ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2022 March 27; 14(3): 211-270

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 3 March 27, 2022

World Journal of Gastrointestinal Surgery

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

PUBLICATION DATE
March 27, 2022

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 March 27; 14(3): 211-220

DOI: 10.4240/wjgs.v14.i3.211

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Case Control Study

Fast-track protocols in laparoscopic liver surgery: Applicability and correlation with difficulty scoring systems

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Specialty type: Surgery

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Zhou S

Received: April 19, 2021
Peer-review started: April 19, 2021
First decision: June 13, 2021
Revised: July 25, 2021
Accepted: February 9, 2022
Article in press: February 9, 2022
Published online: March 27, 2022

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Abstract

BACKGROUND

Few series have reported the utility of fast-track protocols (FTP) in minimally invasive liver surgery.

AIM

To report the applicability of FTP in minimally invasive liver surgery and to correlate with difficulty scores.

METHODS

The series of patients undergoing minimally invasive liver surgery from 2014 was analyzed. Iwate, Southampton and Gayet's scores were compared as predictors of FTP adherence. Accomplishment of FTP was considered within 24-h, 48-h and 72-h. Multivariate models were performed to define discharge < 24 h, < 72 h, complications and readmissions.

RESULTS

From 160 cases, 78 were candidates for FTP, of which 22 (28.2%), 19 (24.4%) and 14 (17.9%) were discharged in < 24-h, 48-h and 72-h, respectively (total = 71.5%). Iwate, Southampton and Gayet's scores achieved area under the receiver operating characteristic values for < 24-h stay of 0.780, 0.687 and 0.698, respectively. Sensitivity and specificity values for the best score (Iwate) were 87.7% and 66.7%, respectively (cutoff = 5.5). In multivariate models, < 72 h stay and complications revealed body mass index as a risk factor independent from difficulty scores.

CONCLUSION

The development of aggressive FTP is feasible and < 24-h stay can be achieved

even in moderate and advanced complexity cases. Difficulty scores, including body mass index value, may be useful to predict which cases may adhere to these protocols.

Key Words: Liver; Fast-track; Enhanced recovery; Laparoscopy

Core Tip: The current manuscript shows how fast-track protocols on laparoscopic liver surgery can be accomplished according to difficulty scoring systems.

Citation: Ciria R, Padial A, Ayllón MD, García-Gaitan C, Briceño J. Fast-track protocols in laparoscopic liver surgery: Applicability and correlation with difficulty scoring systems. *World J Gastrointest Surg* 2022; 14(3): 211-220
URL: https://www.wjgnet.com/1948-9366/full/v14/i3/211.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i3.211

INTRODUCTION

Minimally invasive liver surgery (MILS) has become wide spread in recent years. Nowadays, the feasibility and advantages of MILS have been widely demonstrated[1,2]. Enhanced recovery after surgery (ERAS) protocols are multimodal pathways developed to overcome the deleterious effect of perioperative stress after major surgery. The last guidelines published in 2016 from the ERAS Society performed a systematic review over more than 30 articles in which the classical 23 ERAS items validated for colorectal surgery were analyzed for liver surgery[3,4]. The conclusion was that the application of ERAS protocols in liver surgery could be beneficial although the available evidence was poor and prospective studies were encouraged.

Several difficulty scores have been reported to date in laparoscopic liver surgery (LLS). The primary endpoints of all of them are intraoperative complications, conversions and degree of difficulty. The most widely used is the Iwate score[5]. There are others like the Southampton score[6] and the Gayet's score [7]. However, none of them have been tested to predict early recovery and/or completion of a fast-track protocol (FTP).

Our liver unit adopted MILS in 2014, and since the very beginning has implemented a very aggressive FTP leading to an innovative 1-d stay protocol. The main aim of our manuscript is to report a prospective validation of our FTP in MILS. As secondary aims, we analyzed our experience with 1-d stay surgery in LLS and the results of FTP grouped by the 3 scores of difficulty in LLS currently reported in literature in order to compare the capability of each score to predict FTP accomplishment.

MATERIALS AND METHODS

Inclusion period and population

All patients who underwent MILS since the adoption of the laparoscopic approach (October 2014) at the University Hospital Reina Sofía in Córdoba-Spain were included in the study. All patients signed informed consent for the approval of their personal data for research. All cases were included in a prospectively maintained database. Approval number of the institutional review board of the University Hospital Reina Sofia was 4380 (Code 0000-0002).

Inclusion criteria

The inclusion criteria were unrestricted. We started our FTP at case 40 (to avoid learning curve). Regarding comorbidities, no significant heart disease, body mass index (BMI) < 35 and American Society of Anesthesiologists score < 4 were required. Regarding complexity, Iwate and Southampton scores ≥ 10, living donation and synchronic colorectal and liver resections were excluded. Conversions were also excluded from the analysis, being considered an "a posteriori" variable.

Calculation of difficulty scores

According to their original publications, we considered Iwate, Southampton and Gayet's scores for the calculations and the testing. Iwate score was calculated according to its last update in which an "Expert" category was added and up to 12 points could be reached. Southampton and Gayet's scores were calculated according to their original reports as no further modifications have been reported.

Perioperative FTP

Since the decision of developing an FTP for LLS, two different protocols were considered for both minor and major resections, including a 24-h and a 48-h discharge protocol, respectively. The protocols are depicted in Figure 1A and B. Considering that the main aim is maintaining a low central venous pressure during the surgical procedure, most of the interventions in our protocol are focused on an aggressive preoperative emptying of the intravascular compartment, a fluid restriction during the operation and a rapid postoperative recovery with early intake.

Surgical procedures and recovery area

Our laparoscopic liver resection is based on general principles of open and MILS. Our standard position of the patient is supine with tilt left 30º-45º in case of right posterior resections. Our main transection device is ultrasonic surgical aspiration irrigation device with bipolar sealing forceps for vascular structures. Main vessels are transected using endo-staplers. Following the surgery, the patients are admitted to a postoperative recovery area in which patients are monitored continuously by anesthesiologists. Immediately after arrival, blood tests are obtained, and unless abnormal the patient is discharged to our surgical ward in a 2-4 h period.

Statistical analysis and main endpoints

A prospectively maintained database was screened to obtain complexity scores and to identify potential variables not included in the previously reported scores that would increase their prediction capabilities. Comparisons were performed after normality tests (Shapiro-Wilk) using parametric or non-parametric tests, accordingly. Multivariate models were performed by logistic binary regression tests including variables within 0.1 significance in the major models. The final models included variables below 0.05 significance. Receiver operating curves were performed defining the best cutoff point of the complexity scores. The main endpoints of our study were: (1) Global results and discharge 24h/48h/72 h or FTP not accomplished; (2) Prediction capability of early discharge from difficulty scores; (3) Receiver operating curves for "early discharge" accomplishment of scores; and (4) Multivariate models: discharge-24 h/discharge-72 h/general complications/readmissions.

RESULTS

Overall results and completion of FTP

From a total of 160 LLS, the final dataset for the analysis was 78 cases. Exclusions were defined as depicted in Figure 2. Mean comprehensive complication index was 5.18 ± 11.52 for the group of patients within the FTP. A total of 23% had any kind of complication, from which only 5 cases (6.4%) were major complications (Dindo-Clavien III-IV). Comparisons with the group of patients that were not candidates to enter into a FTP showed that the selection procedure was adequate (Table 1). From the 78 cases of candidates for FTP, 22 (28.2%), 19 (24.4%) and 14 (17.9%) were discharged in less than 24-h, 48-h and 72-h, respectively (total = 71.5%). The rest (29.5%) did not accomplish any kind of FTP because of the following reasons: complication (26.1%), long distance from home > 200 km (17.3%), delay in the discharge from the recovery area > 12 h (34.8%) and weekender/no acceptance from the patients (21.7%). Readmission rate in the whole series was 7.5%. It was lower but did not reach statistical significance in the FTP group compared to the non-FTP group (7.7% *vs* 11.9%; *P* = not significant). In the FTP group, readmissions were related to the surgical procedure but could not be considered a direct consequence of the application of an FTP. One of the cases was a late evisceration that happened 8 d after the discharge.

Accomplishment of the FTP according to difficulty scores

As observed in Figure 3, the accomplishment of an FTP is directly related to the difficulty of the LLS. It should be noted that a low punctuation in the scores predicted a low postoperative stay and that a high difficulty score predicted a non-accomplished FTP. We also analyzed the combination of 2 or 3 scores with equal punctuation in order to find out whether they would benefit and complement each other by adding homogeneity. However, the combination of the scores was lower in the prediction of accomplishment of an FTP. After these findings, a correlation test was performed in order to find out if Iwate and Southampton scores correlated linearly. An $R^2 = 0.2594$ score was obtained. As observed in Figure 4, several cases were not concordant in their punctuation. Several high Iwate score cases were downgraded by the Southampton scoring system.

Predicting early discharge with less than 24-h postoperative hospital stay

By performing receiver operating curves, it could be demonstrated that the difficulty scores could predict early discharge < 24 h. In this sense, it should be noted that the best cutoff points were equivalent for both Iwate and Southampton scores (score = 5.5). The best sensitivity was observed for the Iwate score (S = 85.7%), with a specificity of 66.7% (Figure 5).

Table 1 Baseline data and complications in the groups of candidates and non-candidates for a fast-track protocol

	Whole series (160 cases)	Excluded learning curve (first 40 cases)	Non-candidate for FTP (42 cases)	Candidate for FTP (78 cases)	*P* (FTP *vs* no FTP)
Baseline data					
Age	59 ± 13	59 ± 14	58 ±15	59 ± 14	NS
Sex (M/F ratio)	83/77	66/54	29/13	37/41	0.023
BMI	27.56 ± 4.88	27.51 ± 5.03	27.69 ± 6.21	27.43 ± 4.44	NS
Malignancy, *n* (%)	122 (76.25)	93 (77.50)	32 (76.19)	61 (78.20)	NS
Postoperative stay	4.41 ± 4.68	4.50 ± 5.12	7.40 ± 7.17	2.94 ± 2.46	0.001
Operative time	253.81 ± 91.91	258.41 ± 89.81	294.19 ± 84.82	239.14 ± 86.95	0.001
Tradit minor/major	82/77	58/61	16/25	42/36	NS
Iwate					0.02
Low	26	19	5	14	
Intermediate	60	43	9	34	
Advanced	54	43	13	30	
Expert	19	14	14	0	
Iwate					0.009
I	68	48	13	35	
II	24	18	3	15	
III	67	53	25	28	
Iwate					NS
Low	21	13	3	10	
Moderate	81	58	18	40	
High	52	43	15	28	
Extremely high	4	4	4	0	
Complications					
CCI	8.10 ± 17.53	4.91 ± 12.51	16.57 ± 26.34	5.18 ± 11.52	0.01
No complications, *n* (%)	117 (73.1)	33 (82.5)	24 (57.1)	60 (76.9)	0.024
Redo surgery, *n* (%)	8 (5.0)	1 (2.5)	6 (14.3)	1 (1.3)	0.04
Readmission, *n* (%)	12 (7.5)	1 (2.5)	5 (11.9)	6 (7.7)	NS
Minor complications (I-II), *n* (%)	30 (18.8)	4 (10.0)	13 (31.0)	13 (16.7)	0.024
Major complications (IIIa, IIIb, IV)	13 (8.1)	3 (7.5)	5 (11.9)	5 (6.4)	NS
	6 IIIa	1 IIIa		4 IIIa	
	2 IIIb	1 IIIb		1 IIIb	
	2 Iva		2 Iva		
	1 IVb		1 IVb		
	2 V		2 V		

BMI: Body mass index; CCI: Comprehensive complication index; F: Female; FTP: Fast-track protocols; M: Male; NS: Not significant.

Multivariate analysis

Multivariate models were obtained to find out if complexity scores were independent predictors of early discharge, complications and/or readmissions. A model was performed for each of the complexity scores in order to avoid interactions. Age, BMI, sex, American Society of Anesthesiologists score, previous surgery, malignancy, bilobar spread and liver disease were added as variables. All patients in

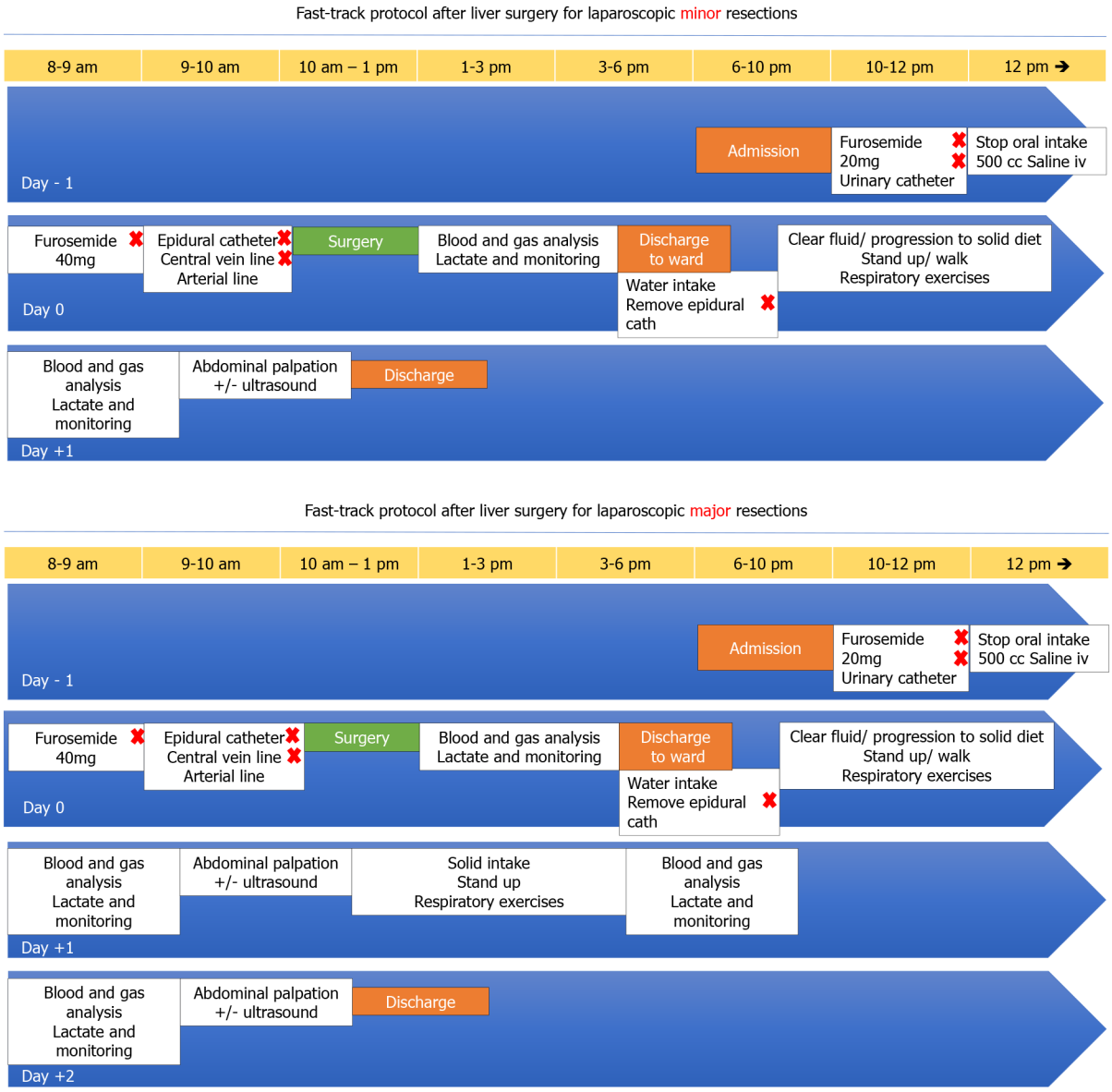

Figure 1 Perioperative protocols of fast-track in laparoscopic minor (A) and major (B) liver resections. The minor (A) and the major (B) laparoscopic liver resections are protocols of 24-h and 48-h postoperative hospital stay. Actions with a red cross are under consideration for removal of this protocol after 5 yr of experience.

the series were included (160 cases). As observed in Table 2, in each model the complexity scores were independent risk scores. Interestingly, BMI was a persistent risk factor added to these scores in both the complications and discharge < 72 h models.

DISCUSSION

Patients undergoing a standard laparoscopic liver resection may be considered as optimal candidates to be included into early recovery protocols, as the surgical procedure needs no anastomosis nor vascular reconstruction. The adoption of LLS by liver teams seems to be clearly exponential, and thus the recovery and postoperative comfort are improving. According to our results, adequate selection may lead to high rates of effectiveness in terms of early discharge, low readmission rates and reduced incidence of complications. Complexity scores may be helpful in the selection process.

Several complexity scores have been reported to date[5-14]. From a technical point of view, most of them have assessed the effect of variables such as tumor location or extent of liver resection. However, liver and patient status have not been considered as important in the scores, and only impaired liver function and previous liver surgery or preoperative chemotherapy have been marginally evaluated. Only Hasegawa *et al*[13] considered BMI score as valuable in a difficulty score. According to our results, BMI score may be considered as important because it may add relevant information about the prognosis

Table 2 Multivariate models

Model					
Iwate					
Discharge 24 h	Sig	OR	Discharge 72 h	Sig	OR
Iwate	0.001	1.626 (1.2-2.18)	Iwate	0.01	1.46 (1.09-1.95)
			BMI 25-30	0.033	6.39 (1.16-35.30)
			BMI 30-35	0.013	8.51 (1.57-46.14)
Complications	Sig	OR	Readmissions	Sig	OR
Iwate	0.02	1.2 (1.03-1.41)	Iwate	0.007	1.58 (1.13-2.22)
BMI > 35	0.008	8.75 (1.76-43.44)			
Southampton					
Southampton	0.015	1.43 (1.07-1.92)			
			BMI 25-30	0.032	6.08 (1.16-31.87)
			BMI 30-35	0.006	9.85 (1.91-50.70)
Complications	Sig	OR	Readmissions	Sig	OR
			Southampton	0.036	1.3 (1.01-1.68)
BMI > 35	0.013	7.09 (1.52-33.04)			
Gayet					
Discharge 24 h	Sig	OR	Discharge 72 h	Sig	OR
Gayet	0.004	1.85 (1.21-2.81)	Gayet	0.043	1.53 (1.01-2.31)
			BMI 25-30	0.042	5.72 (1.06-30.86)
			BMI 30-35	0.014	8.08 (1.52-42.99)
Complications	Sig	OR	Readmissions	Sig	OR
Gayet	0.008	1.48 (1.11-1.98)	Gayet	0.027	2.08 (1.08-4.01)
BMI > 35	0.009	8.56 (1.71-42.85)			

Considering the end-point of discharge in < 24 h and < 72 h, complication rate and readmissions, complexity scores were included and analyzed independently. Age, body mass index, sex, American Society of Anesthesiologists score, previous surgery, malignancy, bilobar spread and liver disease were added as variables. BMI was an independent risk factor added to complexity scores in most of the models analyzed. BMI: Body mass index; OR: Odds ratio; Sig: Significance.

of the patients and the potential adherence to an FTP. In our opinion, liver and patient status have not been adequately considered and should be re-evaluated into difficulty scores. Liver function parameters are only considered by traditional markers (such as Child, platelets or bilirubin). Western and eastern populations are different from a demographical and epidemiological point of view. The main disease, underlying liver impairment and a potential fatty liver or neoadjuvant chemotherapy may surely complement current scores.

A recent meta-analysis performed on 580 laparoscopic liver patients (292 early recovery *vs* 288 traditional) performed on 8 studies highlighted the potential benefit of these protocols in this type of surgery[15]. However, the risk of bias was too high as the authors did not report detailed randomization methods, allocation concealment or blind methods. Moreover, the included studies did not adopt a standard and unified clinical treatment of ERAS programs, and complexity of the resection was not included or controlled as a bias factor. A more recent meta-analysis on ERAS clinical pathways included 4 randomized trials showing several advantages like length of stay and lower complication rates[16]. However, according to the recent recommendations from the ERAS group, liver teams were encouraged to report other components or modifications that could improve results or help spread this clinical pathway.

Our protocol is probably the most aggressive perioperative protocol reported to date in LLS. Our main aim was to reach < 24 h stay in minor hepatectomies and < 48 h in major hepatectomies without any detrimental effect on postoperative outcome. As stated before, about 30% of the cases, if adequately selected, can be discharged in less than 24 h and up to 50% in less than 2 d. It should be noted that 74% of the cases that did not adhere to our FTP were due to non-medical issues or complications. The area to

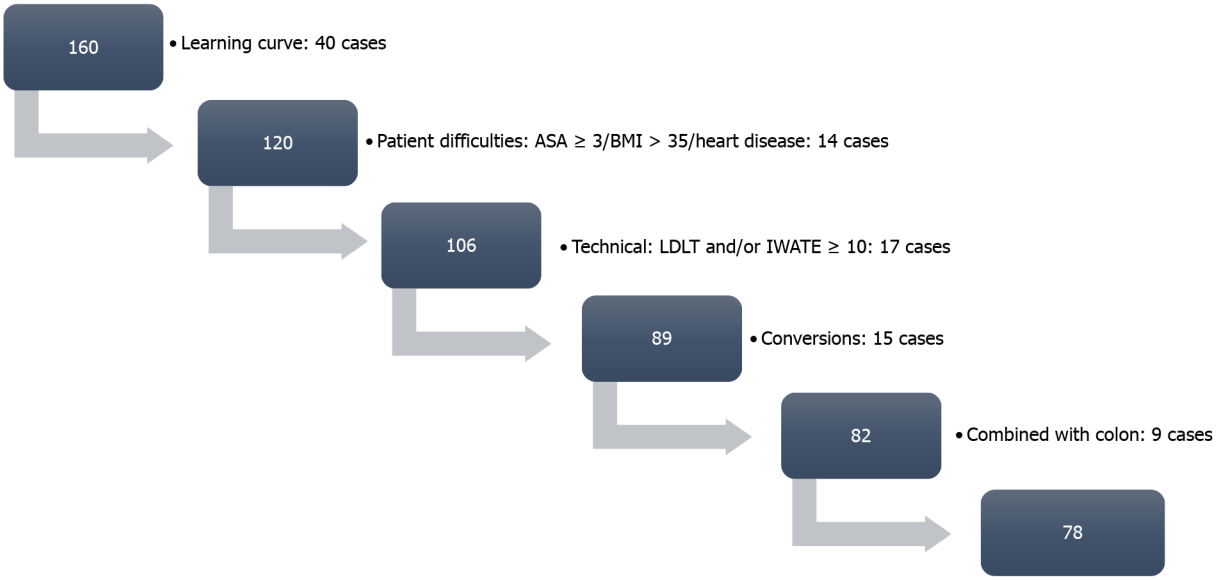

Figure 2 Flowchart of the patients included in the study. After removal of excluded cases, a total of 78 cases was the final dataset of patients amenable for inclusion in a fast-track protocol. ASA: American Society of Anesthesiologists; BMI: Body mass index; LDLT: Living donor liver transplantation.

