CME versus D3 Dissection for Colon Cancer

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Abstract

Keywords

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Over the past 30 years, rectal cancer surgery has been standardized by total mesorectal excision. More recently, some have suggested that colon cancer surgery should be standardized by complete mesocolic excision (CME) with central vascular ligation (CVL), especially in Western countries. Surgeons undertaking CME with CVL report optimal outcomes. Sharp dissection within the embryological plane and high vascular ligation at the vessel origin are essential. In Japan, a similar concept, D3 dissection, has been adopted for decades. Although both surgical procedures are similar, distinct differences exist. Some surgeons are confused about the principles and practice of these two procedures. As well as overviewing the theory behind CME with CVL and D3 dissection, the technical details of both procedures are described.

The concept of total mesorectal excision (TME) was proposed by Heald, following the observation that local recurrence of rectal cancer could arise from residual cancer deposits in the distal mesorectum.^{1–3} At the same time, Quirke et al showed that incomplete tumor resection at the circumferential resection margin predicted a high rate of local recurrence, which was associated with poorer planes of surgery.^{4,5} Since TME decreased local recurrence rates with a long follow-up,² many institutions adopted TME as the standard surgery for rectal cancer. The standardization of the surgical procedure for rectal cancer led to better prognosis and the outcomes after rectal cancer surgery overtook those for colon cancer surgery in some countries.^{6,7} Therefore, the most appropriate surgical procedure for colon cancer was desired. West et al reported the marked variability in the plane of surgery achieved in colon cancer with nonstandardized surgery.⁸ Their study suggested that improving the plane of dissection into the mesocolic plane might improve survival in patients with colon cancer. Hohenberger et al applied the concept of TME to colon cancer and proposed complete mesocolic excision (CME) with central vascular ligation (CVL), in which surgeons performed meticulous dissection in the mesocolic plane with ligation of the supplying vessel at its origin to remove all of the lymph nodes in the regional mesocolon.⁹

Following the excellent outcomes reported by Hohenberger, many institutions adopted CME with CVL as the standard surgical procedure for colon cancer.¹⁰

In Japan, D3 dissection has been standard procedure for colon cancer for several decades. Although the extent of lymph node dissection can be changed according to the patient's condition, the Japanese guidelines 2016 for the treatment of colorectal cancer recommend D2 dissection for T1 tumors and D3 dissection for T2 to T4 tumors.¹¹ The Japanese Classification of Colorectal Carcinoma is a rule-book of colorectal cancer management in Japan, and describes staging, classification of lymph nodes, surgical procedures, pathology, handling of specimens, and so on.¹² Every regional lymph node station is numbered and classified into pericolic, intermediate, or main lymph nodes. D3 dissection includes all regional lymph nodes around the tumor. A recent study, JCOG0205, a noninferiority study comparing oral with infusional fluorouracil with leucovorin as adjuvant chemotherapy for stage III colorectal cancer, demonstrated a 5-year overall survival rate of 87.5% in patients with D2/D3 dissection.¹³ In JCOG0205, 25 and 74% of patients underwent D2 and D3 lymph node dissection, respectively. The patients diagnosed with T1 cancer preoperatively usually underwent D2 dissection.

The aim of this article is to clarify both the similarities and differences between CME with CVL and D3 dissection from the point of view of a surgeon and a pathologist.

Evaluation of Plane in Colon Cancer Surgery

The plane of surgery is one of the most important factors to predict prognostic outcomes in patients undergoing curative resection for colon cancer. It should be evaluated objectively by a pathologist, preferably on the whole fresh specimen. The plane of colon cancer surgery is classified as mesocolic plane (intact mesocolon), intramesocolic plane (significant mesocolic defects that do not expose the muscularis propria), or muscularis propria plane (significant and extensive defects that expose areas of muscularis propria).^{8,14,15} A permanent record of the plane of surgery should be captured by taking photographs of the surgical specimen.

Surgical Procedure of CME with CVL

The concept of CME with CVL consists of mobilization of the colon and mesocolon within the embryological mesocolic plane with a full regional lymph node dissection including central ligation of the supplying vessels.⁹ Sharp dissection of the visceral fascial layer from the parietal one leads to complete mobilization of the entire mesocolon. In the original manuscript, a Kocher maneuver is performed for right colon cancer. Takedown of the splenic flexure is mandatory for left colon cancer. During these mobilizations, the mesocolon should not be damaged.

