BT than in NB group, but it did not reach the statistical significance(WMD: 88.29,95%CI: [-10.82, 187.40], P = 0.08). In the T1+2 > T3+4 subgroup, EBL was greater in in BT than in NB group (WMD: 80.00,95%CI: [1.26, 158.73], P = 0.05); In the T1+2 < T3+4 subgroup, EBL was greater in in BT than in NB group, but it did not reach the statistical significance(WMD: 80.61,95%CI: [-4.84, 166.06], P = 0.06).

As to the 3 −year OS, the Japan subgroup, the 3 −year OS was similar between the two groups(RR: 0.97,95%CI: [0.89, 1.06], P = 0.54); In the other area subgroup, BT group had a higher 3 −year OS than NB group (RR: 1.71,95%CI: [1.08, 2.70], P = 0.02). In the RCT subgroup, the 3-year OS was similar between the two groups(RR: 1.05,95%CI: [0.90, 1.23], P = 0.54).In the NRCT subgroup, the 3-year OS was similar between the two groups(RR: 1.24,95%CI: [0.94, 1.63], P = 0.14). In the T1+2 > T3+4 subgroup, the 3-year OS was similar between the two groups(RR: 1.08,95%CI: [0.96, 1.22],

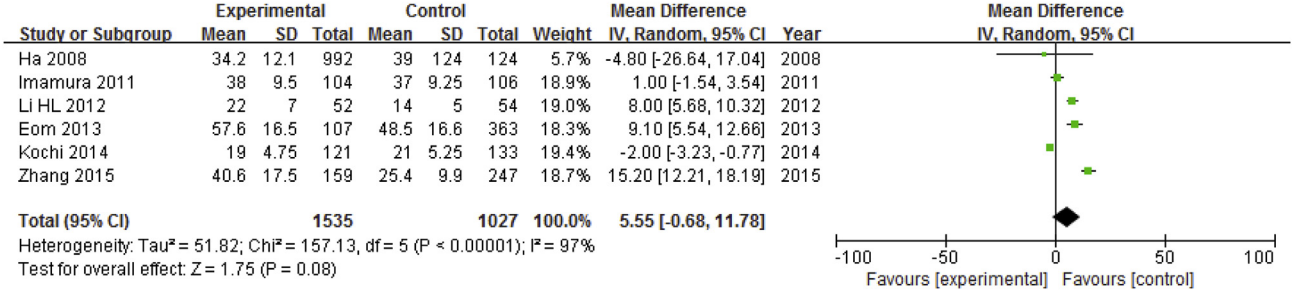
(A) Operative time



(B) EBL



(C) Lymph nodes harvested



(D) LOS

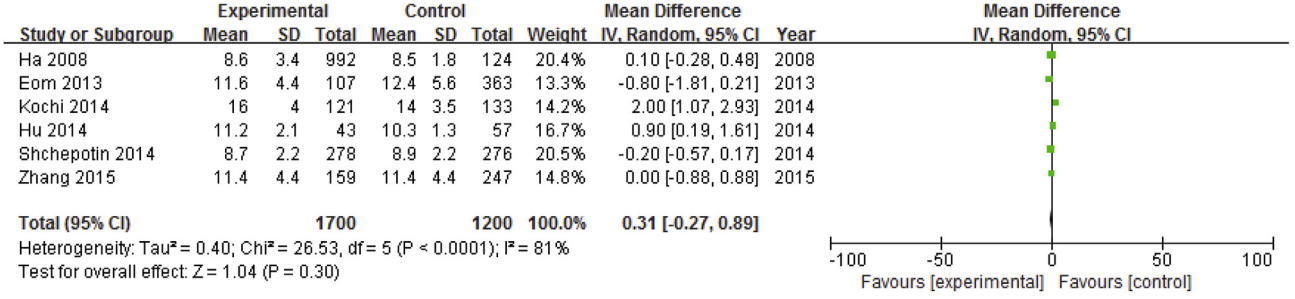
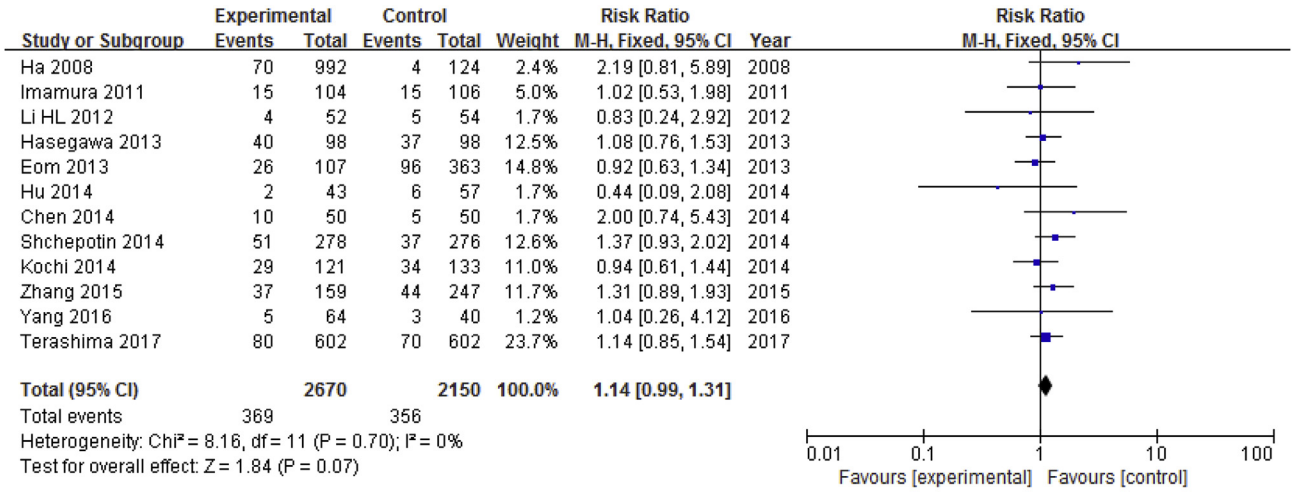


Fig. 2. Forest plot displaying the results of the meta-analysis of(A) Operative time, (B)EBL, (C)Lymph nodes harvested, (D)LOS, (E) Complications, (F) Mortality between BT(Experimental)and NB(Control) group. BT, bursectomy group; NB, non-bursectomy group; EBL, estimated blood loss; LOS, length of stay; SD, standard deviation; CI, confidence interval; OS, overall survival; PFS, progression-free survival; CI: Confidence interval.