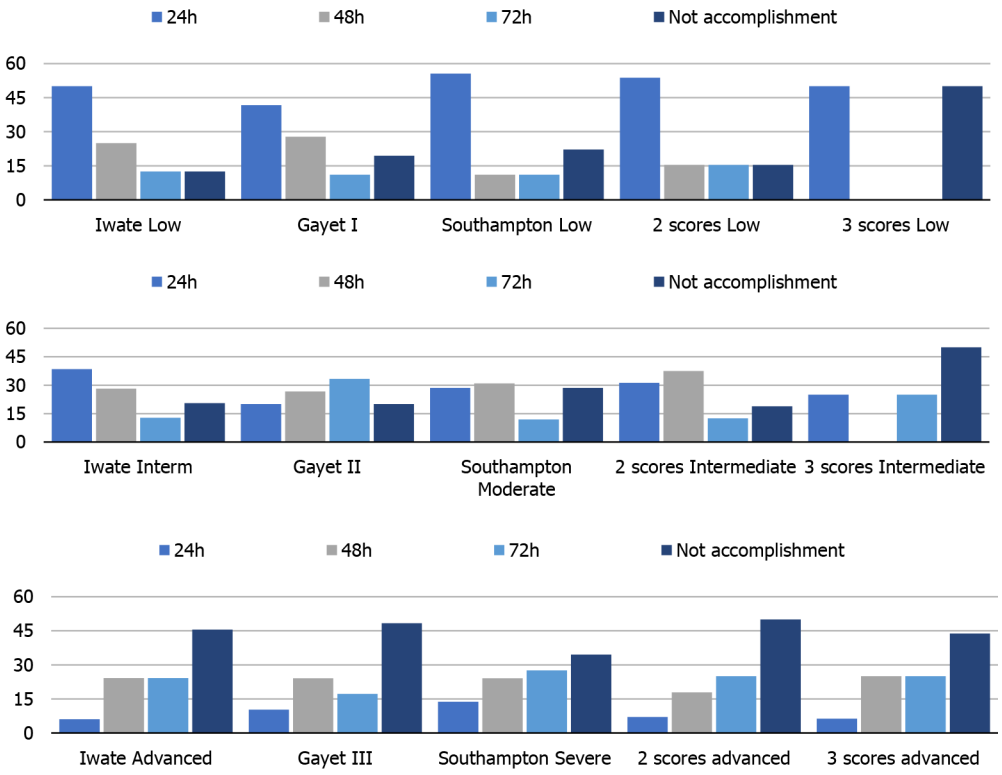

Figure 3 Accomplishment of fast-track protocols according to difficulty scores. The accomplishment of a 24-h, 48-h and 72-h fast-track protocol (blue, green and yellow bars, respectively) was analyzed according to the difficulty scores of Iwate, Gayet and Southampton in their subcategories low (above), intermediate (middle) and severe (below). Interm: Intermediate.

which our hospital gives assistance includes regions more than 200 km away from our city. We detected that people from there were reluctant to early discharge after a major abdominal operation as they felt "unsafe."

The perioperative protocol has experienced some changes mainly due to increased experience. Our most recent cases have been performed without epidural catheter and some of them without central line. Similarly, we have stopped urinary catheterization the night before and discontinued furosemide 12 h before the surgery. These improvements are parallel to the better knowledge from our anesthesiologist, which have perfectly adapted the balance between central venous pressure, pneumoperitoneum

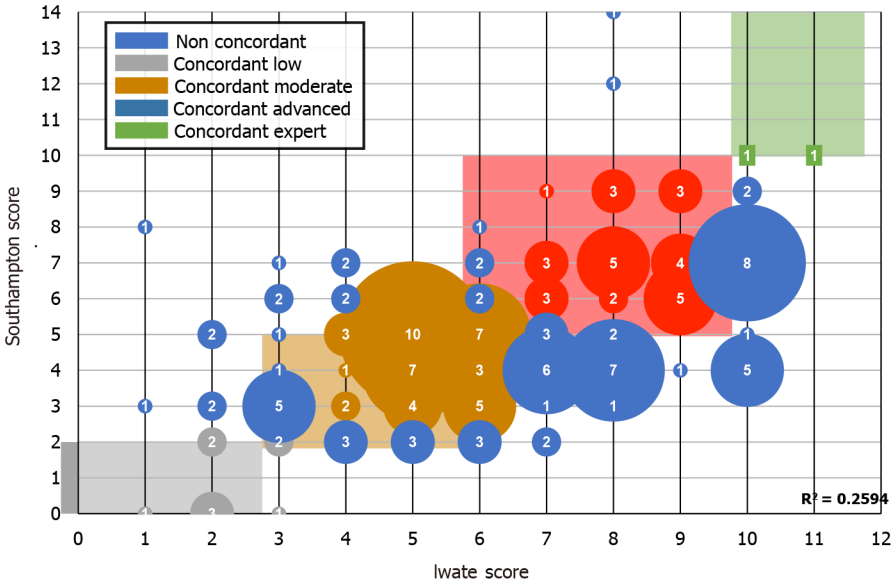

Figure 4 Correlation of difficulty scores. A comparison of Iwate (X-axis) and Southampton (Y-axis) scores was performed. As observed, several cases were upgraded or downgraded (blue circles), meaning a non-concordant classification between both scores.

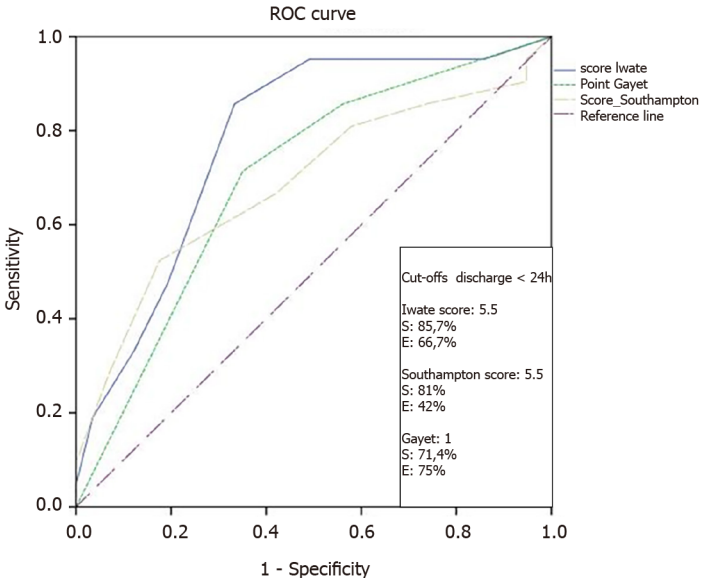

Figure 5 Receiver operating curves for the prediction of 24-h postoperative hospital stay. Iwate score was the best score with a cutoff point scoring of 5.5 with a sensitivity and specificity of 85.7% and 66.7%, respectively.

pressure and airway pressure, making surgery a bloodless field[17]. It should be remarked that anesthesiologists are the cornerstone in our LLS. The intraoperative management based on boluses of inotropes rather than fluid administration is a difficult management that needs expertise and experience.

Some limitations of our research should be highlighted. First, the final population in the study was not extremely large; second, the results may have obviously changed according to our improved experience; and third, complexity has too changed, and thus applicability may be limited. However, we offer a homogeneous population in a brief period of time in a recently developed LLS team. This main advantage may be transferable to several liver teams worldwide and may help them face the same difficulties that we have had in a different way. Alternatively, our protocol is the first incorporating a full perioperative pathway within complexity scoring systems, making a 24 h early discharge possible in the setting of LLS.

CONCLUSION

In conclusion, it is feasible to develop aggressive FTP in LLS, even in high-complexity cases. In fact, our protocols are the first-reported to adequately predict and accomplish a postoperative hospital stay shorter than 24 h. Currently available difficulty scores are useful to define candidates for FTP and may predict a full completion even in aggressive postoperative stay formats. However, we consider that BMI has not been adequately considered and may be added to the scores in order to improve their prediction capabilities.

ARTICLE HIGHLIGHTS

Research background

There is a lack of evidence regarding the correlation between laparoscopic liver surgery (LLS) difficulty scoring systems and accomplishment of fast-track protocols (FTP).

Research motivation

The main motivation is to identify if current difficulty scoring systems may be used to predict early discharging policies and development of complications after LLS within an FTP.

Research objectives

The main objectives are to define if difficulty scoring systems may predict accomplishment of FTPs in LLS and to determine variables that may complement these scoring systems to increase their prediction capabilities.

Research methods

We analyzed out patients included in an FTP and compared Iwate, Southampton and Gayet's scoring systems. Comparisons were also made in some sets of patients who were included in 24-h and 48-h early discharge protocols for both minor and major resections, respectively.

Research results

Our selection criteria was successful with more than 70% of our patients being discharged in less than 72 h. Iwate scoring system was the most accurate to predict 24-h discharge with an area under the receiver operating characteristic = 0.78 and 87.7% and 66.7% for sensitivity and specificity values, respectively, and a cutoff of 5.5 points.

Research conclusions

Iwate difficulty score is the most accurate to predict adhesion to an FTP after LLS. Body mass index was considered as an independent risk factor that should be added to current scoring systems.

Research perspectives

Incoming difficulty scoring systems may be further evaluated to include variables not considered to date.

FOOTNOTES

Author contributions: Ciria R and Ayllón MD designed the research study; Ciria R, Ayllón MD, Padial A and García-Gaitan C performed the research; all authors analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript; Ciria R and Padial A have equally contributed to the development of this manuscript and research.

Institutional review board statement: Approval number of the institutional review board of the University Hospital Reina Sofia was 4380 (Code 0000-0002).

Conflict-of-interest statement: The authors declare no conflict of interest in none of the contents within the development of the manuscript.

Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at rubenciria@gmail.com. Participants gave informed consent for data sharing.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Spain

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S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Wu RR

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World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 March 27; 14(3): 221-235

DOI: 10.4240/wjgs.v14.i3.221

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Case Control Study

Does cranial-medial mixed dominant approach have a unique advantage for laparoscopic right hemicolectomy with complete mesocolic excision?

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: El-Nakeep S, Egypt; Hegazy AA, Egypt

Received: September 1, 2021
Peer-review started: September 1, 2021
First decision: November 7, 2021
Revised: November 14, 2021
Accepted: March 5, 2022
Article in press: March 5, 2022
Published online: March 27, 2022

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Abstract

BACKGROUND

Complete mesocolic excision (CME) with central vascular ligation (CVL) was proposed by Hohenberger in 2009. The CME principle has gradually become the technical standard for colon cancer surgery. How to achieve CME with CVL in laparoscopic right hemicolectomy (LRH) is controversial, and a unified standard approach is not yet available. In recent years, the authors' team has integrated the theory of membrane anatomy, tried to combine the cephalic approach with the classic medial approach (MA) for technical optimization, and proposed a cranial-medial mixed dominant approach (CMA).

AIM

To explore the feasibility of operational approaches for LRH with CME.

METHODS

In this retrospective cohort study, the clinical data of 57 patients with right-sided colon cancer (TNM stage I, II, or III) who underwent LRH with CME from January 2016 to June 2020 were collected and summarized. There were 31 patients in the traditional MA group and 26 in the CMA group.

RESULTS

There were no significant differences in baseline data between the two groups. The operation was shorter and the number of lymph nodes dissected was higher in the CMA group than in the MA group, but there was no significant difference in the number of positive lymph nodes, intraoperative blood loss, postoperative exhaust time, feeding time, postoperative hospital stay or postoperative complication incidence.

CONCLUSION
Our study shows that the CMA is a safe and feasible procedure for LRH with CME and has a unique advantage.

Key Words: Right hemicolectomy; Laparoscopic surgery; Complete mesocolic excision; Mesocolon; Embryology; Colon cancer

Core Tip: This work presents the combination of the cranial approach and the classic medial approach and optimization of the combined approach to propose a cranial-medial mixed dominant approach (CMA) based on embryonic development and membrane anatomy. Our study shows that the CMA is a safe and feasible procedure for laparoscopic right hemicolectomy with complete mesocolic excision and has a unique advantage.

Citation: Lin L, Yuan SB, Guo H. Does cranial-medial mixed dominant approach have a unique advantage for laparoscopic right hemicolectomy with complete mesocolic excision? *World J Gastrointest Surg* 2022; 14(3): 221-235
URL: https://www.wjgnet.com/1948-9366/full/v14/i3/221.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i3.221

INTRODUCTION

Since Heald[1] proposed the total mesorectal excision (TME) principle in 1982, TME has become the international gold standard for rectal cancer[2]. In 1991, Jacobs *et al*[3] first reported laparoscopic colorectal cancer resection. A similar concept of complete mesocolic excision (CME) with central vascular ligation (CVL) was proposed by Hohenberger *et al*[4] in 2009 based on the concepts of TME. The CME principle has gradually become the technical standard for colon cancer surgery[5,6]. The National Comprehensive Cancer Network (NCCN) guidelines for colon cancer recommended laparoscopic surgery for patients with curable colon cancer[7] for years, but it is generally considered that laparoscopic right hemicolectomy (LRH) is relatively complex and difficult[8]. How to achieve CME with CVL in LRH has been controversial, and a unified standard approach is not yet available. Before this procedure can be generally recommended, a consensus is needed on how the operation can be carried out optimally. However, quite a few approaches have been proposed[9-11]. In recent years, the authors' team has integrated the theory of embryonic development and membrane anatomy, combined the cranial approach with the classic medial approach (MA) and optimized the combined approach to propose a cranial-medial mixed dominant approach (CMA). This approach allows better control of surgical risks, is more compliant with CME requirements, and is more standardized and reproducible.

MATERIALS AND METHODS

Materials

All the patients, both those in the CMA group and those in the MA group, were admitted to the Department of Gastrointestinal Surgery of Zhongshan Hospital of Xiamen University and underwent LRH with CME and CVL, which was performed by Professor Sibo Yuan. Between January 2016 and December 2020, adult patients who had a confirmed diagnosis of renal cell carcinoma (RCC), who underwent contrast-enhanced CT of the chest, abdomen, and pelvis for clinical staging (cTNM), and who underwent radical colectomy were selected from the database. The selection criteria were as follows: (1) Patients were 15 years of age or older, with no limitation on sex; (2) Patients had a confirmed diagnosis of clinical stage I, II, or III adenocarcinoma through biopsy of the right colon on colonoscopy, including the caecum, ascending colon, hepatic flexure, and proximal transverse colon; and (3) Patients underwent laparoscopic surgery at a scheduled time rather than emergency surgery due to severe obstruction or perforation. During 2016–2018, 36 patients underwent LRH with the traditional MA. From 2018 to 2020, 33 patients underwent treatment with the CMA. Twelve of the 69 patients were excluded from this study due to resection of local metastases of the organ (stomach, uterus, annex, *etc.*) and simultaneous resection of liver metastases and intestinal polyps, for which we could not assess the operative duration, postoperative recovery or other factors. Professor Yuan primarily used the MA before 2018 and proposed and primarily used the CMA after 2018 to complete LRH. Twenty-six patients

were included in the CMA group, and 31 patients were included in the MA group after exclusion (Figure 1). Postoperative clinical tumour staging was based on the Union for International Cancer Control (UICC) cancer staging manual (version 6). Preoperative blood and albumin (ALB) transfusions were performed in cases of anaemia and hypoproteinaemia, respectively. The basic condition of the patients and the outcome data are shown in Table 1.

Surgical approaches

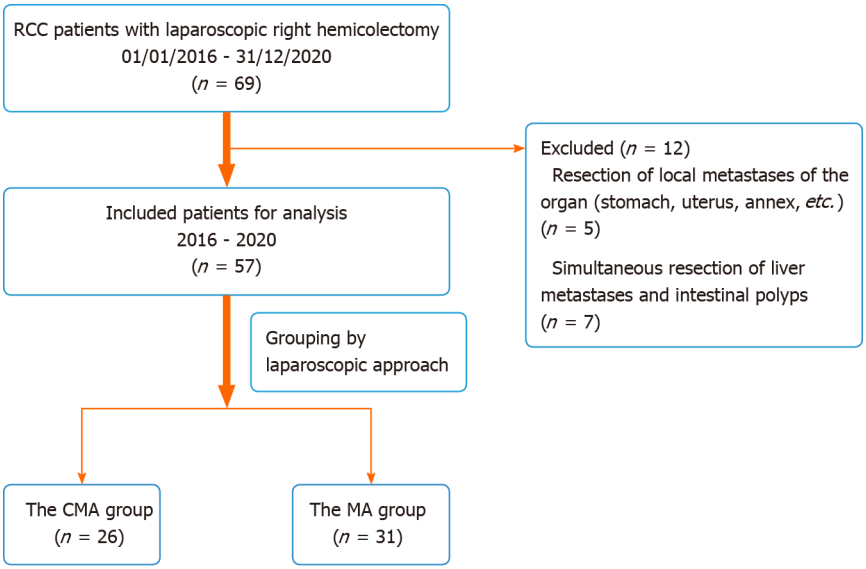
Dissociation of the right colon under laparoscopy was completed in both groups of patients (CMA and MA). Then, the surgeon made a small incision of approximately 4 cm on the right side of the abdomen to complete the anastomosis (routine end-side anastomosis), finally rearranging the bowel.

CMA: (1) Establishment of a laparoscopic system and intraperitoneal exploration: All patients were placed in the lithotomy position after the administration of general anaesthesia, with the left leg lowered as much as possible to avoid affecting the operation of the surgeon. Throughout the procedure, the surgeon stood on the left side of the patient, whereas the first assistant stood on the right side, and the second assistant held a mirror and stood between the legs of the patient. Five trocars were used (three 5 mm, one 12 mm, one 10 mm), with one observation and four operation ports. Among these, one observation port with a 10-mm trocar was located 2 cm lower than the umbilicus. One operation port with a 5-mm trocar was placed at Maxwell's point. The second operation port with a 12-mm trocar was placed near the anti-Maxwell point. The third and fourth operation ports with 5-mm trocars were located approximately 2 cm lower than the edge of the rib arch across the left and right clavicular midline intersections (Figure 2). Laparoscopic exploration of the liver lobe, peritoneum, omentum, spleen, stomach, colon, pelvis, and small intestine was performed; the tumour location and size were evaluated to assess the extent of tumour invasion into the surrounding tissue and determine the scope of surgical resection. Then, the projection of the surgical trunk, the superior mesenteric artery (SMA) on the mesocolon and the root of the middle colic vessels were explored; (2) The greater omentum was split with an ultrasonic knife to the left of the superior edge of the transverse colon, the omental bursa was entered, and the greater omentum outside the gastric omental vascular arch (tumour of the ascending colon or ileocaecum) or inside the vascular arch (tumour of the hepatic curvature or right half of the transverse colon) was longitudinally cut off, revealing the right mesenteric fusion region of the transverse mesocolon, the mesogastrium and the underlying visceral duodenal-pancreatic peritoneum (also called the fusion fascia of Fredet)[12,13]; (3) Cephalic-approach procedure (CAP): The first assistant lifted the gastric body and pulled the mesogastrium upwards laterally, and the surgeon used the right hand to pull the transverse mesocolon downwards, which formed an antagonistic force and satisfactorily exposed the right fusion fascia area of the transverse mesocolon and the mesogastrium. The surgeon first dissected the fusion fascia in the innermost area adjacent to the gastric antrum (Figure 3A), entered the dorsal side of the fusion fascia of Fredet (Figure 3B), and then gently expanded the surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum in a medial-to-lateral direction. After cleavage of the lateral "white line of Toldt" around the hepatic flexure, the fusion fascia was incised between the hepatic curvature of the colon and the second part of the duodenum and expanded downwards and slightly laterally, and the plane between the fusion fascia of Toldt and the subperitoneal deep fascia (Gerota fascia) near the lateral side of the second part of the duodenum was entered. Using the projection of the superior right colic vein (SRCV) on the fusion fascia of Fredet as a landmark, the surgical plane was expanded medially to expose the gastrocolic trunk of Henle (GCTH), and the nonvascularized mesocolic area was expanded on the left side of the root of the middle colonic vessels, completing the dissection of the surgical area of the GCTH[14,15] (SAGCTH), defined as the area of the superior mesenteric vein (SMV) located at the head of the pancreas and including the venous confluence of the right gastroepiploic vein (RGEV), anterosuperior pancreatic-duodenal vein (ASPV), and SRCV. Then, exposure was continue downwards to the second part of the duodenum, the head of the pancreas and the cranial root of the middle colic vessel; a piece of gauze was placed transversely at the lower edge as a landmark. In this procedure, the most important thing was to maintain the surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum and to completely resect the fusion fascia of Fredet (Figure 3C); (4) Medial-approach procedure (MAP): The first assistant pulled up the mesocolon of the middle colic vascular area with the left hand, pulled the mesocolon of the ileocolic vascular area with the right hand, and exposed the projection of the surgical trunk[14,17] on the mesocolon. The surgeon incised the mesentery junction (the fusion point of the mesocolon, the visceral peritoneum, and the intestinal mesentery, approximately 3 cm below the projection of the ileocolic vessels to the confluence of the SMV) with an ultrasonic scalpel (Figure 3D and E), utilized the vapourization effect of the ultrasonic scalpel, sought the fusion fascia of Toldt and then entered the surgical plane between the fusion fascia of Toldt and subperitoneal deep fascia (Figure 3F); then, the surgeon slightly expanded the plane laterally to the white line of Toldt, down to the peritoneal reflexion area of the ileocaecum, and up to the lower margin of duodenum and cut off the right fusion fascia of Toldt at the third portion of the duodenum, where the fusion fascia of Toldt divided into the posterior pancreatic fascia of Treitz and the fusion fascia of Fredet. The dorsal side of the fusion fascia of Fredet was entered to reach a rendezvous of the surgical plane with that of the CAP (Figure 3G and H). The ileocolic artery (ICA) was used as a landmark, revealing the surgical

Table 1 Basic patient preoperative characteristics

Item	CMA group (*n* = 26)	MA group (*n* = 31)	*P* value
Age (yr)	63.12 ± 13.65	61.35 ± 12.27	0.61
Sex			0.794
Male	14	18	
Female	12	13	
BMI (kg/m^2)	21.42 ± 3.15	22.54 ± 3.43	0.209
Tumour size (cm)	5.18 ± 1.80	4.84 ± 2.06	0.52
Previous abdominal surgery			0.488
Yes	3	6	
No	23	25	
Tumour location			0.644
Ileocecal junction	7	6	
Ascending colon	11	12	
Flexura hepatica coli	8	13	
Histological grade			0.185
Well	0	1	
Moderate	18	26	
Poor	8	4	

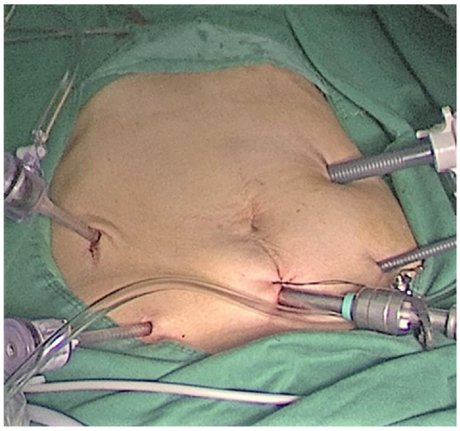
CMA: Cranial-medial mixed dominant approach; MA: Medial approach.



DOI: 10.4240/wjgs.v14.i3.221

Figure 1 Flow chart of clinical data selection.

trunk; the mesenteric radix was sharply dissected from the caudal side (small intestinal venous branch of the SMV) to the cranial side (the left root of the middle colic artery (MCA), with the projection of the gauze used as a landmark), and the roots of the vessels (ileocolic vessels, right colic artery, *etc.*) were ligated simultaneously; (5) Rendezvous of the surgical plane after the CAP and MAP. The rendezvous zone: (a) The nonvascularized mesocolic area on the left side of the root of the MCA was dissected to enter the ventral plane of the pancreas; and (b) The connecting line from the right side of the middle colic vessel to the GCTH was opened up, which connected the dorsal side of the fusion fascias of Fredet



DOI: 10.4240/wjgs.v14.i3.221

Figure 2 The position of the five trocars.

and Toldt. The root of the right branch of the MCA was ligated simultaneously; and (6) Cleavage of the lateral white line of Toldt was performed around the caecum (Figure 3L), along the ascending colon and around the hepatic flexure, connecting the posterior plane of the expanded fusion fascia of Toldt to complete the overall mobilization of the right colon (Figure 3M). The specimen from the operation was in Figure 4.