For cancer of the right and transverse colon, the ileocolic vessels are divided after complete mobilization. Next, the right colic vessels are divided if present. Only the right branch of the middle colic vessels is divided for cancer of

the cecum and ascending colon. However, the middle colic vessels are divided at their root for hepatic flexure and transverse colon cancer. The left colic artery is divided at its root for descending colon cancer. The root of the inferior mesenteric artery is usually preserved. The inferior mesenteric vein is divided below the pancreas. For sigmoid colon cancer, the inferior mesenteric artery is divided at its root.

Surgical Procedure of D3 Dissection

The concept of D3 dissection is similar to CME with CVL. The Japanese Classification of Colorectal Carcinoma defines the extent of lymph node dissection from D0 to D3 as below.

D0: incomplete dissection of pericolic lymph nodes

D1: complete dissection of pericolic lymph nodes

D2: complete dissection of pericolic and intermediate lymph nodes

D3: complete dissection of all regional lymph nodes

As a general rule, both proximal and distal margins should be 10 cm beyond the tumor to remove the regional lymph nodes. However, the longitudinal resection margin also depends on the location and number of the feeding artery.

With D3 dissection, only the ileocolic vessels are divided for cecal cancer if the right colic vessels are not present (►Fig. 1). During right hemicolectomy with D3 dissection for cancers beyond the cecum, the ileocolic vessels, the right colic vessels if present, and the right branch of the middle colic vessels are divided. Lymph node dissection along the surgical trunk, that is, the superior mesenteric vein between the ileocolic vein and the gastroduodenal trunk, is mandatory for right hemicolectomy with D3 dissection. The lymph nodes around the root of the middle colic artery are harvested and the root of the middle colic artery is exposed. Thereafter, the right branch of middle colic artery is divided. The middle

Fig. 1 Schemas describing the extent of bowel resection for cecal cancer in Japanese D3 dissection (A) and complete mesocolic excision with central vascular ligation (B).

colic vein usually branches cranial to the middle colic artery. There exist many variations in the branching of the middle colic vein. The middle colic vein is usually divided at the root or at the same ligation level as the artery. When the feeding artery of a transverse colon cancer is both the left and right branches of the middle colic artery, the middle colic vessels are divided at the root. When a transverse colon cancer is located near the splenic flexure, the left branch of the middle colic vessels and the left colic vessels is divided. The main nodes around the root of the middle colic artery and the inferior mesenteric artery are also harvested. The inferior mesenteric artery is usually preserved. The inferior mesenteric vein is usually divided below the pancreas.

The inferior mesenteric artery is usually divided at the root for sigmoid colon cancer. However, the inferior mesenteric artery is sometimes divided below the left colic artery to preserve proximal blood flow as much as possible. In such a case, the main lymph nodes around the root of the inferior mesenteric artery are harvested. The root of the inferior mesenteric artery is exposed during this process.

Impact of CME

Several studies demonstrated that the implementation of CME with CVL for colon cancer improved the quality of surgery and the outcomes. A retrospective Danish study demonstrated that CME surgery was associated with better disease-free survival than conventional colon cancer resection for patients with stage I to III colon adenocarcinoma.¹⁰ In their study, 4-year disease-free survival for patients with Union for International Cancer Control (UICC) stage I disease in the CME group was 100% compared with 89.8% (83.1–96.6) in the non-CME group ($p = 0.046$). For patients with UICC stage II disease, 4-year disease-free survival was 91.9% (95% confidence interval [CI]: 87.2–96.6) in the CME group compared with 77.9% (71.6–84.1) in the non-CME group ($p = 0.0033$), and for patients with UICC stage III disease, it was 73.5% (63.6–83.5) in the CME group compared with 67.5% (61.8–73.2) in the non-CME group ($p = 0.13$). Merkel et al reported that the implementation of CME for colon cancer improved the quality indicators of process and outcome quality over 30 years.¹⁶ In stage III colon cancer, the 5-year locoregional recurrence rate decreased from 14.8 to 4.1% ($p = 0.046$) and the 5-year cancer-related survival rate increased from 61.7 to 80.9% ($p = 0.010$) in their study. A Chinese study demonstrated that CME was associated with improved local recurrence-free survival without increasing surgical risks.¹⁷ Surgical teaching programs for CME led to better overall and disease-free survivals in the “Stockholm Colon Cancer Project.”¹⁸

Difference between CME and D3 Dissection

We previously reported the comparison between CME with CVL and D3 dissection.¹⁴ A series of resections for primary colon cancer from one European and two Japanese centers were assessed in terms of the plane of surgery, physical characteristics, and lymph node yields. Mesocolic plane resection rates from both series were high; however, Japanese D3

specimens were significantly shorter (162 vs. 324 mm, $p < 0.001$), resulting in a smaller amount of mesentery (8,309 vs. 17,957 mm², $p < 0.001$) and nodal yield (median, 18 vs. 32, $p < 0.001$). The distance from the high vascular tie to the bowel wall (100 vs. 99 mm, $p = 0.605$) was equivalent. These characteristics were similar between left and right colon. From these results, both surgical plane and vascular high tie were similar between CME with CVL and D3 dissection. However, the length of resected bowel was significantly shorter in D3 dissection than in CME with CVL.