(E)Complications



(F) Mortality

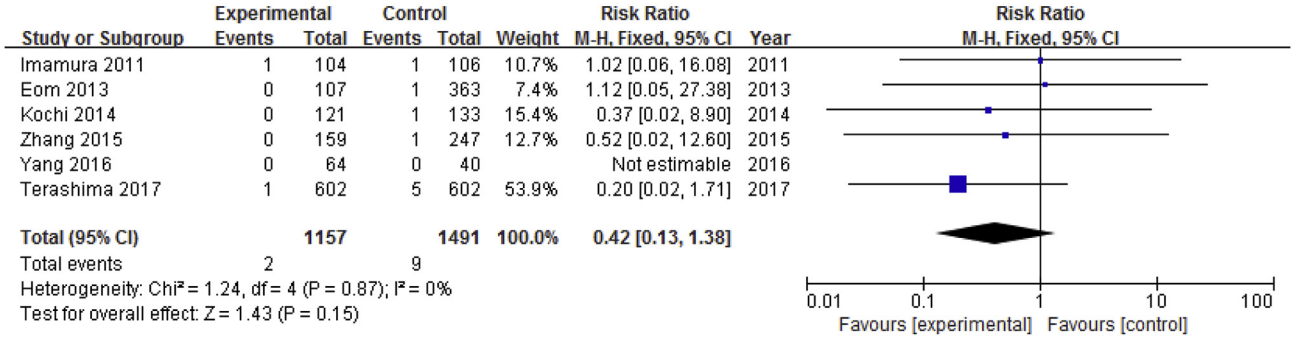


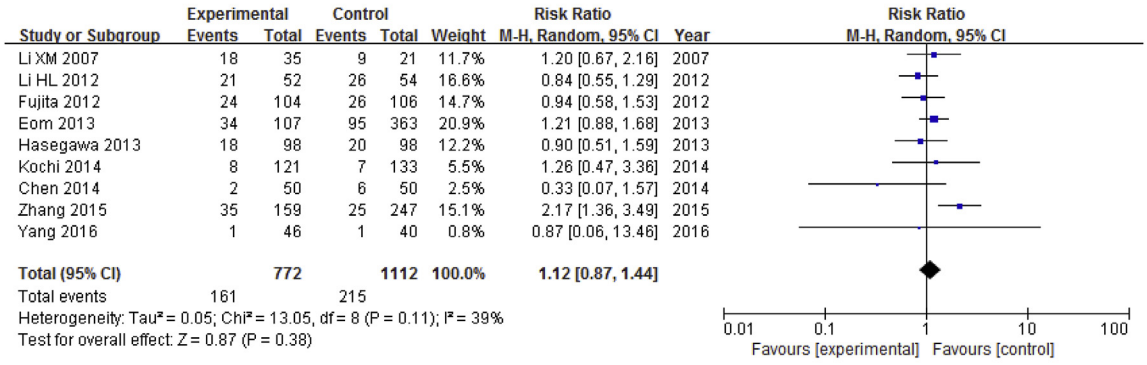
Fig. 2. (*continued*).

Table 2
Summary of primary outcomes for BT *versus* NB.

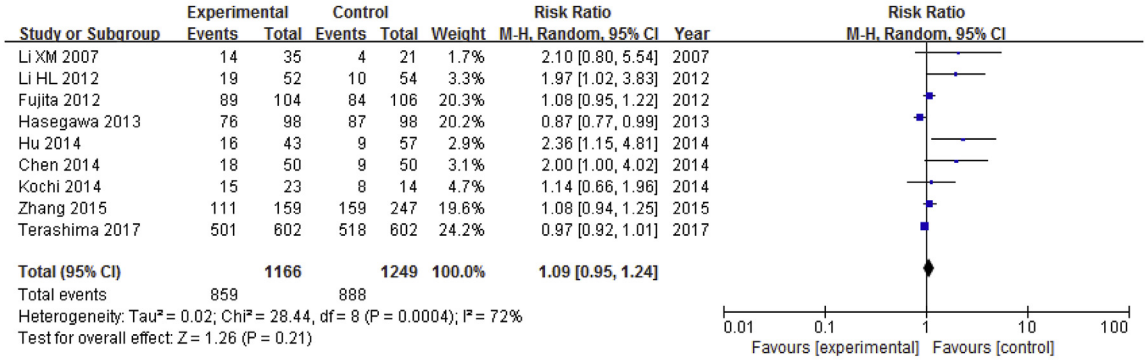
Outcome	Datasets n	Patients, n BT NB	I^{2} (%)	Effect measure	Analysis model	Pooled effect 95% CI	P value
Operative time	11	2602 2100	92	MD	RE	33.95, [23.21,44.69],ghy	P < 0.00001
EBL	7	1408 1502	99	MD	RE	67.18, [22.42, 111.94]	P = 0.003
Lymph nodes harvested	6	1535 1027	97	MD	RE	5.55, [-0.68, 11.78]	P = 0.08
LOS	6	1700 1200	81	MD	RE	0.31, [-0.27, 0.89]	P = 0.30
Complications	12	2670 2150	0	RR	FE	1.14, [0.99, 1.31]	P = 0.07
pancreatic fistula	5	1032 1128	37	RR	RE	1.17, [0.56, 2.44],	P = 0.67