MA: First, we found the anatomic projection of the ileocolic vessel pedicle. We anatomized the SMV from the caudal side to the cranial side and ligated the roots of the vessels [ileocolic vein (ICV), ileocolic artery (ICA), RCV, right colic artery (RCA), *etc.*]. Then, we followed the fusion space of the hepatic flexure of the colon and completely dissected the colonic hepatic flexure (as mentioned above). Finally, we mobilized the right colon along with the expanded fusion fascia of Toldt.

Observational indexes

Intraoperative data were obtained regarding the operative duration (duration of the total operation and the laparoscopic procedure), blood loss, specimen length, and number of resected and positive lymph nodes. Postoperative data, including exhaust time, liquid intake time, postoperative hospitalization (days), and postoperative complications, were recorded. Complications were graded according to the Clavien–Dindo classification[18]. Mortality and short-term postoperative complications within the first 30 postoperative days (or during the entire hospital stay if longer than 30 d) were recorded. Postoperative ileus was defined as no tolerance for solid food and no defecation by postoperative day 6 [19]. Postoperative bleeding was defined as bleeding requiring at least one transfusion of packed red cells during surgery or in the subsequent 48 h.

Statistical analysis

All calculations and analyses were performed by SPSS software, version 22.0 (SPSS, Chicago, IL). Quantitative data are expressed as the mean ± SD. Student's *t* test was used to compare the differences between the two groups; $P < 0.05$ was considered statistically significant.

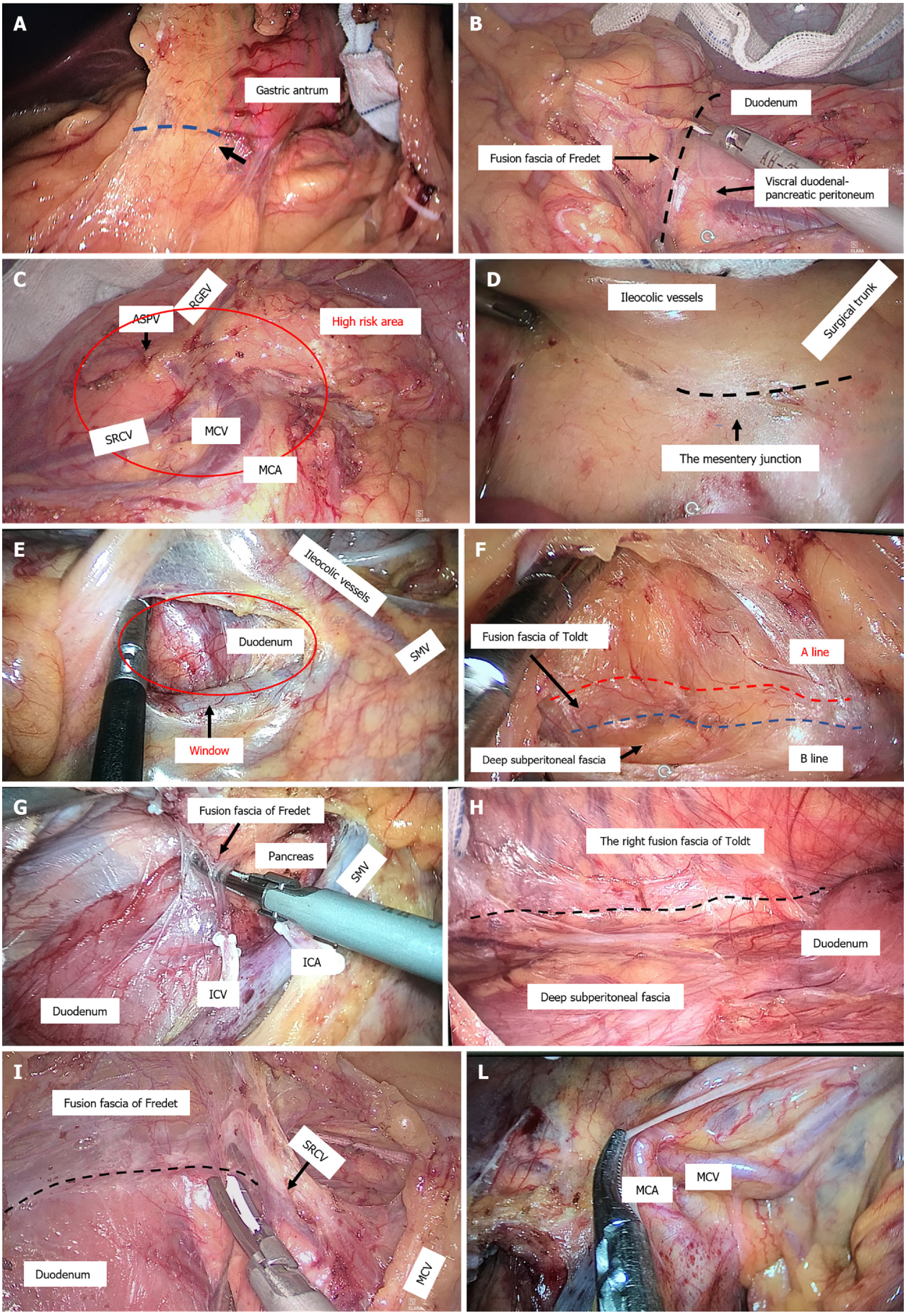
RESULTS

General information

Twenty-six and 31 patients were assigned to the MA and CMA groups, respectively (Table 1). There was no significant difference between the groups in sex, tumour location, tumour classification, laboratory results [carcinoembryonic antigen (CEA) level, haemoglobin (HB) level, white blood cell (WBC) count, ALB level, *etc.*] or body mass index.

Comparison of intraoperative and postoperative conditions

The mean resection sample length in the MA group was 26.95 ± 6.18 cm, which was not different from that in the CMA group (27.926 ± 7.52 cm) ($P = 0.598$). The number of lymph nodes collected in the CMA group was 30.50 ± 15.31, which was significantly greater than that in the MA group (23.81 ± 9.06). The number of positive lymph nodes was similar in both groups. In the CMA group, the operative duration was 135.12 ± 17.47 min, and the laparoscopic procedure time was 69.73 ± 15.13 min, which were significantly lower ($P < 0.05$) than those in the MA group (150.61 ± 26.01 min and 84.81 ± 21.48 min,


A
Gastric antrum
B
Duodenum
Fusion fascia of Fredet
Viscral duodenal-pancreatic peritoneum
C
RGEV
ASPV
High risk area
SRCV
MCV
MCA
D
Ileocolic vessels
Surgical trunk
The mesentery junction
E
Ileocolic vessels
Duodenum
SMV
Window
F
Fusion fascia of Toldt
A line
Deep subperitoneal fascia
B line
G
Fusion fascia of Fredet
Pancreas
SMV
ICA
ICV
Duodenum
H
The right fusion fascia of Toldt
Duodenum
Deep subperitoneal fascia
I
Fusion fascia of Fredet
SRCV
Duodenum
MCV
L
MCA
MCV

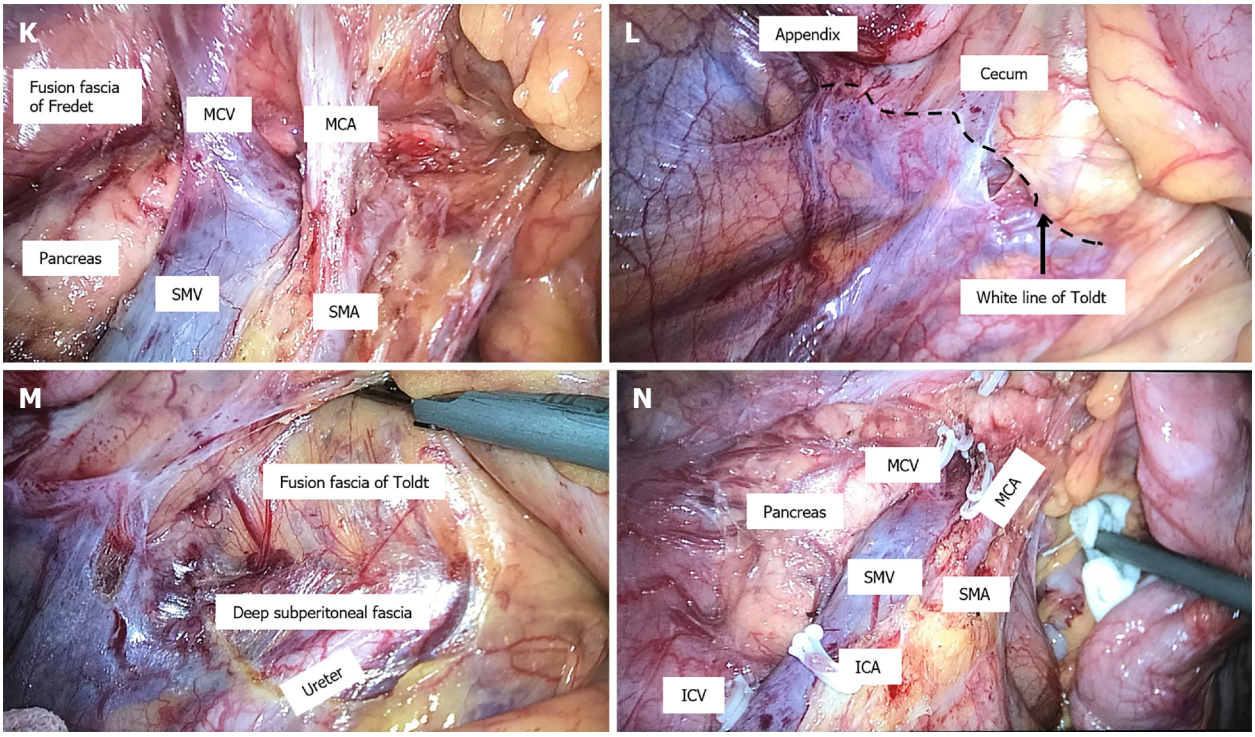


Figure 3 The cranial-medial mixed dominant approach. A: The right fusion fascia area of the transverse mesocolon and the mesogastrium. The black arrow indicates the position of the first cut with dissection along the dotted line; B: Expanded surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum; C: High-risk area using the superior right colic vein as a landmark included the gastrocolic trunk of Henle, middle colic vein (MCV), and middle colic artery (MCA); D: The mesentery junction fusion point of the mesocolon and the intestinal mesentery, approximately 3 cm below the projection of ileocolic vessels to the confluence of the superior mesenteric vein (SMV); E: The mesocolic window was opened to enter the right retrocolic space; F: Expanded surgical plane of the right retrocolic space between the ventral side of the fusion fascia of Toldt and deep subperitoneal fascia. A line: Red dotted line, B line: Blue dotted line, as indicated by Shinohara[15]; G: Fusion fascia of Fredet; H: Right retrocolic space after resection between the fusion fascia of Toldt and deep subperitoneal fascia; I: Rendezvous view of the surgical plane after the cephalic-approach procedure and medial-approach procedure, cut along the black dotted line on the fusion fascia of Fredet; J: Complex three-dimensional anatomical structure of the root of medial colic vessels; K: Three-dimensional dissection of the mesocolon around the root of the MCVs; L: Lateral white line of Toldt around the ileocaecum; M: Cleavage of the lateral white line of Toldt around the caecum connected to the posterior plane of the expanded fusion fascia of Toldt; N: SMV after lymph node dissection. RGEV: Right gastroepiploic vein; ASPV: Anterosuperior pancreatic-duodenal vein; SRCV: Superior right colic vein; ICA: Ileocolic artery; ICV: Ileocolic vein; SMA: Superior mesenteric artery.

respectively). There was no significant difference in the intraoperative blood loss, feeding fluid time, exhaust time, length of hospital stay or postoperative laboratory results (seven days after the operation) between the two groups ($P > 0.05$) (Table 2).

Operational complications

The incidence of complications in the CMA group was 23%, while that in the CA group was 13%, but the difference was not significant ($P = 0.486$). The 30 d mortality rate was 0 in both groups. However, there were 3 cases of lymphatic fistula in the CMA group, all of which were cured by conservative treatment (Table 3).

DISCUSSION

Multiple cohort studies have confirmed the oncological effectiveness and surgical safety of CME with CVL[20-22], in which the embryologic tissue planes are resected along the entire enveloped mesocolon. There is a multicentre, prospective, randomized trial comparing conventional (laparoscopic) right hemicolectomy with robotic CME for patients with right-sided colon cancer at 4 centres in the UK currently underway, and we are very much looking forwards to its results[23]. Although there are still some doubts[8], laparoscopic CME has gradually become the technical standard for colon cancer[5]. However, there is no consensus on which standard surgical approach should be used to perform LRH with CME.

The representative approaches of LRH with CME include the MA, cephalic approach, caudal approach and other mixed approaches. European randomized controlled trials (RCTs) have suggested that[24] the MA has advantages in LRH and is both widely used in clinical practice and representative. However, Liang *et al*[9] suggested that the MA is difficult and commonly leads to bleeding due to

Table 2 Comparison of intraoperative and postoperative conditions between the two groups

Item	CMA group (*n* = 26)	MA group (*n* = 31)	*P* value
Sample length (cm)	26.95 ± 6.18	27.926 ± 7.52	0.598
No. of lymph nodes collected	30.50 ± 15.31	23.81 ± 9.06	0.046
No. of positive lymph nodes	2.15 ± 2.99	1.45 ± 2.32	0.323
Nerve invasion			0.524
Yes	20	26	
No	6	5	
Vessel carcinoma embolus			0.432
Yes	14	20	
No	12	11	
Invasive depth			0.021
T1	2	1	
T2	0	1	
T3	8	1	
T4	16	28	
Lymph node metastasis			0.658
N0	13	19	
N1	9	9	
N2	4	3	
pTNM			
0	0	1	0.339
I	1	0	
II	12	16	
III	11	14	
IV	2	0	
Total operation time (min)	135.12 ± 17.47	150.61 ± 26.01	0.01
Laparoscopic procedure time (min)	69.73 ± 15.13	84.81 ± 21.48	0.003
Intraoperative blood loss (mL)	48.46 ± 30.07	67.10 ± 87.88	0.309
Exhaust time (d)	3.81 ± 1.92	4.45 ± 1.15	0.123
Liquid intake time (d)	5.27 ± 1.87	4.81 ± 1.22	0.266
Postoperative hospitalization (d)	12.23 ± 2.23	11.29 ± 2.02	0.101

CMA: Cranial-medial mixed dominant approach; MA: Medial approach.

variation in the surgical trunk and its branches. Matsuda *et al*[4] proposed a cranial-to-caudal approach in 2015 and considered that it is easy to expose the pancreas and the root of the middle colic vessels and facilitate lymph node dissection along the surgical trunk for advanced right-sided colon cancer. Zou *et al*[11] proposed a caudal-to-cranial approach and showed that it was easier to enter the dorsal side of the fusion fascia of Toldt. These approaches all have some limitations. In clinical practice, based on the universal principle of embryonic development and fusion fascia theory, is there a more optimized surgical approach?

In recent years, the authors' team has proposed and practised the CMA to perform LRH with CME, with satisfactory results. Compared with the MA group, the CMA group had obvious advantages in the total operative duration, laparoscopic procedure duration and the number of lymph nodes dissected, while the intraoperative blood loss and the incidence of postoperative complications were basically the same between the two groups.

Table 3 Comparison of complication rates between the two groups, *n* (%)

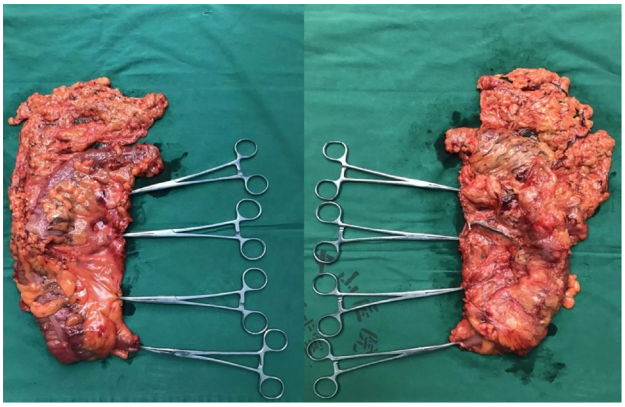
Item	CMA group (*n* = 26)	MA group (*n* = 31)	*P* value
Complications	6(23)	4(13)	0.486
Anastomotic fistula	0	0	
Anastomotic stenosis	0	0	
Bleeding	0	1	
Lymphatic fistula	3	1	
Ileus	2	0	
Incisional hernia	0	1	
Acute urine retention	0	0	
Incision infection prevention	1	1	
Intra-abdominal infection	0	0	
Pulmonary infection	0	0	

CMA: Cranial-medial mixed dominant approach; MA: Medial approach.

The theoretical framework of the CMA is derived from four aspects. First, the fascia of the primitive gut (which develops into the mesogastrium, mesocolon, mesostenium, *etc.*) is continuous during embryonic development[25,26]. Second, during embryological development, the midgut loop rotates 270 counterclockwise around the primary SMA, and the greater omentum and transverse mesocolon overlay the frontal surface of the mesoduodenum[27-29]. The peritoneal membrane at the attachment site fuses and degenerates to form membranous connective tissue called the fusion fascia[29]. Third, the right fusion fascia of Toldt is divided into the posterior pancreatic fascia of Treitz dorsally and the anterior pancreatic fascia of Fredet ventrally at the second portion of the duodenum[13,17]. These fusion fascias are delineated by the posterior layer of the ascending mesocolon ventrally (the mesofascial interface) and by the prerenal fascia, representing the posterior parietal peritoneum covering the retroperitoneum (the retrofascial interface) dorsolaterally[28]. Finally, CME with CVL was defined as follows[4,13]: (1) Dissection between the right mesocolon and the retroperitoneum, following the embryological plane, the dorsal side of the fusion fascia of Toldt and the fusion fascia of Fredet (the retrofascial interface); (2) High ligation of ileocolic vessels, right colic vessels, and the right branches of middle colic vessels; and (3) Removal of a sufficient length of the colon.

In the CAP, after entering the omental bursa, we emphasized the anatomical function of the first cut of the ultrasonic knife and produced the bubble effect when dissecting the fusion fascia in the innermost area adjacent to the gastric antrum (Figure 2A). The bubble effect allows the "angel fair" to form and the surgical space to be confirmed; then, the fusion fascia of the dorsal leaf of the transverse mesocolon and the dorsal mesogastrium can be separated, easily exposing the surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum and allowing entry. Garcia-Granero *et al*[14] indicated that the fusion fascia of Fredet should be removed completely. Mike and Kano[17,30] proposed that there are three fusion modes between the transverse mesocolon and mesoduodenum. That is, fusion between the ventral leaf of the transverse mesocolon and mesoduodenum, between the dorsal leaf of the transverse colon and mesoduodenum, and almost no fusion. We found that regardless of which mode was found, through the CAP, we could obtain a clear surgical plane and achieve a bloodless field.

The GCTH enters the SMV, dividing it into the distal "surgical trunk" and proximal "Henle's trunk area" (SAGCTH). The difficulty of LRH lies in the SAGCTH. Due to the anatomy of this region, the risk of injury to the SMV and perioperative bleeding is considered to be high. Causes of bleeding or injury include vascular variations in the GCTH[31-33], improper traction during the operation, and an uneven pancreatic surface. In most cases, the GCTH is close to the lower edge of the pancreas, joining the SMV at the uncinate process of the pancreas. The right gastroepiploic vein is near the upper edge of the pancreatic head, sometimes closely associated with the pancreas, and the signs are difficult to identify. The course of the SRCV is special in that it bridges the gap between the transverse mesocolon and the mesogastrium before it merges into the GCTH[34], and inappropriate tension needs to be avoided in dissection of the SRCV. How can this anatomical region be dissected under laparoscopy? We suggest that the SRCV can be used as a landmark, as its inflow mode is relatively constant[35]. By tracking the direction of SRCV inflow into the GCTH from the outermost side of the pancreatic head and performing ligation at its root, the risk of bleeding caused by anatomical relationships and improper techniques can be avoided. In addition, the dorsal side of the transverse mesocolon can be fully exposed at the lower edge of the uncinate process to overcome the obstacle of the visual field under the traditional MA.



DOI: 10.4240/wjgs.v14.i3.221

Figure 4 The specimen from the operation.

In the MAP, we first incised the mesocolon in the ileocolic area approximately 3 cm below the projection of ileocolic vessels to the confluence of the SMV, where a natural depression with colour distinction (yellow–white junction), which is the boundary between the intestinal mesentery and the right mesocolon, can be seen under high-definition laparoscopy. Some experts[36] have called this site the "trijunction", *i.e.*, the fusion point of the mesocolon, the visceral peritoneum, and the intestinal mesentery. Through the incision of this trijunction, we can enter the posterior space of the colon (the dorsal side of the fusion fascia of Toldt) behind the whole ascending colon and ileocecal part and can gently anatomize the whole plane of the posterior space of the colon. There is some controversy about the ideal surgical plane for colon separation. Zhang *et al*[37] considered the right retrocolic space to be ideal but did not define the level of the surgical plane. The separation plane should be behind the fusion fascia of Toldt, that is, between the fusion fascia of Toldt and the deep layer of the posterior subperitoneal fascia, as suggested by Mike M[17,30]. Based on autopsy experience, Culligan *et al*[38] proposed the view that the retrocolic space can be divided into two planes, the mesofascial plane and the retrofascial plane. Shinohara[16] pointed out the A line and the B line. The A line runs along the plane of the ventral side of the fusion fascia of Toldt without cutting it open. It does not affect the degree of lymph node dissection, but in most cases, the fusion fascia of Toldt is cut open, and it is easier to enter and expand the plane along the B line (dorsal side of the fusion fascia of Toldt). Therefore, he recommended dissociating along the B line. Our understanding is that we entered the mesofascial plane following the A line and the retrofascial plane following the B line. Coffey *et al*[39] suggested that the origin and termination of fascial lymphatics should be determined to partly address this question. A previous study[40] found that the fusion fascia of Toldt may serve a barrier function, as rarely in colorectal cancer does one observe the spread of colon cancer through the fascia into the retroperitoneum. Even where the mesocolon has been directly involved, spread through the fascia is unusual. Therefore, we agree with Mike M that complete removal of the fusion fascia of Toldt is necessary.

