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Complete Mesocolic Excision in Colon Cancer: A Systematic Review and Meta Analysis

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Abstract

Objectives: To compare the outcomes of patients undergoing open and laparoscopic right hemicolectomy with complete mesocolic excision to outcomes following standard open and laparoscopic right hemicolectomy.

Introduction: The surgical treatment of colorectal cancer stands at a crossroads with alternative strategies for lymphadenectomy currently being evaluated. Right hemicolectomy and complete mesocolic excision is an alternative to standard right hemicolectomy.

Design, methods and data sources: The preferred reporting items for systematic reviews and meta analyses guidelines were followed in undertaking this study. Medline was searched to identify all studies describing open and laparoscopic right hemicolectomy with complete mesocolic excision from 2008 to 2018. Statistical analysis was performed using the 'Meta' and 'Metafor' packages in R statistical software.

Study selection: Systematic review and meta analysis.

Patients: A total of 1,048 adult male and female patients with age ranges from 35 to 96 years were evaluated during this study.

Primary and secondary outcome measures: This study aims to evaluate open and laparoscopic right hemicolectomy with complete mesocolic excision and compare 30 day morbidity and mortality, duration of surgery, intra operative blood loss, lymph node harvest, disease free survival, local recurrence and rates of anastomotic leaks to similar outcomes following standard open and laparoscopic right hemicolectomy to determine whether this technique should be the recommended nodal harvesting strategy during right hemicolectomy.

Setting: Not applicable

Results: 14 studies with a total of 1,048 patients were included in this review. Complete mesocolic excision offered reduced local recurrence (2% *vs.* 14%) and improved disease free survival (95% *vs.* 75.8%), however duration of surgery and post operative stay were increased (130 to 288 *vs.* 130 min) and (8 days vs. 5 days) respectively.

Conclusion: Complete mesocolic excision might upstage and could improve prognosis in colorectal cancer, however this procedure could increase patient morbidity and mortality. Further research is necessary to definitively evaluate this technique.

Keywords: Colon cancer; Right hemicolectomy; D2 lymphadenectomy; Complete mesocolic excision; CME; Hohenberger

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Introduction

Patients with early stage colorectal cancer have 5 yr survival rates of between 82% and 93%; this decreases to 59% in the presence of lymph node metastases [1]. Traditionally a segmental colectomy with D2 lymphadenectomy (high ligation of feeding artery, i.e. ileocolic pedicle in right hemicolectomy) was performed based on the oncological principle that local control of disease determined survival. Lymphadenectomy was performed for pathological staging purposes and prognostication, rather than actual survival benefits [2].

Of the patients with stage 2 and stage 3 colorectal cancers who are treated with potentially curative surgery, 20% to 30% will die of this disease within 5 yrs; this may be explained by under-staging of the disease due to an insufficient lymph node yield [3].

Decisions regarding adjuvant chemotherapy are largely based on nodal status. Adjuvant chemotherapy in patients with lymph node infiltration has decreased mortality by more than 30% [4].

The American Joint Committee on Cancer (AJCC) recommends analyzing at least 10 to 14 lymph nodes for accurate staging of disease [5]. Lower lymph node harvests may under stage disease resulting in patients potentially not receiving adjuvant therapy [6].

Right hemicolectomy and CME is an alternative to standard right hemicolectomy with D2 lymphadenectomy.

Right hemicolectomy and CME

A standard right hemicolectomy for a caecal or ascending colon cancer involves either a laparoscopic or an open procedure with removal of the distal ileum, caecum, ascending colon and proximal transverse colon including the mesentery with high ligation of the ileocolic, right colic (when present) and right branch of the middle colic arteries with removal of central (D2) lymph nodes [6].

Right hemicolectomy with CME was introduced by Hohenberger in 2008 [7].

