D2 lymphadenectomy with complete mesogastrium excision *vs.* conventional D2 gastrectomy for advanced gastric cancer

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Abstract

Background: The complete mesogastrium excision (CME) based on D2 radical gastrectomy is believed to significantly reduce the local-regional recurrence compared with D2 radical gastrectomy in advanced gastric cancer, and it is widely used in China. This study aimed to explore whether D2 + CME is superior to D2 on surgical outcomes during gastrectomy from Chinese data.

Methods: Feasible studies comparing the D2 + CME (D2 + CME group) and D2 (D2 group) published up to March 2020 are searched from electronic databases. The data showing surgical and complication outcomes are extracted to be pooled and analyzed.

Results: Fourteen records including 1352 patients were included. The D2 + CME group had a shorter mean operative time (weighted mean difference [WMD] = −16.72 min, 95% confidence interval [CI]: −26.56 to − 6.87 min, $P < 0.001$), lower mean blood loss (WMD = −39.08 mL, 95% CI: −49.94 to −28.21 mL, $P < 0.001$), higher mean number of retrieved lymph nodes (WMD = 2.13, 95% CI: 0.58–3.67, $P = 0.007$), shorter time to first flatus (WMD = −0.31 d, 95% CI: −0.53 to − 0.10 d, $P = 0.005$), and postoperative hospital days (WMD = −1.09, 95% CI: −1.92 to −0.25, $P = 0.010$) than the D2 group. Subgroup analysis suggested that the advantages from the D2 + CME group were obvious in traditional open radical gastrectomy, proximal gastrectomy, and distal gastrectomy compared with D2 group. The evaluations of post-operative complications showed that the patients who underwent D2 + CME had a lower incidence of post-operative complications than the patients who underwent D2 surgery alone (relative risk [RR] = 0.65, 95% CI: 0.45–0.87, $P = 0.003$). The D2 radical gastrectomy plus CME improved 3-year overall survival (OS) (RR = 1.16, 95% CI: 1.02–1.32, $P = 0.020$) and lowered the local recurrence rate (RR = 0.51, 95% CI: 0.28–0.94, $P = 0.030$). The patients undergoing laparoscopic surgery or total gastrectomy had more significant advantages compared between D2 + CME and D2 groups in 3-year OS.

Conclusion: The data from China show that D2 radical gastrectomy plus CME are reliable procedures and safety compared to D2 radical gastrectomy with faster recovery, lower risk, and better prognosis.

Keywords: Complete mesogastrium excision; Lymphadenectomy; Advanced gastric cancer; Review; Meta-analysis

Introduction

Gastric cancer (GC) remains the fifth most common cancer and the third leading cause of cancer-related deaths worldwide. Approximately, 50% of GC cases occur in East Asia, especially in China, and usually present as an advanced-stage disease.[1] R0 resection combined with D2 lymphadenectomy has been widely accepted as the standard surgical treatment for locally advanced GC in Asian countries.[2] However, this seemingly extensive resection does not reduce locoregional recurrence in patients with GC, even in those with N0 stage GC.[3] Post-operative recurrence still occurs in 40% to 70% of patients with GC. Some reports have shown that the dissemination of cancer cells in the mesogastrium, termed metastasis V,[4] is the main reason for tumor relapse.[5,6] Thus, en bloc resection of the mesogastrium is necessary during radical gastrectomy.

As total mesorectal excision (TME) and complete mesogastrium excision (CME), based on embryology and anatomy, have been applied in colorectal cancer and have achieved good clinical results, complete meso-gastric excision has also gained attention. In 2000, Gullino *et al*[7] first reported the advantages of the mesogastrium procedure for treating GC

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by summarizing the results of 61 patients who underwent surgery. Since then, CME has been widely performed in Asia, especially in China. D2 gastrectomy, along with the CME procedure (D2 + CME), has been proven to reduce free intraperitoneal cancer cells and improve short-term outcomes compared to conventional D2 gastrectomy.[8] Nevertheless, this complicated and technique-dependent approach was conducted at the expense of more extensive trauma and resection than conventional D2 lymphadenectomy. Consequently, whether patients with GC benefit from D2 + CME remains uncertain. Since this novel surgery has been widely used in East Asian countries, especially in China, we collected data from China and performed a meta-analysis to evaluate the safety and feasibility of D2 + CME compared to D2 alone in the treatment of GC.

