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The Oncological Reasons for Performing A Complete Mesocolic Excision: A Systematic Review and Meta-analysis

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Abstract

Background

While complete mesocolic excision (CME) has been shown to have an oncological benefit as compared to conventional colonic surgery for colon surgery, this benefit must be weighed up against the risk of major intra-abdominal complications. This paper aimed to assess the comparative oncological benefits of CME.

Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, a systematic review of the literature until May 2020 was performed. Comparative studies assessing CME versus conventional colonic surgery for colon cancer were compared, and outcomes were pooled.

Results

A total of 700 publications were identified, of which 19 were found to meet the inclusion criteria. A total of 25,886 patients were compared, with 14,431 patients in the CME arm. CME was associated with a significantly higher rate of vascular injury (odds ratio (OR) 3, $p<0.001$). Rates of local and distant recurrence were lower in the CME group (OR 0.66 and 0.73 respectively, both $p<0.001$). CME patients had a significantly higher lymph node yield ($p<0.001$). While no significant differences were noted between the two groups in terms of pooled 3-year or 5-year disease-free survival, pooled 5-year overall survival was significantly higher in the CME group (relative risk 0.82, $p<0.001$).

Conclusion

Based on the available evidence, CME is associated with improved oncologic outcomes at the expense of higher complication rates, including vascular injury. The oncological benefits need to weighed up against a multitude of factors including the level of hospital support, surgeon experience, patient age, and associated comorbidities.

Keywords: Complete mesocolic excision, complete mesocolic rection, D3 resection, colorectal cancer

Introduction

Complete mesocolic excision (CME) for the treatment of colorectal cancer is a surgical technique that was first proposed in 2009.[1] The caecum, ascending, transverse, descending, and sigmoid colon are all enveloped by visceral fascia and attached to the retroperitoneum by the mesocolon. The mesocolon contains blood vessels, lymphatic vessels, and lymph nodes, which are all structures that can potentially facilitate metastatic spread.[1] The idea of CME was conceived from this anatomical understanding, in performing a meticulous sharp dissection along the visceral plane, and mobilising the mesocolon away from the retroperitoneum without breaching the fascial layer.[1] A key component of CME as described by Hohenberger et. al is central vascular ligation (CVL); this entails a D3 dissection, thus maximizing lymph node clearance.[1]

Several publications have shown an oncological benefit to performing CME. [2-4] However, this benefit must be weighed up against the risk of major intra-abdominal complications such as vascular injury. This systematic review and meta-analysis aimed to assess the comparative oncological benefits of CME, as compared to traditional colon surgery for colonic cancer, by pooling the outcomes from several comparative studies published on this topic.

Methods

A meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Three authors (JCK, SP, KTC) were responsible for the literature search and data extraction. A systematic research was performed in PubMed and Medline, and the last search date was 29 May 2020. The following keywords were used: “complete mesocolic resection” OR “complete mesocolic excision” OR “D3 resection” OR “extended lymphadenectomy” AND “colon cancer”.

Comparative studies comparing CME and standard colonic resection which reported at least one outcome of interest were included. Studies were excluded if they were video vignettes, letters, conference abstracts, systematic reviews, or technical descriptions of CME. The outcomes of interest were mean blood loss, mean lymph node yield, mean length of stay (LOS), mean operating time, oncological outcomes such as the rates of distant and local recurrence, disease-free and overall survival, the rate of overall complications and mortality, and the rate of specific complications such as vascular injury, ileus, and anastomotic leak.

Statistical analysis

Any continuous data that was reported as median and range was converted to mean and standard deviation. Categorical data was collected as absolute numbers; overall survival (OS) and disease-free survival (DFS) was collected as a percentage. Any data that reported zero events was replaced with 0.5 to allow for computation of statistical calculation. A pooled odds ratio (OR) and relative risk (RR) was calculated based on the Cochran-Mantel-Haenszel test and random effect model analysis respectively. I^2 statistics were performed to assess for inter-study heterogeneity. The Newcastle-Ottawa Scale and the Jadad score were used to assess the

quality of non-randomised and randomised studies respectively. A p-value of <0.05 was considered significant. All data analysis was performed in R Studio Team (2015). RStudio: Integrated Development for R Studio, Inc., Boston, MA using the metaphor package for meta-analysis.[5]

Results

After an extensive search in accordance with the PRISMA guidelines, a total of 700 publications were identified (Figure 1). Of these, a full text review was performed for 72 publications following title and abstract review. A total of 19 publications met the inclusion criteria, and these were included in the final analysis (Table 1).[2-4,6-22] There was a total of 25,688 patients who underwent surgery for colorectal cancer, who were dichotomised into two groups; patients who underwent CME, and those who underwent traditional colectomy. 14,431 patients (56.2%) underwent CME. Of these, 6159 (42.7%) had right-sided cancers. The two groups were compared in terms of operative complications, oncological outcomes, and survival.

Overall complications were significantly more common in the CME group, with a pooled OR of 1.21 (95% CI 1.06 – 1.37, $p = 0.006$), whereas vascular injury had the highest pooled OR of 3 (95% CI 1.56 – 5.76, $p < 0.001$) when compared to non-CME resection (Figure 2, Supporting Information). However, other complications did not show any statistical differences including mean operative blood loss (SMD -0.21, 95% CI -1.09 – 0.68, $p = 0.649$), operative time (SMD 0.22, 95% CI -0.30 – 0.73, $p = 0.409$), anastomotic leak rate (OR 1.12, 95% CI 0.85 – 1.49, $p = 0.483$), post-operative ileus (OR 1.04, 95% CI 0.65 – 1.66, $p = 0.956$), and mean length of stay in hospital (SMD -0.36, 95% CT -0.98 – 0.26, $p = 0.255$) (Supporting Information).

In terms of oncological outcomes, rates of local and distant recurrence favoured the CME group, with a pooled OR of 0.66 (95% CI 0.52 – 0.83, $p < 0.001$) and 0.73 (95% CI 0.61 – 0.87, $p < 0.001$) respectively as compared to the non-CME group (Table 2, Figure 3 & 4). In one study with 45 patients, there were no instances of local recurrence, and another study had just one patient with local recurrence among a pool of 56 patients.[4,16] There was a significant

difference between lymph node yield between the two groups with a standard mean difference (SMD) of 1.31 favouring CME (95% CI 0.66 – 1.95, $p < 0.001$) (Supporting Information).

There were no significant differences between the two groups in terms of pooled 3-year DFS (RR 0.92, 95% CI 0.82 – 1.04, $p = 0.174$), 5-year DFS (RR 0.99, 95% CI 0.90 – 1.09, $p = 0.827$), and overall mortality (OR 1.19, 95% CI 0.86 – 1.66, $p = 0.335$), but pooled 5-year OS was significantly higher in the CME group (RR 0.82, 95% CI 0.77 – 0.87, $p < 0.001$). (Table 2, Figure 5, Supporting Information).

