Int J Clin Exp Med 2017;10(8):11616-11625
www.ijcem.com /ISSN:1940-5901/IJCEM0053087

Original Article

Surgical and pathological outcomes of complete mesocolic excision compared with conventional surgery in right colon cancers

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Received July 1, 2016; Accepted July 3, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: To compare the surgical and pathological outcomes of complete mesocolic excision (CME) with conventional surgery in colon cancers. Methods: 125 patients with right colon cancer received surgical treatment were enrolled in the retrospective study, of whom, 59 underwent CME surgery (CME group) and 66 underwent conventional radical surgery (control group). Surgical specimens of the CME group were then prepared as pathological large format with the complete mesocolon. Hematoxylin-eosin staining and subsequent pathological analyses were conducted. Results: The number of dissected lymph node was larger in the CME group than that in the control group (29.7 ± 6.1 *vs.* 19.3 ± 5.3, $P < 0.05$). Similar results were observed in subgroups of stage I, II, and III colon cancers (25.2 ± 5.7 *vs.* 13.2 ± 5.6, 31.3 ± 7.7 *vs.* 19.6 ± 6.2, 30.3 ± 8.4 *vs.* 25.2 ± 7.2, respectively; $P < 0.05$). And also, larger mesocolon area, longer distance from vascular high ligation point to intestinal wall, and longer distance from vascular high ligation point to tumor center were observed in CME group ($P < 0.05$). The pathological large format could be used to identify mesenteric lymphatic metastasis (59.32%) and observe the dynamics of continuous and skip metastases of colon cancer along with the lymphatic vessels in a single slice. Conclusions: CME is appropriate in colon cancer surgery and it reveals the status of lymph node metastasis more precisely. The pathological large format is potential for illustrating the biological behavior of colon cancer. This technique is worth considering as a quality control standard for colon cancer surgery.

Keywords: Colon cancer, complete mesocolic excision, fusion fascia, pathological large format, circumferential resection margin

Introduction

In recent years, the incidence and mortality rates of colon cancer have gradually risen and rank the third among all malignant tumors [1]. In 1982, Heald et *al.* identified the importance of the mesorectum (i.e., the mesentery supporting the rectum) in the recurrence of rectal cancer, and proposed the surgery strategy of total mesorectal excision (TME) [2]. Then in 1986, Quirke *et al.* proposed a concept of circumferential resection margin (CRM) for rectal cancer to prevent lateral spread of the tumor, decrease subsequent local recurrence, and improve the prognosis [3].

Complete mesocolic excision (CME) was firstly applied in treatment of colon cancer by Hohenberger and his colleagues in 2009 [4], who also suggested that CME should be considered as standard strategy in the surgical management of colon cancer. Their retrospective study revealed that CME could minimize intraperitoneal tumor dissemination, resulting in lower local recurrence rates and better survival outcomes. However, CME is still considered to be at a preliminary stage. More evidences are required to verify the existence of a complete posterior mesocolic fusion fascia and its potential for tumor invasion and diffusion. Furthermore, no quality assessment of CME including the circumferential margin has been reported.

Materials and methods

Subjects

A total of 125 patients undergoing surgery for right colon cancer from January 1, 2012 to