This procedure can be performed *via* open or laparoscopic surgery. In CME the dissection commences laterally by identifying the lateral peritoneal fold; an embryonic fusion plane that facilitates mesofascial and retrofascial separations. Anatomically and histologically, there is a single fascial layer separating the overlying mesocolon from the underlying retroperitoneum (Toldt's fascia). The dissection continues medially in the mesofascial interface. The mesenteric root up to the origin of the superior mesenteric pedicle is mobilized, and the dissection continues over the duodenum and pancreatic uncinate process to allow complete access to the superior mesenteric vein, as well as to the medially and inferiorly located superior mesenteric artery. Continuing medially, the small intestinal mesentery, ileocecal junction, right colon, right mesocolon and mesenteric confluence are fully mobilized and entirely intact from the underlying fascia and retro-peritoneum. The autonomic nervous plexus is identified and preserved. After the complete mobilization, the ligation of the supplying vessels follows. Initially, the ileocolic and the right colic vessels (if present) are divided at their origin from the superior mesenteric vessels. Sharp dissection is then carried out centrally along the superior mesenteric artery, ensuring clearance of all associated lymph nodes. To expose the middle colic vessels; the lesser sac is entered by breaching the omentum caudal to the gastroepiploic arcade. For caecal and ascending colon cancers, only the right branch of the middle colic vessels is divided. The transverse mesocolon dissection is continued vertically to meet the dissection along the superior mesenteric vascular pedicle, producing a rectangular specimen with an intact mesocolic envelope containing all central lymph nodes. At that point, the colon is divided at the level of the middle colic vessels [7].

Since introducing colectomy with CME into routine practice Hohenberger has reduced local recurrence rates from 6.5% to 3.6% and increased 5 yr cancer related survival from 82.1% to 89.1% compared to standard right hemicolectomy with D2 lymphadenopathy [7].

Despite these impressive results international uptake of this technique has been less than enthusiastic. This may be because this procedure is more technically challenging with a longer duration of surgery than that of standard right hemicolectomy [8]. Further resistance to the widespread utilization of this technique is based on claims that the procedure may be associated with increased patient morbidity and mortality [9].

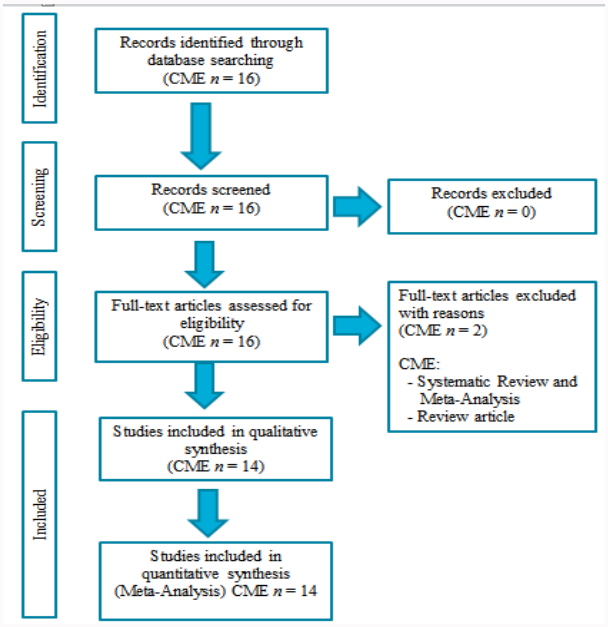

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow chart utilized in this study.

This study aims to evaluate the technique of open and laparoscopic right hemicolectomy with CME and compare outcomes of this technique to those of standard open and laparoscopic right hemicolectomy to determine whether this technique should be the recommended surgical resection for right hemicolectomy.

Methods

Inclusion and exclusion criteria

The Preferred Reporting Items for systematic Reviews and Meta Analyses (PRISMA) guidelines were followed in undertaking this sytematic review and meta-analysis (Figure 1) [10].