Coffey *et al*[41] proposed that attention should be given to maintenance of the surgical plane during LRH to meet the requirements of CME. How should the right plane be maintained? Our clinical viewpoint and theoretical basis are as follows: (1) In the process of embryonic development, the peritoneum and mesentery at the attachment site fuse and degenerate to form a single sheet of connective tissue called the fusion fascia at the end of intestinal rotation (the fusion fascias of Toldt and Fredet)[42,43], and the inside of the fusion fascia cannot be dissected by definition. It is easy to enter and expand the surgical plane behind the ascending colon from the dorsal side of the fusion fascia of Toldt; (2) The medial border of the fusion fascia of Fredet is the SMV and GCTH[13]. A safe surgical plane with better exposure can be obtained by entering from the dorsal side of the fusion fascia of Fredet, which can reduce the risk of injury to this area and especially prevent tearing and thus bleeding of the SMV, which can lead to life-threatening complications[43]; and (3) Although Shinohara[16] suggested that separation from the ventral side of the fusion fascia does not affect lymph node dissection, there is no evidence-based medical evidence that this procedure can ensure the integrity of lymphatic dissection. More importantly, this method can easily lead to fascia fragmentation and residue. Our conclusion is that to achieve CME in right-sided colon surgery, complete resection of the fusion fascias of Toldt and Fredet is necessary. How do we judge whether we entered the ventral side of the fusion fascia of Toldt under laparoscopy? First, the plane covered by the smooth, deep subperitoneal fascia (Gerota fascia) can be seen in the operation field, the reproductive vessels and peristaltic ureter can be seen behind this fascia, and the white line of Toldt can be seen faintly laterally. Second, a thin layer of relatively dense connective tissue membrane can be seen below the duodenum when the plane is expanded cephalad, and the duodenal wall can be seen vaguely behind this membrane. Third, the whole dissection process is bloodless. Bleeding indicates entry of the incorrect plane.

Where is the core anatomical area in the rendezvous process of the surgical plane of the CAP and MAP? Matsuda *et al*[10,44] noted that lymph node dissection around the middle colic vessels is technically demanding. The difficulty comes from the fusion of the transverse mesocolon in the middle colic vessel region with the greater omentum, pancreas and duodenum during embryonic development, forming a complex three-dimensional anatomical structure (Figure 2J). A substantial mesenteric tissue mass occurs at the root of the middle colic vessel region formed by midgut rotation during embryonic development. Although the fascia is contiguous, it is interrupted at points where vessels enter or leave the mesentery[39]. The position of the points is the edge of the envelope structure of the mesocolon. There is concentrated lymphatic flow and complex vascular variation at the lower edge of the uncinate process of the pancreas and the root of middle colic vessels[15,45-47]. Therefore, in LRH with CME, the dissection of the mesenteric area at the root of the middle colic vessels is the core anatomical area of the whole operation, and a simple approach such as the MA is difficult to complete. Under the CMA, we treated the cephalic part of the mesocolon of the middle colic vessel region first in the CAP, fully exposed the surgical plane behind the anterior pancreatic fascia to avoid pancreatic injury and safely exposed the GCTH and its branches; we exposed the mesenteric inner and lower boundaries of the SAGCTH and middle colic vessel region; and then we treated the caudal part of the middle colic vessel region to reach the rendezvous region of the surgical plane. Therefore, the mesentery in this area can be dissected in three dimensions to avoid residual mesenteric tissue, pancreatic injury, and injury to vessels such as the GCTH, which may lead to serious intraoperative bleeding.

Different researchers have different understandings of membrane anatomy but achieve the same result by different methods. Mike and Kano[17] have suggested that the membrane is continuous and that the membrane plane is continuous. Zhao *et al*[48] proposed the concept of a "mesenteric window". After incising the inferior edge of the ileocolic vascular pedicle, we could easily enter the natural right retrocolic space and extend the space laterally and cranially. Shinohara[16] affirmed that the SRCV and its confluence with the GCTH constituted the rotation centre of the mesocolon during embryonic development. Coffey *et al*[39] considered that the central mechanism of fixation of the mesocolon and posterior abdominal wall, that is, the connection point of the mesentery and blood vessels, constitutes the "hilum" of the mesentery, which determines the medial boundary of dissection, just as right peritoneal reflection (the white line of Toldt) determines the lateral boundary. Garcia-Granero *et al*[14] found that the medial limit of the fascia of Fredet is represented by the SMV and GCTH, which is also the hilum of the mesocolon. The above research results strongly promote the accuracy of surgery in LRH. According to our understanding, the right mesocolon is fan-shaped, and the SMV axis is the core anatomical marker of the right mesocolon, which connects the mesenteric window and hilum. These two landmarks are the result of fusion of the gastrointestinal mesentery after rotation during embryonic development and are also the important theoretical basis of membrane anatomy for the CMA.

Although this study discusses the surgical approach, the ultimate pursuit of the surgeon is oncological benefits for the patient. An early study by West *et al*[49] suggested that attention should be given to the quality classification of surgical specimens in the surgical treatment of colon cancer, as colon cancer patients who undergo resection with an intact mesocolon achieve 15% better 5-year overall survival than those with defects in the mesocolic specimens. Xie *et al*[50] recommended that in gastrointestinal surgery, the mesentery should be removed completely to prevent cancer leakage. Benz *et al*[51] proposed a new classification system for CME in right-sided colon cancer, with the following distribution: type 0 (best), type I, type II, and type III (poorest). In type 0, the true CME specimen, the stalks of the ileocolic vessels and middle colic vessels are connected by tissue of the surgical trunk (lymphatic tissue package covering the SMV), and the mesocolic window has a complete medial frame of mesocolic tissue. Bertelsen *et al*[52] recently reported five-year outcomes for right-sided colon cancer across the capital region, demonstrating a significant reduction in recurrence in the CME group (9.7% *vs* 17.9%) and the potential for improved long-term outcomes after the resection of all UICC stage I-III right-sided colon adenocarcinomas. The original intention of presenting the CMA was to standardize the surgical procedure and to obtain better specimen quality.

CONCLUSION

The CMA is based on the theory of embryonic development and membrane anatomy, and the technical route itself weakens the vascular and lymphoid anatomy. The unique advantages of LRH with the CMA are as follows: (1) The team learning curve can be significantly shortened; (2) The operation can be performed with little to no bleeding, with a reduced probability of conversion to laparotomy and improved safety and efficiency; and (3) Higher-quality specimens can be obtained. Therefore, we believe that the CMA is the dominant approach for laparoscopic radical resection of the right colon. However, the CMA currently lacks RCT-based evidence and needs to be validated in further multicentre prospective studies.

ARTICLE HIGHLIGHTS

Research background

Complete mesocolic excision (CME) with central vascular ligation (CVL) is the technical standard for colon cancer surgery. How to achieve CME with CVL in laparoscopic right hemicolectomy (LRH) is controversial. Several approaches have been proposed, but a unified standard approach is not yet available.

Research motivation

The authors' team has proposed and practised the cranial-medial mixed dominant approach (CMA) to perform LRH with CME for years. We would like to confirm that the CMA does have unique technical advantages through data rather than subjective opinionssby comparing it with the classic medial approach (MA).

Research objectives

To compare the CMA with the classic MA to prove that the CMA has unique advantages in performing LRH.

Research methods

We compared the two groups (CMA and MA) by intraoperative data (operative duration, blood loss, specimen length, number of resected and positive lymph nodes, and postoperative data (exhaust time, liquid intake time, postoperative hospitalization, postoperative complications). Additionally, we described the procedure and technical points of the CMA in detail to facilitate the reader's understanding.

Research results

There were no significant differences in baseline data or the number of positive lymph nodes, intraoperative blood loss, postoperative exhaust time, feeding time, postoperative hospital stay or postoperative complication incidence between the two groups. The operation was shorter and the number of lymph nodes dissected was higher in the CMA group.

Research conclusions

The CMA weakens the vascular and lymphoid anatomy and has unique advantages for LRH with CME and CVL.

Research perspectives

More RCT-based evidence and further multicentre prospective studies are needed to validate the CMA.

FOOTNOTES

Author contributions: Lin L and Yuan SB designed, performed the research study, contributed new reagents and analytic tools and wrote the manuscript; Lin L and Guo H analyzed the data; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the scientific research sub-committee of the medical ethics committee Institutional Review Board of Zhongshan Hospital Affiliatedto Xiamen University (Approval No. xmzsyyky-2021-159).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflict of interest.

Data sharing statement: The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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S-Editor: Wang LL
L-Editor: A
P-Editor: Li X

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World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 March 27; 14(3): 236-246

DOI: 10.4240/wjgs.v14.i3.236

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

New common bile duct morphological subtypes: Risk predictors of common bile duct stone recurrence

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Specialty type: Gastroenterology and Hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Awai K, Japan; Thacoor A, United Kingdom

Received: November 1, 2021
Peer-review started: November 1, 2021
First decision: December 4, 2021
Revised: December 12, 2021
Accepted: March 6, 2022
Article in press: March 6, 2022
Published online: March 27, 2022

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Abstract

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) is the primary treatment for removing common bile duct (CBD) stones. The risk factors for CBD stone recurrence after ERCP have been discussed for many years. However, the influence of CBD morphology has never been noticed.

AIM

To evaluate CBD morphology and other predictors affecting CBD stone recurrence in average patients.

METHODS

A retrospective analysis of 502 CBD stone patients who underwent successful therapeutic ERCP for stone extraction at our centre from February 2020 to January 2021 was conducted. CBD morphology and other predictors affecting CBD stone recurrence were examined by univariate analysis and multivariate logistic regression analysis.

RESULTS

CBD morphology ($P < 0.01$), CBD diameter ≥ 1.5 cm [odds ratio (OR) = 2.20, 95%CI: 1.08-4.46, $P = 0.03$], and endoscopic biliary sphincterotomy with balloon dilation (ESBD) (OR = 0.35, 95%CI: 0.17-0.75, $P < 0.01$) are three independent risk factors for CBD stone recurrence. Furthermore, the recurrence rate of patients with the S type was 6.61-fold that of patients with the straight type (OR = 6.61, 95%CI: 2.61-16.77, $P < 0.01$). The recurrence rate of patients with the polyline type was 2.45-fold that of patients with the straight type (OR = 2.45, 95%CI: 1.14-5.26, $P = 0.02$). The recurrence rate of S type patients was 2.70-fold that of patients with

the polyline type (OR = 2.70, 95%CI: 1.08-6.73, P = 0.03). Compared with no-ESBD, ESBD could decrease the risk of recurrence.

CONCLUSION

CBD diameter ≥ 1.5 cm and CBD morphology, especially S type and polyline type, were associated with increased recurrence of CBD stones. In addition, ESBD was related to decreased recurrence. Patients with these risk factors should undergo periodic surveillance and standard prophylactic therapy.

Key Words: Endoscopic retrograde cholangiopancreatography; Common bile duct stones; Recurrence; Common bile duct morphology; Risk factors

Core Tip: Endoscopic retrograde cholangiopancreatography (ERCP) is the primary treatment for removing common bile duct (CBD) stones. The risk factors for CBD stone recurrence after ERCP have been discussed for many years. However, the influence of CBD morphology has never been reported. We demonstrate that CBD morphology was an independent risk factor for CBD stone recurrence in patients. Furthermore, the S type and polyline type were associated with an increased risk of recurrent CBD stones. This information represents a new perspective by defining the shape of the common bile duct on cholangiograms, which could redefine the risk factors and models of recurrence and predict periodic follow-up.

Citation: Ji X, Yang Z, Ma SR, Jia W, Zhao Q, Xu L, Kan Y, Cao Y, Wang Y, Fan BJ. New common bile duct morphological subtypes: Risk predictors of common bile duct stone recurrence. *World J Gastrointest Surg* 2022; 14(3): 236-246

URL: https://www.wjgnet.com/1948-9366/full/v14/i3/236.htm

DOI: https://dx.doi.org/10.4240/wjgs.v14.i3.236

INTRODUCTION

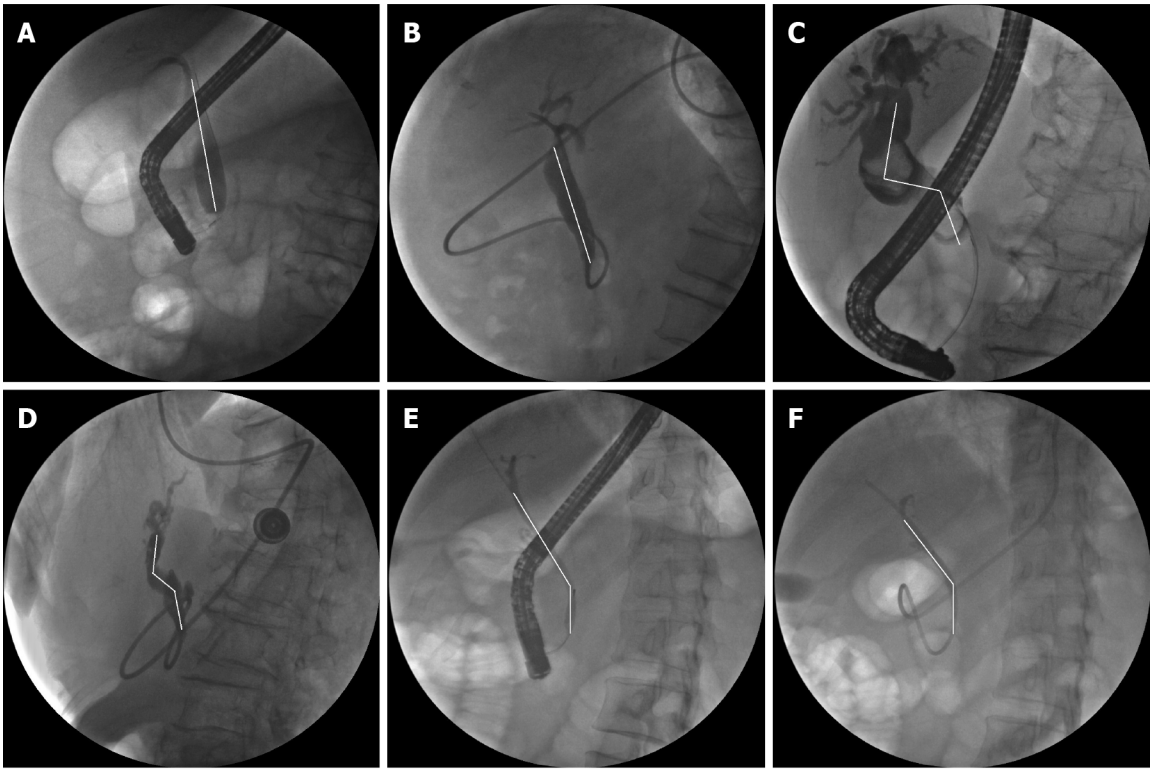
As a minimally invasive endoscopic procedure, endoscopic retrograde cholangiopancreatography (ERCP) is widely performed to treat common bile duct (CBD) stones. However, challenging problems, such as patients with gastrectomy who require multiple procedures and post ERCP complications, are typically encountered[1]. Choledocholithiasis recurrence is a long-term complication[2-5], and the recurrence rate after therapeutic ERCP was 2%-22% in the literature[6-9]. My previous studies reported that CBD morphology in Billroth II anatomy patients is an independent risk factor for CBD stone recurrence[10]. Therefore, we also aim to investigate CBD morphology in average patients with or without gastrectomy and clarify the association between CBD morphology and stone recurrence.

To date, there are a wide range of risk factors for recurrent CBD stones, and the most common predictors are operative related factors, such as age[11], periampullary diverticulum (PAD)[12,13], CBD diameter[14,15], CBD stone diameter[11,16], multiple CBD stones[12,17], endoscopic biliary sphincterotomy (EST)[11,16,18], endoscopic papillary balloon dilation (EPBD)[11], endoscopic papillary large balloon dilation (EPLBD)[19,20], EST with balloon dilation (ESBD)[15,21,22], cholecystectomy[23], gastrectomy[24,25], and CBD angulation[26-28]. However, there have been no reports concerning CBD morphology before my previous study. This is also the first study to report the best evidence regarding CBD morphology in average patients. In the present study, CBD morphology was defined as cholangiogram morphology from the confluence of the left and right hepatic ducts to the distal CBD entering the duodenum, including straight type, S type, and polyline type (Figure 1)[10].

MATERIALS AND METHODS

Patients

From February 2020 to January 2021, 790 patients underwent ERCP at the General Hospital of Northern Theater Command, and 502 patients were included in this study. The exclusion criteria were as follows: (1) patients with tumours of the duodenal papilla, CBD, liver, or gallbladder; (2) patients without specific stones during ERCP; (3) patients who had not removed their stones completely after the first ERCP; and (4) patients with incomplete data. Stone recurrence was defined as the presence of CBD stones at least 6 mo after previous CBD stones were completely removed by ERCP. At least two stone



DOI: 10.4240/wjgs.v14.i3.236

Figure 1 Common bile duct morphology on cholangiograms. A, B: Straight type; C, D: S type; E, F: Polyline type.

recurrences were defined as multiple recurrences after the first ERCP[27]. Patients with CBD stones who visited our hospital were confirmed by abdominal computed tomography and ERCP.

ERCP procedure

All endoscopists performed the ERCP procedures with at least 500 cases of experience. In our institution, prophylactic antibiotics are used in patients without evidence of cholangitis before ERCP. Firstly, the patient was sedated in the left lateral decubitus position. Endoscopists used a side-viewing duodenoscope or a forward-viewing gastroscope (Olympus Medical, Tokyo, Japan) entering the stomach. The first step was to perform the wire-guided biliary cannulation. Precut sphincterotomy or the double-wire technique can be prepared after biliary cannulation failed. As selective biliary cannulation was achieved, depending on CBD stones, the operator executed the therapeutic intervention, which included EST, ESBD, EPBD, and EPLBD. After the therapeutic intervention, the operator chose to remove stones with a retrieval balloon and/or a retrieval basket with or without mechanical lithotripsy. After CBD stone removal, an endoscopic nasobiliary drainage (ENBD) tube was placed in all patients to determine the complete clearance of CBD stones. After 3-5 d of observation, endoscopists confirmed that no residual stones were present and identified the CBD morphology again by cholangiography.

Parameter measurements on cholangiograms

Assessed factors, such as the CBD morphology, the largest stone, and the diameter of the CBD, were measured with the patient placed in the left lateral decubitus position during the operation. Furthermore, cholangiography was performed to determine the CBD morphology and the clearance of CBD stones through an ENBD tube before the tube was removed. CBD morphology was identified by at least two experienced endoscopists with operative and postoperative cholangiograms. The definition of CBD morphology was cholangiogram morphology from the confluence of the left and right hepatic ducts to the distal CBD entering the duodenum. We classified the CBD morphology as follows: straight type, the CBD was straight without bending; S type, the CBD was S-shaped with two bends; and polyline type, the CBD had one bend.

Statistical analysis

Statistical analyses were performed with SPSS 26.0. Univariate analysis was performed using Student's t test, Fisher's exact test and χ^2 test. Independent risk factors were analyzed by multivariate logistic regression analysis with a backwards likelihood ratio. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 502 patients with CBD stones were retrospectively identified from the collected database. The average follow-up was 19 mo. Among the 502 patients, recurrence was detected in 43 patients, and multiple recurrences were detected in 9 patients. The rates of recurrence and multiple recurrences were 8.6% (43/502) and 1.8% (9/502), respectively. No statistically significant differences in patient characteristics, such as sex, PAD, CBD diameter, largest CBD stone diameter ≥ 1.5 cm, CBD stone number ≥ 2, muddy stones, initial ampullary intervention (EST), cholecystectomy, and procedure time, were observed between the recurrence group and nonrecurrence groups (Table 1 and Table 2).

Patient characteristics according to CBD morphology

As shown in Table 3, the presence of a CBD diameter ≥ 1.5 cm (P = 0.01) differed significantly among different CBD morphologies and was detected in 96 (33.2%), 22 (48.9%), and 42 (25.0%) patients with straight type, S type, and polyline type, respectively. The proportion of patients with a CBD diameter ≥ 1.5 cm in the straight type group was the highest of all the groups. Other factors showed no significant difference.

Patient characteristics according to multiple recurrences

Characteristics of patients with single recurrence and multiple recurrences are shown in Table 4. All factors were not related to multiple recurrences given that significant differences were noted (P > 0.05). The results regarding PAD (P = 0.06) and ESBD (P = 0.07) were probably limited by the small sample size.

Risk factors for CBD stone recurrence

In univariate analysis, age ≥ 70 years (P = 0.01), CBD diameter ≥ 1.5 cm (P < 0.01), EPBD/EPLBD (P < 0.01), ESBD (P < 0.01), gastrectomy (P = 0.03), and CBD morphology (P < 0.01) were significant factors for CBD stone recurrence.

Multicollinearity analysis showed all the results were VIF < 5, which represented no relationship among age ≥ 70 years, CBD diameter ≥ 1.5 cm, EPBD/EPLBD, ESBD, gastrectomy, and CBD morphology.

In multivariate analysis, CBD morphology (P < 0.01), CBD diameter ≥ 1.5 cm [odds ratio (OR) = 2.20, 95%CI: 1.08-4.46, P = 0.03], and ESBD (OR = 0.35, 95%CI: 0.17-0.75, P < 0.01) were identified as independent risk factors. Moreover, the recurrence rate of patients with the S type was 6.61-fold that of patients with the straight type (OR = 6.61, 95%CI: 2.61-16.77, P < 0.01). The recurrence rate of patients with the polyline type was 2.45-fold that of patients with the straight type (OR = 2.45, 95%CI: 1.14-5.26, P = 0.02), and the recurrence rate of S type patients was 2.70-fold that of patients with the polyline type (OR = 2.70, 95%CI: 1.08-6.73, P = 0.03) (Table 5).

DISCUSSION

ERCP remains the primary choice to extract CBD stones given its minimally invasive nature. However, risk factors for recurrent CBD stones have not been thoroughly defined. In our previous study, we hypothesized that the altered anatomy that resulted from gastrectomy could affect the shape of the CBD. Therefore, we classified the CBD morphology into straight type, S type, and polyline type. The results showed that CBD morphology was related to CBD stone recurrence in gastrectomy patients[10]. As the present study shows, CBD morphology was also related to recurrence in patients without gastrectomy. This clinical observation assumed that the biliary system could undergo anatomic variations as it developed from the primitive midgut and was further changed by surgery, such as gastrectomy. The complexity of CBD development potentially influences its normal function[29,30].

The incidence of CBD stone recurrence in this study was 8.6% with a median 19-month follow-up, which is compatible with previous studies. In multivariate analysis, CBD morphology, CBD diameter ≥ 1.5 cm, and ESBD represent three independent risk factors. More specifically, the recurrence rate of patients with the S type was greater than that of patients with other types. As reported, bile stasis, duodenal-biliary reflux, and bacterial infection are essential factors in the pathogenesis of CBD stone recurrence[31,32]. Given the pathophysiology and the clinical significance of CBD morphology, we can assume the mechanism of recurrence caused by the S type and polyline type. First, a curved CBD is prone to bile stasis, which also predisposes patients to bacterial infection. Second, different shapes of the CBD enter the duodenum at different angles. S-type and polyline-type CBDs enter the duodenum at angles close to a right angle and are prone to intestinal fluid reflux. Duodenal-biliary reflux may cause changes in the bile duct loop and bacterial infection[33].

Our study demonstrated that a CBD diameter ≥ 1.5 cm was an independent risk factor for recurrence. However, the mechanism of CBD dilation is unclear. Some studies assumed that CBD dilation could

Table 1 Patient characteristics

Characteristics	*n* (%)
Patients	502
Recurrence	43 (8.6)
Multiple recurrences	9 (1.8)
Male	287 (57.2)
Age (mean ± SD, yr)	65.2 ± 15.6
Age 70 yr	201 (40.0)
PAD	243 (48.4)
CBD diameter (mean ± SD, cm)	1.3 ± 0.7
CBD diameter 1.5 cm	160 (31.9)
Largest CBD stone diameter 1.5 cm	83 (16.3)
CBD stone number 2	189 (37.6)
Muddy stones	131 (26.1)
Initial ampullary intervention	
EST	141 (28.1)
EPBD/EPLBD	31 (6.2)
ESBD	315 (62.7)
CBD morphology	
Straight type	289 (57.6)
S type	45 (9.0)
Polyline type	168 (33.5)
Cholecystectomy	26 (5.2)
Gastrectomy	9 (1.8)
Procedure time (mean ± SD, min)	20.0 ± 13.7

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

lead to CBD stone formation[34-36]. The decreased hydrostatic force of bile and loss of normal CBD functional movement may predispose patients to stone reformation[37].