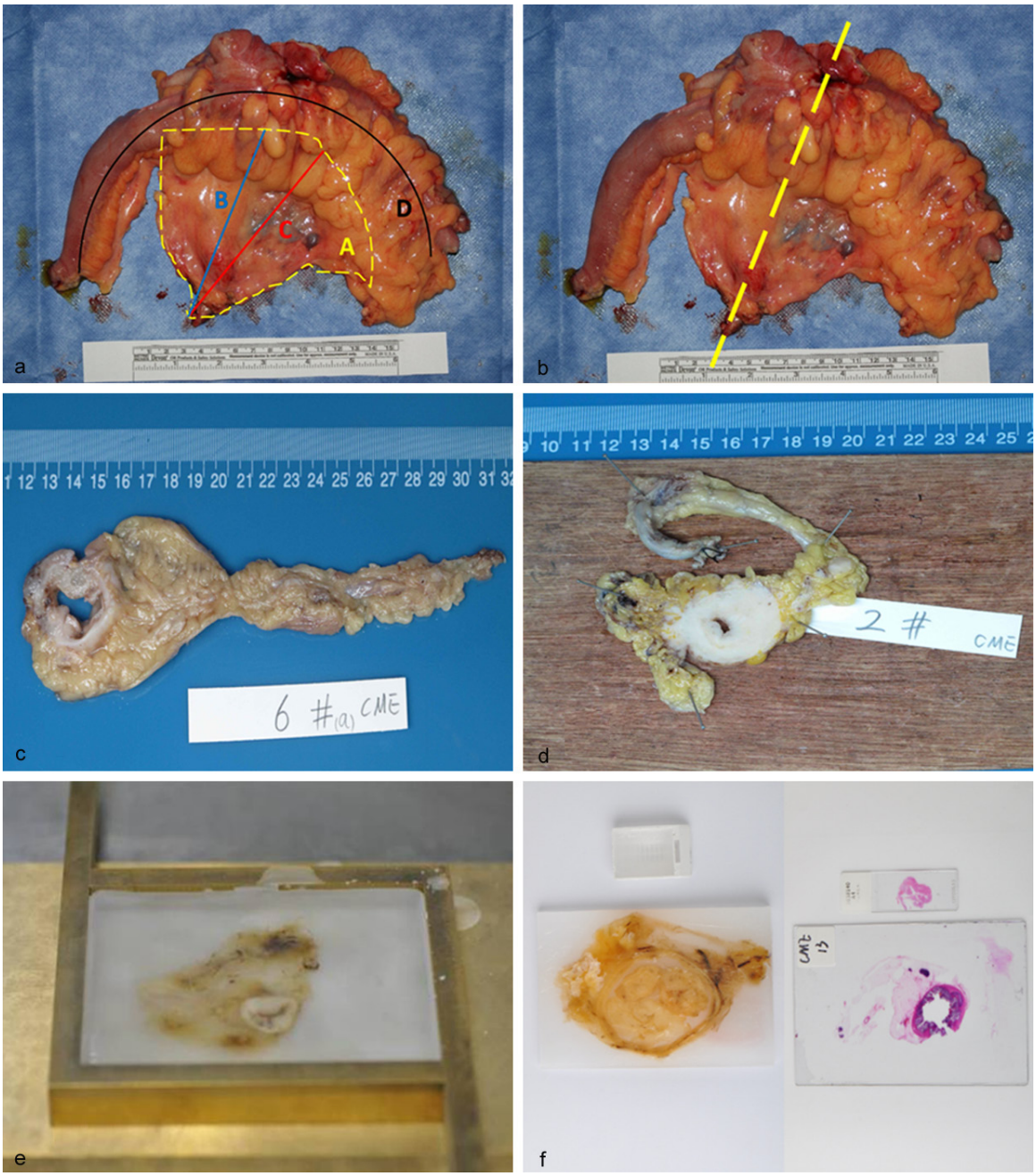

Figure 1. (a and b) A high ligation of vessels was conducted along the intestinal coronal arteries at the mesangial stem and the stump specimens was collected; A. The area of mesentery (area within yellow dash line); B. The distance between tumor and vessel ligation (blue line); C. The shortest distance between tumor and colon wall (red line); D. The length of dissected colon (black line); The dissection for fixed sample (yellow dash line in b). (c-e) The fresh specimens were fixed. (f) The comparison of pathological large section and routine section.

January 1, 2015 in Beijing Friendship Hospital Affiliated to the Capital University of Medical Sciences were retrospectively enrolled in this study.

The inclusion criteria for the study: cancer of the ileocecum, ascending colon, or hepatic flexure of the colon without preoperative distant metastasis; no history of abdominal surgery; patients underwent open or laparoscopic surgery within 4 weeks of diagnosis. The exclusion criteria: the presence of other malignant diseases; non-cancer patients who underwent similar procedures; extensive infiltration to ad-

Table 1. The clinical and pathological characteristics of CME and control groups*

		CME	Control	P
Subjects, n		59	66	-
Gender	Male	38 (64.4)	39 (59.1)	0.584
	Female	21 (35.6)	27 (40.9)	-
Age, y	Median	57	55	0.547
	Range	28-75	46-72	-
Tumor location	Ileocecum	20 (34.0)	19 (28.8)	0.817
	Ascending colon	28 (47.4)	33 (50.0)	
	Hepatic flexure of colon	11 (18.6)	14 (21.2)	
Tumor staging	Stage I	10 (17.0)	11 (15.9)	0.961
	Stage II	29 (49.1)	33 (50.0)	
	Stage III	20 (33.9)	25 (34.1)	
Tumor differentiation	Well	8 (13.6)	11 (15.9)	0.786
	Moderate	31 (52.5)	36 (54.5)	
	Poor	20 (33.9)	19 (29.6)	

*Reported as n (%) unless indicated otherwise.

jacent tissues and organs; major blood vessel invasion; emergency surgery; incomplete medical records; history of chemotherapy.

Based on the surgical procedure, the enrolled subjects were apportioned to CME surgical treatment group (CME group) and conventional colon cancer radial operation group (control group).