Discussion

In this meta-analysis consisting of predominantly non-randomised studies, CME was associated with an improvement in intermediate oncological outcomes, with a reduced rate of both local and distant recurrence, when compared to conventional colonic resection technique. However, the risk of vascular injury, and other surgical complications was higher with CME than with traditional colectomy. While no significant differences were identified between patients undergoing CME and traditional colon surgery in terms of pooled DFS, pooled 5-year OS was significantly higher in the CME group

Vascular injury is a potentially catastrophic complication that is associated with performing CME for colon cancer. For right colon cancers, CME requires radial dissection along embryological planes up to the middle colic artery (MCA) and middle colic vein (MCV) with central ligation of the ileocolic vein (ICV) and artery (ICA), and the right branch of the MCA.[23,24] In doing so, the superior mesenteric vein (SMV) needs to be exposed and may be inadvertently injured when performing nodal clearance of the D3 lymph node basin, potentially leading to bowel ischemia.[23] Other mechanisms for vascular injury include the avulsion of the ICV near its origin along the SMV as a result of excessive retraction, inadvertent injury to the gastrocolic trunk, MCA, or MCV as a result of anatomical variations, or traction of the colon to be resected through a proportionally small incision whilst performing this procedure in a minimally invasive fashion, causing possible life-threatening venous bleeding.[23,24] Prevost et al. reported that most vascular injuries occurred around the SMV.[14] As with all procedures, there is a learning curve that can mitigate the risk of such operative complications, with the learning curve estimated to be between 23 and 25 cases in published literature.[25,26] While the rate of vascular injury was significantly higher with

CME in our study, other technical markers were reassuring, with no differences noted between the CME and non-CME groups with regards to intra-operative blood loss, operative time, post-operative anastomotic leak, or length of stay in hospital.

As expected, our study showed a significant increase in pooled lymph node harvest when a CME was performed as opposed to traditional colectomy. Additional lymph node yield from another nodal basin could improve staging, allowing clinicians to accurately understand the potential risk of distant recurrence prior to advocating for adjuvant chemotherapy. This is particularly important, as some studies have found there is a potential risk of skip lymph node metastasis to the D3 basin (in which D1 and D2 lymph node basins are negative) in approximately 1-5% of patients.[27] The benefits of D3 lymphadenopathy are still being studied, with one study showing a positive D3 lymph node basin is a poor prognostic indicator and long-term outcome, regardless of having a more aggressive surgical approach.[28]

There were two randomised controlled trials (RCTs) included in this meta-analysis. Yan et al. found that lymph node yield was significantly higher with CME, and that CME was found to have markedly increased overall survival and tumour-free survival rates as compared to traditional radical operation for colon cancer.[21] These results are similar to ours of significantly higher lymph node harvest, and improved overall survival with CME. Conversely, Karachan et al. did not find a significant difference in lymph node yield despite performing CME. However, they did note that there was a significant increase in nodal positivity in the CME group. The authors of this study thought that this potential for better nodal staging in CME was a contributing factor to improved survival.

The benefits of CME in terms of the potentially reduced risk of local and distant recurrence, need to be weighed up against the risk of intra-operative complications. Patient selection for CME should be based, among other individual factors, on the cancer stage at time of surgical resection. There has been a lack of consensus on how to select the most appropriate patients to benefit from CME. The Japanese Society for Cancer of the Colon and Rectum published guidelines for the treatment of colorectal cancer in 2019, which included an algorithm to assist with this decision, which is based on radiological staging.[29] The recommendations included an assessment of mesocolic lymph nodes for any suspicious micro metastasis. If there is no suspicious lymph node micro metastasis, the decision would be based on the depth of tumour invasion (Figure 6).[29]

Our study did not differentiate the outcomes between different approaches (open, laparoscopic or robotic) to performing a CME, but this is an area that is quickly evolving in the last few years, with increasing uptake of robotic CME. There is some suggestion that robotic CME may contribute to safer vessel and lymph node dissection as compared to laparoscopic or open CME. Robotic CME allows for more precise vessel dissection with articulated instruments and is not subject to human tremors. It also incorporates a stable camera platform allowing for optical three-dimensional vision to clearly identify accurate dissection planes.[30,31] A direct comparison of robotic CME with laparoscopic CME has shown a lower conversion rate with robotic CME, which was found to be beneficial for dissection and performing an intracorporeal anastomosis[32]. This remains an area for future study.

There are some limitations to this study, namely that it is limited by the quality of the individual studies contributing to this pooled analysis. Only two randomised studies were included in this analysis. Furthermore, there was significant inter-study heterogeneity. The finding of a

reduction in the rate of local and distant recurrence was based on pooled data from only a few studies, and therefore must be interpreted with caution. 5-year DFS, which was not statistically different between the two groups, was pooled from a larger number of studies. Additionally, the expertise of the surgeons would have potentially impacted on the rate of complications, particularly in the non-randomised studies. Lastly, the absence of individual patient data precluded adjustment for potential confounders in this study.

Conclusion

This study shows that CME for colon cancer is associated with improved oncologic outcomes at the expense of higher morbidity rates including vascular pedicle injury. The oncological benefits need to weighed up against a multitude of factors including hospital support, surgeon experience, patient age, and associated comorbidities. Studies should not only focus on long-term oncological outcomes, but also appropriate patient selection that will allow maximum oncological benefit.

Tables

Table 1: Studies included in the meta-analysis

No.	Author	Year	Patient Selection	Study Type	No. of Patients (Right)		NOS/ Jadad†
					CME	Non-CME	
1	An et al.	2018	All right hemicolectomies	Retrospective OS	34	81	6
2	Bertelsen et al.	2015	All resections for Stage I – III colonic adenocarcinomas	RSFPMD	364 (145)	1031 (429)	8
3	Bertelsen et al.	2016	All resections for Stage I – III colonic adenocarcinomas	RSFPMD	529 (212)	1701 (731)	8
4	Galizia et al.	2013	Consecutive resections for right sided colonic adenocarcinomas	Prospective OS	45	58	7
5	Gao et al.	2020	All radical resections for colon cancer	Prospective, non-randomised, double blind controlled trial	220 (128)	110 (57)	7
6	Ishihara	2016	Curative resections for Stage I – III colonic adenocarcinomas	RSFPMD	3756 (1347)	2185 (564)	8
7	Karachun et al.	2019	Colonic resections for primary colonic cancer - T1–4aN0–2M0–1 (resectable metastases)	Randomised controlled trial	56 (21)	43 (21)	3
8	Kotake et al.	2014	Curative resections for pT3 or pT4 colon cancer	RSFPMD	6580 (3358)	3518 (1923)	9
9	Kotake et al.	2015	All curative resections for pT2 colon cancer	RSFPMD	774 (343)	659 (309)	9
10	Merkel et al.	2016	All consecutive resections for primary colon cancer	Retrospective OS	1099 (335)	920 (405)	7
11	Prevost et al.	2018	All elective right colectomies	RSFPMD	71	84	7
12	Rinne et al.	2020	All laparoscopic resections for Stage I-III colon cancers	RSFPMD	325 (168)	340 (168)	6
13	Sammour et al.	2019	Consecutive laparoscopic or	RSFPMD	141	56	6

			robotic right or extended-right hemicolectomy for primary colon adenocarcinoma				
14	Storli et al.	2014	All consecutive resections for Stage I-II colon cancer	Prospective OS	84 (27)	105 (39)	6
15	Tagliacozzo et al.	1997	All curative colorectal resections for right colon cancer	Retrospective OS	60	84	7
16	Thorsen et al.	2016	All consecutive curative resections for right colon cancer	Case control study	49	49	9
17	West et al.	2009	Consecutive resections for colon adenocarcinoma	Prospective OS	49 (30)	40 (16)	7
18	Yan et al.	2020	All resections for stage III colon cancer	Randomised controlled trial	98 (45)	98 (51)	3
19	Zurleni et al.	2017	All consecutive curative resections for right colon cancer	Retrospective OS	97	95	7