Some studies have shown that age ≥ 70 years is clinically significant for CBD stone recurrence[30,38]. However, this facto was significant in univariate analysis and insignificant in multivariate analysis in our study. Park *et al*[39] reported that cholecystectomy could be routinely recommended to prevent newly developed gallstones, but it should be considered carefully in patients ≥ 70 of age due to high surgical comorbidity. However, the differences in cholecystectomy were not statistically significant in our study, which was probably limited by the small sample size. Patients aged ≥ 70 years and without cholecystectomy were suggested to undergo careful follow-up for CBD stone recurrence.

Several studies have proposed that gastrectomy patients have an increased risk of cholelithiasis, and the incidence of CBD stones is 10%-25%[24,40-42]. However, gastrectomy did not reach a significant difference due to the small sample size in multivariate analysis. Sugiyama *et al*[43]. reported that patients with CBD stone recurrence were prone to subsequent recurrence. Our study showed that the subsequent recurrence rate in patients with recurrent CBD stones was greater than the CBD stone recurrence rate (20.9% *vs* 8.6%). However, significant differences between single recurrence and multiple recurrences were not observed in our study.

EST, EPLBD, EPBD, and ESBD are important ERCP techniques for stone removal. Dong *et al*[44] conducted a meta-analysis to demonstrate that ESBD exhibited better efficacy and fewer early complications than EST. Another network meta-analysis showed that pancreatitis among ESBD, EPBD and EST did not reach a statistically significant difference. The risk of bleeding in ESBD and EST was higher than that in EPBD[45]. However, neither of them investigated the influence of initial ampullary interventions on recurrent CBD stones. Furthermore, several studies reported that different interventions were unrelated to CBD stone recurrence[30,46,47]. However, our study presented the result that ESBD was an

Table 2 Patient characteristics of patients with and without common bile duct stone recurrence, *n* (%)

Characteristics	Recurrence (*n* = 43)	Nonrecurrence (*n* = 459)	*P* value
Sex (male/female)	23/20	264/195	0.61
Age ≥ 70 yr	25 (58.1)	176 (38.3)	0.01
PAD	23 (53.5)	220 (47.9)	0.49
CBD diameter (mean ± SD, cm)	1.5 ± 0.5	1.3 ± 0.7	0.06
CBD diameter ≥ 1.5 cm	23 (53.5)	137 (29.8)	< 0.01
Largest CBD stone diameter ≥ 1.5 cm	11 (25.6)	71 (15.5)	0.09
CBD stone number ≥ 2	15 (34.9)	174 (37.9)	0.70
Muddy stones	12 (27.9)	119 (25.9)	0.78
Initial ampullary intervention			
EST	13 (30.2)	128 (27.9)	0.74
EPBD/EPLBD	9 (20.9)	22 (4.8)	< 0.01
ESBD	17 (39.5)	298 (64.9)	< 0.01
CBD morphology			< 0.01
Straight type	14 (32.6)	275 (59.9)	
S type	11 (25.6)	34 (7.4)	
Polyline type	18 (41.9)	150 (32.7)	
Cholecystectomy	5 (11.6)	21 (4.6)	0.06
Procedure time (mean ± SD, min)	19.3 ± 14.2	20.1 ± 13.6	0.71
Gastrectomy	3 (7.0)	6 (1.3)	0.03

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

independent risk factor for stone recurrence. Compared with no-ESBD, ESBD decreased the risk of recurrence.

In some studies, the potential contributors influencing ERCP technical difficulty have included the size and number of CBD stones, tapering distal CBD, and the distal CBD arm and angulation[48-50]. However, CBD morphology has never been defined as an independent risk factor for technical difficulty. Prospective and multicentric clinical trials should be conducted to explore the influence of CBD morphology on the ERCP process. Information on CBD morphology should be reported by endoscopists to predict the efficacy of certain devices and therapeutic interventions for CBD stone removal by ERCP and to achieve complete stone clearance.

Ando *et al*[6] and Cheon *et al*[51] recommended specific periodic follow-up after therapeutic ERCP, but these authors were not focused on CBD morphology. The exploration of CBD morphology leads to an accurate understanding of potential contributors to recurrent CBD stones. Comprehensive risk factors and a model could provide specific guidance for endoscopists and patients.

To date, our research is the first to evaluate CBD morphology as a risk factor for CBD stone recurrence in average patients. By comparing operative cholangiograms and postoperative ENBD cholangiograms, our study implied that pulling the duodenoscope during the operation could affect CBD angulation and CBD morphology. Therefore, we identified CBD morphology using postoperative ENBD cholangiograms to eliminate bias. During cholangiography, patients were all placed in the left lateral decubitus position. Postoperative cholangiography with ENBD could improve the accuracy of CBD morphology assessment and determine the clearance of CBD stones.

There are several limitations to this study. First, this study was retrospective. Second, we did not evaluate stone components, and this information might have clinical significance for stone recurrence. Third, the follow-up period was short, and a prospective study with a long follow-up could be performed to explore CBD stone recurrence in the future.

Table 3 Patient characteristics of patients with different common bile duct morphologies, *n* (%)

Characteristics	Straight type (*n* = 289)	S type (*n* = 45)	Polyline type (*n* = 168)	*P* value
Sex (male/female)	166/123	30/15	91/77	0.32
Age ≥ 70 yr	104 (36.0)	20 (44.4)	77 (45.8)	0.10
PAD	136 (47.1)	20 (44.4)	87 (51.8)	0.53
CBD diameter (mean ± SD, cm)	1.3 ± 0.4	1.5 ± 0.5	1.4 ± 0.9	0.14
CBD diameter ≥ 1.5 cm	96 (33.2)	22 (48.9)	42 (25.0)	0.01
Largest CBD stone diameter ≥ 1.5 cm	42 (14.5)	8 (17.8)	32 (19.0)	0.44
CBD stone number ≥ 2	105 (36.3)	17 (37.8)	67 (39.9)	0.75
Muddy stones	78 (27.0)	11 (24.4)	42 (25.0)	0.87
Initial ampullary intervention				
EST	84 (29.1)	11 (24.4)	46 (27.4)	0.79
EPBD/EPLBD	18 (6.2)	3 (6.7)	10 (6.0)	0.98
ESBD	180 (62.3)	30 (66.7)	105 (62.5)	0.85
Cholecystectomy	19 (6.6)	2 (4.4)	5 (3.0)	0.24
Procedure time (mean ± SD, min)	19.8 ± 11.7	19.7 ± 13.1	20.6 ± 16.7	0.81
Gastrectomy	5 (1.7)	0 (0.0)	4 (2.4)	0.38

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

Table 4 Characteristics of patients with single recurrence and multiple recurrences, *n* (%)

Characteristics	Single recurrence (*n* = 34)	Multiple recurrences (*n* = 9)	*P* value
Sex (male/female)	19/15	4/5	0.71
Age (mean ± SD, yr)	71.3 ± 13.7	68.6 ± 12.2	0.59
Age ≥ 70 yr	21 (61.8)	4 (44.4)	0.46
PAD	21 (61.8)	2 (22.2)	0.06
CBD diameter (mean ± SD, cm)	1.5 ± 0.5	1.6 ± 0.6	0.43
CBD diameter ≥ 1.5 cm	18 (52.9)	5 (55.6)	1.00
Largest CBD stone diameter ≥ 1.5 cm	10 (29.4)	1 (11.1)	0.41
CBD stone number ≥ 2	12 (35.3)	3 (33.3)	1.00
Muddy stones	10 (29.4)	2 (22.2)	1.00
Initial ampullary intervention			
EST	10 (29.4)	3 (33.3)	1.00
EPBD/EPLBD	6 (17.6)	3 (33.3)	0.37
ESBD	16 (47.1)	1 (11.1)	0.07
CBD morphology			0.22
straight type	12 (35.3)	2 (22.2)	
S type	10 (29.4)	1 (11.1)	
polyline type	12 (35.3)	6 (66.7)	
Cholecystectomy	5 (14.7)	0 (0.0)	0.57
Gastrectomy	3 (8.8)	0 (0.0)	1.00
Procedure time (mean ± SD, min)	19.9 ± 15.7	17.0 ± 6.3	0.60

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

Table 5 Risk factors for common bile duct stone recurrence

Factor	B	OR (95%CI)	*P* value	B	OR (95%CI)	*P* value
Age ≥ 70yr	0.69	1.99 (0.99-4.00)	0.06			
CBD diameter ≥ 1.5 cm	0.79	2.20 (1.08-4.46)	0.03			
EPBD/EPLBD	0.92	2.51 (0.89-7.06)	0.08			
ESBD	-1.04	0.35 (0.17-0.75)	< 0.01			
Gastrectomy	1.46	4.29 (0.84-21.83)	0.08			
CBD morphology			< 0.01			< 0.01
Straight type		Reference		-0.90	0.41 (0.19-0.88)	0.02
S type	1.89	6.61 (2.61-16.77)	< 0.01	0.99	2.70 (1.08-6.73)	0.03
Polyline type	0.90	2.45 (1.14-5.26)	0.02		Reference	

CBD: Common bile duct; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation; OR: Odds ratio.

CONCLUSION

In conclusion, CBD morphology was a unique risk factor, and CBD morphology, CBD diameter ≥ 1.5 cm, and ESBD represent three independent risk factors. Further study is needed to reveal the mechanism, predict the procedure difficulty, and instruct the postoperative follow-up.

ARTICLE HIGHLIGHTS

Research background

Preventing recurrent common bile duct (CBD) stones is an indispensable study. However, the risk factors for CBD stone recurrence after Endoscopic retrograde cholangiopancreatography (ERCP) are unclear.

Research motivation

The CBD on the cholangiogram is common in every ERCP operations. But CBD morphology has never been classified and discussed.

Research objectives

The aim was to investigate the relationship between CBD morphology and recurrent CBD stones in patients after ERCP.

Research methods

From February 2020 to January 2021, 502 patients after ERCP at our center were included in the retrospective case-control study. Univariate analysis and multivariate logistic regression analysis were performed to identify risk factors for CBD stone recurrence.

Research results

CBD morphology, CBD diameter ≥ 1.5 cm, and endoscopic biliary sphincterotomy with balloon dilation (ESBD) are three independent risk factors for CBD stone recurrence. Furthermore, CBD diameter ≥ 1.5 cm could increase the risk of recurrence and ESBD could decrease the risk of recurrence.

Research conclusions

Of the three CBD morphology, patients with the S type had the highest risk of recurrent CBD stones, followed by those with the polyline type and the lowest were the straight type.

Research perspectives

A large-scale prospective study should be performed to verified patients with above risk factors could prevent recurrence with medical treatment, such as Ursodeoxycholic acid. And the surveillance period needs further research.

ACKNOWLEDGEMENTS

The study was supported by the Digestive Endoscopy Centre at General Hospital of Northern Theater Command.

FOOTNOTES

Author contributions: Ji X and Yang Z contributed to drafting the final manuscript; Ji X, Ma SR, Jia W, Zhao Q, Xu L, Ka Y, Cao Y, Wang Y, Fan BJ, Yang Z contributed to study design, data collection, statistical analysis, and reading and approving the final manuscript.

Supported by Key Research and Development Program of Liaoning Province, China, No. 2019JH2/10300026.

Institutional review board statement: The study was reviewed and approved by the General Hospital of Northern Theater Command Institutional Review Board [No. Y(2021)067].

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors disclose no conflicts.

Data sharing statement: No additional data are available.

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S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 March 27; 14(3): 247-259

DOI: 10.4240/wjgs.v14.i3.247

ISSN 1948-9366 (online)

META-ANALYSIS

Peroral endoscopic longer *vs* shorter esophageal myotomy for achalasia treatment: A systematic review and meta-analysis

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Beraldo RF, Cabezuelo AS, Oda M

Received: September 27, 2021
Peer-review started: September 27, 2021
First decision: December 4, 2021
Revised: December 9, 2021
Accepted: February 16, 2022
Article in press: February 16, 2022
Published online: March 27, 2022

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Abstract

BACKGROUND

Peroral endoscopic myotomy (POEM) has been demonstrated to be safe and effective in the treatment of achalasia. Longer myotomy is the standard POEM procedure for achalasia but when compared with shorter myotomy, its effectiveness is not as well known.

AIM

To compare the clinical effectiveness of longer and shorter myotomy.

METHODS

PubMed, EmBase, Cochrane Library, web of science and clinicaltrials.gov were queried for studies comparing shorter and longer POEM for achalasia treatment. The primary outcome was clinical success rate. Secondary outcomes comprised of operative time, adverse events (AEs) rate, gastroesophageal reflux disease (GERD) and procedure-related parameters. The Mantel-Haenszel fixed-effects model was primarily used for the analysis. Publication bias was assessed.

RESULTS

Six studies were included in this analysis with a total of 514 participants. During the follow-up period of 1-28.7 mo, longer and shorter myotomy in treating

achalasia showed similar excellent effectiveness [overall clinical success (OR = 1, 95%CI: 0.46-2.17, P = 1, I^2: 0%; subgroup of abstract (OR = 1.19, 95%CI: 0.38 to 3.73; P = 0.76; I^2: 0%); subgroup of full text (OR = 0.86 95%CI: 0.30 to 2.49; P = 0.78; I^2: 0%)]. Shorter myotomy had significantly reduced mean operative time compared with the longer procedure. There were no statistically significant differences in AEs rates, including GERD (overall OR = 1.21, 95%CI: 0.76-1.91; P = 0.42; I^2: 9%; subgroup of abstract OR = 0.77, 95%CI: 0.40-1.47; P = 0.43; I^2: 0%; subgroup of full text OR = 1.91, 95%CI: 0.98-3.75; P = 0.06; I^2: 0%), hospital stay (overall MD = -0.07, 95%CI: -0.30 to 0.16; P = 0.55; I^2: 24%; subgroup of abstract MD = 0.20, 95%CI: -0.25 to 0.65; P = 0.39; I^2: 0; subgroup of full text MD = -0.16, 95%CI: -0.42 to 0.10; P = 0.23; I^2: 42%), and major bleeding (overall OR = 1.25, 95%CI: 0.58-2.71; P = 0.56; I^2: 0%) between the two procedures. These differences remained statistically non-significant in all sensitivity analyses.

CONCLUSION

POEM was effective in treating achalasia. Shorter and longer myotomy procedures provided similar therapeutic effects in terms of long-term effectiveness. In addition, shorter myotomy reduced the operative time.

Key Words: Endoscopy; Meta-analysis; Myotomy; Peroral endoscopic myotomy; Gastroesophageal reflux disease

Core Tip: We evaluated the peroral endoscopic longer *vs* shorter myotomy for achalasia treatment in our study. To our knowledge, this is the first meta-analysis aiming to compare longer and shorter myotomy during peroral endoscopic myotomy for the treatment of achalasia regarding clinical success, safety and procedure-related outcomes. Shorter and longer myotomy procedures showed similar therapeutic effects in terms of long-term effectiveness. In addition, shorter myotomy reduced the operative time.

Citation: Weng CY, He CH, Zhuang MY, Xu JL, Lyu B. Peroral endoscopic longer *vs* shorter esophageal myotomy for achalasia treatment: A systematic review and meta-analysis. *World J Gastrointest Surg* 2022; 14(3): 247-259
URL: https://www.wjgnet.com/1948-9366/full/v14/i3/247.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i3.247

INTRODUCTION

Achalasia is a rare esophageal motor disease with a prevalence of approximately 1 case/100000 adults. The pathophysiology of achalasia disorder involves incomplete relaxation of the lower esophageal sphincter (LES) and impaired esophageal peristalsis[1]. Its clinical manifestations comprise dysphagia, regurgitation, chest pain and weight loss. Currently, endoscopic botulinum toxin injection or pneumatic dilation and laparoscopic Heller myotomy (LHM) are used to treat achalasia[2]. Inoue and colleagues[3] carried out the first peroral endoscopic myotomy (POEM) surgery to treat 17 achalasia patients in 2010 with 100% technical success. POEM is a novel, minimally invasive therapeutic modality for achalasia and related disorders, which was first reported by Inoue *et al*[3] in 2010. Since then, POEM has been widely used in the treatment of achalasia in many studies and achieves excellent efficacy[4-7].

However, the technique of POEM has changed very little since its introduction[3]. During POEM, the variable extent of gastric myotomy and esophageal myotomy range from 2 cm to 3 cm and 6 cm to 10 cm, respectively. Meanwhile, previous studies have demonstrated the significance of the extent of the myotomy on the gastric side[8,9]. However, the clinical relevance of myotomy length on the esophagus remains unknown. Some researchers have also adopted shorter myotomy in POEM and achieved similar efficacy in recent years[10].

The existing literature lacks high-quality evidence to compare the clinical outcomes of short-length and long-length POEM for achalasia treatment. Furthermore, for shorter or longer myotomy in POEM, which is more effective remains unknown. In this study, we compared the two myotomy modalities based on clinical outcomes and the incidence of postoperative adverse events.

MATERIALS AND METHODS

Data source and search strategy

The present systematic review and meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, EmBase, Web of Science, Cochrane Library and clinicaltrials.gov databases were searched for relevant studies published from January 2010 to October 2020, because POEM was first reported in humans in 2010[3]. The searching language of publications was restricted to English. The Medical Subject Headings (MESH) terms employed included Achalasia's, Esophageal OR Esophageal Achalasia's OR Cardiospasm OR Cardiospasms OR Achalasia OR Achalasia's OR Achalasia, Esophageal OR Megaesophagus OR Esophageal Achalasia AND POEM OR Peroral endoscopic myotomy OR esophageal myotomy OR Peroral endoscopic myotomy AND shorter OR longer OR modified. The reference lists of eligible articles were further assessed for additional studies of interest. Two investigators independently performed the search and data extraction, assessed the quality of the articles and the discrepancies were resolved by consensual discussion. The third investigator reviewed the extracted data. Discussion with senior authors solved any arising issues. Randomized clinical trials (RCTs) and retrospective studies were qualified for the search.

Study selection

Article title and abstract eligibility screening was performed in an independent way by two investigators. Open-label double-blinded RCTs, as well as retrospective trials evaluating patients and comparing peroral endoscopic shorter and longer myotomy for the treatment of achalasia were included. Exclusion criteria were: (1) Experimental studies; (2) Publication language other than English; and (3) An editorial, a case report, a review or case series.

The data parameters obtained from each study were: (1) Trial features such as study design, sample size, follow-up duration and publication year; (2) Primary outcome, *i.e.* clinical success; and (3) Secondary outcomes, including (i) operative time, (ii) GERD (the main indicator was endoscopic reflux esophagitis), (iii) total number of adverse events (AEs) such as major bleeding, and (iv) procedure-related parameters.

Quality assessment

The Cochrane "risk of bias" tool and the Newcastle-Ottawa Scale (NOS) were employed for assessing methodological quality of included studies[11]. Discrepancies between the two investigators were resolved by consensual discussion.

Statistical analysis

Review Manager 5.3 (RevMan) was utilized to analyze the extracted data and determine odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity was determined by inspection of forest plots, the Cochrane Q test, and the I^2 statistic. A Q test with $P<0.10$ was considered significant. According to the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook), I^2 values were categorized as: < 30%, low heterogeneity; 30%-50%, moderate heterogeneity; > 50%, substantial heterogeneity; > 75%, high heterogeneity.

RESULTS

Patient baseline features

Details of the selection process were outlined in Figure 1. Overall, 711 articles were initially selected. After ruling out duplicates, reviews, case series, irrelevant and nonstandard records, 6 studies were included which involved 3RCTs and 3 retrospective trials[12-17] and covered 545 patients. Their features are summarized in Table 1. The quality assessment of the studies was depicted in Figure 2. No significant differences were found in age, sex, American Society of Anesthesiologists (ASA) classification and previous interventions[18]. The detailed study quality evaluation items were presented in Table 2. Compared with the long myotomy (LM) group, the length of esophageal myotomy in the short myotomy (SM) group was significantly reduced. The total incision range of the LM group was 8-25 cm, including 6-20 cm on the esophagus and 2-5 cm on the stomach. For the SM group, the cut range was 3-7cm, including 2-6 cm on the esophagus and 1-3 cm on the stomach.

Clinical success

All patients were followed up for clinical success rate and Eckardt score. Data on clinical success after POEM were available in six studies (Figure 3) [overall clinical success (OR = 1, 95%CI: 0.46-2.17, P = 1, I^2: 0%; subgroup of abstract (OR = 1.19, 95%CI: 0.38 to 3.73; P = 0.76; I^2: 0%); subgroup of full text (OR = 0.86 95%CI: 0.30 to 2.49; P = 0.78; I^2: 0%)]. Therefore, clinical success of POEM showed no statistically significant difference between the two groups.

Table 1 Articles' features

Ref.	Total sample	Sex, male/female, *n*	Age, yr	Symptoms duration, yr or mo	MBI	Classification, *n* (%)	Pre-ECK scores	LESP, mmHg	IRP, mmHg
Familiari *et al*[15], 2016	LM: 38 SM: 35	NA	NA	NA	NA	NA	NA	NA	NA
Gao *et al* [16], 2017	LM: 53	LM: 29/24; SM: 25/22	LM: 37.83 ± 14.36	LM: 5.23 ± 5.87	LM: 19.76 ± 3.07	NA	LM: 6.75 ± 1.86	LM: 43.03 ± 13.73	NA
	SM: 47		SM: 43.96 ± 11.69	SM: 5.30 ± 4.87	SM: 20.25 ± 2.97		SM: 6.34 ± 1.74	SM: 41.93 ± 14.93	
Gong *et al* [17], 2016	LM: 59; SM: 38	Female; LM: 29; SM: 19	LM: 39.8 ± 12.4; SM: 41.5 ± 7.2	LM: 6.5 ± 5.5; SM: 7.9 ± 4.3	LM: 20.7 ± 2.6; SM: 20.1 ± 3.2	ASAC I: LM: 47; SM: 29; II: LM: 11; SM: 7; III: LM: 1; SM: 2; CC I: LM: 21; SM: 12 II: LM: 38; SM: 26	LM: 7.2 ± 2.4; SM: 6.8 ± 1.7	LM: 42.1 ± 12.9; SM: 44.6 ± 13.2	NA
Gu *et al* [14], 2020	LM: 48; SM: 46	LM: 23/25; SM: 21/25	LM: 42.8 ± 10.2; SM: 43.6 ± 11.4	LM: 4.1(0.3~31.0); SM: 5.0(0.3~34.0□	NA	CC II: LM: 48; SM: 46	LM: 7.1 ± 1.6; SM: 7.5 ± 1.5	LM: 32.4 ± 5.3; SM: 33.5 ± 5.0	LM: 21.5 ± 4.6; SM: 23.2 ± 4.8
Huang *et al* [13], 2020	LM: 74; SM: 36	Female; LM: 34; SM: 17	LM: 37.7 ± 13.0; SM: 40.8 ± 11.1	LM: 8.9 ± 5.8; SM: 8.8 ± 5.5	LM: 19.4 ± 3.1; SM: 20.3 ± 2.6	ASAC I: LM: 58; SM: 33; II: LM: 15; SM: 2; III: LM: 1; SM: 1; CC I: LM: 26; SM: 12; II: LM: 48; SM: 24	LM: 7.5 ± 1.9; SM: 7.1 ± 1.6	LM: 39.8 ± 13.7; SM: 41.8 ± 14.3	NA
Nabi *et al* [12],2020	LM: 37; SM: 34	LM: 24/13; SM: 18/16	LM: 41.3 ± 14.4; SM: 40.1 ± 16.8	LM: 3;SM: 3	NA	ASAC I: LM: 13; SM: 12; II: LM: 24; SM: 22	LM: 6.75 ± 1.32; SM: 6.02 ± 1.33	NA	LM: 28.50 ± 11.01; SM: 26.40 ± 13.9

Data are presented as mean ± standard deviation or *n* (%). ASAC: American Society of Anesthesiologists classification; BMI: Body mass index; CC: Chicago classification; IRP: Integrated relaxation pressure; LESP: Lower esophagus sphincter pressure; LM: Long myotomy; NA: Not Applied; Pre-ECK scores: Preoperative- peroral endoscopic myotomy Eckardt scores; SM: Short myotomy.