The Ethics Board of Beijing Friendship Hospital Affiliated to the Capital University of Medical Sciences approved this study. All enrolled patients signed a research consent form.

Surgery

CME procedure was performed according to the reports of Hohenberger *et al.* [4]. In brief, the operation is consisted of a surgical separation by sharp dissection of the visceral fascia layer from the parietal. This resulted incomplete mobilization of the entire mesocolon covered by an intact visceral fascial layer on both sides ensuring safe exposure. The supplying arteries were tied at their origin. The extent of the surgery was determined by the location of the cancer and the pattern of potential lymphatic spread.

The conventional radical treatment was conducted in accordance with the Specification for Diagnosis and Treatment of Colorectal Cancer (2010 version) issued by the Department of Medical Administration, Ministry of Health of the People's Republic of China [5].

Surgical specimens and lymph node dissection

The surgical specimens taken from patients in the CME group were fixed and prepared for pathological large format, with the complete mesocolon for the observation of CRM. Digital photographs of the fresh surgical specimens from CME group and Control group were recorded, which were subsequently submitted to image analysis using Image-Pro Plus 6.0 (Media Cybernetics, Georgia Avenue Silver Spring, MD, USA). Features of the mesocolic excision were measured and analyzed, such as the length of intestine, the mesangial area, and the shortest distance from the vascular high ligation point to the tumor and intestine.

Pathological analyses

Surgical specimens were processed and prepared for pathological large format, including the complete mesocolon of the cancer from CME group. Firstly, the fresh specimens were fixed with formalin for 12 h. Then, a high ligation of vessels was conducted along the intestinal coronal arteries at the mesangial stem, and the stump specimens were collected and fixed on a wood plate for two days. Finally, the specimens were dehydrated, waxed, and paraffin embedded with "S" hook. A push-full slicing machine, REM-710 (Yamato Kohki Industrial, Japan) with macrotome (180 mm, S35LL, Feather Safety Razor, Japan), was used for sectioning. Full humidification was ensured during the slicing process to achieve the desired quality, and the glass slides were prepared with album. All dried slices were stained with hematoxylin and eosin and sealed properly (**Figure 1b-f**). The slices were analyzed by 2 pathologists (Dr. Li and Dr. Chen, with 15 and 13 years of experience, respectively) using an

Table 2. Lymph nodes dissected in the CME and control groups

		CME	Control	P
Subjects, n		59	66	
Total lymph nodes, n		29.7 ± 6.1	19.3 ± 5.3	< 0.001[a]
Tumor staging	Stage I	25.2 ± 5.7	13.2 ± 5.6	< 0.001[a]
	Stage II	31.3 ± 7.7	19.6 ± 6.2	< 0.001[a]
	Stage III	30.3 ± 8.4	25.2 ± 7.2	< 0.001[a]
Positive lymph nodes, n[b]		4 (8.0-1.0)	1.5 (3.0-1.0)	0.032[a,c]
Positive lymph nodes, %[c]		11.6 (34.1-7.8)	9.9 (23.2-4.3)	0.796[c]

[a]*P* < 0.05; [b]median (IQR); [c]Mann-Whitney U test.

Table 3. Features of surgical specimen resections in CME and control groups

	CME	Control	P
Subjects, n	59	66	
Mesangial area, mm^2	15423 ± 4187.2	9660 ± 2063.2	< 0.001[a]
Intestine length, mm	286 ± 56.7	267 ± 47.6	0.044[a]
Vascular high ligation to intestine wall, mm[b]	97 ± 15.2	74 ± 13.7	< 0.001[a]
Vascular high ligation to tumor, mm[b]	133 ± 31.2	115 ± 23.5	< 0.001[a]

[a]*P* < 0.05; [b]minimum distance.

optical microscope (OLYMPUS CX31, Olympus Optical, Japan).

Statistical analyses

SPSS19.0 software (SPSS, Chicago, USA) was used for all statistical analyses. Quantitative data with normal distribution were recorded as mean ± standard deviation, and unpaired t-test was used to compare the differences between CME and Control groups if both populations have the same SD, otherwise, unpaired t-test with Welch's correction was used. For non-normally distributed numerical data, the median was reported and the Mann-Whitney U test was applied for comparisons between the groups. The chi-squared test was used to analyze categorical variables. Fisher's exact test was employed for data with small sample size. A *P*-value less than 0.05 was considered statistically significant. Nominal data of pathology results was presented by description.

Results

Number of lymph nodes and the characteristics of surgical specimens

According to the surgical procedure and criteria of inclusion and exclusion, 59 cases were apportioned to CEM group and 66 cases were apportioned to conventional group (Control group). The clinicopathological characteristics such as gender, age, tumor location, tumor staging, tumor differentiation between the CEM and control groups were comparable (**Table 1**).