Methods

Literature search

A comprehensive literature search was conducted up to 27 March, 2020 using PubMed, Embase, the Cochrane Library, Wanfang data, VIP database, SinoMed, and China National Knowledge Infrastructure. The following search terms and keywords were used in the search strategy: "(gastric/stomach) AND (cancer/neoplasm/tumor)," and "mesangial resection/mesogastric excision/ mesogastrium excision." Full articles published in English and Chinese were included. In addition, related studies, potentially relevant articles, and references of the included articles were also searched.

Inclusion and exclusion criteria

Studies that met the following inclusion criteria were selected: (1) published retrospective case-control studies; (2) the included studies were compared between standard D2 radical gastrectomy (D2 group) and a combination of CME and D2 gastrectomy (D2 + CME group), including open or laparoscopic surgery, all of which were performed by the same experienced surgeon; and (3) the related data could be reported and extracted directly or calculated indirectly from the original studies. Case reports, reviews, conference abstracts, and fundamental research studies were excluded.

Data extraction and quality assessment

Three authors independently selected the trials and extracted the data according to the above-mentioned criteria. The following data were collected: author information; year; sample size; median follow-up period; surgical form and method; surgical outcomes (operation time, blood loss, mean number of retrieved lymph nodes [LNs], time taken for the first flatus, time taken till a semi-liquid diet intake, time taken to get out of bed, and postoperative hospital days); post-operative complications; overall survival (OS); and recurrence-free survival (RFS). Two authors independently conducted the quality assessment based on the Newcastle-Ottawa scale of case-control studies. Studies with ≥7 points were regarded as "high quality," studies with 4 to 6 points were regarded as "moderate quality," and studies with ≤3 points were regarded as "low quality." The assessment was done in duplicate, and disagreements were handled by discussion to reach a consensus.

Statistical analysis

Data analysis was conducted using Review Manager, version 5.3.0 (Cochrane Collaboration, UK). Continuous variables were evaluated using weighted mean difference (WMD) and 95% confidence intervals (CIs), and are shown as mean ± standard deviation. Categorical variables were evaluated using relative risk (RR) and 95% CIs. Heterogeneity was assessed using the chi-squared test based on the Q-statistic and I^2 statistics ($I^2 \leq 25\%$, low heterogeneity; $25\% < I^2 < 50\%$, moderate heterogeneity; $I^2 \geq 50\%$, high heterogeneity). In cases where $I^2 < 50\%$ and $P > 0.1$ were seen, the fixed model was used; otherwise, a random model was selected. The Mantel–Haenszel method was used for categorical variables, while the inverse variance method was used for continuous variables. Subgroup analysis based on the form (open *vs.* laparoscopic) and method of surgery (total gastrectomy [TG] *vs.* no-TG) was performed to find the potential heterogeneity among the included studies. Subgroup differences were shown as *P* for the test. Sensitivity analysis was performed to evaluate the robustness of the results by excluding each study and obtaining the pooled estimates from the remaining studies. The possibility of publication bias was assessed using a funnel plot through a visual inspection of its symmetry. Statistical significance was set at $P < 0.05$. Forest plots were used to determine the pooled effect sizes and 95% CIs.