Five studies presented pre-POEM Eckardt score as a quantitative variable. The score was 6.75 ± 1.86, 7.2 ± 2.4, 7.1 ± 1.6, 7.5 ± 1.9, 6.75 ± 1.32 in the LM group, respectively. In the SM group, the score was 6.34 ± 1.74, 6.8 ± 1.7, 7.5 ± 1.5, 7.1 ± 1.6 and 6.02 ± 1.33, respectively. Six studies provided postoperative Eckardt scores, which were also comparable between the LM and SM group. The postoperative Eckardt score in the LM group was 0.5 ± 0.8; 0.98 ± 1.14; 1.2 ± 1.2; 0.72 ± 0.42; 1.6 ± 1.3; 0.818 ± 0.983, respectively. Similarly, the score in the SM group was 0.5 ± 0.8; 1.06 ± 1.42; 1.0 ± 0.9; 0.76 ± 0.51; 1.3 ± 1.2 and 0.935 ± 0.929, respectively.

Procedure-related outcomes

Operative time: Total procedure duration was available in all six articles including a total of 521 patients. The operative time in the LM group was 59.2 ± 16.7, 63.13 ± 26.50, 68.5 ± 23.2, 45.6 ± 16.2, 62.1 ± 25.2 and 72.43 ± 27.28, respectively. For the SM group, the time was 47.7 ± 13.2, 50.62 ± 20.02, 44.2 ± 16.3, 31.2 ± 15.3, 46.6 ± 18.5 and 44.03 ± 13.78, respectively. Obviously, the operative times in the SM group were shorter than that in the LM group (Figure 4).

Length of myotomy: A total of 3 RCTs and 2 retrospective studies involving 421 cases were meta-analyzed, with 180 cases in the SM group and 241 cases in the LM group. Myotomy length in POEM included the span of esophageal and gastric myotomy. The total length of myotomy in the LM group was 11.10 ± 2.0, 11.5 ± 3.1 and 11.7 ± 2.4 cm, respectively. Among them, the esophageal myotomy length was 8.42 ± 2.13, 8.2 ± 2.7, 10.14 ± 0.54, 7.97 ± 2.40 and 8.5 ± 2.6 cm, respectively, and the gastromyotomy length was 2.49 ± 0.70, 3.2 ± 1.4, 3.2 ± 1.2 and 2.84 ± 0.63 cm, respectively. The following myotomy values were obtained in the SM group of six studies: total length in three studies, 6.04 ± 0.69, 6.1 ± 0.5 and 6.0 ± 0.6 cm, respectively; esophageal length in five studies, 3.87 ± 0.61, 4.0 ± 0.9, 5.66 ± 0.14, 4.0 ± 0.7 and 2.76 ± 0.41 cm, respectively; and gastric length in four studies, 2.21 ± 0.41, 2.1 ± 0.3, 3.2 ± 1.2 and 2.70 ± 0.73 cm, respectively.

Manometry outcomes: Preoperative LES pressure in POEM was available in four articles with a total of 401 patients, and five articles including 450 individuals assessed postoperative LES pressure. The level of preoperative LES pressure in the LM group was 43.03 ± 13.73, 42.1 ± 12.9, 32.4 ± 5.3 and 39.8 ± 13.7 mmHg respectively, and the value was 41.93 ± 14.93, 44.6 ± 13.2, 33.5 ± 5.0 and 41.8 ± 14.3 mmHg,

Table 2 The detailed study quality evaluation items

Ref.	Follow-up sample	Length of the myotomy, cm	Operative time, min	Myotomy length, cm	Follow-up time, mo	Clinical success	GERD, %	LESP, mmHg	HRM, mmHg	Post-ECK scores	Adverse events
Familiari *et al*[15], 2016	LM: 23 SM: 26	LM: 13 SM: 8	LM: 59.2 ± 16.7 SM: 47.7 ± 13.2	ES: LM: 8.42 ± 2.13 SM: 3.87 ± 0.61 ST: LM: 2.49 ± 0.70 SM: 2.21 ± 0.41 TO: LM: 10.94 ± 2.11 SM: 6.04 ± 0.69	8	LM: 100% SM: 100%	LM: 42.9% SM: 65%	LM: 17 ± 9.7 SM: 11.4 ± 6.5	LM: 8.6 ± 4.9 SM: 5.9 ± 5.0	LM: 0.5 ± 0.8 SM: 0.5 ± 0.8	No
Gao *et al*[16], 2017	LM: 53 SM: 47	LM: > 7 SM: ≤7	LM: 63.13 ± 26.5 SM: 50.62 ± 20.02	NA	3,6,12	LM: 96.2% SM: 93.6%	LM: 11.3% SM: 12.8%	LM: 16.51 ± 5.01 SM: 17.41 ± 3.69	NA	LM: 0.98 ± 1.14 SM: 1.06 ± 1.42	MB: LM: 0, SM: 0 MP: LM: 1; SM: 0 HS: LM: 10.19 ± 4.03 SM: 10.21 ± 3.78
Gong *et al* [17], 2016	LM: 59 SM: 38	LM: > 7 SM: ≤7	LM: 68.5 ± 23.2 SM: 44.2 ± 16.3	ES: LM: 8.5 ± 2.6 SM: 4.0 ± 0.9 ST: LM: 3.2 ± 1.4 SM: 2.1+0.3 TO: LM: 11.7 ± 2.4 SM: 6.1 ± 0.5	NA	LM: 91.5% SM: 92.1%	LM: 18.6% SM: 15.8%	LM: 19.3 ± 8.5 SM: 16.7 ± 4.3	NA	LM: 1.2 ± 1.2 SM: 1.0 ± 0.9	MB: LM: 3; SM: 2 MP: LM: 1; SM: 0 HS: LM: 6.6 ± 1.1 SM: 6.4 ± 1.2
Gu *et al*[14], 2020	LM: 48 SM: 46	LM: 7-8 SM: 3-4	LM: 45.6 ± 16.2 SM: 31.2 ± 15.3	ES: LM: 10.14 ± 0.54 SM: 5.66 ± 0.14	1,3,6,12	LM: 93.8% SM: 95.7%	LM: 22.9% SM: 15.2%	LM: 12.1 ± 3.9 SM: 11.8 ± 4.4	LM: 9.7 ± 2.6 SM: 10.1 ± 2.4	LM: 0.72 ± 0.42 SM: 0.76 ± 0.51	HS: LM: 6: 5 ± 1.6 SM: 7.0 ± 0.9
Huang *et al* [13], 2020	LM: 74 SM: 36	LM > 7 SM≤ 7	LM: 62.1 ± 25.2 SM: 46.6 ± 18.5	ES: LM: 8.2 ± 2.7 SM: 4.0 ± 0.7 ST: LM: 3.2 ± 1.2 SM: 3.2 ± 1.2 TO: LM: 11.5 ± 3.1 SM: 6.0 ± 0.6	28.7	LM: 91.9% SM: 94.4%	LM: 14.9% SM: 8.3%	LM: 13.3 ± 5.7 SM: 15.9 ± 3.2	NA	LM: 1.6 ± 1.3 SM: 1.3 ± 1.2	MB: LM: 3; SM: 2 MP: LM: 1; SM: 0 HS: LM: 9.3 ± 2.9 SM: 9.9 ± 2.4
Nabi *et al* [12], 2020	LM: 37 SM: 34	LM: ≥ 6 SM: ≤ 3	LM: 72.43 ± 27.28 SM: 44.03 ± 13.78	ES: LM: 7.97 ± 2.40 SM: 2.76 ± 0.41 ST: LM: 2.84 ± 0.63 SM: 2.70 ± 0.73	12	LM: 96.97% SM: 93.55%	LM: 56.67%SM: 44.4%	NA	LM: 7.44 ± 4.30 SM: 8.60 ± 1.30	LM: 0.818 ± 0.983 SM: 0.935 ± 0.929	MB: LM: 17; SM: 12 HS: LM: 2.81 ± 0.70 SM: 2.82 ± 0.67

Data are presented as mean ± standard deviation or *n* (%). Eck: Eckardt score; ES: Esophageal; HS: Hospitalization, mean days; MB: Major bleeding; MP: Mucosal perforation; Post-ECK scores: Postoperative- peroral endoscopic myotomy Eckardt scores; POEM: Peroral endoscopic myotomy; GERD: Gastroesophageal reflux disease; LM: Long myotomy; NA: Not Applied; SM: Short myotomy; ST: Stomach; TO: Total.

respectively, in the SM group. Postoperative LES pressure level in the LM group was 17 ± 9.7, 16.51 ± 5.01, 19.3 ± 8.5, 12.1 ± 3.9 and 13.3 ± 5.7 mmHg, respectively, and the pressure level was 11.4 ± 6.5, 17.41 ± 3.69, 16.7 ± 4.3, 11.8 ± 4.4 and 15.9 ± 3.2 mmHg, respectively, in the SM group.

Integrated relaxation pressure: Preoperative integrated relaxation pressure (IRP) in POEM was available in two articles with a total of 165 patients, and three articles including 214 individuals assessed postoperative IRP pressure. The levels of preoperative IRP in the LM group were 21.5 ± 4.6 mmHg and 28.50 ± 11.01 mmHg, and in the SM group, the values were 23.2 ± 4.8 mmHg and 26.40 ± 13.9 mmHg. Postoperative IRP level in the LM group was 8.6 ± 4.9, 9.7 ± 2.6, and 7.44 ± 4.30 mmHg, respectively, and this pressure level was 5.9 ± 5.0, 10.1 ± 2.4 and 8.60 ± 1.30 mmHg, respectively, in the SM group.

Endoscopic reflux esophagitis: This meta-analysis found no difference in endoscopic reflux esophagitis between the two procedures (total OR = 1.21, 95%CI: 0.76-1.91; P = 0.42; I^2: 9%; subgroup of abstract OR = 0.77, 95%CI: 0.40-1.47; P = 0.43; I^2: 0%; subgroup of full text OR = 1.91, 95%CI: 0.98-3.75; P = 0.06; I^2: 0%), with low heterogeneity found. Hence, random- and fixed-effects models yielded identical results (Figure 5A).

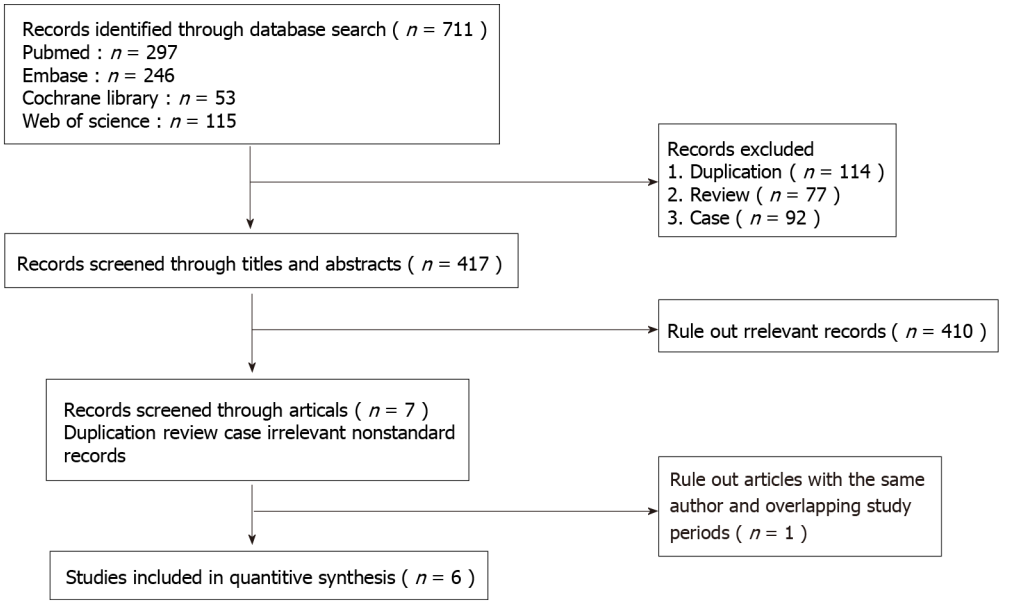

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Figure 1 Flow diagram of the study selection process.

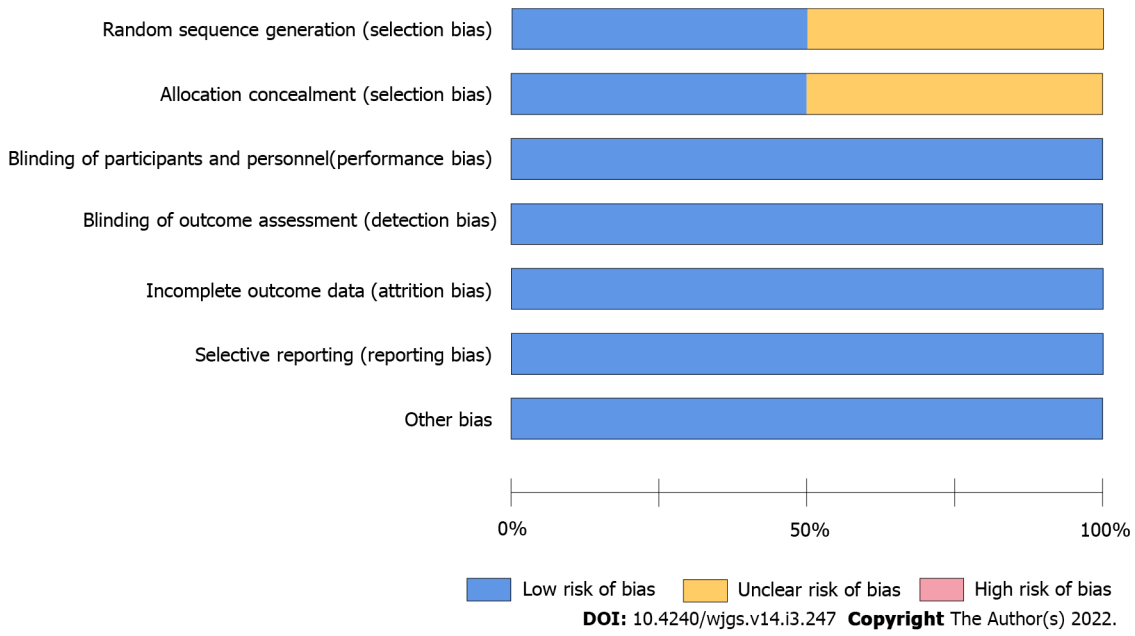

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Figure 2 Risk of bias of the enrolled studies. The methodological quality of the included studies was similar. No study had a high risk for confounding variables.

AEs: The incidence rates of AEs in different studies are detailed in Table 2. No procedure-related deaths were recorded. The rate of hospitalization showed no difference between the two procedures (total MD = -0.07, 95%CI: -0.30 to 0.16; P = 0.55; I^2: 24%; subgroup of abstract MD = 0.20, 95%CI: -0.25 to 0.65; P = 0.39; I^2: 0; subgroup of full text MD = -0.16, 95%CI: -0.42 to 0.10; P = 0.23; I^2: 42%), with no heterogeneity detected (Figure 5B). The incidence rate of major bleeding was similar comparing the two groups (total OR = 1.25, 95%CI: 0.58-2.71; P = 0.56; I^2: 0%) (Figure 5C). These differences remained statistically significant in all sensitivity analyses.

DISCUSSION

In this meta-analysis, we critically assessed the available RCTs and retrospective studies comparing SM and LM during POEM for the treatment of achalasia. Our main findings were that both approaches

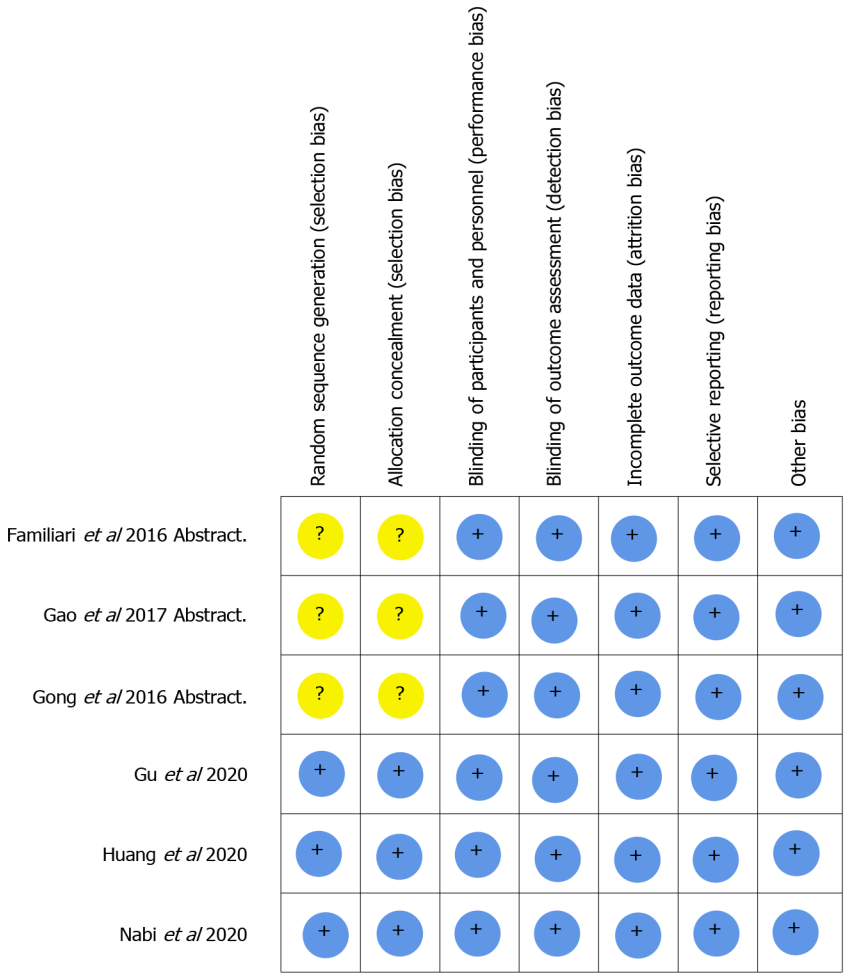
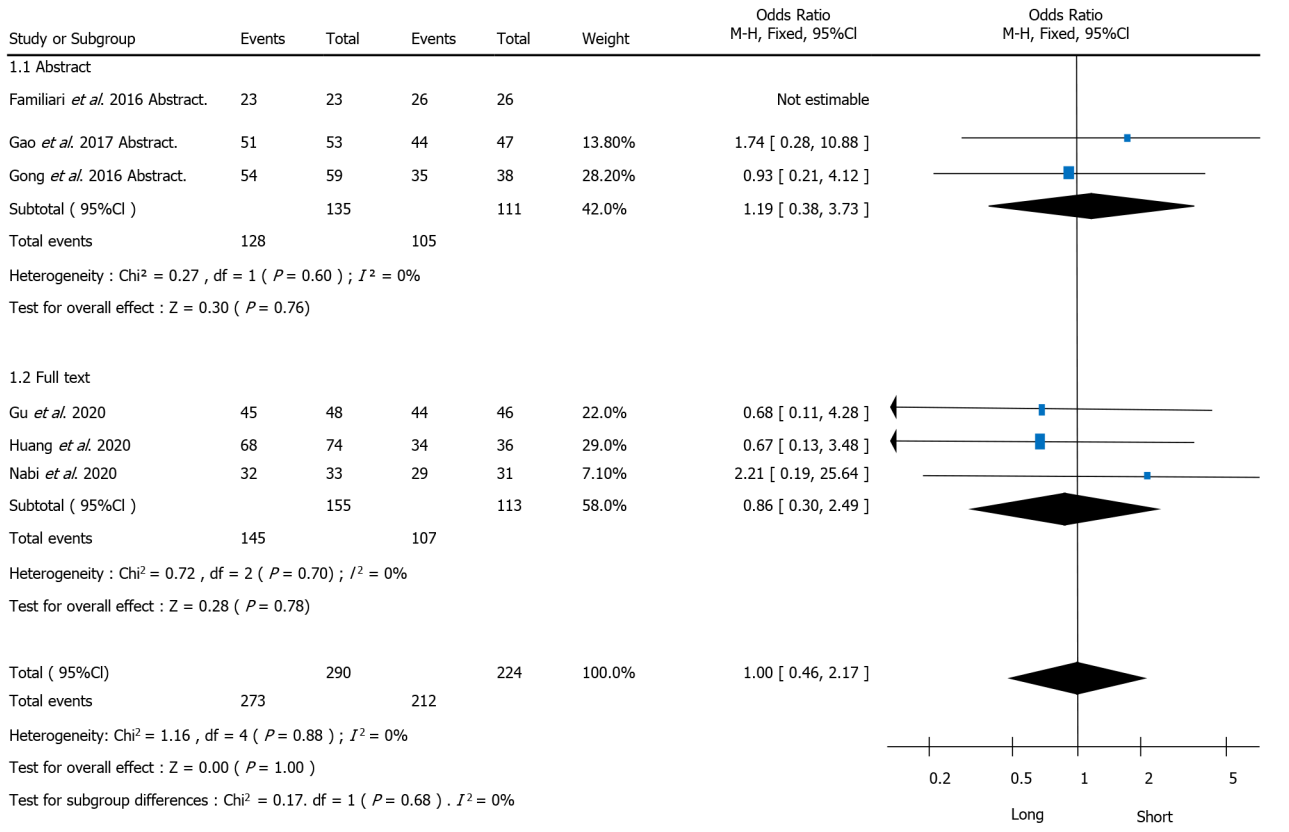


Figure 3 Long *vs* short myotomy. Meta-analysis of primary outcomes (clinical success rate).

were equally effective yet the shorter procedure required reduced operation time. Heterogeneity across the studies was low and a comprehensive sensitivity analysis was consistent with our primary findings. No publication bias was detected.