Then the lymph node dissections of the surgical specimens in the two groups were compared (**Figure 1** and **Table 2**). The number of lymph nodes in the CME group was significantly higher than in the control group (P < 0.001). When the CME and control groups were stratified by pathological stage, the number of lymph nodes at each stage was consistently higher in the CME group than the control. The number of positive lymph nodes in the CME group was significantly higher.

The size of the mesangial area was significantly larger in the CME group relative to the control group (P < 0.001), and significant difference was observed in the length of intestine (P < 0.05, **Table 3**). The minimum distance from the vascular high ligation point to either the tumor or the intestine was significantly longer in the CME group compared with the control group.

Circumferential resection margin

The pathological large formats were successfully fixed, embedded, sectioned, and evenly

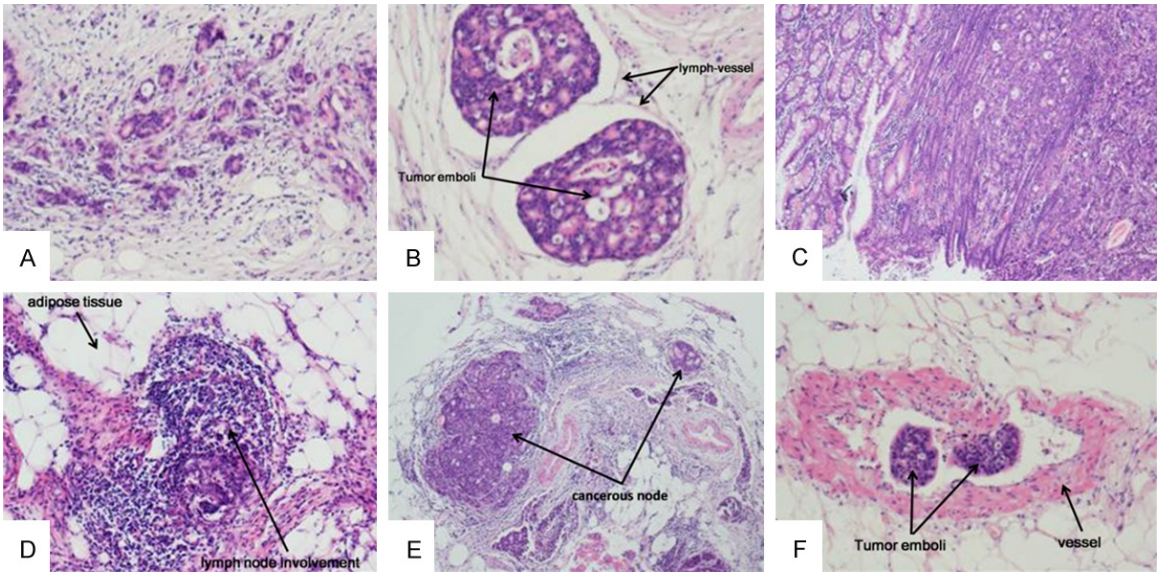

Figure 2. A. Tumor invasion in superficial myometrium, full-thickness and adenoma canceration (60X). B. Tumor metastasis bypassing the lymphatic vessels (150X). C. Atypical hyperplasia (60X). D. Tumor penetrates muscularis and invades lymph nodes in the adipose tissues of paracolic mesentery (150X). E. Lymph nodes in mesentery (60X). F. Cancer embolus in the vessels of mesentery (150X).

Table 4. Circumferential resection margin of colon cancer by CME pathological complete section

		n (%)
Total		59 (100)
Depth of invasion	Superficial	21 (35.59)
	Myometrium	32 (53.23)
	Full colon wall	6 (11.18)
Tumor differentiation	Well	15 (25.42)
	Moderate	27 (45.76)
	Poor	10 (16.94)
	Mucinous	7 (11.88)
Lymphatic vessel invasion	Yes	32 (54.23)
	No	27 (45.77)
Severe dysplasia of adjacent mucosa	Yes	23 (38.98)
	No	36 (61.02)
Mesangial lymph node metastasis	Yes	35 (59.32)
	No	24 (40.68)
Mesangial microinvasion	Yes	5 (8.47)
	No	54 (91.53)

stained, which could be applied for further observation, including the histological type, tumor grade, and the depth of tumor invasion. Compared to standard pathological small sections, the larger format could provide more detailed information such as the mesocolic position of the colon cancer metastasis, as well as the relationship between the mesocolic and the primary tumor/colon wall. With the help of pathological large format, we identified that, of the 59 CME cases, 21 were superficial, 32 invaded into myometrium, and 6 invaded into full colon wall; 15 were well differentiated , 27 were moderate differentiated, 10 were poor differentiated, and seven were mucinous differentiated; 32 presented lymphatic vessel invasion; 23 presented severe dysplasia of adjacent mucosa; 35 exhibited mesangial lymph node metastasis; and five cases exerted mesangial microinvasion (**Figure 2** and **Table 4**).