Abbreviations
RSFPMD: Retrospective study from a prospectively maintained database
OS: Observational study
† Newcastle-Ottawa score for non-randomised studies and Jadad score for randomised studies

Table 2: Recurrence rates and survival of patients

Author and Year	No of patients		Age				Advanced cancer (AJCC III or Duke C)				Local Recurrence				5 year DFS		5 year OS	
	CME	Non-CME	CME	Range	Non-CME	Range	CME	Range	Non-CME	Range	CME		Non-CME		CME	Non-CME	CME	Non-CME
An et al.	34	81	NR				7	20.6%	28	34.6%	NR				94.2%	89.0%	100%	89.5%
Bertelsen et al.	364	1031	71.5	64.3-77.8	73	66-79.9	140	38%	365	35%	NR				NR		74.8%	69.6%
Bertelsen et al.	529	1701	71.7	65-78.3	72.9	66-80.1	194	36.7%	587	34.5%	NR				NR		NR	
Galizia et al.	45	58	67	13	68	11	19	42.2%	20	34.5%	0	0	12	20.7%	90%	74%	NR	
Gao et al.	220	110	68	58-77	73	57-79	94	42.7%	42	38.2%	NR				NR		NR	
Ishihara.	3756	2185	64	-	67.5	-	1616	43%	562	25.7%	NR				91.0%	93.5%	NR	
Karachun et al.	56	43	NR				37	66%	22	51%	NR				NR		NR	
Kotake et al.	6580	3518	62.2	-	65.01	-	2906	44.2%	1397	39.7%	NR				NR		79.2%	74.6%
Kotake et al.	774	659	NR				172	22.2%	129	19.6%	NR				NR		91.7%	90.3%
Merkel et al.	1099	920	66.7	-	64	-	370	33.7%	382	41.5%	146	13.3%	204	22.2%	78.0%	73.4%	78%	73.4%
Prevost et al.	71	84	73.6	33-88.9	73.8	21-88.9	18	30.5%	33	46.5%	NR				NR		NR	
Rinne et al.	325	340	72	11	72	18	124	38.5%	122	35.9%	NR				85.6%	89.2%	72.9%	77.9%
Sammour et al.	141	56	64	12	64	14	48	34%	15	26.8%	0	0	1	1.8%	79.2%	84.4%	77.8%	62.4%

Storli et al.	84	105	72.5	11.3	72.6	12.6	0	0	0	0	1	1.2%	3	2.9%	82.3%	64.8%	87.9%	66.1%
Tagliacozzo et al.	60	84	63	6.5	61	7	26	43.3%	32	38.1%	NR				43.8%	36.3%	64.3%	62.8%
Thorsen et al.	49	49	67	27-75	65	28-75	NR				NR				NR		NR	
West et al.	49	40	68	60-79	76	67-80	20	40.8%	20	50.0%	NR				NR		NR	
Yan et al.	98	98	59.5	10.1	60.7	9.8	98	100%	98	100%	NR				59.8%	49.9%	73.8%	47.7%
Zurleni et al.	97	95	71	-	73	-	32	33%	33	34.7%	NR				NR		NR	