Results

Study characteristics

The characteristics of the included studies are listed in Table 1, and the flow chart of the literature search is shown in Supplementary Figure 1, http://links.lww.com/CM9/A957. A total of 560 articles were collected from the database and othersources. After screening the titles and abstracts of 560 articles, the full texts of 76 articles were assessed. Fourteen articles[9-22] were eventually eligible for the meta-analysis, including 1352 patients: 670 in the D2 group and 682 in the D2 + CME group. These 14 articles were retrospective case-control studies published between 2011 and 2020 and conducted between 2006 and 2020. All the included articles focused on advanced GC. Surgeons in six articles[9,10,12,13,19,21] performed traditional open surgery, while those in seven articles[11,14,15,17,18,20,22] performed laparoscopic surgery, and the researchers of one article[16] showed the use of both surgeries. Four studies (two each) reportedly performed distal gastrectomy (DG)[11,18] and proximal gastrectomy (PG).[9,20] Five articles[12,15-17,22] included patients undergoing TG. Five articles[10,13,14,19,21] studied these two or three types of gastrectomy. Quality scores ranged from six to eight. All included records were regarded as having moderate to high quality [Supplementary Table 1, http://links.lww.com/CM9/A957].

Surgical outcomes

As shown in Table 2, significant heterogeneity was observed and a random model was used. The pooled meta-analysis suggested that patients undergoing

Table 1: Characteristics of included studies comparing D2 lymphadenectomy with complete mesogastrium excision and conventinal D2 gastrectomy for advanced GC.

Study	Year	Study design	Study period	Median follow-up (m)	Sample size Total	D2	D2 + CME	Surgical form	Surgical method	NOS score
Kong *et al*[9]	2011	Retro study	2010–2011	NR	120	58	62	O	PG	6
Liu *et al*[10]	2014	Retro study	2007–2013	36	100	50	50	O	PG/DG/TG	7
Li *et al*[11]	2015	Retro study	2006–2011	36	120	60	60	L	DG	7
Ji *et al*[12]	2016	Retro study	2013–2015	12	98	48	50	O	TG	8
Liang *et al*[13]	2016	Retro study	2010–2013	36	80	40	40	O	PG/DG/TG	8
Xie *et al*[14]	2016	Retro study	2014–2015	NR	53	27	26	L	PG/DG/TG	8
Guo *et al*[15]	2017	Retro study	2011–2014	36	100	50	50	L	TG	8
Liu *et al*[16]	2018	Retro study	2016–2017	6	84	42	42	L/O	TG	7
Luo *et al*[17]	2018	Retro study	2013–2015	36	66	33	33	L	TG	7
Shen *et al*[18]	2018	Retro study	2014–2017	NR	92	44	48	L	DG	8
Ma *et al*[19]	2019	Retro study	2014–2016	36	96	48	48	O	DG/TG	8
Dang *et al*[20]	2020	Retro study	2018–2019	12	98	49	49	L	PG	8
Yu *et al*[21]	2020	Retro study	2020–2017	36	80	40	40	O	PG/DG/TG	8
Zheng *et al*[22]	2020	Retro study	2015–2017	(30–48) *vs*. (12–30)	165	81	84	L	TG	8

AG: Advanced gastric cancer; CME: Complete mesogastrium excision; DG: Distal gastrectomy; L: Laparoscopic; NOS: Newcastle–Ottawa Scale; NR: Not reported; O: Open; PG: Proximal gastrectomy; Retro: Retrospective; TG: Total gastrectomy.

D2 + CME had a shorter operation time (WMD = –16.72 min, 95% CI: –26.56 to –6.87 min, $P < 0.001$), lower blood loss (WMD = –39.08 mL, 95% CI: –49.94 to –28.21 mL, $P < 0.001$), higher number ofretrieved LNs (WMD = 2.13, 95% CI: 0.58–3.67, $P = 0.007$), a shorter time to first flatus (WMD = –0.31 d, 95% CI: –0.53 to –0.10 d, $P = 0.005$), and shorter post-operative hospital days (WMD = –1.09, 95% CI: –1.92 to –0.25, $P = 0.010$), as compared with patients in the D2 group. No significant difference between the two groups was observed in detecting the time to get out of bed (WMD = –0.32 d, 95% CI: –0.72 to 0.07 d, $P = 0.110$) and time taken till semi-liquid diet intake (WMD = –0.59 d, 95% CI: –1.44 to 0.26 d, $P = 0.170$).