Lymph node metastasis in mesentery

This study showed that pathological large formats stained with hematoxylin and eosin could provide more intuitive observation of the continuous process of colon cancer metastasis, compared with routine pathological sections (**Figure 3**). The tumor was observed to appear firstly at the intestinal wall, from where it transferred to the mesentery along the lymph-vessel. The invasion then moved to the paracolic lymph nodes, and then the first-station lymph nodes. While

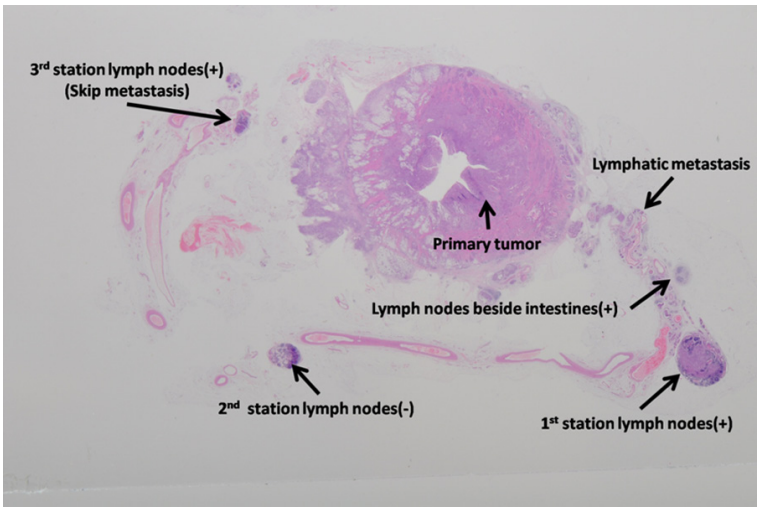

Figure 3. The continuous process of colon cancer metastasis can be observed in the pathological large section. The tumor is firstly identified at the intestine wall, from where it transfers to mesentery along the lymph-vessel. The invasion then further moves to paracolic lymph nodes, followed by the first station lymph nodes. The second station lymph nodes are negative in some cases, however, skip metastases could be identified in the third station lymph nodes.

the second-station lymph nodes were negative in some cases, skip metastases could be identified in third-station lymph nodes. The dynamic process of lymph node metastasis in colon cancer can be observed easily, providing direct evidence for the study of lymph node metastasis in colon cancer (**Figure 4**).

Complete membrane structure in posterior mesocolic peritoneum

A continuous and complete membrane structure was found in the posterior mesocolic fusion fascia visceralis (**Figure 5**), which mainly consisted of blood vessels and fibrous tissues, with a clear boundary and the adipose tissue in the mesentery. Mesothelial cells were also observed in the mesenteric film, providing pathological evidence for the concept of a complete mesocolon in CME. The integrity of the posterior mesocolic fusion fascia visceralis and mesenteric film could be used as an indication for CME, and further applied as a quality control standard of CME specimen (**Figure 6**).

Discussion

For the past decades, the concept of mesorectum and total mesorectal excision surgery first proposed by Heald *et al.* [2] has significantly changed in colorectal cancer treatment in clinical practice. The surgical significance of the mesorectum, which refers to loose retrorectal space, devoid of blood vessels between the hindgut peritoneum and parietal fascia that mentioned as the Holy plane by Heald *et al.* [6], provides a clear and safe site for surgical dissection and prevents cancer metastasis. Later, Quirke and his colleagues [3] reported that circumferential margin involvement significantly influenced the rate of postoperative local recurrence and survival. According to Quirke, the status of the lateral edge and its distance to the tumor were independent prognostic factors for local recurrence and survival, indicating the importance of obtaining negative lateral and surrounding margins besides the distal mesangial margin. The circumferential resection margin and circumferential margin involvement provide a quality control standard for TME surgery, which significantly reduces the local recurrence rate of colorectal cancer and improves the prognosis [7].