Figure Legends

Figure 1: Study Selection from PRISMA Guidelines

Figure 2: Pooled odds ratio of vascular injury

Figure 3: Pooled odds ratio of local recurrence

Figure 4: Pooled odds ratio of distant recurrence

Figure 5: Pooled relative risk of 5-year overall survival

Figures 6: Algorithm for patient selection for CME

Supporting information: Additional statistical data

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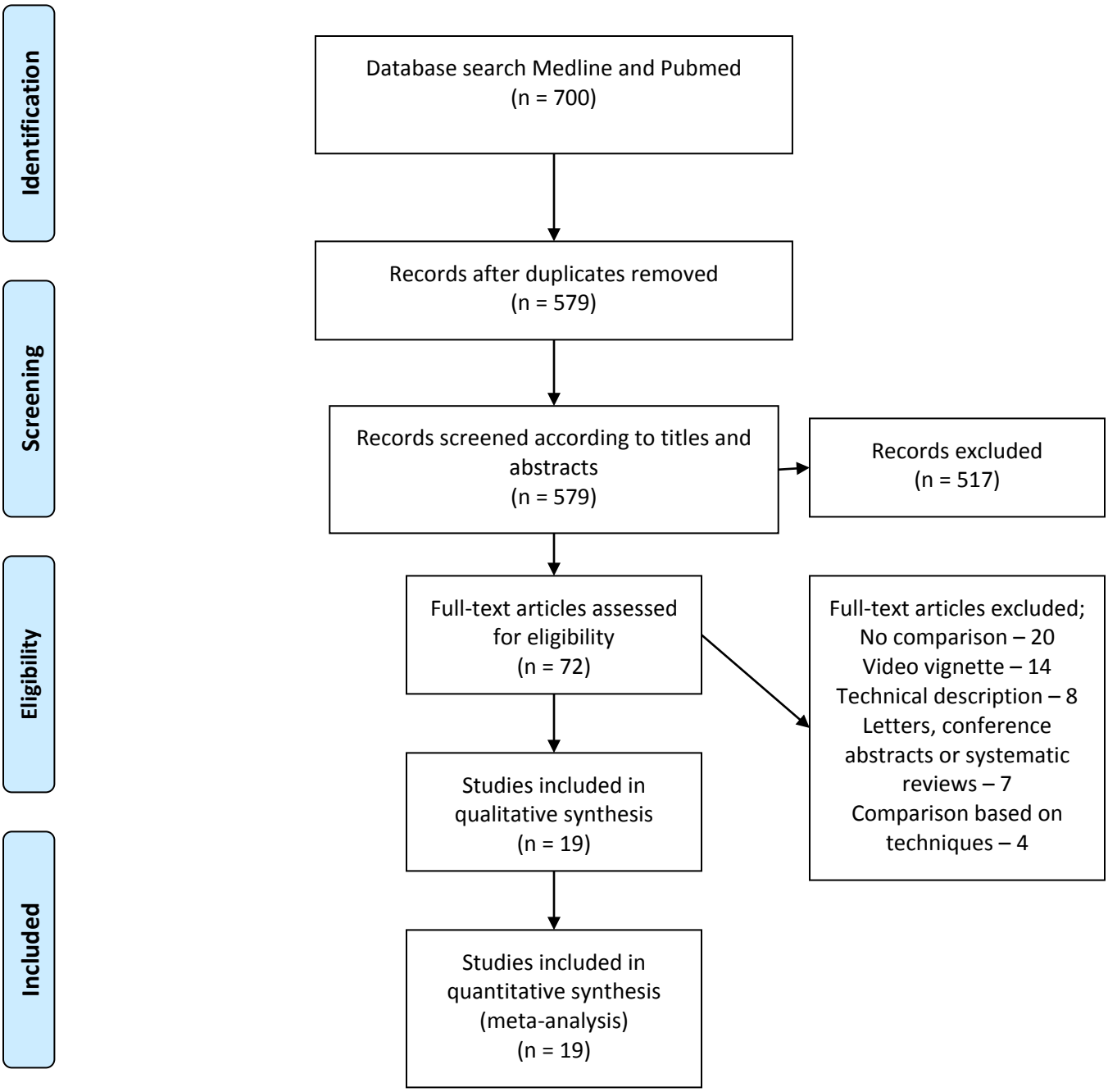
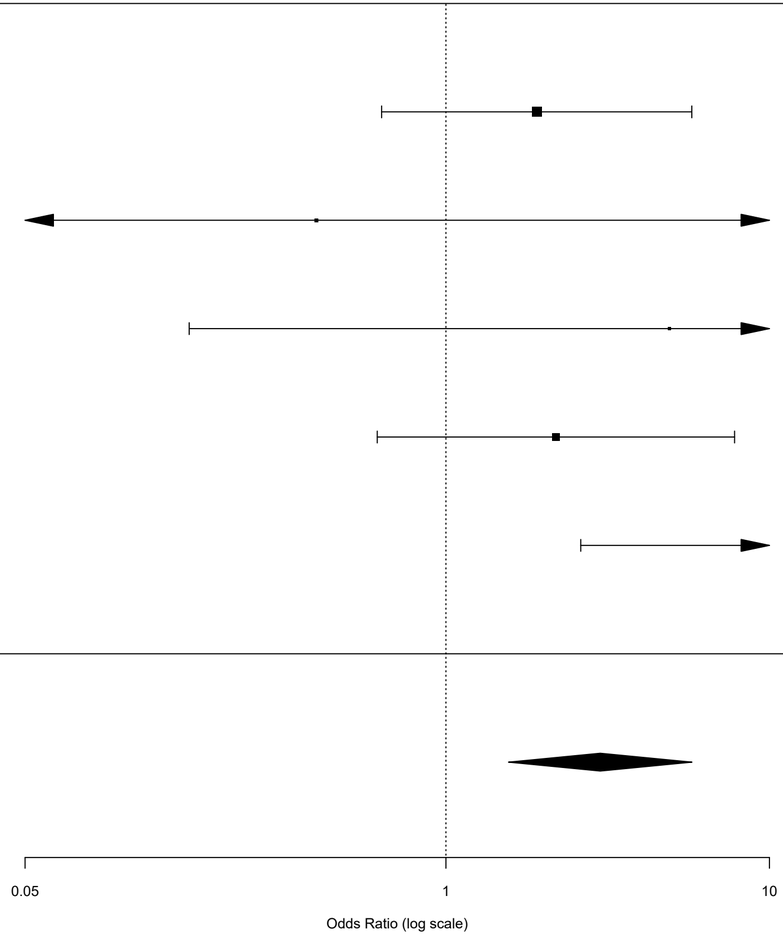
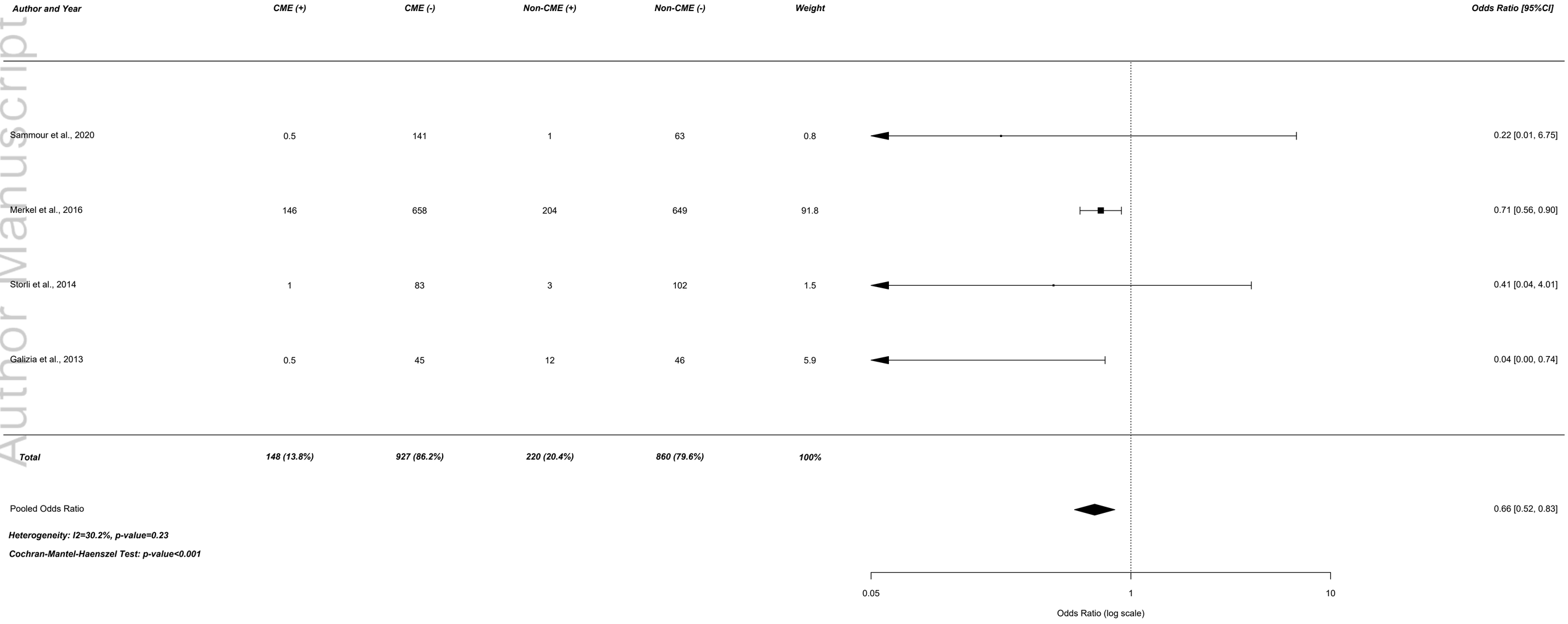


Author and Year	CME (+)	CME (-)	Non-CME (+)	Non-CME (-)	Weight	Odds Ratio [95%CI]
Rinne et al., 2020	9	316	5	335	44.3	1.91 [0.63, 5.76]
Sammour et al., 2020	0.5	141	0.5	56	6.7	0.40 [0.01, 20.26]
An et al., 2018	1	33	0.5	81	2.7	4.91 [0.16, 149.89]
Prevost et al., 2018	7	64	4	80	30.8	2.19 [0.61, 7.80]
Bertelsen et al., 2016	9	520	4	1967	15.5	8.51 [2.61, 27.75]
Total	***26.5 (2.2%)***	***1166 (97.8%)***	***14 (0.5%)***	***2623 (99.5%)***	***100%***	
Pooled Odds Ratio						3.00 [1.56, 5.76]