The MOOSE checklist was used when writing this systematic review and meta-analysis [11]. All published studies on open or laparoscopic right hemicolectomy with CME from 2008 until 2018 were reviewed. Studies were included that measured any or all of the following primary and/or secondary outcomes: 30 day morbidity, 30 day mortality, anastomotic leak, intra operative blood loss, 5 yr overall survival, disease free survival, local recurrence, length of surgery, post operative ileus, duration of post operative stay and number of lymph nodes harvested. Definitions of the end-points were based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [12]. 30 day morbidity was defined as significant morbidity (intra-abdominal abscesses, post operative bleeding, respiratory complications and wound infection) within 30 days of surgery that required conservative, operative or radiological management. Anastomotic leak required evidence from either a CT scan or an intra operative diagnosis. Ileus was defined as an inability to tolerate an oral diet more than 24 h after the operation, despite regular anti-emetics; or dilatation of the bowel on CT scan without a mechanical transition point, requiring placement of a nasogastric tube.

Systematic reviews and Meta-analyses, editorial comments,

Tables 1: Data from studies examining right hemicolectomy with complete mesocolic excision.

Right Hemicolectomy with CME														
Study	**Patient Age (Yrs.)**	**BMI (kg/m²)**	**Patient Numbers**	**30 Day Morbidity**	**30 Day Mortality**	**Anastomotic Leak**	**Intra-op Blood loss**	**5yr overall Survival**	**Disease free Survival**	**Local Recurrence**	**Length of Surgery (Minutes)**	**Post - op ileus**	**Post - op length of stay**	**LN Harvested**
Wu QB [18]	61	22	31	0	0	0	45 mLS	N/R	N/R	N/R	130	4days	6 days	34
Xie D [19]	57	22	36	25%	0	0	5 mLs	100% at 12 months	100% at 12 months	0 at 12 months	N/R	Feb-36	10 days	20
Matsuda T [20]	N/R	N/R	28	0	0	N/R	15 mLs	N/R	100% at 17 months	0 at 17 months	208	N/R	N/R	21
Uematsu D [21]	73	22 - 32	35	11	0	0	20 mLs	N/R	N/R	3 at 14 months	263	2days	7 days	34
Kim CW [22]	66.4	23.5	64	11%	0	0	50 mLs	N/R	N/R	0 at 20.1months N/R	178.7	3days	6 days	28.4
Benz S [23]	70.7	25.1	28	N/R	0	0	N/R	N/R	N/R		202.5	N/R	8 days	59
Huang JL [24]	56	N/R	102 (53 Lap, 49 open)	4%	0	0	94 mLs	N/R	100% at 24 months	0 at 24 months	194	3 days	11 days	14
Matsuda T [25]	N/R	N/R	18	0	0	0	82 mLs	N/R	100% at 24 months	0 at 24 months	288	N/R	N/R	24
Melich G [26]	63.7	23.3	81	3.60%	0	2.50%	116 mLs	N/R	N/R	N/R		N/R	N/R	31.3
Kang J [27]	66	23.5	128	4.60%	0	0	N/R	N/R	7 recurrences in 25.5 months	0 at 25.5 months	192	3d ays	5 days	28
Ogino T [28]	55	22.9	81	N/R	N/R	N/R	57.1 mLs	N/R	N/R	N/R	181.5	N/R	N/R	21.6
Galizia G [29]	67 - CE 68 - D2	26-CME 25-D2	45 - CME **58 - D2**	13% - CME **12% - D2**	0 - CME **0 - D2**	2 - CME **3 - D2**	280 mLs - CME 200 mLs - D2	93.3% - CME 75.8% - D2	93.3% - CME 75.8% - D2	13% - CME 14% - D2	178 - CME 130 - D2	N/R	N/R	20 - CME **15 - D2**
Bertelsen CA [30]	70.2 - CME 72.6 - D2	N/R	198 93 - CME **105 - D2**	26.90%	6.5% - CME **7.6% - D2**	8.6% - CME 7.6% - D2	250 mLs - CME 270 mLs - D2	N/R	N/R	N/R	N/R	N/R	5 days - CME 4 days - D2	26.7 - CME 24.5 - D2
Pramateftakis MG [31]	65.6	N/R	115	13%	0	0.90%	N/R	72.40%	72.40%	0.90%	N/R	N/R	N/R	N/R

reviews and responses to articles were excluded. Studies were restricted to those published in the english language.