In 2003, the idea of CME first appeared in the work of Hohenberger *et al.* [8], and was later formally proposed [4]. The success of CME requires the achievement of several crucial goals during radical resection of colon cancer: sharp dissection of the visceral fascia layer resulting in complete mobilization of the entire mesocolon; safe exposure and blockage of the supplying arteries at their origin; and the proper extent of the surgical procedures, determined by the location of the cancer and the pattern of potential lymphatic spread [4]. Some scholars believed that CME should be introduced as a standard surgical approach for the treatment of colon cancer [9]. In 2009, Hohenberger *et al.* [4] and West *et al.* [10] reported their collaborative results, in which the standard CME specimen provided by the Hohenberger group remedied West's previous studies [10]. The above study indicates the challenge and impor-

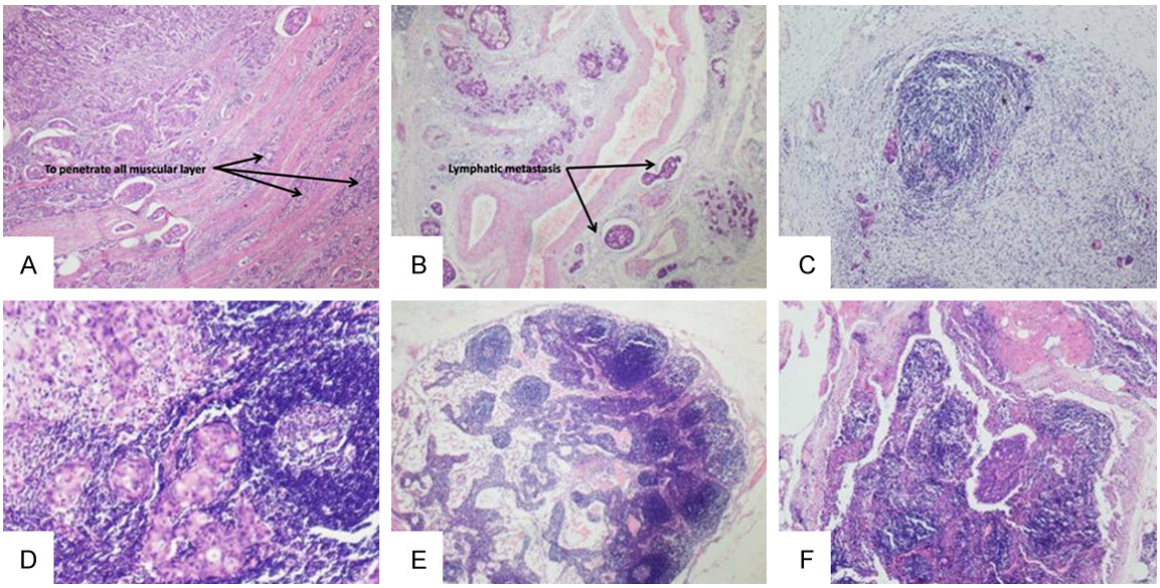

Figure 4. (A) Tumor invasion at muscularis with full penetration to the colon wall (60X). (B) Tumor penetrates colon wall and invades mesentery along the lymphatic vessels (30X). (C) Tumor invasion at paracolic lymph nodes (60X) and (D) the first station lymph nodes (150X). (E) Negative second station lymph nodes (30X) and (F) skip metastasis in the third station lymph nodes (30X).

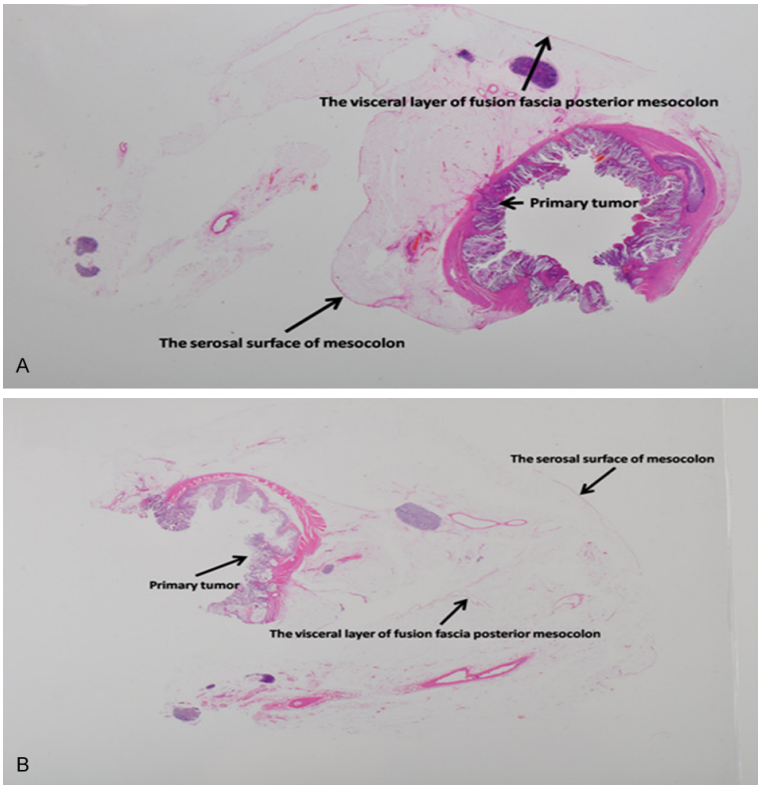

Figure 5. A and B. Complete fusion fascia visceralis at posterior mesocolon.

tance of collaboration between surgeons and pathologists to improve the quality of surgery [8].