Heterogeneity:I2=19.3%, p-value=0.29

Cochran-Mantel-Haenszel Test: p-value<0.001

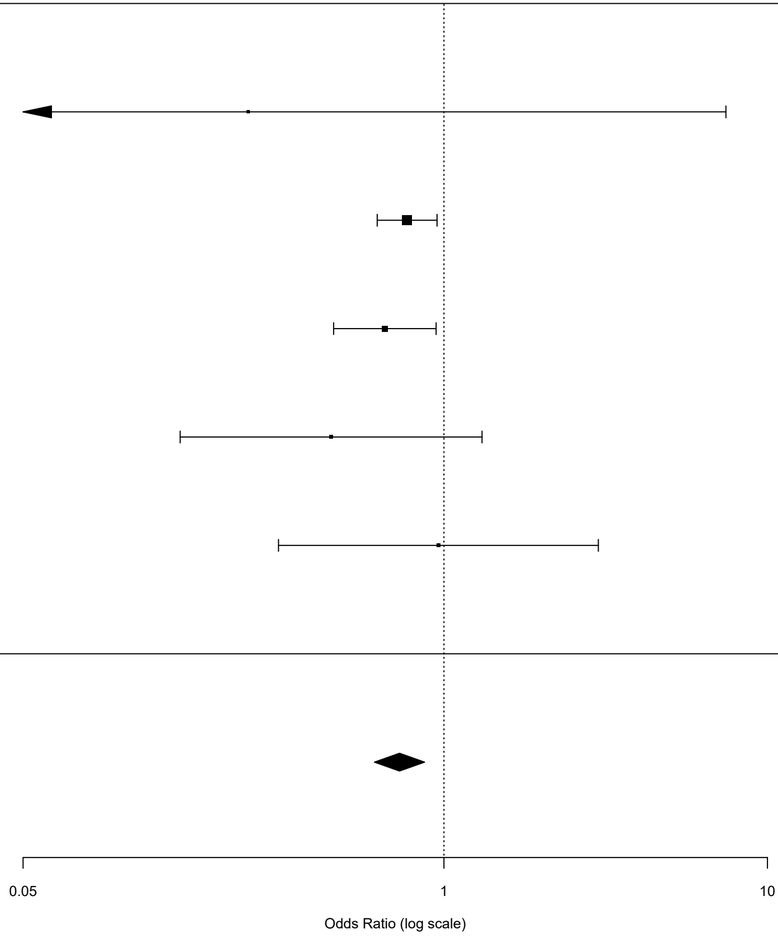




Author and Year	CME (+)	CME (-)	Non-CME (+)	Non-CME (-)	Weight	Odds Ratio [95%CI]
Gao et al., 2020	0.5	220	1	109	0.5	0.25 [0.01, 7.44]
Merkel et al., 2016	207	625	266	618	67	0.77 [0.62, 0.95]
Bertelsen et al., 2015	41	323	167	864	26.7	0.66 [0.46, 0.95]
Storli et al., 2014	5	79	13	92	3.7	0.45 [0.15, 1.31]
Galizia et al., 2013	6	39	8	50	2.1	0.96 [0.31, 3.00]
Total	***259.5 (16.8%)***	***1286 (83.2%)***	***455 (20.8%)***	***1733 (79.2%)***	***100%***	
Pooled Odds Ratio						0.73 [0.61, 0.87]