Search and selection strategy

A search of Medline *via* Pubmed and Medline *via* Ovid SP was undertaken to identify all studies describing the use of 'open or laparoscopic CME and right hemicolectomy' in patients with colorectal cancer. The search terms used were: 'complete mesocolic excision and right hemicolectomy' searched as both keywords and MeSH headings where available. Search results were first screened by title and abstract, after which the full texts of potentially relevant articles were retrieved and underwent a further round of screening for inclusion. The references of included studies and relevant review articles were manually searched for additional suitable publications.

Inclusion criteria were:

- All publications evaluating patients with colorectal cancer undergoing open or laparoscopic right hemicolectomy with complete mesocolic excision
- Adult patients only
- Studies in the English language only
- Studies published in full form in peer-reviewed literature

Data extraction and validity assessment

Data was extracted and quality control was performed by the author. Any discrepancies in the data were resolved by involvement of the senior author. Where additional data was required, the corresponding author of the relevant article was contacted by email in an attempt to obtain the necessary data.

For each included article, the following data and outcomes were extracted in a structured information sheet: author of study, study design, study centre/country, type of resection, use of Enhanced Recovery After Surgery (ERAS) protocol [13], primary outcome, follow-up duration, main findings from the study. Additionally data was collated on: patient demographics (age, Body Mass Index [BMI]), numbers of patients in the study, 30 day morbidity, 30 day mortality, rates of anastomotic leak, volume of intra operative blood loss, 5 yr overall survival, disease free survival, local recurrence, length of surgery, duration of post operative ileus, post operative duration of hospital stay and the number of lymph nodes harvested (Table 1).

Data analysis

Outcome measures were calculated as pooled proportions of patients (with 95% confidence intervals) developing the outcomes of interest. The fixed effects (Mantel-Haenszel) and random effects (Der Simonian-Laird) models were used for pooling [14].

Heterogeneity was determined using the Q statistic of I^2 which describes the percentage of total variation across studies attributable to heterogeneity rather than to chance [14]. An I^2 value of 0% to 25% was taken to represent low heterogeneity, 26% to 50% moderate heterogeneity, and values above 50% represented high heterogeneity. Heterogeneity was assessed by examining the Forest plots for obvious outliers and by attempting appropriate subgroup analyses. In general, the fixed effects model was used in analyses with low heterogeneity while the random effects model was used in instances of high heterogeneity. Statistical analysis was carried out using the 'Meta' and 'Metafor' packages in R statistical software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [15,16]. Quality assessment of the included studies was carried out using the NHLBI Study Quality Assessment Tools for Observational Cohort and Cross-Sectional Studies and Case-Control Studies [17].

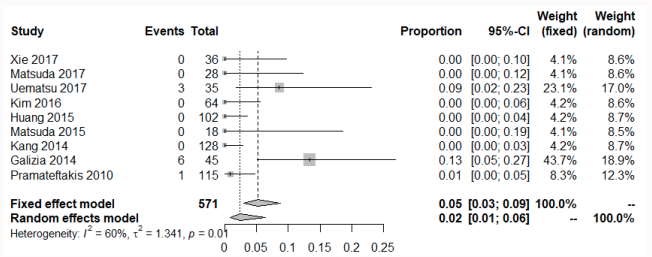

Figure 2: Forest plot displaying the results of the Meta-analysis analysing local recurrence rate with right hemicolectomy and CME.

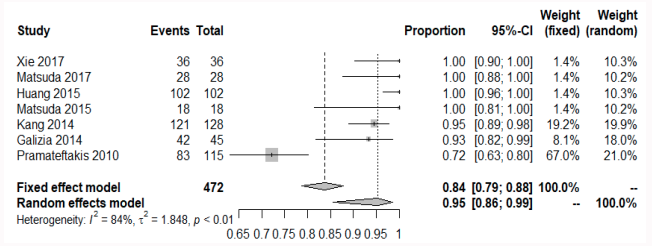

Figure 3: Forest plot displaying the results of the meta analysis on disease free survival with right hemicolectomy and CME.