Lymphatic drainage in the colon is confined to the mesentery by the mesocolic serosa and fusion fascia visceralis, with an opening in the vascular root. D3 resection can normally be achieved in CME by high nutrient vessel ligation, which helps to reduce the possibility of residual positive lymph nodes. The theoretical basis of achieving better prognosis after CME is that the procedure reduces the probability of intraoperative disseminated tumor and extends lymph node dissection. A previous study showed that, after receiving conventional radical surgery, an additional mesentery resection with CME detected residual positive lymph nodes in the resected mesentery of 18.18% of patients with right colon cancer [11]. It is still controversial whether the number of positive lymph nodes dissected should be considered as a standard for surgical quality [12, 13]. However, most researchers agree that the number of positive lymph nodes dissected is not only

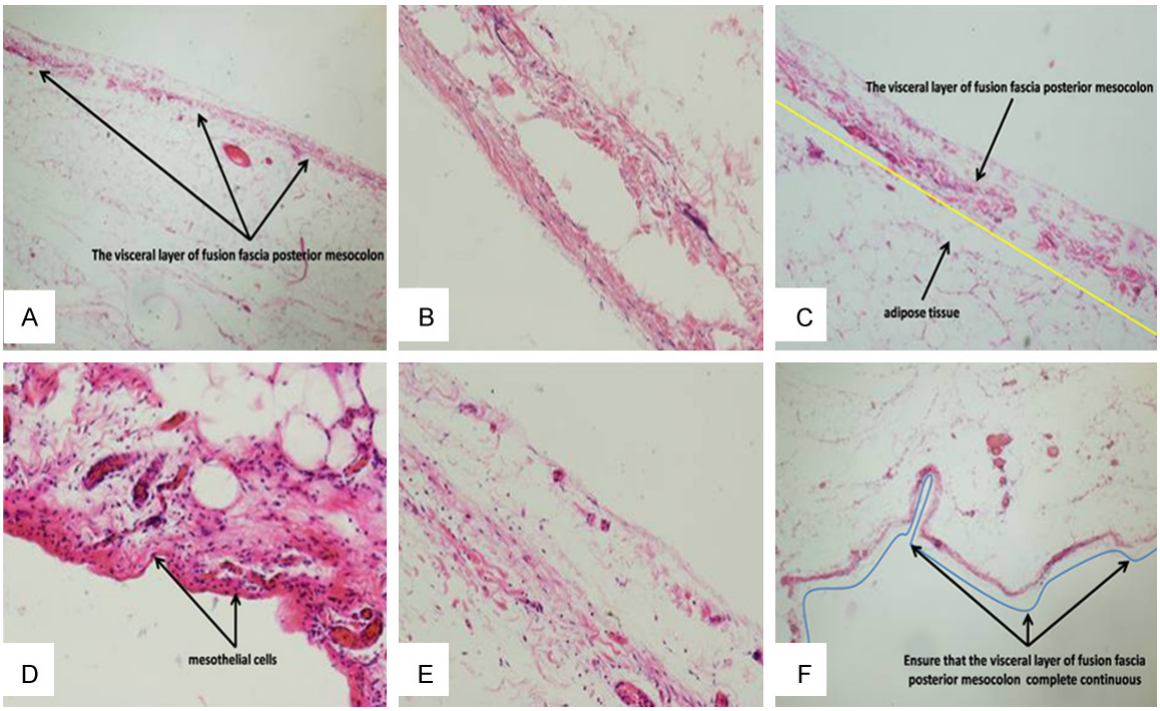

Figure 6. (A) A continuous and complete membrane structure is found in the posterior mesocolic fusion fascia visceralis (30X), and (B) it is mainly consisted of fibrous connective tissues (150X). (C) There is a clear boundary between fusion fascia visceralis and the adipose tissue in the mesentery (30X). (D and E) The mesenteric film contains mesothelial cells, which differs from the posterior mesocolic fusion fascia visceralis (150X). (F) The integrity of the posterior mesocolic fusion fascia visceralis could be applied as a quality control standard of CME specimen (30X).

related to surgical quality, but also related to the pathologists. That is, the management of the surgical specimens and the technique and experience of the pathologist both influence the number of dissected lymph nodes. Although some scholars disagree with this view point [14, 15], there were reports proving that the experience of pathologists and the number of dissected lymph node were closely related [16, 17].