Anastomotic leakage	3	384 468	0	RR	FE	1.27, [0.47, 3.46]	P = 0.64
Ileus	5	590 947	0	RR	RE	0.96, [0.59, 1.55]	P = 0.86
Wound infection	3	387 743	0	RR	FE	0.93, [0.45, 1.95]	P = 0.86
Bleeding	3	263 353	0	RR	FE	2.67, [0.73, 9.77]	P = 0.41
Anastomotic Stenosis	2	228 496	69	RR	RE	0.98, [0.14, 6.94]	P = 0.99
Abdominal abscess	3	384 486	0	RR	FE	0.81, [0.27, 2.48]	P = 0.71
Pneumonia	3	384 486	0	RR	FE	1.19, [0.67, 2.11]	P = 0.55
Mortality	6	1157 1491	0	RR	FE	0.42, [0.13, 1.38]	P = 0.15
Recurrence rate	9	772 1112	46	RR	RE	1.12, [0.86, 1.46],	P = 0.44
3-year OS	9	1116 1249	72	RR	RE	1.09, [0.95, 1.24]	P = 0.21
5-year OS	4	601 613	80	RR	RE	1.06, [0.90, 1.26]	P = 0.49
3 −year RFS	3	225 218	0	RR	FE	1.00, [0.89, 1.12]	P = 0.99
5 −year RFS	3	323 337	0	RR	FE	1.05, [0.97, 1.15]	P = 0.25