We also compared the specimens of stage III colon cancer between CME with CVL, D3 dissection, and conventional surgery.¹⁹ The length of resected bowel and the area of mesentery were longer and larger in the order of CME with CVL, conventional surgery, and D3 dissection. The length of the vascular tie was similar between CME with CVL and D3 dissection, which was longer than that of conventional surgery. The rate of mesocolic plane excision was equivalent between CME with CVL and D3 dissection, which was higher than that of conventional surgery.

Laparoscopic CME and D3 Dissection

Laparoscopic surgery for colon cancer has prevailed since Jacobs et al reported the first case of laparoscopic colectomy.²⁰ Several studies demonstrated that laparoscopic CME and D3 dissection were comparable to open CME and D3 dissection. A Greek study reported that laparoscopic and open CME with CVL were equivalent except for the length from tumor to high tie and the length from tumor to bowel in transverse colon.²¹ Bae et al reported that laparoscopic CME with CVL was superior to open in short-term outcomes such as the time to soft diet and the length of hospital stay.²² In their study, the 5-year overall survival rates of the open and laparoscopic CME groups were 77.8 and 90.3% ($p = 0.028$), and the 5-year disease-free survival rates were 71.8 and 83.3% ($p = 0.578$), respectively. West et al also demonstrated that laparoscopic CME can be performed to the same standard as open surgery by supervised trainees.²³ A meta-analysis including one randomized and seven case-control trials was reported.²⁴ In their study, there was no difference in short-term mortality (odds ratio = 2.16 [95% CI: 0.73–6.41]; $p = 0.16$), anastomotic leakage, ileus, and deep-seated infection/abscess. There was a trend for longer operative time ($p = 0.05$) and shorter length of hospital stay ($p = 0.09$) with the laparoscopic approach. In addition, no statistically significant difference was found in overall survival (hazard ratio = 0.85 (95% CI: 0.69–1.06); $p = 0.15$), disease-free survival, local recurrence, and distant metastases.

As for D3 dissection, a randomized controlled trial JCOG0404 was conducted to evaluate the noninferiority of laparoscopic D3 dissection compared with open surgery for colon and rectosigmoid cancer.²⁵ In JCOG0404, the patients with stage II or stage III cancer were randomly assigned to laparoscopic ($n = 529$) and open ($n = 528$) D3 dissection group. Noninferiority of laparoscopic D3 dissection was not proven, because the overall survival rates were better than originally expected. The 5-year overall survival in JCOG0404

was 90.4% (95% CI: 87.5–92.6) for open surgery and 91.8% (89.1–93.8) for laparoscopic surgery. Yamamoto et al reported the short-term outcomes in JCOG0404.²⁶ In their study, the conversion rate from laparoscopic to open surgery was 5.4%. The patients assigned to laparoscopic surgery had less blood loss ($p < 0.001$), although laparoscopic surgery lasted 52 minutes longer ($p < 0.001$). Laparoscopic surgery was associated with a shorter time to pass first flatus, decreased use of analgesics after 5 postoperative days, and a shorter hospital stay. Morbidity (14.3 vs. 22.3%, $p < 0.001$) was lower in the laparoscopic surgery arm. From these results, the safety and the better short-term outcomes of laparoscopic CME with CVL and D3 dissection for colon cancer have been established.

The Optimal Surgery for Colon Cancer

The good prognosis after CME with CVL or D3 dissection for colon cancer has been reported.^{9,25} However, the optimal surgery for colon cancer is still unclear and which patients benefit from high ligation is unknown. To solve this problem, a randomized controlled study will be necessary to compare the long-term outcomes between CME with CVL, D3 dissection, and conventional surgery. An international prospective observational cohort study for optimal bowel resection extent and central radicality for colon cancer (T-REX study) is ongoing, including centers undertaking both CME with CVL and D3 surgery. The primary end point of the T-REX study is distribution of metastatic lymph nodes. The second end point is prognostic outcomes according to the length of bowel resection and the central radicality.