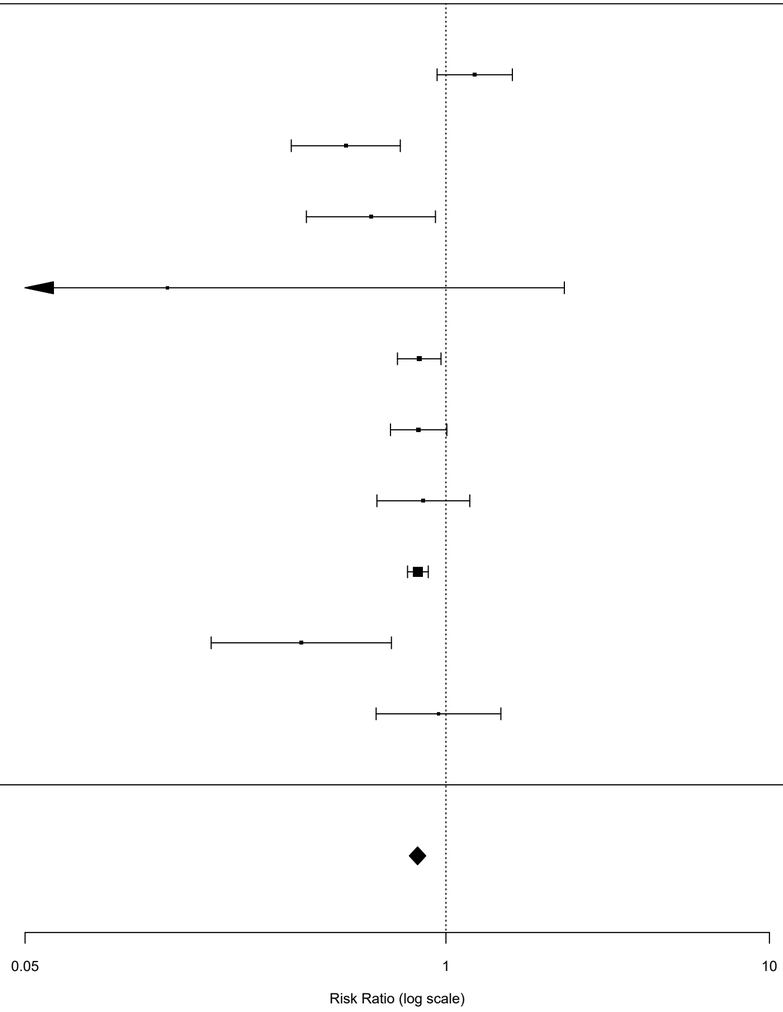
Heterogeneity : I2=0% , p-value=0.74

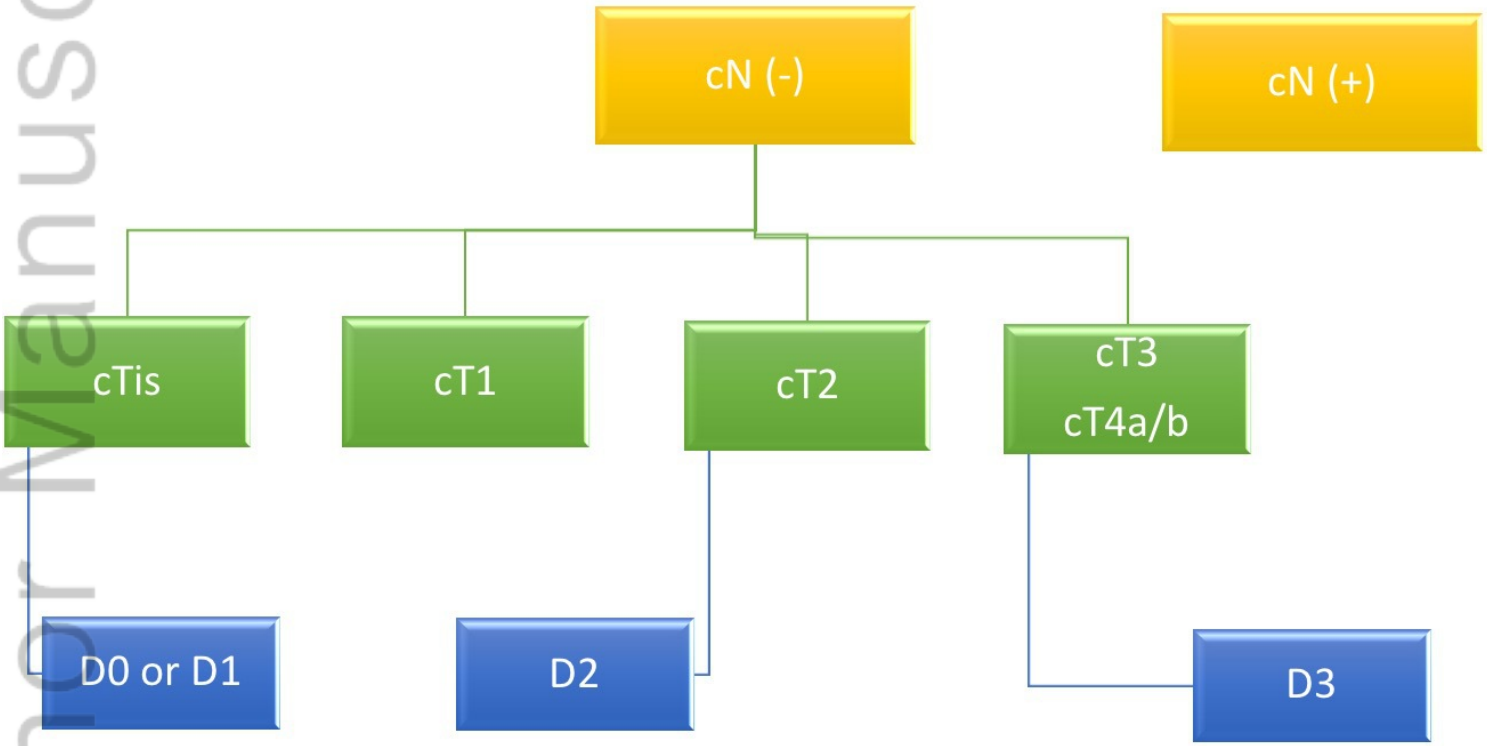
Cochran-Mantel-Haenszel Test: p-value<0.001



Author and Year	*CME (+)*	*CME (-)*	*Non-CME (+)*	*Non-CME (-)*	*Weight*	*Relative Risk [95%CI]*
Rinne et al., 2020	88	237	75	265	3.9	1.23 [0.94, 1.60]
Yan et al., 2020	25	73	51	47	2.7	0.49 [0.33, 0.72]
Sammour et al., 2020	31	110	21	35	1.6	0.59 [0.37, 0.93]
An et al., 2018	0	34	8	73	0.3	0.14 [0.01, 2.32]
Merkel et al., 2016	241	858	244	676	14.1	0.83 [0.71, 0.97]
Bertelsen et al., 2015	91	273	313	718	8.7	0.82 [0.67, 1.01]
Kotake et al., 2015	64	710	64	595	3.7	0.85 [0.61, 1.18]
Kotake et al., 2014	1368	5212	893	2625	62	0.82 [0.76, 0.88]
Storli et al., 2014	10	74	35	70	1.7	0.36 [0.19, 0.68]
Tagliacozzo et al., 1997	21	39	31	53	1.3	0.95 [0.61, 1.48]
Total	***1939 (20.3%)***	***7620 (79.7%)***	***1735 (25.2%)***	***5157 (74.8%)***	***100%***	
Pooled Relative Risk						0.82 [0.77, 0.87]

Heterogeneity: I2=65.3%, p-value<0.01
RE Model: p-value<0.001





ANS_16518_Figure 6.jpg

The Oncological Reasons for Performing A Complete Mesocolic Excision: A Systematic Review and Meta-analysis

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Figures: 6

Table: 2

Supporting information: Additional statistical data

Abstract

Background

While complete mesocolic excision (CME) has been shown to have an oncological benefit as compared to conventional colonic surgery for colon surgery, this benefit must be weighed up against the risk of major intra-abdominal complications. This paper aimed to assess the comparative oncological benefits of CME.

Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, a systematic review of the literature until May 2020 was performed. Comparative studies assessing CME versus conventional colonic surgery for colon cancer were compared, and outcomes were pooled.

Results

A total of 700 publications were identified, of which 19 were found to meet the inclusion criteria. A total of 25,886 patients were compared, with 14,431 patients in the CME arm. CME was associated with a significantly higher rate of vascular injury (odds ratio (OR) 3, $p<0.001$). Rates of local and distant recurrence were lower in the CME group (OR 0.66 and 0.73 respectively, both $p<0.001$). CME patients had a significantly higher lymph node yield ($p<0.001$). While no significant differences were noted between the two groups in terms of pooled 3-year or 5-year disease-free survival, pooled 5-year overall survival was significantly higher in the CME group (relative risk 0.82, $p<0.001$).

Conclusion

Based on the available evidence, CME is associated with improved oncologic outcomes at the expense of higher complication rates, including vascular injury. The oncological benefits need to weighed up against a multitude of factors including the level of hospital support, surgeon experience, patient age, and associated comorbidities.

Keywords: Complete mesocolic excision, complete mesocolic rection, D3 resection, colorectal cancer

Introduction

Complete mesocolic excision (CME) for the treatment of colorectal cancer is a surgical technique that was first proposed in 2009.[1] The caecum, ascending, transverse, descending, and sigmoid colon are all enveloped by visceral fascia and attached to the retroperitoneum by the mesocolon. The mesocolon contains blood vessels, lymphatic vessels, and lymph nodes, which are all structures that can potentially facilitate metastatic spread.[1] The idea of CME was conceived from this anatomical understanding, in performing a meticulous sharp dissection along the visceral plane, and mobilising the mesocolon away from the retroperitoneum without breaching the fascial layer.[1] A key component of CME as described by Hohenberger et. al is central vascular ligation (CVL); this entails a D3 dissection, thus maximizing lymph node clearance.[1]

Several publications have shown an oncological benefit to performing CME. [2-4] However, this benefit must be weighed up against the risk of major intra-abdominal complications such as vascular injury. This systematic review and meta-analysis aimed to assess the comparative oncological benefits of CME, as compared to traditional colon surgery for colonic cancer, by pooling the outcomes from several comparative studies published on this topic.

Methods

A meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Three authors (JCK, SP, KTC) were responsible for the literature search and data extraction. A systematic research was performed in PubMed and Medline, and the last search date was 29 May 2020. The following keywords were used: “complete mesocolic resection” OR “complete mesocolic excision” OR “D3 resection” OR “extended lymphadenectomy” AND “colon cancer”.

Comparative studies comparing CME and standard colonic resection which reported at least one outcome of interest were included. Studies were excluded if they were video vignettes, letters, conference abstracts, systematic reviews, or technical descriptions of CME. The outcomes of interest were mean blood loss, mean lymph node yield, mean length of stay (LOS), mean operating time, oncological outcomes such as the rates of distant and local recurrence, disease-free and overall survival, the rate of overall complications and mortality, and the rate of specific complications such as vascular injury, ileus, and anastomotic leak.