BT, bursectomy group; NB, non-bursectomy group; EBL, estimated blood loss; LOS, length of stay; OS, overall survival rate; RFS, recurrence-free survival; CI, confidence interval.
MD, mean difference; RR, relative ratio; FE, fixed effect; RE, random effect.

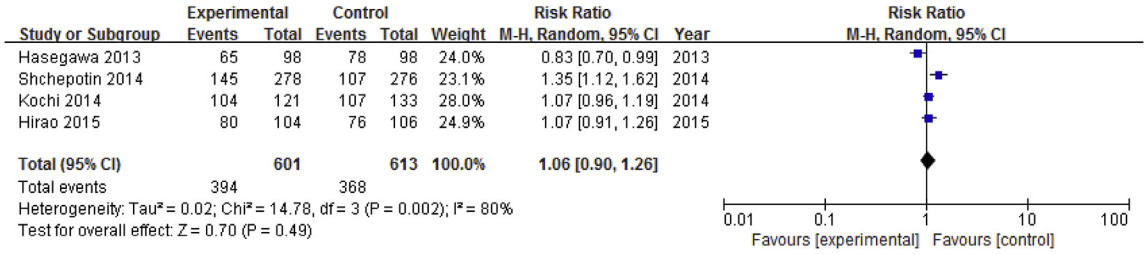
(A) Recurrence rate



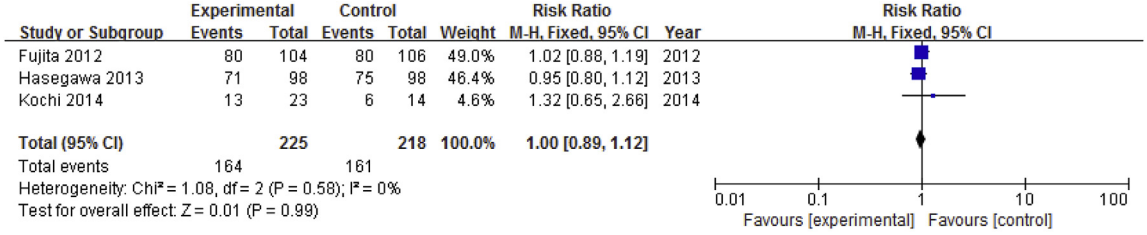
(B) 3–year OS



(C) 5–year OS



(D)3 –year RFS



(E) 5 –year RFS

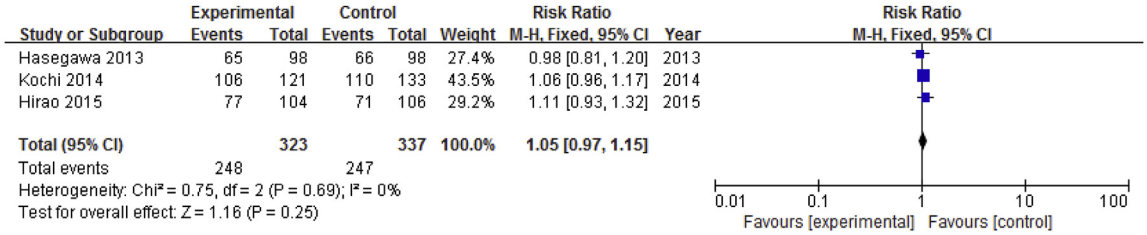


Fig. 3. Forest plot displaying the results of the meta-analysis of(A) Recurrence rate, (B) 3-year OS, (C) 5-year OS, (D) 3 –year RFS, (E) 5 –year RFS between BT(Experimental)and NB(Control). SD, standard deviation; CI, confidence interval; OS, overall survival; PFS, progression-free survival; BT, bursectomy group; NB, non-bursectomy group; CI: Confidence interval.