Post-operative complications

Our results revealed that the incidence of total postoperative complications was lower in patients who underwent D2 + CME than in those who underwent D2 alone (RR = 0.65, 95% CI: 0.49–0.87, $P = 0.003$). Except for incision infection (RR = 0.26, 95% CI: 0.09–0.77, $P = 0.01$), there were no significant differences in the incidence of gastroparesis, pancreatic fistula, lymphatic leakage, anastomotic fistula, hemorrhage, intraperitoneal hemorrhage and infection, intestinal obstruction, and pulmonary infection between the two groups [Table 3].

OS and RFS in 3 years

Eight studies compared the 3-year OS between the D2 + CME and D2 groups. A random-effects model was used based on statistical homogeneity ($P < 0.001$, $I^2 = 79\%$). As shown in Figure 1, CME based on D2 radical gastrectomy significantly improved the 3-year OS of patients compared with traditional D2 radical gastrectomy (RR = 1.16, 95% CI: 1.02–1.32, $P = 0.020$).

Table 2: The meta-analysis of surgical outcomes between D2 + CME and D2 groups.

Outcomes	No. of studies	Sample size D2 + CME	D2	Model for meta-analysis	Heterogeneity (P, I^2)	WMD	95% CI of overall effect	P value
Operation time (min)	13	632	620	R	<0.001, 95%	–16.72	–26.56, –6.87	<0.001
Blood loss (mL)	13	633	621	R	<0.001, 97%	–39.08	–49.94, –28.21	<0.001
Mean N of retrieved LNs	11	539	527	R	<0.001, 88%	2.13	0.58, 3.67	0.007
Time to first flatus (days)	9	437	429	R	0.006, 63%	–0.31	–0.53, –0.10	0.005
Time to semi-liquid diet (days)	6	304	299	R	<0.001, 79%	–0.32	–0.72, 0.07	0.110
The first time to get out of bed (days)	6	275	271	R	<0.001, 96%	–0.59	–1.44, 0.26	0.170
Post-operative hospital days	10	477	469	R	<0.001, 85%	–1.09	–1.92, –0.25	0.010

CI: Confidence interval; CME: Complete mesogastrium excision; F: Fixed model; LNs: Lymph nodes; R: Random-effect model; WMD: Weighted mean difference.

Table 3: The meta-analysis of post-operative complications between D2 + CME and D2 groups.

Outcomes	No. of studies	Sample size: D2 + CME Event	Sample size: D2 + CME Total	Sample size: D2 Event	Sample size: D2 Total	Model for meta-analysis	Heterogeneity (P, I^2)	RR	95% CI of overall effect	P value
Gastroplegia	3	0	138	3	138	F	1.000, 0%	0.33	0.05, 2.08	0.240
Pancreatic fistula	1	2	62	0	58	R	–	4.68	0.23, 95.52	0.320
Lymphatic leakage	5	4	284	8	277	F	0.960, 0%	0.55	0.19, 1.61	0.270
Anastomotic fistula	3	8	134	16	129	F	0.610, 0%	0.49	0.22, 1.09	0.080
Incision infection	3	4	151	15	147	F	0.820, 0%	0.26	0.09, 0.77	0.010
Intra-abdominal infection	2	1	107	5	98	F	0.280, 15%	0.25	0.04, 1.51	0.130
Ileus	2	3	99	8	99	F	0.410, 0%	0.35	0.09, 1.37	0.130
Intra-abdominal hemorrhage	2	0	146	4	139	F	0.690, 0%	0.19	0.02, 1.60	0.130
Anastomotic hemorrhage	1	1	45	1	40	R	–	0.89	0.06, 13.75	0.930
Pulmonary infection	7	16	369	23	357	F	0.920, 0%	0.67	0.36, 1.24	0.200
Total post-operative complications	13	65	644	98	635	F	0.290, 16%	0.65	0.49, 0.87	0.003

CI: Confidence interval; CME: Complete mesogastrium excision; F: Fixed-effects model; R: Random-effects model; RR: Relative risk.