The notion of endoscopic myotomy was first put forward by Ortega and collaborators[19], with an electrosurgical knife utilized for dissecting the lower esophageal rosette without manipulating the distal anti-reflux zone. Nevertheless, direct endoscopic myotomy has serious complications, and it has been abandoned. POEM was first reported by Pasricha and collaborators[20] in 2007 with pigs and utilized a submucosal tunnel for LES myotomy. In 2010, Inoue and collaborators[3] first applied POEM clinically using seven individuals who received a relatively shorter myotomy (mean length of 4.9 cm and 1.0 cm on the gastric side) but had worse clinical outcomes compared with the 10 cases undergoing a longer myotomy (mean length of 10.4 cm). With regard to myotomy length in POEM, Inoue and colleagues recommended to use a length of > 10 cm (average 13 cm) as the standard[21]. Since then, POEM has been considered as an emerging treatment modality and is the preferred therapeutic option for achalasia and has shown success in all age groups and different types and stages of achalasia[22]. In addition, POEM is promising in the treatment for spastic esophageal motility ailments. Avoiding abdominal incisions could reduce surgical invasiveness, improve cosmetic effects and shorten convalescence time [23]. Moreover, POEM has been widely used clinically due to its advantages over LHM[24] including no abdominal cut, faster recovery and the possibility of avoiding general anesthesia. In addition, unlike LHM, POEM does not involve GEJ dissection[25].

The major differences in the implementation of POEM worldwide include myotomy orientation (anterior or posterior), thickness (full or partial) and length (shorter and longer). With regard to myotomy length in POEM surgery, Von Renteln and colleagues (Germany), Costamagna and collaborators (Italy), Chiu and co-workers (Hong Kong, China) and Minami and colleagues (Japan), all performed LM to treat achalasia with a mean incision length of 12, 10, 10.8 or 14.4 cm, and promising efficacy and safety have been achieved[26-29]. However, these trials adopted the original LM POEM technique by Inoue *et al*[21], with a myotomy length of about 10 cm. Meanwhile, the average LES length was only 3.2 cm, ranging from 2.4 to 4.0 cm in healthy and achalasia individuals[30]. According to the



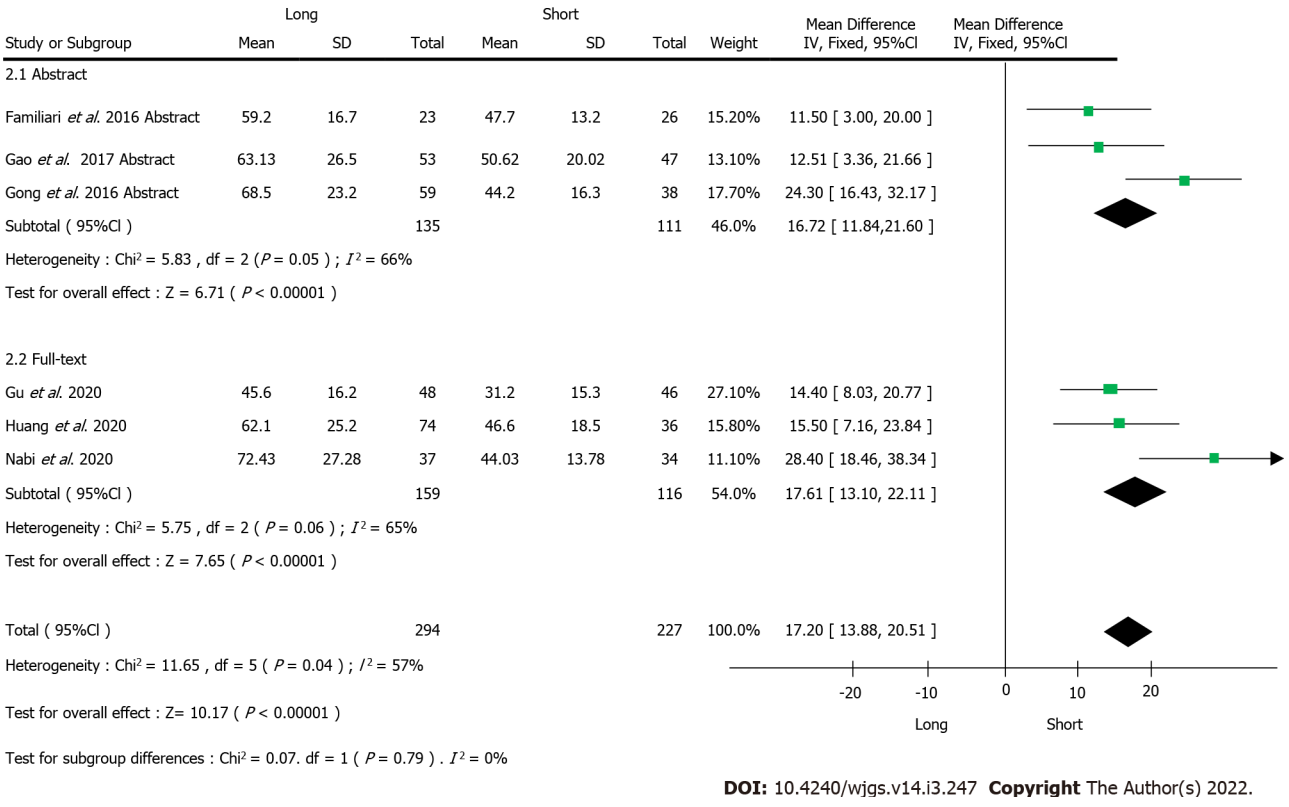


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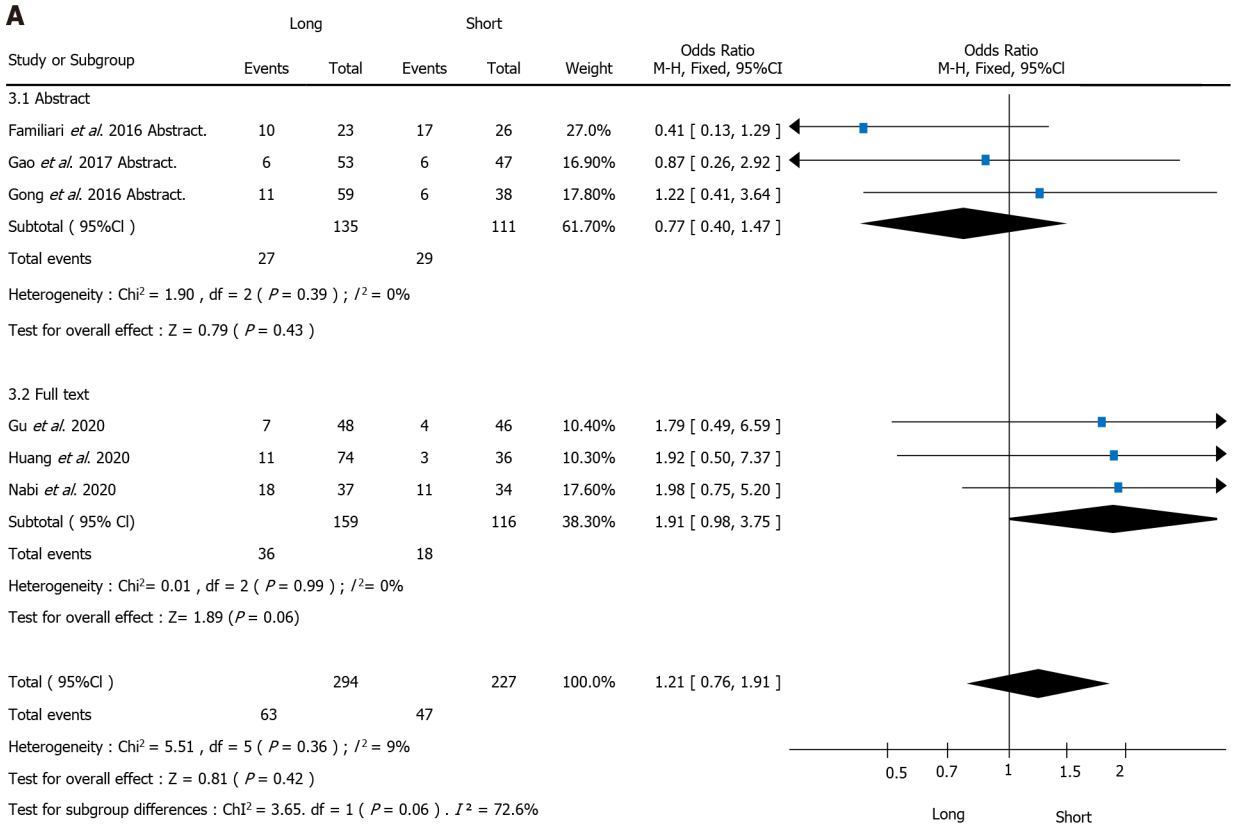
Figure 4 Operative time of long *vs* short myotomy.

guidelines of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), for cases of achalasia, esophageal myotomy length should be ≥ 4 cm and the gastromyotomy length should be 1-2 cm[31]. Therefore, it was hypothesized that a modified POEM procedure with a LM might be as effective as the LM procedure in achalasia treatment as it ensured sufficient LES cutting while ameliorating complications and decreasing operation time. To test this hypothesis, Wang *et al*[10] enrolled 46 patients who underwent modified POEM with shorter submucosal tunnel (average length

A



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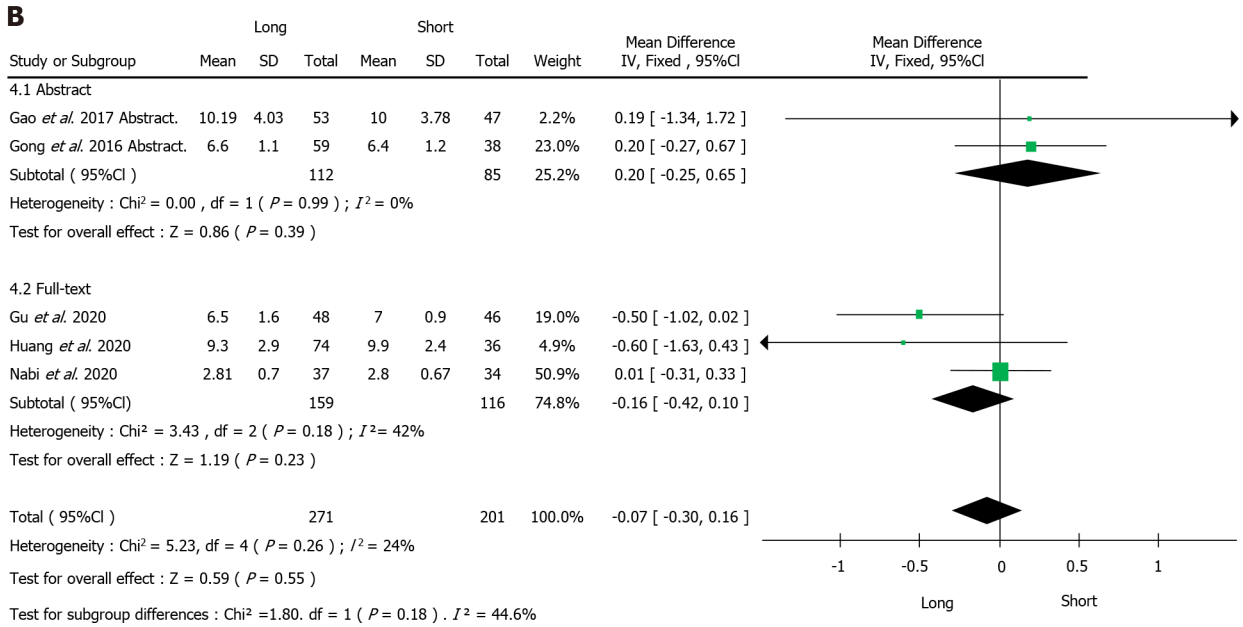

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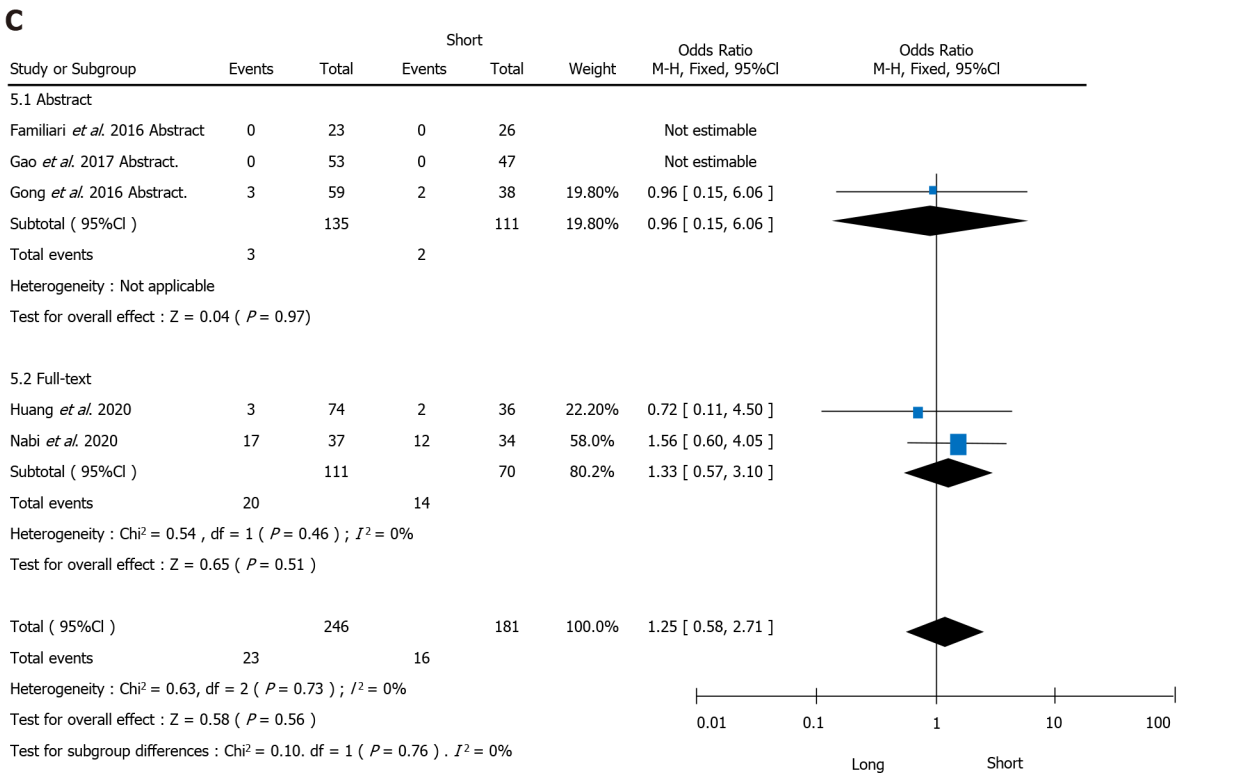

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Figure 5 Long *vs* short myotomy. Meta-analysis of secondary outcomes. A: Endoscopic reflux esophagitis; B: Hospitalization; C: Major bleeding.

6.8 cm) and endoscopic myotomy of muscle bundles (total average length 5.4 cm). They reported that modified POEM with LM showed great safety and commendable short-term efficacy in treating achalasia. However, for patients with type I and II achalasia, a short esophageal myotomy may be sufficient[10].

The present analysis, which was based on RCTs and a retrospective study, confirmed that POEM offered excellent efficacy with a high clinical success rate. The treatment efficacy was similar between the SM and LM procedures, regardless of the definition used, length of myotomy, publication type and the statistical method employed to pool the data. The meta-analysis of manometric outcomes, where no significant disparities were detected, further endorsed the lack of clinical differences between LM and SM.

Another matter of debate is GERD after POEM[32]. Several technical refinements have been attempted to decrease the odds of post-POEM GERD, including a selective myotomy of the inner circular muscle[33], endoscopic fundoplication[34], or limiting the length of gastromyotomy[35]. The proper location of the gastroesophageal junction (GEJ) is critical in ensuring the procedure's effectiveness and may have an impact on GERD[36,37]. Many reports showed a lower GERD incidence after POEM due to the preservation of the pharyngoesophageal ligament[38,39]. In the present meta-analysis, the incidence rate of GERD was similar between the SM and LM procedures.

Regarding POEM-related AEs, multicenter studies showed that the technique was associated with a low incidence of severe AEs (< 1%)[40,41]. Interestingly, we found that the total incidence rate of AEs, including hospitalization and major bleeding, were comparable between the two groups. Procedure-related outcomes were also evaluated. As expected from our clinical experience, the SM took much less time compared with the LM but the treatment effects were similar.

This meta-analysis had some limitations. First, the number of studies was very small and three RCTs were only retrieved as abstracts. Although we conducted subgroup analysis based on abstract and full-text, more studies were still needed to analyze the results. Second, only three articles evaluated IRP after POEM treatment. Third, a longer myotomy is thought to be more effective on controlling symptoms caused by the esophageal spasm of type III achalasia. However, in this meta-analysis, due to the small number of patients with type III achalasia and recent literature[18], our conclusions might not apply to type III achalasia treatment and a short myotomy could not be recommended. We expected more RCTs to examine the effect of shorter or longer in the treatment of type III achalasia. Due to the lack of relevant research articles, we did not evaluate the postoperative efficacy of POEM for achalasia subtypes. Fourth, the follow-up duration was relatively short so this study was unable to compare the long-term efficacy and AES between LM and SM procedures.

CONCLUSION

In conclusion, short myotomy has the advantage of reduced procedure time in the treatment of achalasia compared to long myotomy, but the clinical success rate, AEs, and reflux rate were comparable. Thus, peroral endoscopic shorter myotomy could have a great clinical application prospect. Our results are restricted by the small number of patients, short follow-up duration, and a lack of specific definition of short myotomy. Future studies with a larger sample size and longer follow-up duration are warranted to evaluate the long-term efficacy and safety of these two procedures in POEM.

ARTICLE HIGHLIGHTS

Research background

For a long time, peroral endoscopic myotomy (POEM) has been demonstrated to be safe and effective in the treatment of achalasia.

Research motivation

Longer myotomy is the standard POEM procedure for achalasia, but its effectiveness compared with shorter myotomy is not well known. Thus, we want to provide an analysis to assess the clinical outcomes of shorter and longer myotomy.

Research objectives

To conduct a meta-analysis to compare the clinical effectiveness of the two procedures.

Research methods

The PubMed, Web of Science, Cochrane Library, clinicaltrials.gov, and EMBASE databases were used to search for relevant studies to compare shorter and longer myotomy in POEM for achalasia treatment.

Research results

Longer and shorter myotomy groups in treating achalasia had similar excellent effectiveness. Shorter myotomy had significantly reduced mean operative time compared with the longer procedure. There were no statistically significant differences in AE's rates, including gastroesophageal reflux diseases, hospital stay and major bleeding between the two procedures.

Research conclusions

Short myotomy has the advantage of shorter procedure time in the treatment of achalasia compared to long myotomy, but the clinical success rate, adverse events , and reflux rate were comparable.

Research perspectives

Future randomized clinical trials should determine whether the benefits remain comparable after years of follow-up.

FOOTNOTES

Author contributions: Weng CY and He CH collected data; Zhuang MY analyzed the data and wrote the first draft of the manuscript; Xu JL and Lyu B were major contributors in editing the manuscript; All authors read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 8177030774.

Conflict-of-interest statement: The authors declare they have no competing financial and non-financial interests.

PRISMA 2009 Checklist statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wu RR

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World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 March 27; 14(3): 260-267

DOI: 10.4240/wjgs.v14.i3.260

ISSN 1948-9366 (online)

CASE REPORT

Successful treatment with laparoscopic surgery and sequential multikinase inhibitor therapy for hepatocellular carcinoma: A case report

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Specialty type: Surgery

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Luo XZ, China; Mukthinuthalapati VVPK, United States; Nenu I, Romania

Received: November 30, 2021
Peer-review started: November 30, 2021
First decision: December 26, 2021
Revised: January 8, 2022
Accepted: March 16, 2022
Article in press: March 16, 2022
Published online: March 27, 2022

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) with massive portal vein tumor thrombosis (PVTT) and distant metastasis is considered unresectable. However, due to recent developments in systemic chemotherapy, successful cases of conversion therapy for unresectable diseases have been reported. Herein, we report a successful multidisciplinary approach for treatment of multi-visceral recurrence with sequential multikinase inhibitor and laparoscopic surgery.

CASE SUMMARY

A 63-year-old woman with chronic hepatitis B virus infection was diagnosed with HCC. Subsequently, she underwent two rounds of laparoscopic partial hepatectomy, laparoscopic left adrenalectomy, and transcatheter arterial chemoembolization plus sorafenib for recurrence. Four years after initial hepatectomy, she presented with a 43-mm mass in the spleen and tumor thrombus involving the main portal vein trunk with ascites. Her liver function was Child-Pugh B (8), and protein induced by vitamin K absence or antagonist II (PIVKA II) levels were elevated up to 46.291 mAU/mL. Since initial treatment with regorafenib for three months was unsuccessful, the patient was administered lenvatinib. Ten months post-treatment, there was no contrast enhancement of PVTT or splenic metastasis. Chemotherapy was discontinued due to severe diarrhea. Afterward, splenic metastasis became viable, and PIVKA II increased. Therefore, hand-assisted laparoscopic splenectomy was performed. She experienced no clinical recurrence 14 mo after resection.

CONCLUSION
Conversion surgery after successful multikinase inhibitor treatment might be considered an effective treatment option for advanced HCC.

Key Words: Hepatocellular carcinoma; Lenvatinib; Portal vein; Venous thrombosis; Splenic neoplasms; Case report

Core Tip: A 63-year-old woman had chronic hepatitis B virus infection and previous treatment history of hepatocellular carcinoma. She developed a 43-mm splenic mass and tumor thrombus involving the right portal branch and an umbilical portion extending down to the main trunk with severe ascites. She was initially treated with regorafenib and then lenvatinib. Ten months post-treatment, there was no contrast enhancement of portal vein tumor thrombosis or splenic metastases. However, after lenvatinib discontinuation due to severe diarrhea, splenic metastases showed partial contrast enhancement. Subsequently, hand-assisted laparoscopic splenectomy was performed with no remarkable postoperative complications. She experienced no recurrence for 14 mo.

Citation: Endo Y, Shimazu M, Sakuragawa T, Uchi Y, Edanami M, Sunamura K, Ozawa S, Chiba N, Kawachi S. Successful treatment with laparoscopic surgery and sequential multikinase inhibitor therapy for hepatocellular carcinoma: A case report. *World J Gastrointest Surg* 2022; 14(3): 260-267
URL: https://www.wjgnet.com/1948-9366/full/v14/i3/260.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i3.260

INTRODUCTION

Treatment strategy recommendations for hepatocellular carcinoma (HCC) have been introduced in various guidelines. These guidelines include the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan[1], Barcelona Clinic Liver Cancer (BCLC) Guidelines[2], and American Association for the Study of the Liver Diseases Guidelines[3]. According to these guidelines, indications for liver resection are limited by tumor progression. Moreover, many cases with distant metastasis or local major vessel invasion are not eligible for resection. Recently, development of effective molecular-targeted agents, including sorafenib[4], regorafenib[5], ramucirumab[6], and lenvatinib (LEN)[7] has prolonged patient survival and occasionally enabled multidisciplinary treatments combined with chemotherapy and liver resection for HCC. Among these agents, LEN, which is an oral multikinase inhibitor targeting kinases, is known to achieve a higher rate of objective response rate (ORR)[7]. These kinases include vascular endothelial growth factor receptor 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor receptor-α (PDGFR), RET, and KIT. Therefore, there have been a limited number of reports on conversion surgery after LEN treatment[8-17]. However, to the best of our knowledge, there are only a few reports on long-term remission with portal vein tumor thrombus[8,16].

Herein, we report a successful multidisciplinary approach for treatment of unresectable HCC recurrence with sequential multikinase inhibitor therapy and laparoscopic surgery.