Statistical analysis

Any continuous data that was reported as median and range was converted to mean and standard deviation. Categorical data was collected as absolute numbers; overall survival (OS) and disease-free survival (DFS) was collected as a percentage. Any data that reported zero events was replaced with 0.5 to allow for computation of statistical calculation. A pooled odds ratio (OR) and relative risk (RR) was calculated based on the Cochran-Mantel-Haenszel test and random effect model analysis respectively. I^2 statistics were performed to assess for inter-study heterogeneity. The Newcastle-Ottawa Scale and the Jadad score were used to assess the

quality of non-randomised and randomised studies respectively. A p-value of <0.05 was considered significant. All data analysis was performed in R Studio Team (2015). RStudio: Integrated Development for R Studio, Inc., Boston, MA using the metaphor package for meta-analysis.[5]

Results

After an extensive search in accordance with the PRISMA guidelines, a total of 700 publications were identified (Figure 1). Of these, a full text review was performed for 72 publications following title and abstract review. A total of 19 publications met the inclusion criteria, and these were included in the final analysis (Table 1).[2-4,6-22] There was a total of 25,688 patients who underwent surgery for colorectal cancer, who were dichotomised into two groups; patients who underwent CME, and those who underwent traditional colectomy. 14,431 patients (56.2%) underwent CME. Of these, 6159 (42.7%) had right-sided cancers. The two groups were compared in terms of operative complications, oncological outcomes, and survival.

Overall complications were significantly more common in the CME group, with a pooled OR of 1.21 (95% CI 1.06 – 1.37, $p = 0.006$), whereas vascular injury had the highest pooled OR of 3 (95% CI 1.56 – 5.76, $p < 0.001$) when compared to non-CME resection (Figure 2, Supporting Information). However, other complications did not show any statistical differences including mean operative blood loss (SMD -0.21, 95% CI -1.09 – 0.68, $p = 0.649$), operative time (SMD 0.22, 95% CI -0.30 – 0.73, $p = 0.409$), anastomotic leak rate (OR 1.12, 95% CI 0.85 – 1.49, $p = 0.483$), post-operative ileus (OR 1.04, 95% CI 0.65 – 1.66, $p = 0.956$), and mean length of stay in hospital (SMD -0.36, 95% CT -0.98 – 0.26, $p = 0.255$) (Supporting Information).

In terms of oncological outcomes, rates of local and distant recurrence favoured the CME group, with a pooled OR of 0.66 (95% CI 0.52 – 0.83, $p < 0.001$) and 0.73 (95% CI 0.61 – 0.87, $p < 0.001$) respectively as compared to the non-CME group (Table 2, Figure 3 & 4). In one study with 45 patients, there were no instances of local recurrence, and another study had just one patient with local recurrence among a pool of 56 patients.[4,16] There was a significant

difference between lymph node yield between the two groups with a standard mean difference (SMD) of 1.31 favouring CME (95% CI 0.66 – 1.95, $p < 0.001$) (Supporting Information).

There were no significant differences between the two groups in terms of pooled 3-year DFS (RR 0.92, 95% CI 0.82 – 1.04, $p = 0.174$), 5-year DFS (RR 0.99, 95% CI 0.90 – 1.09, $p = 0.827$), and overall mortality (OR 1.19, 95% CI 0.86 – 1.66, $p = 0.335$), but pooled 5-year OS was significantly higher in the CME group (RR 0.82, 95% CI 0.77 – 0.87, $p < 0.001$). (Table 2, Figure 5, Supporting Information).

Discussion

In this meta-analysis consisting of predominantly non-randomised studies, CME was associated with an improvement in intermediate oncological outcomes, with a reduced rate of both local and distant recurrence, when compared to conventional colonic resection technique. However, the risk of vascular injury, and other surgical complications was higher with CME than with traditional colectomy. While no significant differences were identified between patients undergoing CME and traditional colon surgery in terms of pooled DFS, pooled 5-year OS was significantly higher in the CME group

Vascular injury is a potentially catastrophic complication that is associated with performing CME for colon cancer. For right colon cancers, CME requires radial dissection along embryological planes up to the middle colic artery (MCA) and middle colic vein (MCV) with central ligation of the ileocolic vein (ICV) and artery (ICA), and the right branch of the MCA.[23,24] In doing so, the superior mesenteric vein (SMV) needs to be exposed and may be inadvertently injured when performing nodal clearance of the D3 lymph node basin, potentially leading to bowel ischemia.[23] Other mechanisms for vascular injury include the avulsion of the ICV near its origin along the SMV as a result of excessive retraction, inadvertent injury to the gastrocolic trunk, MCA, or MCV as a result of anatomical variations, or traction of the colon to be resected through a proportionally small incision whilst performing this procedure in a minimally invasive fashion, causing possible life-threatening venous bleeding.[23,24] Prevost et al. reported that most vascular injuries occurred around the SMV.[14] As with all procedures, there is a learning curve that can mitigate the risk of such operative complications, with the learning curve estimated to be between 23 and 25 cases in published literature.[25,26] While the rate of vascular injury was significantly higher with

CME in our study, other technical markers were reassuring, with no differences noted between the CME and non-CME groups with regards to intra-operative blood loss, operative time, post-operative anastomotic leak, or length of stay in hospital.

As expected, our study showed a significant increase in pooled lymph node harvest when a CME was performed as opposed to traditional colectomy. Additional lymph node yield from another nodal basin could improve staging, allowing clinicians to accurately understand the potential risk of distant recurrence prior to advocating for adjuvant chemotherapy. This is particularly important, as some studies have found there is a potential risk of skip lymph node metastasis to the D3 basin (in which D1 and D2 lymph node basins are negative) in approximately 1-5% of patients.[27] The benefits of D3 lymphadenopathy are still being studied, with one study showing a positive D3 lymph node basin is a poor prognostic indicator and long-term outcome, regardless of having a more aggressive surgical approach.[28]

There were two randomised controlled trials (RCTs) included in this meta-analysis. Yan et al. found that lymph node yield was significantly higher with CME, and that CME was found to have markedly increased overall survival and tumour-free survival rates as compared to traditional radical operation for colon cancer.[21] These results are similar to ours of significantly higher lymph node harvest, and improved overall survival with CME. Conversely, Karachan et al. did not find a significant difference in lymph node yield despite performing CME. However, they did note that there was a significant increase in nodal positivity in the CME group. The authors of this study thought that this potential for better nodal staging in CME was a contributing factor to improved survival.

The benefits of CME in terms of the potentially reduced risk of local and distant recurrence, need to be weighed up against the risk of intra-operative complications. Patient selection for CME should be based, among other individual factors, on the cancer stage at time of surgical resection. There has been a lack of consensus on how to select the most appropriate patients to benefit from CME. The Japanese Society for Cancer of the Colon and Rectum published guidelines for the treatment of colorectal cancer in 2019, which included an algorithm to assist with this decision, which is based on radiological staging.[29] The recommendations included an assessment of mesocolic lymph nodes for any suspicious micro metastasis. If there is no suspicious lymph node micro metastasis, the decision would be based on the depth of tumour invasion (Figure 6).[29]

Our study did not differentiate the outcomes between different approaches (open, laparoscopic or robotic) to performing a CME, but this is an area that is quickly evolving in the last few years, with increasing uptake of robotic CME. There is some suggestion that robotic CME may contribute to safer vessel and lymph node dissection as compared to laparoscopic or open CME. Robotic CME allows for more precise vessel dissection with articulated instruments and is not subject to human tremors. It also incorporates a stable camera platform allowing for optical three-dimensional vision to clearly identify accurate dissection planes.[30,31] A direct comparison of robotic CME with laparoscopic CME has shown a lower conversion rate with robotic CME, which was found to be beneficial for dissection and performing an intracorporeal anastomosis[32]. This remains an area for future study.