The 3-year RFS rates from five studies were also assessed between the two groups. The meta-analysis result suggested that the recurrence in the D2 + CME group was significantly lower than that in the D2 group (RR = 0.51, 95% CI: 0.28–0.94, P = 0.03) [Figure 2].

Subgroup analyses

Surgical outcomes

In the subgroup of traditional open surgery, compared with the D2 group, patients in the D2 + CME group had a shorter operation time and shorter time to semi-liquid diet intake post-operation. There was no significant difference in the operation time between the D2 + CME and D2 groups in the laparoscopic subgroup. In terms of blood loss and the time to first flatus, among both the traditional open and laparoscopic surgery subgroups, the D2 + CME group showed significant advantages over the D2 group. While analyzing LN dissection, D2 + CME under laparoscopy showed more obvious advantages than D2 + CME under traditional open laparotomy. A significant difference was observed in the time to semi-liquid diet intake when comparing the traditional open surgery and laparoscopic surgery subgroups Supplementary Table 2, http://links.lww.com/CM9/A957.

For no-TG cases, the operation time of the D2 + CME group was significantly shorter than that of the D2 group, and fewer complications were seen in the D2 + CME group, including a shorter time to first flatus. Regarding LN dissection, the D2 + CME group showed superior radical treatment than the D2 group in the no-TG (PG/TG) operation. Regardless of the subgroup (no-TG or TG), lower blood loss was observed in the D2 + CME group than in the D2 group. A significant difference was observed in the evaluation of blood loss and the mean number of retrieved LNs between no-TG and TG subgroups. The above results

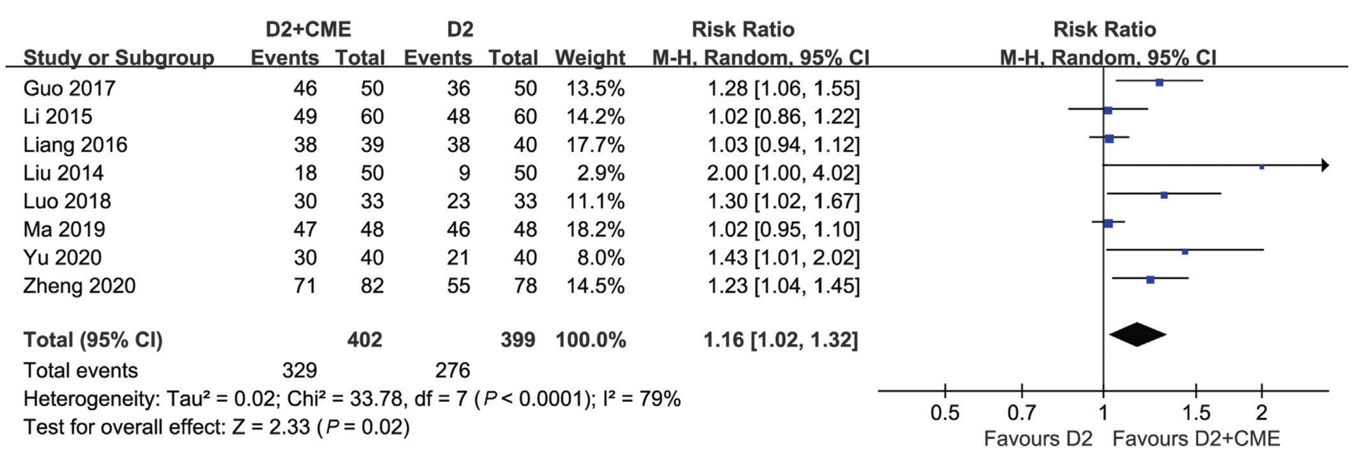

Figure 1: Three-year overall survival of CME based on D2 radical gastrectomy (D2 + CME) *vs.* traditional D2 radical gastrectomy (D2). CI: Confidence interval; CME: Complete mesogastrium excision.