Table 3
Sensitivity analysis of operation time.

Excluded studies	MD (95%CI)	P value	$I^{2(\%)}$	Analysis model
Yang 2016, 26	35.31, [23.76, 46.86]	<0.00001	93	RE
Terashima 2017, 27	34.69, [22.17, 47.21]	<0.00001	93	RE
14,15,21,26	47.06, [32.99, 61.13]	<0.00001	87	RE

MD, mean difference; CI, confidence interval; RR, relative ratio; FE, fixed effect; RE, random effect.

P = 0.20). In the T1+2 < T3+4 subgroup, the 3-year OS was similar between the two groups(RR: 1.09,95%CI: [0.92, 1.29], P = 0.32).

Heterogeneity

The heterogeneity of included trials was assessed. Significant heterogeneity was detected between studies with respect to the following factors: operation time, EBL, LOS and lymph nodes harvested, 3 −year OS, 5 −year OS.

Publication bias

Funnel plot analysis of the studies was performed in the meta-analysis reporting on overall complication, operative time, EBL and 3 −year OS in BT group as compared with NB group. None of the studies lay outside the limits of the 95% CIs, and there was no evidence of publication bias or heterogeneity among the studies on complications (I [2] = 0%, $P = 0.70$, Fig. 4C). However, the included studies were asymmetrical in the Funnel plot on operative time, EBL and 3 −year OS, so there was publication bias or heterogeneity among the studies on operative time, EBL and 3 −year OS (I [2] = 92%,$P < 0.00001$; $I^2 = 99\%$,$P < 0.00001$; $I^2 = 72\%$, P = 0.0004,respectively, Fig. 4A,B,D).

Discussion

In the 1960s, bursectomy is seen as an essential component of radical surgery for serosa-involved GC in Japan. At that time, additional prophylactic resection of the omentum, the peritoneum over the posterior lesser sac, the pancreas and/or spleen had been justified as the standard procedure to perform during complete radical gastectomy. Then, prophylactic routine resections of the pancreas and/or spleen were abandoned because of the high incidence of postoperative complications [28]. However, omentectomy and bursectomy continued to be standard parts of traditional radical gastrectomy. Bursectomy was routinely recommended in the GACA Gastric Cancer Treatment Guidelines as a part of radical surgery for GC without any supporting evidence, but was included due to traditional acceptance (version 1, 2001) [29]. The GACA revised the GC treatment guidelines three years after the first version and recommended bursectomy only for serosa-invading tumors (version 2, 2004) [30]. In 2011, they changed the guidelines again and this time they limited the indication of bursectomy only to posterior gastric wall tumors penetrating the serosa, and it should be avoided in T1/T2 tumors to prevent injury to the pancreas and/or adjacent blood vessels. (version 3, 2010) [7]. The guidelines of 2014 (ver. 4) [31] had no change the indication of bursectomy. At that time, JCOG 1001 was launched and has completed accrual. Now the results of JCOG 1001 have been revealed. However, the effect of complete bursectomy in treatment of GC patients remains inconsistent. Therefore, we performed a meta-analysis of combined RCTs and NRCTs to evaluate the safety and efficiency.

Surgical safety and oncologic benefits are necessary factors in order to make sure bursectomy as a potential useful therapeutic procedure in the GC surgery according to the viewpoints today [23]. Bursectomy is a complicated and technique-dependent procedure, which may increase the operative time and account for more blood loss during the operation. The meta-analysis revealed that bursectomy was associated with longer operative time and more blood loss. The extra time consuming of the operations was mainly on account of the dissection of the anterior of mesocolon of transverse and capsule of the pancreas. However, longer operative time and more intraoperative blood loss do not mean the unsafety of the surgical bursectomy procedures although with the potential injury of the vessels of the mesocolon of transverse.