Results

Selection and quality assessment

Sixteen studies were retrieved from the initial search, however after removal of one Systematic review and Meta analysis and one review article, 14 studies remained for the systematic review (Figure 1).

All studies were published between 2008 and 2018. The majority of the studies were conducted in Japan, China and South Korea. Patient ages ranged from 35 to 96 yrs and BMIs ranged from 16.9 kg/m^2 to 40.5 kg/m^2. A total of 1,048 patients across the included studies underwent right hemicolectomy with CME (Table 1).

Meta analysis: Right hemicolectomy and CME

Local recurrence: Using the random effects model, the pooled proportion of local recurrence was 2% with a 95% confidence interval of 1% to 6% (Figure 2). This compares to a local recurrence following right hemicolectomy and D2 lymphadenectomy of 14% as reported in the study by Galizia et al. [29].

Disease free survival: In patients undergoing right hemicolectomy and CME, pooled disease free survival was 95% (confidence interval 86% to 99%) using the random effects model (Figure 3). This compared to a disease-free survival of 75.8% following standard right hemicolectomy as reported in the study by Galizia et al. [29].

Anastomotic leak: Using the fixed effects model, the pooled proportion of patients developing post operative anastomotic leak was 4% with a 95% confidence interval of 2% to 6% (Figure 4). This compares to an anastomotic leak following standard right hemicolectomy and D2 lymphadenectomy of 7.6% in the study by Bertelsen et al. [30].

30 day mortality: Using the fixed effects model, the pooled 30 day mortality in patients undergoing right hemicolectomy and CME was 2% with a 95% confidence interval of 1% to 4% (Figure 5). This compares to a 30 day mortality of 7.6% following right hemicolectomy with D2 lymphadenectomy as reported in the study by Bertelsen et al.

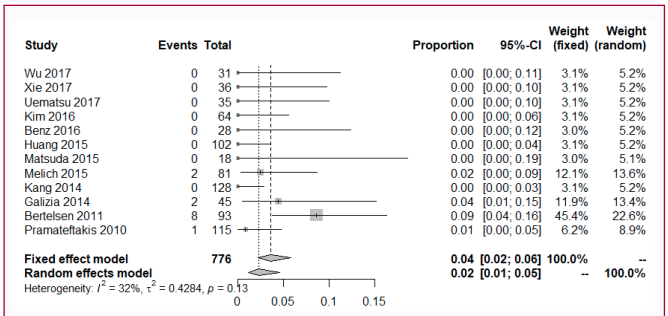

Figure 4: Forest plot demonstrating the results of the meta analysis on anastomotic leak following right hemicolectomy and CME.

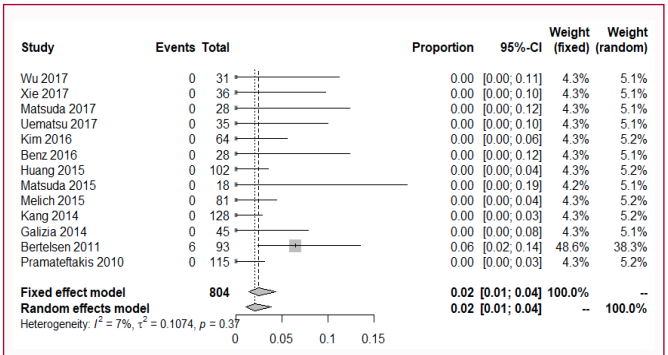

Figure 5: Forest plot displaying the results of the meta analysis on 30 day mortality following right hemicolectomy and CME.