Study or Subgroup	D2+CME Events	D2+CME Total	D2 Events	D2 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guo 2017	5	50	7	50	27.1%	0.71 [0.24, 2.10]
Liang 2016	2	39	1	40	3.8%	2.05 [0.19, 21.72]
Luo 2018	3	33	5	33	19.4%	0.60 [0.16, 2.31]
Ma 2019	2	48	8	48	31.0%	0.25 [0.06, 1.12]
Yu 2020	3	40	3	10	18.6%	0.25 [0.06, 1.06]
Total (95% CI)		**210**		**181**	**100.0%**	**0.51 [0.28, 0.94]**
Total events	15		24			

Heterogeneity: Chi² = 3.58, df = 4 (P = 0.47); I² = 0%

Test for overall effect: Z = 2.15 (P = 0.03)

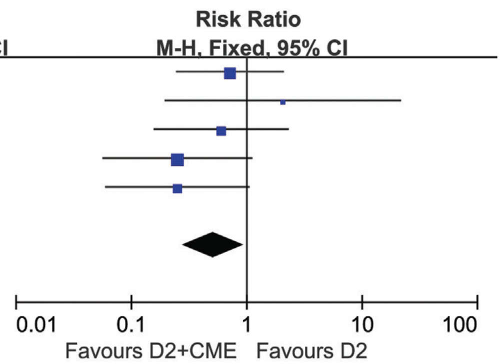

Figure 2: Three-year recurrence-free survival of CME based on D2 radical gastrectomy (D2 + CME) *vs*. traditional D2 radical gastrectomy (D2). CI: Confidence interval; CME: Complete mesogastrium excision.

are shown in Supplementary Table 2, http://links.lww.com/CM9/A957.

Three-year OS

The results from the subgroup analysis showed that in the case of laparoscopic surgery or radical TG, the 3-year OS in the D2 + CME group was significantly superior to that of the D2 group. The results are shown in Supplementary Table 3, http://links.lww.com/CM9/A957.

Heterogeneity analysis

The subgroup analysis shown in Supplementary Table 2, http://links.lww.com/CM9/A957 indicates significant heterogeneity in the traditional open surgery subgroup when we analyzed the operation time, blood loss, and the mean number of retrieved LNs. Significant heterogeneity was seen in the laparoscopic surgery subgroup when we analyzed the time to first flatus, time to semi-liquid diet intake, first time to get out of bed, and post-operative hospital days. However, lower heterogeneity was observed in the TG subgroup when all surgical outcomes were analyzed. Supplementary Table 2, http://links.lww.com/CM9/A957 indicates lower heterogeneity in the TG and laparoscopic surgery subgroups when subgroup analysis was performed to measure the 3-year OS. It could be seen that these sources of heterogeneity might be caused due to various forms and methods of surgery.

Sensitivity and publication bias

Sensitivity analyses were performed by removing individual studies from the data. We found that excluding the studies did not alter the overall results. Funnel plots were used to evaluate publication bias. No significant publication bias was found in the total complications and 3-year RFS evaluations. However, a significant asymmetry was found in the other funnel plots, as described in Supplementary Figure 2, http://links.lww.com/CM9/A957.

Discussion

To date, even after performing the two principal treatments of cancer, i.e., primary lesion removal and LN dissection, a large number of patients still experience postoperative recurrence and even distant metastasis, which seriously affects the prognosis of patients with cancer.[23] CME is now considered the third principal cancer treatment due to its unique advantages in reducing local tumor recurrence. In colorectal cancer, TME has been shown to remarkably reduce the regional recurrence rate and improve the survival of patients.[24] The concept of TME and CME has been widely applied in colorectal cancer. A meta-analysis of 12 studies involving 8586 patients showed that radical surgery in combination with CME improved the quality and long-term survival of patients with colon cancer.[25] These facts suggest that CME may be necessary for radical gastrectomy in GC patients. However, the direct application of such mesentery-based surgery during GC surgery was restricted due to several anatomical restrictions related to the stomach. Nevertheless, some surgeons have continued to adopt CME in radical gastrectomy and put forward detailed surgical procedures.[26-30] Some related reports have been published successively, proving the value of CME in radical gastrectomy. In a study by Shinohara *et al*,[31] the similarities between mesogastric and mesorectal excision were systematically described in terms of anatomical layers and LN dissection, providing evidence supporting the application of CME in radical gastrectomy. Especially for peripancreatic LN dissection, CME could significantly increase the number of peripancreatic LNs and avoid the serious risk associated with pancreatectomy, compared with adverse events, severe complications, and unsatisfactory prognosis associated with TG combined with pancreatectomy.[32] A wide resection was conducive to the thorough removal of potential metastatic lesions, but the scope of resection was enlarged, resulting in increased trauma, prolonged operation time, and gradually increasing difficulty of resection. These factors may lead to serious complications and higher post-operative morbidity after surgery.[25] Therefore, whether to include the CME procedure remains controversial for D2 gastrectomy.