There are some limitations to this study, namely that it is limited by the quality of the individual studies contributing to this pooled analysis. Only two randomised studies were included in this analysis. Furthermore, there was significant inter-study heterogeneity. The finding of a

reduction in the rate of local and distant recurrence was based on pooled data from only a few studies, and therefore must be interpreted with caution. 5-year DFS, which was not statistically different between the two groups, was pooled from a larger number of studies. Additionally, the expertise of the surgeons would have potentially impacted on the rate of complications, particularly in the non-randomised studies. Lastly, the absence of individual patient data precluded adjustment for potential confounders in this study.

Conclusion

This study shows that CME for colon cancer is associated with improved oncologic outcomes at the expense of higher morbidity rates including vascular pedicle injury. The oncological benefits need to weighed up against a multitude of factors including hospital support, surgeon experience, patient age, and associated comorbidities. Studies should not only focus on long-term oncological outcomes, but also appropriate patient selection that will allow maximum oncological benefit.

Tables

Table 1: Studies included in the meta-analysis

No.	Author	Year	Patient Selection	Study Type	No. of Patients (Right)		NOS/ Jadad†
					CME	Non-CME	
1	An et al.	2018	All right hemicolectomies	Retrospective OS	34	81	6
2	Bertelsen et al.	2015	All resections for Stage I – III colonic adenocarcinomas	RSFPMD	364 (145)	1031 (429)	8
3	Bertelsen et al.	2016	All resections for Stage I – III colonic adenocarcinomas	RSFPMD	529 (212)	1701 (731)	8
4	Galizia et al.	2013	Consecutive resections for right sided colonic adenocarcinomas	Prospective OS	45	58	7
5	Gao et al.	2020	All radical resections for colon cancer	Prospective, non-randomised, double blind controlled trial	220 (128)	110 (57)	7
6	Ishihara	2016	Curative resections for Stage I – III colonic adenocarcinomas	RSFPMD	3756 (1347)	2185 (564)	8
7	Karachun et al.	2019	Colonic resections for primary colonic cancer - T1–4aN0–2M0–1 (resectable metastases)	Randomised controlled trial	56 (21)	43 (21)	3
8	Kotake et al.	2014	Curative resections for pT3 or pT4 colon cancer	RSFPMD	6580 (3358)	3518 (1923)	9
9	Kotake et al.	2015	All curative resections for pT2 colon cancer	RSFPMD	774 (343)	659 (309)	9
10	Merkel et al.	2016	All consecutive resections for primary colon cancer	Retrospective OS	1099 (335)	920 (405)	7
11	Prevost et al.	2018	All elective right colectomies	RSFPMD	71	84	7
12	Rinne et al.	2020	All laparoscopic resections for Stage I-III colon cancers	RSFPMD	325 (168)	340 (168)	6
13	Sammour et al.	2019	Consecutive laparoscopic or	RSFPMD	141	56	6

			robotic right or extended-right hemicolectomy for primary colon adenocarcinoma				
14	Storli et al.	2014	All consecutive resections for Stage I-II colon cancer	Prospective OS	84 (27)	105 (39)	6
15	Tagliacozzo et al.	1997	All curative colorectal resections for right colon cancer	Retrospective OS	60	84	7
16	Thorsen et al.	2016	All consecutive curative resections for right colon cancer	Case control study	49	49	9
17	West et al.	2009	Consecutive resections for colon adenocarcinoma	Prospective OS	49 (30)	40 (16)	7
18	Yan et al.	2020	All resections for stage III colon cancer	Randomised controlled trial	98 (45)	98 (51)	3
19	Zurleni et al.	2017	All consecutive curative resections for right colon cancer	Retrospective OS	97	95	7

Abbreviations
RSFPMD: Retrospective study from a prospectively maintained database
OS: Observational study
† Newcastle-Ottawa score for non-randomised studies and Jadad score for randomised studies

Table 2: Recurrence rates and survival of patients

Author and Year	No of patients		Age				Advanced cancer (AJCC III or Duke C)				Local Recurrence				5 year DFS		5 year OS	
	CME	Non-CME	CME	Range	Non-CME	Range	CME	Range	Non-CME	Range	CME		Non-CME		CME	Non-CME	CME	Non-CME
An et al.	34	81	NR				7	20.6%	28	34.6%	NR				94.2%	89.0%	100%	89.5%
Bertelsen et al.	364	1031	71.5	64.3-77.8	73	66-79.9	140	38%	365	35%	NR				NR		74.8%	69.6%
Bertelsen et al.	529	1701	71.7	65-78.3	72.9	66-80.1	194	36.7%	587	34.5%	NR				NR		NR	
Galizia et al.	45	58	67	13	68	11	19	42.2%	20	34.5%	0	0	12	20.7%	90%	74%	NR	
Gao et al.	220	110	68	58-77	73	57-79	94	42.7%	42	38.2%	NR				NR		NR	
Ishihara.	3756	2185	64	-	67.5	-	1616	43%	562	25.7%	NR				91.0%	93.5%	NR	
Karachun et al.	56	43	NR				37	66%	22	51%	NR				NR		NR	
Kotake et al.	6580	3518	62.2	-	65.01	-	2906	44.2%	1397	39.7%	NR				NR		79.2%	74.6%
Kotake et al.	774	659	NR				172	22.2%	129	19.6%	NR				NR		91.7%	90.3%
Merkel et al.	1099	920	66.7	-	64	-	370	33.7%	382	41.5%	146	13.3%	204	22.2%	78.0%	73.4%	78%	73.4%
Prevost et al.	71	84	73.6	33-88.9	73.8	21-88.9	18	30.5%	33	46.5%	NR				NR		NR	
Rinne et al.	325	340	72	11	72	18	124	38.5%	122	35.9%	NR				85.6%	89.2%	72.9%	77.9%
Sammour et al.	141	56	64	12	64	14	48	34%	15	26.8%	0	0	1	1.8%	79.2%	84.4%	77.8%	62.4%

Storli et al.	84	105	72.5	11.3	72.6	12.6	0	0	0	0	1	1.2%	3	2.9%	82.3%	64.8%	87.9%	66.1%
Tagliacozzo et al.	60	84	63	6.5	61	7	26	43.3%	32	38.1%	NR				43.8%	36.3%	64.3%	62.8%
Thorsen et al.	49	49	67	27-75	65	28-75	NR				NR				NR		NR	
West et al.	49	40	68	60-79	76	67-80	20	40.8%	20	50.0%	NR				NR		NR	
Yan et al.	98	98	59.5	10.1	60.7	9.8	98	100%	98	100%	NR				59.8%	49.9%	73.8%	47.7%
Zurleni et al.	97	95	71	-	73	-	32	33%	33	34.7%	NR				NR		NR	

Figure Legends

Figure 1: Study Selection from PRISMA Guidelines

Figure 2: Pooled odds ratio of vascular injury

Figure 3: Pooled odds ratio of local recurrence

Figure 4: Pooled odds ratio of distant recurrence

Figure 5: Pooled relative risk of 5-year overall survival

Figures 6: Algorithm for patient selection for CME

Supporting information: Additional statistical data

Author's contribution

Contributions	**By which author**
Substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data	All authors
Drafting and revising the article	All authors
Final approval of the version to be published	All authors

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