Conclusions

An overview of CME with CVL and D3 dissection for colon cancer has been provided. For both techniques, sharp dissection along the embryological plane is essential. The role of pathologists is crucial to validate the plane of colon cancer surgery by assessing the quality of the specimen. At this moment, lymphadenectomy with vascular high tie is promising by either CME with CVL or D3 surgery, with both resulting in optimal outcomes. However, the optimal length of bowel resection for colon cancer is an important issue to be resolved in the future.

Conflict of Interest

None.

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References

- Heald RJ. The 'Holy Plane' of rectal surgery. *J R Soc Med* 1988;81(09):503–508
- Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg* 1982;69(10):613–616
- Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg* 1998;133(08):894–899
- Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986;2(8514):996–999
- Quirke P, Steele R, Monson J, et al; MRC CR07/NCIC-CTG C016 Trial Investigators; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG C016 randomised clinical trial. *Lancet* 2009;373(9666):821–828
- Birgisson H, Talbäck M, Gunnarsson U, Pahlman L, Glimelius B. Improved survival in cancer of the colon and rectum in Sweden. *Eur J Surg Oncol* 2005;31(08):845–853
- Iversen LH, Nørgaard M, Jepsen P, et al; Northern Danish Cancer Quality Assessment Group. Trends in colorectal cancer survival in northern Denmark: 1985–2004. *Colorectal Dis* 2007;9(03):210–217
- West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. *Lancet Oncol* 2008;9(09):857–865
- Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation—technical notes and outcome. *Colorectal Dis* 2009;11(04):354–364, discussion 364–365
- Bertelsen CA, Neuenschwander AU, Jansen JE, et al; Danish Colorectal Cancer Group. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. *Lancet Oncol* 2015;16(02):161–168
- Watanabe T, Muro K, Ajioka Y, et al; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol* 2018;23(01):1–34
- Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma. Tokyo: Kanehara & Co., Ltd.; 2009
- Shimada Y, Hamaguchi T, Mizusawa J, et al. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and leucovorin in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. *Eur J Cancer* 2014;50(13):2231–2240
- West NP, Kobayashi H, Takahashi K, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. *J Clin Oncol* 2012;30(15):1763–1769
- West NP, Sutton KM, Ingeholm P, Hagemann-Madsen RH, Hohenberger W, Quirke P. Improving the quality of colon cancer surgery through a surgical education program. *Dis Colon Rectum* 2010;53(12):1594–1603
- Merkel S, Weber K, Matzel KE, Agaimy A, Göhl J, Hohenberger W. Prognosis of patients with colonic carcinoma before, during and after implementation of complete mesocolic excision. *Br J Surg* 2016;103(09):1220–1229
- Gao Z, Wang C, Cui Y, et al. Efficacy and safety of complete mesocolic excision in patients with colon cancer: three-year results from a prospective, nonrandomized, double-blind, controlled trial. *Ann Surg* 2018
- Bernhoff R, Martling A, Sjövall A, Granath F, Hohenberger W, Holm T. Improved survival after an educational project on colon cancer management in the county of Stockholm—a population based cohort study. *Eur J Surg Oncol* 2015;41(11):1479–1484
- Kobayashi H, West NP, Takahashi K, et al. Quality of surgery for stage III colon cancer: comparison between England, Germany, and Japan. *Ann Surg Oncol* 2014;21(Suppl 3):S398–S404
- Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991;1(03):144–150

- 21 Gouvas N, Pechlivanides G, Zervakis N, Kafousi M, Xynos E. Complete mesocolic excision in colon cancer surgery: a comparison between open and laparoscopic approach. *Colorectal Dis* 2012;14(11):1357–1364
- 22 Bae SU, Saklani AP, Lim DR, et al. Laparoscopic-assisted versus open complete mesocolic excision and central vascular ligation for right-sided colon cancer. *Ann Surg Oncol* 2014;21(07):2288–2294
- 23 West NP, Kennedy RH, Magro T, et al. Morphometric analysis and lymph node yield in laparoscopic complete mesocolic excision performed by supervised trainees. *Br J Surg* 2014;101(11):1460–1467
- 24 Athanasiou CD, Markides GA, Kotb A, Jia X, Gonsalves S, Miskovic D. Open compared with laparoscopic complete mesocolic excision with central lymphadenectomy for colon cancer: a systematic review and meta-analysis. *Colorectal Dis* 2016;18(07):O224–O235
- 25 Kitano S, Inomata M, Mizusawa J, et al. Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2017;2(04):261–268
- 26 Yamamoto S, Inomata M, Katayama H, et al; Japan Clinical Oncology Group Colorectal Cancer Study Group. Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. *Ann Surg* 2014; 260(01):23–30