The prevalence of colon cancer varies in different regions. The increasing incidence of right colon cancer [18] contributes to our research interest in this group of patients. The high prevalence ensures a relatively large sample size. In addition, the embryological origin and complicated anatomic structure of the right colon makes it representative of various parts of the colon. Our present study confirmed that CME of right colon cancer helped to identify more positive lymph nodes compared with conventional surgery. Moreover, CME provided better observation of the specimen, including mesangial area, the distance from the high vascular ligation point to the intestinal wall, and the minimum distance from the high vascular ligation point to the tumor center. Hence, the procedure significantly improved quality of surgical specimen.

Pathological large format is a conventional slicing technique. However, its clinical application has been limited due to complexities such as difficult collection, prolonged fixation, and higher cost. But this technique was considered as an irreplaceable role in circumferential margin involvement and other research fields. The mesocolon has a fan-like morphology. Nonetheless, the CRM is shaped as a cone, while its mesentery is at the lateral intestine. These differences result in extreme difficulty when preparing the pathological large format. In our work, we have explored a variety of fixation and embedding methods, and finally the techniques of circumvoluted fixation on wood plate, Shook-assisted embedding and waxing, vaporized slicing, and egg white preparation were adopted. These techniques helped us to successfully manufacture the pathologi-

cal large format of the entire mesocolon of colon cancer.

Our study revealed that, compared with conventional pathological section, the pathological large format provided more detailed information regarding the constitution of the colon cancer. This included the primary tumor, adjacent atypical hyperplasia, surrounding normal tissues, complete mesangial serosa, posterior mesocolic fusion fascia visceralis, and mesangial tissues. The large format also better revealed the three-dimensional structure of the cancer, especially for those with large tumor volume and varied morphology, resulting in a higher rate of tumor detection and better understanding of tumor invasion. Our results also showed that tumor invasion to surrounding tissues could vary, in which direct penetration to the serosa and mesangial or distant metastases by passing the lymphatic/blood vessels could both be detected.

A typical feature of colon cancer is the skip metastasis of lymph nodes, which means that the third station lymph node could be positive although metastasis in the second station lymph node is absent. Our work first reported skip metastasis of lymph nodes within the same pathological section, providing direct evidence of this special feature in colon cancer. Conventional radical surgery could not reveal the surgical trunk of the mesocolic vessels, neither could it ligate the root to cut off the corresponding artery and vein, nor achieve lymph node dissection at the third station. These disadvantages result in merely a radical surgery of D1 or D2, while the remaining lymph nodes at Toldt's fascia may contain residual disease. This may be an important cause for colon cancer recurrence [19]. On the contrary, CME helps to achieve complete dissection of the involved lymph nodes, including the paracolic, intermediate, and central lymph nodes. Compared with the results of other indirect methods, the total mesocolic section provides stronger and more direct evidence for investigating lymph node metastasis in colon cancer.

This study confirmed the existence of a complete membrane structure in the posterior mesocolic fusion fascia visceralis, which mainly consisted of fibrous connective tissues with a clear boundary and adipose tissues. This continuous membrane extends from the intestine to the vascular high ligation point at the root of the mesocolon, while it also combines with the intestinal and ventral mesocolic serosa to circumvent the mesocolon, forming a relatively airtight envelop-like structure, termed "envelop" by Hohenberger *et al.* [8]. The results in this study also provided further histopathological evidence for the surgical basis of CME. The integrity and continuity of the fusion fascia visceralis is crucial to the surgery; any damage to the envelop will result in intraoperative blood loss, an unclear surgical field, or even residual tumor in the mesocolon, which becomes the origin of local recurrence.

In this study, we demonstrated that CME is appropriate in colon cancer surgery and reveals more precisely the status of lymph node metastasis. Further multi-center, prospective, and randomized studies are warranted to verify the application of CME. Nonetheless, the accuracy of this concept has been proved by the solid pathological evidence in this work. The pathological large format is potential for illustrating the biological behavior of colon cancer. This technique is worthy to be considered routine for identifying surgical margins and could be considered a quality control standard for colon cancer surgery.

Acknowledgements

The study was supported by the basic and clinical scientific research cooperation fund from Capital University of Medical Science (No. 16JL37) and Beijing "215" High-Level Health Technique Personnel Training Project.

Disclosure of conflict of interest

None.

Authors' contribution

Yang Y. and Zhang Z.: study concept and design; Lan J., Li J., Chen G., Wang K., Zhao X., and Wu G.: acquisition of data; Yang Y., Zhang Z., and Wang J.: drafting of the manuscript.

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