In our meta-analysis, the pooled analysis showed that the incidence of overall postoperative complications and mortality was comparable with the two groups. Of the postoperative complications of bursectomy, gastrointestinal surgeons are most concerned about the possible damage of the pancreas and potential trend increase the incidence of pancreatic fistula and postoperative intestinal obstruction. Injury to the pancreatic parenchyma may occur when dissecting the pancreatic capsule and lead to the probable incidence of pancreatic fistula. There was no difference in the incidence of pancreatic fistulas and amylase levels in the postoperative drainage fluid between the bursectomy group and non-bursectomy group [15]. They concluded that pancreatic fistula may not be caused by the dissection of the pancreatic capsule but owing to the lymphadenectomy of those lymph nodes adjacent to the pancreas parenchyma. Generally, the resection of the pancreatic capsule is experienced cumulative procedures, and the experienced surgeons in an experienced center can rarely induce injury to the pancreas and reduce the potential incidence of pancreatic fistula [32]. Therefore, despite the fact that the bursectomy is a time-consuming procedure, the D2 lymphadenectomy with gastrectomy plus bursectomy can be performed safely in high-volume experienced centers or by experienced surgeons [16,23].

Generally, recurrence refers to the growth of cancer lesions pertinent to the primary caner after radical resection is performed according to the objective decision of surgeons. The recurrence

Table 4
Sub-group analysis of operation time.

Sub-group	Number of studies	MD (95%CI)	P value	$I^{2(\%)}$	Analysis model
Area					
Japan	4(15,19,21,27)	40.09, [14.15, 66.03]	0.002	92	RE
the other countries	7(14,18,20,23–26)	31.45, [18.27, 44.64]	<0.00001	93	RE
Study type					
RCT	5(15,18,24,26,27)	23.24, [15.53, 30.94]	<0.00001	72	RE
NRCT	6(14,19–21,2325)	48.50, [24.02, 72.99]	0.0001	96	RE
T stage					
T1+2 > T3+4	4(14,15,21,26)	16.80, [-2.22, 35.81]	0.08	88	RE
T1+2 < T3+4	6(18–20,23,25,27)	47.06, [32.99, 61.13]	<0.00001	87	RE

CI, confidence interval; MD, mean difference; RCT, randomized comparative trials; NRCT, non-randomized comparative studies; RR, relative ratio; FE, fixed effect; RE, random effect; NA, not applicable.