CME refers to the en bloc removal of all tissues in the ventral and dorsal mesenterium of the stomach, including the stomach, blood vessels, and lymphoid adipose tissue.[7] After around 20 years of discovery, CME has been widely used in radical gastrectomy practices in China.[33] However, randomized controlled trials (RCTs) with a large sample size are still lacking to elucidate the safety and efficacy of CME. Therefore, this meta-analysis aimed to evaluate the safety and effectiveness of D2 + CME and to provide evidence supporting the wide application of D2 + CME surgery in GC patients. Our evaluation found that D2 + CME showed better results in terms of surgical time, trauma, and LN dissection. Patients undergoing D2 + CME had faster post-operative recovery. Regarding safety, D2 + CME showed no significant differences from D2. Notably, patients undergoing D2 + CME showed significant benefits in both OS and RFS.

Due to the mutual fusion of the mesogastrium during development, blood vessels and LNs are also fused in the mesogastrium, which generates tissue space. CME is mainly performed by separating the mesogastrium with en bloc resection.[34] In this way, vascular disconnection is more orderly and smoother, reducing the operation time, avoiding unnecessary vascular injury, and reducing surgical trauma. As per the conclusions of our meta-analysis, the post-operative recovery of patients undergoing CME + D2 surgery was significantly better than that of patients undergoing conventional D2 surgery. Importantly, the results of the subgroup analysis indicated that this advantage in rapid recovery was manifested not only in patients undergoing laparoscopic surgery but also in those undergoing traditional open surgery. Although open surgery has many disadvantages (such as extensive trauma, delayed recovery, and increased risk of post-operative metastasis and spread of tumor),[35] with the addition of CME, the incidence of these adverse factors will be significantly reduced, and the surgical safety will also be improved. Studies on CME have suggested that CME does not increase the risk of post-operative morbidity.[22] Our results also suggested that there were no significant differences between the D2 + CME and D2 groups in terms of post-operative complications. These also conformed to the principles of the Enhanced Recovery After Surgery, which reduces the stress responses caused by the surgery itself and ensures the intake of nutrients, thus speeding up the post-operative recovery process.[36] Although the study by Zheng *et al*[22] demonstrated that the mean operative time of the D2 + CME group was prolonged owing to the complicated CME procedure, our pooled data suggested that the operation time in the CME + D2 group did not increase; on the contrary, the CME + D2 group showed a shorter operation time compared with the D2 group, especially in the no-TG subgroup (DG or PG). It is worth noting that these operations must be performed by experienced surgeons to obtain such results.