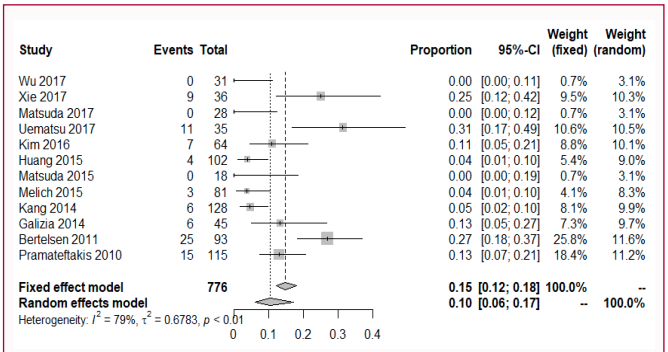

Figure 6: Forest plot displaying the results of the meta analysis on 30 day morbidity following right hemicolectomy and CME.

[30].

30 day morbidity: Using the random effects model, the pooled 30 day morbidity following right hemicolectomy and CME was 10% with a 95% confidence interval of 6% to 17% (Figure 6). This compared to a 30 day morbidity of 12% following right hemicolectomy and D2 lymphadenectomy as reported in the study by Galizia et al. [29].

Discussion

This systematic review and meta analysis has analysed all peer reviewed studies printed in English on the subject since Hohenberger first described the procedure in 2008 [7]. To date no randomised controlled trials exist that compare right hemicolectomy and CME with right hemicolectomy and standard D2 lymphadenectomy, however the data presented represents a combined patient number of 1,048 and hence accurate meaningful, results and conclusions can be drawn from this review.

This Meta analysis calculates that the pooled 30 day morbidity

of 10% for right hemicolectomy with CME is better than the 30 day morbidity of 12% quoted by Galizia et al. [29] for standard right hemicolectomy.

The pooled 30 day mortality of 2% in patients undergoing right hemicolectomy with CME is much better that the 30 day mortality of 7.6% following standard right hemicolectomy reported in the study by Bertelsen et al. [30].

The meta analysis also concluded that the pooled proportion of patients developing post operative anastomotic leak was 4% and this is an improvement on the rates of anastomotic leak of 7.6% following standard laparoscopic right hemicolectomy in the study by Bertelsen et al. [30].

Much of the resistance to right hemicolectomy with CME is based on concerns regarding a more dangerous surgical resection with increased intra operative blood loss compared to standard right hemicolectomy with D2 lymphadenectomy. This Systematic review does not however support an increased intra operative blood loss with right hemicolectomy and CME compared to standard right hemicolectomy with average intra operative blood loss ranging from only 5 mls to 280 mls.

Surgeons who are opposed to right hemicolectomy with CME argue that this procedure is associated with a prolonged intra operative duration, causes a prolonged post operative ileus, and leads to a prolonged post operative duration of stay.

This systematic review records a duration of surgery of between 130 min and 288 min for laparoscopic right hemicolectomy with CME compared to 130 min for standard right hemicolectomy suggesting there is a marked increase in operating time for CME. However this does not appear to predispose to an increase in morbidity or mortality.

Certainly the proponents of right hemicolectomy with CME argue that it is associated with increased 5 yr survival, improved disease free survival, reduced local recurrence and an increased lymph node harvest. These claims are supported by this Systematic review and Meta analysis.

Five yr overall survival was reported in the study by Galizia et al. [29] as 93.3% in those patients who had underwent right hemicolectomy with CME *vs.* 75.8% in those who had underwent right hemicolectomy with standard D2 lymphadenectomy. The results from this systematic review confirm a significant improvement in 5 yr overall survival when right hemicolectomy with CME is performed compared to standard right hemicolectomy.

The Meta analysis calculated a disease free survival of 95% which is an improvement in the disease free survival of 75.8% following standard right hemicolectomy as reported in the study by Galizia et al. [29].

In addition when right hemicolectomy with CME was performed the pooled proportion of local recurrence was 2% which is certainly an improvement on the local recurrence following standard right hemicolectomy of 14% as reported in the study by Galizia et al. [29].