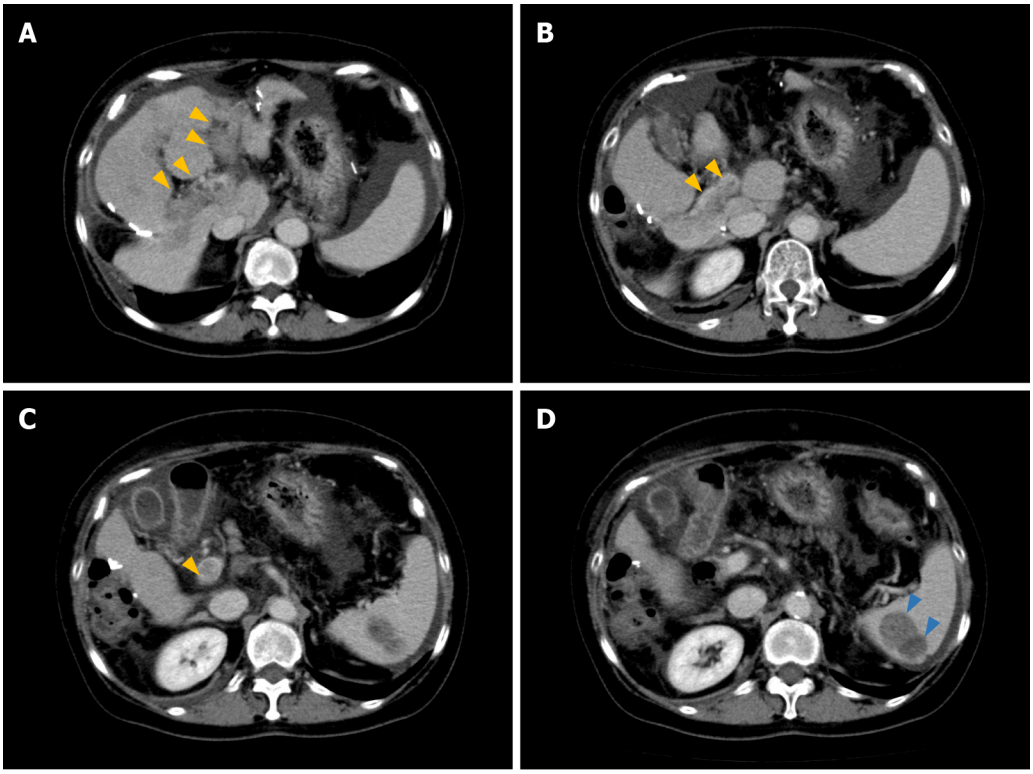
CASE PRESENTATION

Chief complaints

A 63-year-old woman with chronic hepatitis B virus infection was referred to our clinic due to incidental detection of a hepatic mass. Alpha-fetoprotein and protein induced by vitamin K absence or antagonist II (PIVKA II) levels were 25.24 ng/mL and 3021 mAU/mL, respectively. The patient was diagnosed with HCC in December 2014. Thereafter, she underwent hand-assisted laparoscopic partial hepatectomy for a solitary tumor with 5 cm in diameter in the right posterior sector. Pathological findings showed that the lesion was 40 mm in size, moderately differentiated, solitary HCC without any macroscopic vascular invasion (T1bN0M0 and stage IB, based on the 8th Union for International Cancer Control staging of HCC). Liver fibrosis was evident during initial surgery (METVIR F2-3).

History of present illness

Six months after initial surgery, multiple recurrent lesions in the liver were observed. Consequently, the



DOI: 10.4240/wjgs.v14.i3.260

Figure 1 Radiological findings of hepatocellular carcinoma with portal vein tumor thrombosis and splenic metastasis. A: Hypervascular lesion in the left and right anterior portal branches (yellow arrows) suggesting portal vein tumor thrombosis. Ascites are located around the spleen. Dynamic computed tomography (CT), portal phase; B and C: Hypervascular lesions in the main portal branch (yellow arrows). Dynamic CT, portal phase; D: Heterogenic, largely a hypodense lesion with high contrast enhancement in the lower pole of the spleen (blue arrows). Dynamic CT, portal phase.

patient was treated with lipiodol-transcatheter arterial chemoembolization (TACE). After this successful TACE, sorafenib (400 mg per day) was administered. Six months later, she underwent laparoscopic left adrenalectomy for adrenal metastasis (pathology revealed metastatic, moderately differentiated HCC). Eight months after the adrenalectomy, the patient underwent laparoscopic partial hepatectomy for a solitary recurrence in the lateral sector (pathology revealed moderately differentiated HCC, background liver condition; METAVIR F3). Eight months after the second hepatectomy, the patient was treated with sorafenib (400 mg per day, followed by 600 mg per day) for increased PIVKA II levels. Despite 9-mo treatment with sorafenib, she was found to have a 43-mm mass in the spleen and portal vein tumor thrombosis (PVTT) that involved both the right and left portal branches down to the main trunk (Vp4) on computed tomography (CT) (Figure 1).

History of past illness
Hepatitis B infection.

Personal and family history
Her personal and family history was unremarkable.

Physical examination
Her vital signs were normal. There were no remarkable findings other than abdominal distention.

Laboratory examinations
PIVKA II levels increased tremendously up to 46.291 mAU/mL. The BCLC staging system classified the patient into stage C. Aspartate aminotransferase, alanine aminotransferase, and platelet count were 49 IU/L, 40 IU/L, and 14.7 × 10^4/μL, respectively. The FIB-4 index was calculated as 3.71, suggesting that she was likely to be cirrhotic. Her cirrhosis was classified into Child-Pugh B (8) and modified albumin-bilirubin grade 1.

Imaging examinations
CT findings revealed moderate ascites, which indicated portal hypertension due to tumor thrombosis. This also demonstrated irregularity of the external contour of the left lobe of the liver, suggesting cirrhosis.

MULTIDISCIPLINARY EXPERT CONSULTATION

Seishi Nakatsuka, MD, PhD, Assistant Professor, Department of Radiology, Keio University

On contrast enhanced CT scan, a hypodense mass with a size of 43 mm in the spleen and PVTT that involved the right anterior, posterior, and left portal branches down to main trunk (Vp4) were seen. Moreover, moderate ascites was observed. No obvious liver masses were recognized.

FINAL DIAGNOSIS

HCC with PVTT and splenic metastases, which led to massive ascites, possibly due to portal hypertension, was observed.

TREATMENT

Initially, she was treated with regorafenib (400 mg/d) and tolvaptan for ascites.

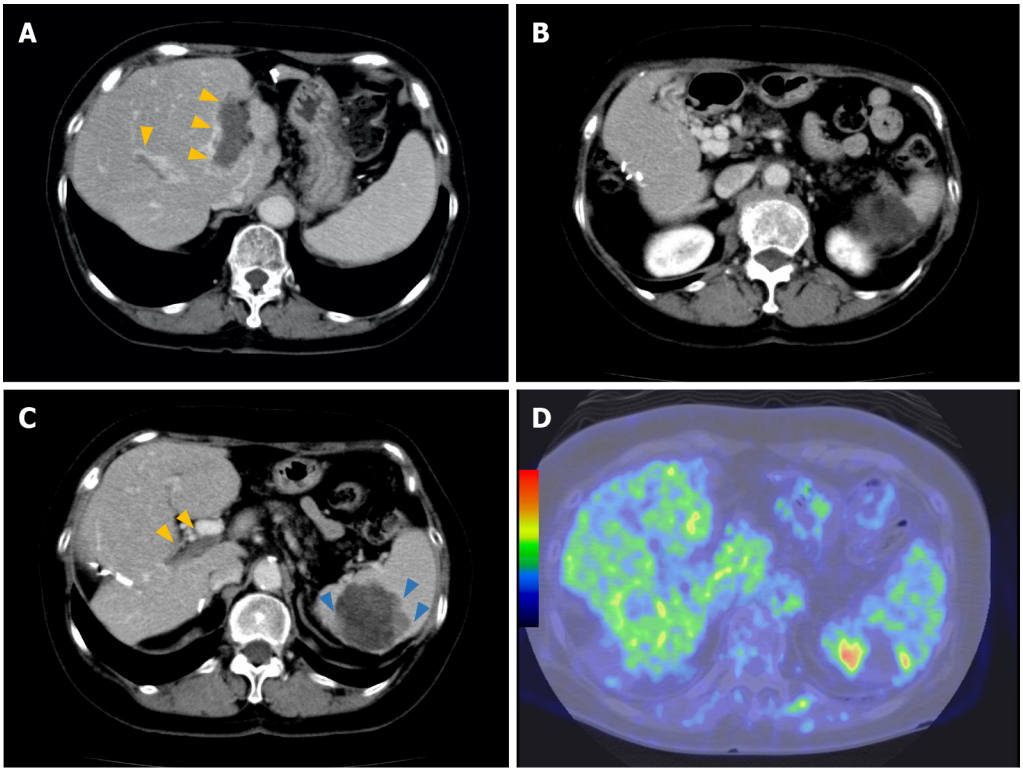
OUTCOME AND FOLLOW-UP

Three months after initiation of regorafenib treatment, the tumor thrombus and spleen metastasis continued to increase in size with elevated PIVKA II levels (129.815 mAU/mL). However, improvement of liver function by resolution of portal hypertension due to cavernous transformation occurred. Her ascites and liver function improved [Child-Pugh A (5)]. Therefore, LEN was orally administered at a dose of 8 mg/d. No severe side effects were observed, except for grade 2 hypertension and anorexia. Ten months after initiation of LEN therapy, the patient had a clinically complete response, according to radiological findings (Figure 2A and B). Additionally, PIVKA II level markedly decreased from 1.637 to 4 mAU/mL and was sustained within the normal range with continued therapy. After 18 mo, LEN treatment was ceased because the patient developed severe diarrhea. At that time, a follow-up CT examination revealed that the tumor burden had significantly decreased. However, after 7 mo, PIVKA II levels increased again, with contrast-enhancement of the splenic lesion on CT and positron emission tomography (PET) findings (Figure 2C and D). Splenectomy was required to control the disease. Therefore, a hand-assisted laparoscopic splenectomy was performed for solitary spleen metastasis. The patient's postoperative course was uneventful. Macroscopic and microscopic histopathological examinations showed necrosis of HCC with slightly viable tumor cells. Surgical margins were negative (Figure 3). There was no clinical evidence of recurrence 14 mo after splenectomy and 81 mo after initial hepatectomy. Levels of PIVKA II remained within the normal range.

DISCUSSION

Based on our experience, LEN therapy could successfully lead to a hypovascular status of PVTT 10 mo after its initiation. In addition, conversion surgery was performed effectively for progression of solitary splenic metastasis after LEN discontinuation. To the best of our knowledge, there have been few reports regarding successful conversion surgery after multikinase inhibitor treatment for HCC with massive tumor thrombus[8,16].

We experienced good control of PVTT with LEN administration. In our case, PVTT became hypovascular 10 mo after LEN administration, along with a necrosis of the splenic lesion. After LEN discontinuation, PVTT continued to be hypovascular, whereas the splenic lesion progressed. There have been two case reports showing disappearance of PVTT[8,16]. Takeda *et al*[8] reported a female patient with advanced HCC and PVTT who was treated with LEN monotherapy and experienced a long-term antitumor effect. Rapidly, LEN caused hypovascularity in the main hypervascular target lesion, and PVTT became undetectable 11 mo after LEN initiation. Takahashi *et al*[16] also reported a 59-year-old male patient with a recurrent liver mass diffusely located at the lateral segment with a massive Vp4 PVTT extending from the umbilical portion to the main and contralateral third-order portal branches. Three months after starting LEN, PVTT critically regressed and retreated to the contralateral first-order portal branch. After LEN cessation for 7 d, radical left lobectomy and PVTT thrombectomy were performed. The majority of PVTT cases showed necrosis. They argued that LEN may have a relatively strong antitumor effect not only on main tumor, but also on PVTT, which is attributed to an antiangiogenic effect. According to two previous reports, LEN exerts both immediate antiangiogenic and long-term antitumor effects on PVTT. According to previous basic studies[18-20], FGFR plays an important role in this antitumor effect *via* inhibition of FGF19-FGFR autocrine loop and antiangiogenic effects



DOI: 10.4240/wjgs.v14.i3.260

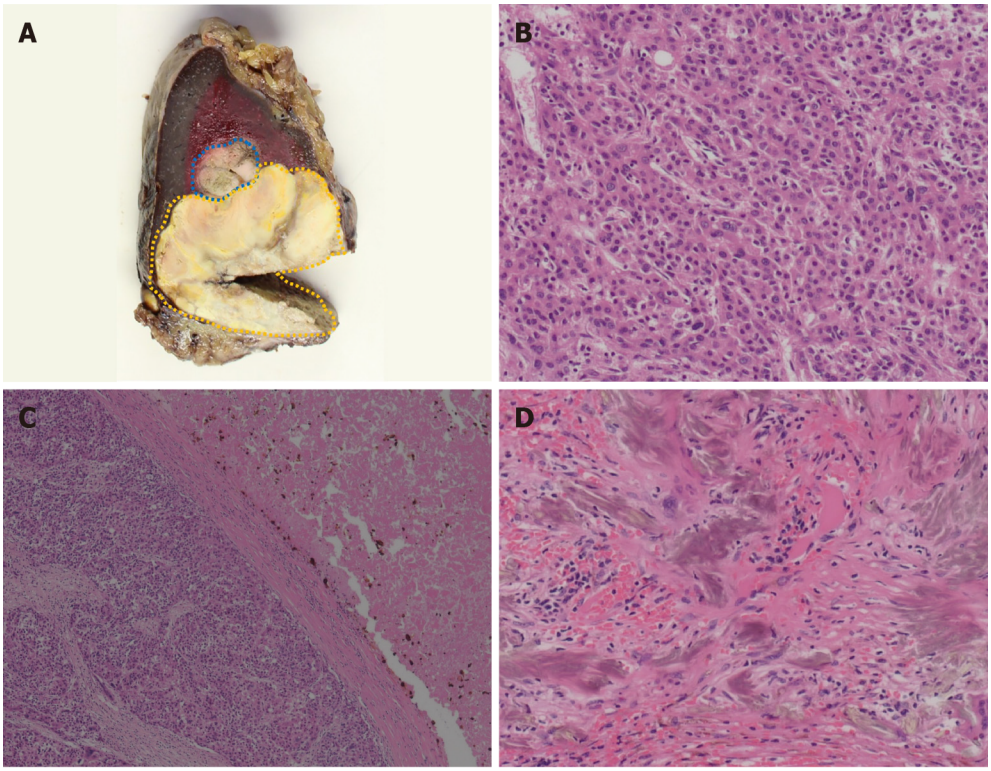
Figure 2 Radiological findings after the lenvatinib treatment. A: Portal vein tumor thrombus (PVTT) becomes hypovascular (yellow arrows) 10 mo after the administration of lenvatinib. Dynamic computed tomography (CT), portal phase; B: The main portal vein is hypovascular, suggesting the organization of PVTT 10 mo after the administration of lenvatinib. Numerous collateral veins are seen around the portal vein. Dynamic CT, portal phase; C: PVTT remains hypovascular (yellow arrows), whereas hypervascular lesions increase the peripheral lesions of the spleen metastases (blue arrows) 8 mo after the cessation of lenvatinib. Dynamic CT, portal phase; D: Fluorodeoxyglucose (FDG) uptakes in the lower pole of the spleen (blue arrows) corresponding to hypervascular lesions on CT. FDG-positron emission tomography.

through inhibition of FGFR/PDGFR. This explains why PVTT and hepatic lesions became hypovascular in 10 mo and continued to be in a hypovascular status approximately 2 years after LEN cessation in our patient.

Importantly, the safety of LEN administration for main PVTT (Vp4) has not been established. Kuzuya *et al*[21] compared the outcomes of advanced HCC with Vp3/4 between sorafenib and LEN as the first-line systemic therapy. The ORR was significantly higher in the LEN group than in the sorafenib group (53.8% *vs* 14.3%, P = 0.0193), and the median overall survival (OS) and time to progression were significantly longer in the LEN group than in the sorafenib group. None of these patients discontinued LEN treatment due to treatment-related adverse events in their series. Chuma *et al*[22] recently have reported the safety and efficacy of LEN treatment in highly advanced HCC. In this report, 20 patients with Vp4 HCC were included, and 12 patients (60%) experienced grade ≥ 3 adverse effects. The ORRs were 26.7% in patients with Child-Pugh A and 0% in those with Child-Pugh B. These findings suggest that LEN administration with close monitoring of patients' live conditions would be acceptable.

It was notable that regorafenib, which has also anti-angiogenic properties did not have any impact on cavernous transformation of the portal vein and portal vein thrombosis. Although they have not been fully elucidated, the various reactions of regorafenib and LEN may originate from the different mechanisms of action between the two agents. The genes downregulated by regorafenib might be different from those manipulated by LEN. That would lead to their different effects. There have been few cases regarding regorafenib and conversion therapy for HCC with PVTT, despite REFLECT trial included patients with macrovascular invasion[5].

Since metastatic splenic lesions became viable after LEN cessation, splenectomy was necessary to control the disease. There have been a few cases of spleen metastases resection[23-26]. The spleen is an important organ in the immune system, and metastases to this organ usually involve multiple lesions, and solitary splenic metastasis seems rare. According to previous reports[23-25], splenectomy for spleen metastases led to favorable outcomes, despite some patients having dismal outcomes (OS, 2-84 mo). Kim *et al*[26] have reported lesions detected by fluorodeoxyglucose-PET, which was similar to those in our patient. It has been assumed that splenic metastasis could be transformed into poor differentiation through multiple treatments.



DOI: 10.4240/wjgs.v14.i3.260

Figure 3 Pathological findings of metastatic splenic lesions. A: Macroscopic finding shows that splenic lesions surrounded by fibrous capsule, and a border part (blue area) is distinguished from other parts (yellow area) with its color, suggesting viable lesions; B: Microscopic finding of viable tumor lesion shows moderately to poorly differentiated hepatocellular carcinoma. Hematoxylin-eosin stain, high-power field (× 200); C: Microscopic findings of mixed component of viable cells and necrotic tissue demonstrated that coagulative and partially liquefactive necrosis (right-side) is surrounded by fibrous capsule, and viable cells (left-side). Hematoxylin-eosin stain, low-power field (× 50); D: Gamma-Gandy bodies shown in the splenic lesions, suggesting previous history of portal hypertension due to portal vein tumor thrombosis. Hematoxylin-eosin stain, high-power field (× 200).

CONCLUSION

We report the rare case of a patient with advanced HCC in whom LEN monotherapy showed long-term antitumor activity. Clinicians should be aware of radiological changes suggestive of intratumoral vascularity during treatment with the novel antiangiogenic agent LEN in patients with advanced HCC. Further studies are needed to elucidate the background of patients' favorable outcomes.

ACKNOWLEDGEMENTS

We would like to thank Dr. Hiromi Serizawa from the Department of Pathology, Hachioji Medical Center Tokyo Medical University for their insightful comment on pathological findings; Dr. Seishi Nakatsuka from the Department of Radiology, Keio University for his precise comment on radiological findings.

FOOTNOTES

Author contributions: Endo Y participated in the patient care, conceptualization, data curation, visualization and wrote the original article; Shimazu M participated in the patient care, reviewed the article, and supervised this report; Ozawa S, Kawachi S, Chiba N, Sakuragawa T, Uchi Y, Sunamura K reviewed the article; Edanami M participated in the patient care.

Informed consent statement: Written informed consent was obtained from this patient.

Conflict-of-interest statement: The authors have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 March 27; 14(3): 268-270

DOI: 10.4240/wjgs.v14.i3.268

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

Is it sufficient to evaluate only preoperative systemic inflammatory biomarkers to predict postoperative complications after pancreaticoduodenectomy?

Semra Demirli Atici, Erdinc Kamer

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Shah OJ, India; Xu X, China

Received: November 21, 2021
Peer-review started: November 21, 2021
First decision: December 27, 2021
Revised: January 7, 2022
Accepted: March 6, 2022
Article in press: March 6, 2022
Published online: March 27, 2022

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Abstract

Postoperative morbidity and mortality rates are still very high among patients undergoing pancreaticoduodenectomy (PD). However, mortality rates secondary to morbidities that are detected early and well-managed postoperatively are lower among patients undergoing PD. Since early detection of complications plays a very important role in the management of these patients, many ongoing studies are being conducted on this subject. Recent endoscopic retrograde cholangiopancreatography and biliary drainage history of the patient study group is important for comparison of C-reactive protein (CRP), an inflammatory parameter evaluated in the retrospective study by Coppola *et al* published in the *World Journal of Gastrointestinal Surgery* and titled "Utility of preoperative systemic inflammatory biomarkers in predicting postoperative complications after pancreaticoduodenectomy: Literature review and single center experience". Therefore, it may be more appropriate to compare CRP values in randomized patients.

Key Words: Pancreaticoduodenectomy; Biliary drainage; Complications; C-reactive protein; CRP; Postoperative pancreatic fistula; Preoperative inflammatory markers

Core Tip: Predicting the complications that may develop after pancreaticoduodenectomy is very important in the management of patients. Preoperative and intraoperative scoring of patients with the combination of many parameters, such as pancreatic structure, pancreatic duct diameter, preoperative biliary drainage history and laboratory parameters, can guide the estimation of postoperative morbidity and management. Inflammatory biomarkers are easily affected by preoperative treatment. In order to discuss such situations, we think that it would be more appropriate to prospectively randomize patients in whom dynamic changes of inflammatory parameters can be observed with reported risk factors, including not only C-reactive protein value but also other inflammatory parameters, rather than these preoperative values.

Citation: Demirli Atici S, Kamer E. Is it sufficient to evaluate only preoperative systemic inflammatory biomarkers to predict postoperative complications after pancreaticoduodenectomy? *World J Gastrointest Surg* 2022; 14(3): 268-270
URL: https://www.wjgnet.com/1948-9366/full/v14/i3/268.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i3.268

TO THE EDITOR

Coppola *et al*[1] recently published a retrospective study on the role of preoperative inflammatory markers to detect the predictive efficiency of postoperative morbidity and mortality in pancreaticoduodenectomy (PD) patients.

Most patients diagnosed with pancreatic cancer undergo preoperative endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes. Preoperative biliary drainage (PBD) can be performed in addition to ERCP in these patients, who may also present with the complaint of obstructive jaundice[2].

PBD itself, duration of the PBD and the ERCP procedure can each increase the inflammatory response [3,4]. Coppola *et al*[1] found that preoperative C-reactive protein (CRP) level of > 8.81 mg/dL was a high-risk factor for general complications and abdominal collection, which was associated with the inflammatory parameters examined prior to PD operations. Unfortunately, the authors did not report the number of PBD procedures performed on the individual patients included in their study, nor did they provide information on the duration of time before the ERCP procedure was performed for any. This missing information may preclude our ability to make conclusions on the effectiveness of the baseline CRP value, since the recent history of ERCP and the history of PBD are unknown for the study's patients. A history of PBD will cause an increased inflammatory response. In addition, increased postoperative complication rates have been demonstrated in relation to a history of PBD and duration of biliary drainage. Prospective randomized controlled trials would be more instructive in determining the efficacy of preoperative inflammatory markers and their importance in the rates of postoperative complications due to PD.

FOOTNOTES

Author contributions: Demirli Atici S and Kamer E wrote the manuscript; Kamer E reviewed and supervised the manuscript preparation; Both authors read and agreed to the published version of the manuscript.

Conflict-of-interest statement: The authors declare having no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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S-Editor: Wu YXJ

L-Editor: A
P-Editor: Wu YXJ

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