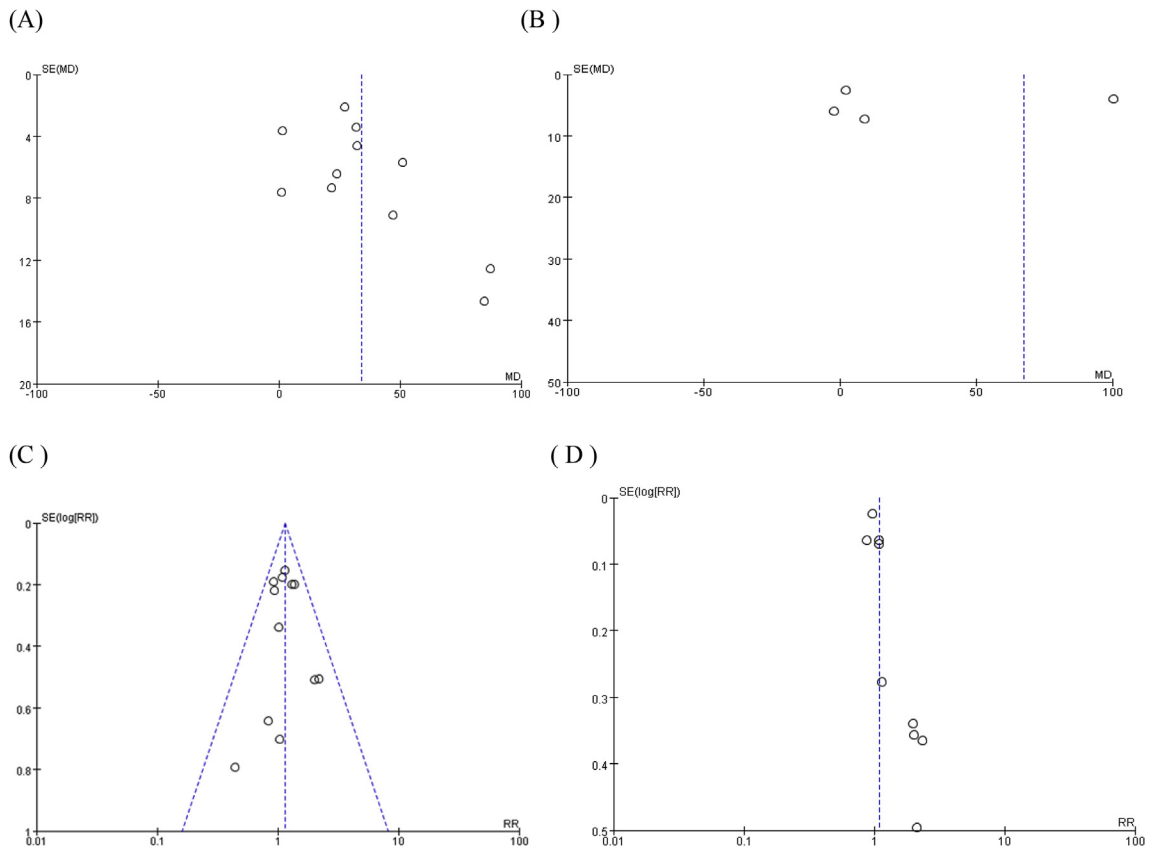


Fig. 4. Funnel plot of (A) operation time, (B)EBL, (C)overall postoperative complication rate, (D) 3 −year OS in patients between BT(Experimental)and NB(Control) group. EBL, estimated blood loss; BT, bursectomy group; NB, non-bursectomy group; OS, Overall survival; RR, relative ratio; SE, standard error; MD, mean difference.

patterns were classified as local recurrence,peritoneal recurrence and hematogenous recurrence. In most studies, recurrence has been classified as the early recurrence group and the late recurrence group based on 2 years and 3 years, respectively. Recurrence patterns were classified as locoregional,peritoneal, hematogenous, or combined metastasis . Meta-analysis of pooled analysis showed that the recurrence rate was similar between the two groups.Choi [33]found that compared with the late recurrence group, the early recurrence group showed an older age, a more advanced stage, a poorly differentiated type of cancer and a significantly higher tendency to have lymphatic invasion, vascular invasion and perineural invasion. Especially in the GC patients with a more advanced stage (stage III and IV), the early recurrence group was characterized by a significantly higher preoperative serum carcinoembryonic antigen level, perineural invasion and a relatively small number of dissected lymph nodes. They think the clinicopathologic characteristics of recurrent GC are significantly different according to the stage of disease, and even in the same stage. Kang [34]demonstrated that intraoperative chemotherapy, as well as postoperative chemotherapy, age, pT stage, pN stage, Lauren histotype, and lymphovascular invasion were found to be independent predictors of early recurrence of pT2-4a stage GC.

With regard to the long-term survival outcomes, there were inconsistent results on it [16,17,20,21,24,25,27].The present meta-analysis demonstrated that there was no significant difference in 3 −year OS, 5 −year OS, 3-year RFS, 5-year RFS between BT group and NB group. In the serosa-positive (pT3−T4) patients, the pooled analysis of two studies showed that 3-year OS [16,21]and 5-year OS [17,21] was similar between the two groups(data not shown).It may suggested that bursectomy can't improve the survival of patients with serosa-positive (pT3−T4) gastric cancer.

The meta-analysis had several limitations. First, the number of included studies was fewer, the size was small in some studies, and thus it decreased the power of the test. Second, different country, adjuvant chemotherapy or not, differences in the type of gastrectomy, different rate of T3/4 stage, different histologic type and different tumor location may increase the clinical heterogeneity of the meta-analysis, but it was impossible to match patient characteristics in all studies. Third, some studies didn't report the long outcomes, and none of the studies reported on the quality of life, none studies talked about economic costs either.

In conclusion, bursectomy was associated with longer operative time and more blood loss, complications and hospital stay were equivalent between the bursectomy and non-bursectomy groups. Bursectomy did not show superiority to non-bursectomy in terms of survival, it is not recommended as a standard surgery for resectable cT3 or cT4 gastric cancer.

Conflict of interest statement

All the authors declare that there is no financial interest or any other potential conflict of interest except the grant of Doctor Research Fund Project of First Affiliated Hospital of Kunming Medical University(2015BS010), Yunnan Provincial Science and Technology Department -Kunming Medical University Applied Basic Research Project Union Foundation (No. 2017FE468(-053)) and Yunnan Provincial Education Department Science Research Fund Project(No.2016ZZX092).

Disclosure information

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