This review demonstrates a significant variation in the number of lymph nodes harvested, this ranged from 14 nodes in the study by Huang et al. [24] to 59 nodes in the study by Benz et al. [23]. This compares to an average number of lymph nodes harvested of 15 during standard right hemicolectomy reported in the study by Galizia et al. [29]. The increased number of lymph nodes retrieved during right hemicolectomy with CME may be the reason that 5 yr survival and disease free survival are higher and why local recurrence is lower than that observed with standard right hemicolectomy.

This review recorded a post operative duration of stay of between 5 and 11 days following right hemicolectomy with CME. In the study by Bertelsen et al. [30] patients who had undergone standard open right hemicolectomy remained in hospital for only 4 days post operatively.

This systematic review and meta analysis gives a thorough evaluation of the literature currently available comparing standard right hemicolectomy *vs.* right hemicolectomy with CME, however this study has several limitations.

This systematic review and meta analysis examined all peer review studies published in the English language over the ten yr period from 2008 until 2018. Studies from 2008 were examined during the literature review as this was when Hohenberger published his results on right hemicolectomy with CME [7]. It is possible that earlier reports of a similar technique to that described by Hohenberger are available in the literature and by reviewing the literature from 2008 onwards these have been inadvertently omitted.

Bertelsen et al. [32] in a Danish population based study published in 2015 concluded that colectomy with CME is associated with better disease free survival than conventional colon cancer resection for patients with stage I to III colon adenocarcinoma, and based on this study Bertelsen et al. [32]. Suggested that colectomy with CME might improve outcomes for patients with colon cancer. The results of this study are supported by the results of this meta-analysis but this study examined the outcomes of right hemicolectomy and CME only whilst Bertelsen et al. [32]. Examined the outcomes of all colonic cancers following colectomy and CME. A further limitation of this systematic review and meta analysis is the language bias that has been introduced. By examining all peer reviewed literature published in the English language only, potentially important studies may have been omitted.

An additional criticism of this paper is the lack of a suitable control as there is a paucity of recent literature examining right hemicolectomy with D2 lymphadenectomy. Hence the controls were generated from the papers examining right hemicolectomy with CME and we accept the limitations of this comparison and acknowledge that this may have introduced bias with interpretation of results and conclusions generated.

Conclusion

The alternative nodal harvesting technique during right hemicolectomy with CME has many advantages but certainly there are obvious disadvantages and clear risks associated with this technique. This is especially the case in the United Kingdom patient cohort who tend to have elevated BMIs. To thoroughly and appropriately evaluate this techniques, it is would be essential to analyse the results of a double blind randomised control trial comparing right hemicolectomy and CME with standard right hemicolectomy.

The 'Radical Extent of lymphadeneactomy D2 dissection *vs.* complete mesocolic excision of Laparoscopic Right Colectomy For Right-Sided Colon Cancer (RELARC)' trial is currently being undertaken [1]. This is a prospective, multi centre, randomised controlled trial in which 1,072 eligible patients will be randomly assigned to the CME or the D2 lymphaenectomy group. This trial

will evaluate 3 yr disease free survival, 3 yr survival, post-operative complication rates, peri-operative mortality rates and numbers of positive central lymph nodes. The results of this randomised controlled trial will provide level 1B evidence on the optimal extent of lymphadenectomy during laparoscopic segmental colectomy and allow definitive conclusions to be made regarding oncological outcome and peri operative safety.

Summary of Findings

In reviewing the literature and the data from this systematic review and meta analysis this study concludes that right hemicolectomy with CME offers comparable 30 day morbidity and mortality and an improved 5 yr survival with a substantially reduced local recurrence rate due to an increased lymph node harvest compared to standard right hemicolectomy. The procedure is however associated with an increased duration of surgery and prolonged post operative inpatient stay, however with continued experience with the procedure both operating time and post operative duration of stay will be reduced and as such the technique of right hemicolectomy and complete mesocolic excision should be considered by the colorectal surgical fraternity.

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