LN dissection during the radical resection of GC is crucial and technically challenging. CME has unique advantages for LN dissection. The subgroup analysis suggested that the D2 + CME group had more LNs than the D2 group, especially in the no-TG group (DG or PG), which might be due to the complete removal of LNs from groups No. 10 and No. 11d in the PG during left gastric mesentery resection in the CME procedure.[26,37] In addition, our meta-analysis indicated that more LNs could be obtained by laparoscopic surgery than by conventional open surgery during the CME procedure. As known already, in addition to the advantages of minimal injury and complications, laparoscopic surgery had an amplification effect and was significantly better than traditional open surgery in showing the actual morphology of the removed tissues and organs. In particular, the widely used 3D laparoscopy could provide better image quality, stereoscopic vision, and hand-eye coordination for surgeons during laparoscopic surgery.[38] To some extent, this clearer approach was advantageous for LN dissection, which explains why the D2 + CME group could harvest more LNs compared to the D2 group in laparoscopic surgery. Many guidelines recommend that >15 LNs be retrieved to determine nodal classification accurately. Our previous report indicated that the appropriate number of retrieved LNs could serve as a tool to predict OS in stage N3b GC patients.[39] Thus, a sufficient number of LNs are critical to determine the prognosis of GC. Traditional D2 lymphadenectomy is usually associated with a poor harvest of LNs, especially in obese patients, because the gastric mesentery could be broken during the sharp dissection of the vasculature, resulting in the remnants of mesenteric tissues containing LNs. On the one hand, this procedure could tamper with the principle of en bloc excision, and fewer LNs would be harvested, whereas non-en bloc resection might result in detachment of tumor cells and residue during operation so that the patients undergoing D2 LNs might not obtain long-term survival benefits.[40] Tavares *et al*[41] demonstrated that occult tumor cells (OTCs) in the LNs, including micrometastases and isolated tumor cells, are regarded as a key factor in the development of GC recurrence and are associated with poor prognosis. A lower number of LNs detected might lead to an increased incidence of OTCs and an increased risk of post-operative recurrence and metastasis, proving that the number of post-operative recurrences is significantly higher in patients receiving traditional D2 surgery than that in patients receiving D2 + CME. Therefore, patients who underwent D2 did not show an advantage in OS compared to those undergoing D2 + CME. Notably, this non-en bloc resection also increases the risk of peritoneal metastasis. More significantly, our subgroup analysis showed that patients undergoing D2 + CME had a better prognosis in laparoscopic surgery or TG. It has been shown that laparoscopic surgery or TG could provide greater survival benefits for GC patients undergoing CME, which might be due to better exposure of the perigastric interfacial space during laparoscopic or TG, allowing more LNs to be dissected. For instance, Zheng *et al*[22] indicated that the separation of the superior recess and splenic recess was straightforward during CME in laparoscopic TG. The separation of the superior recess during CME could obtain better surgical landmarks to make the dissection of LNs number 8 and number 12 more sufficient. The separation of the splenic recess during CME could provide more room and a better view for subsequent splenic hilar lymphadenectomy. These results were consistent with the conclusion that the increased number of LNs detected increased the survival benefit of GC patients.

Although we reported the safety and effectiveness of CME in GC for the first time as a meta-analysis, the present study has some limitations. First, all included studies were retrospective studies, and the number of studies on CME conducted in East Asia, especially in China, was very limited. We did not find any studies in other countries that met the inclusion criteria of this meta-analysis. Therefore, we could only consider the Chinese population for analysis. These results might be affected by analytical bias. To date, the detailed and accurate standards of CME in treating GC have not been completely unified. Second, the surgical technique and experience of the surgeons for the D2 + CME procedure could have affected the results. However, most of the D2 + CME operations by laparoscopic or open surgery were conducted by experienced surgeons in the included studies, and the operation and technique were stable. Third, we also observed large heterogeneity in this study, and some low-quality studies might have affected the final results of the analysis, including lax randomization, and significant publication bias was found in most of the analysis Supplementary Figure 2, http://links.lww.com/CM9/A957. Meanwhile, because none of the included studies conducted a multivariable regression analysis, the harzard risk or RR from every study could not be obtained, making the pooled results and our conclusions limited. However, considering the important role and rapid development of CME in radical gastrectomy for GC, we sought to explore some valuable aspects of the application of CME in radical gastrectomy for GC from limited evidence. Therefore, more high-quality RCTs with a larger patient cohort should be investigated in the future, and we aim to continue focusing on this research area.

Conclusions

This meta-analysis is the first to demonstrate that D2 radical gastrectomy in combination with CME is safer and more effective than D2 radical gastrectomy alone in terms of surgical outcomes, post-operative complications, and prognosis. Some prospective RCTs are needed to evaluate long-term outcomes.[42]

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Conflicts of interest

None.

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