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Observational Study

Detection of metastatic cancer cells in mesentery of colorectal cancer patients

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Abstract**AIM**

To detect the existence of isolated cancer cells in the mesentery of colorectum (named as Metastasis V), and investigate its clinical significance in colorectal cancer (CRC) patients.

METHODS

Sixty-three CRC patients who received radical excision between January 2012 and September 2015 were included. All the patients underwent laparoscopy-assisted radical colectomy or proctectomy [with complete mesocolic excision (CME) or total mesorectal excision (TME)] with R0 dissections at the Department of Gastrointestinal Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The location and size of the primary lesions were recorded immediately after the tumor was removed, with the surrounding mesentery completely separated along the intestinal wall. Each dissected mesentery sample was analyzed for hematoxylin-eosin staining and immunohistochemistry using cytokeratin 19 antibody. Image Pro Plus Software 6.0 (Media Cybernetics, CA, United States) was used

to semi-quantitatively measure the concentration of the cytokeratin 19 immunohistochemistry. The correlation between metastasis found in mesentery and clinicopathological characteristics was examined. The prognosis of patients was also evaluated by preoperative serum CEA level.

RESULTS

Metastasis V was detected in 14 of 63 (22.2%) CRC patients who underwent laparoscopy-assisted radical colectomy or proctectomy (with CME or TME) with R0 dissection in our hospital between January 2012 and September 2015. There was no significant difference in age, gender, tumor size, and tumor location in patients with Metastasis V ($P > 0.05$). Metastasis V was more likely to occur in poorly differentiated tumor (5/11; 45.5%) than moderately (8/46; 17.4%) and well-differentiated one (1/6; 16.7%). The Metastasis V in N2 stage (9/14; 64.3%) was more frequent than in the N0 stage (3/35; 8.6%) or N1 stages (2/14; 14.3%). In addition, Metastasis V was positively related to the tumor invasive depth (T1:0/1, 0%; T2:1/12, 8.3%; T3:7/39, 17.9%; T4:6/11, 54.5%). Furthermore, preoperative serum CEA level in Metastasis V-positive patients was significantly higher than in Metastasis V-negative patients (4.27 ng/mL *vs* 3.00 ng/mL).

CONCLUSION

Metastasis V might be associated with a poor prognosis of CRC patients.

Key words: Colorectal cancer; Colorectal mesentery; Serum CEA level; Radical surgery; Metastasis V

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Core tip: Local-regional recurrence of colorectal cancer (CRC) is common in patients who received R0 resection. Our previous study proposed a novel type of metastasis designated as "Metastasis V" in gastric cancer. Metastasis V is defined as the appearance of cancer cells in the mesentery in broad sense, and may be a risk factor for the poor prognosis after radical surgery. In this study, Metastasis V was also detected in the mesentery of colorectum, and it might be associated with the poor prognosis of CRC patients.

Luo XL, Xie DX, Wu JX, Wu AD, Ge ZQ, Li HJ, Hu JB, Cao ZX, Gong JP. Detection of metastatic cancer cells in mesentery of colorectal cancer patients. *World J Gastroenterol* 2017; 23(34): 6315-6320 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i34/6315.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i34.6315>

INTRODUCTION

Three decades ago, RJ Heald introduced the total

mesorectal excision (TME) in the treatment of rectal cancer^[1]. Subsequently, complete mesocolic excision (CME) was popularized by W Hoehenbuerg to reduce tumor relapse and improve prognosis in colon cancer patients^[2]. These new approaches greatly contributed to the complete mesentery excision and improved lymph node harvest. Furthermore, with the development of surgical technology, neo-adjuvant chemotherapy and efficient perioperative management, the prognosis of patients with colorectal cancer (CRC) has been improved. However, local-regional recurrence of CRC is still often noted in the patients who received radical R0-resection with no lymphatic metastasis^[3].

Direct invasion, lymphatic drainage, hematogenous spread and peritoneal dissemination are the four classical routes for local-regional recurrence or distant implantation of cancer cells. In addition to these pathways, the existence of metastatic cancer cells in the mesentery of colorectum has also been reported, and this type of metastasis was named as "extra-capsular spreads" or "extra-nodal metastasis"^[4-7]. In our previous study, we proposed a novel type of tumor metastasis designated as Metastasis V in gastric cancer. Metastasis V is defined as the appearance of cancer cells in the mesogastrium with perigastric adipose tissue, and it may be a risk factor for patient survival after radical surgery^[8]. Here, in this study, we further determined whether Metastasis V can be detected in the mesocolorectum, and examined its clinical significance.

MATERIALS AND METHODS

Patients, samples, and sectional tissue analysis

Sixty-three patients who underwent surgery for CRC at the Department of Gastrointestinal Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between January 2012 and September 2015 were included in this study. The patients consisted of 25 female patients and 38 male patients. All of these patients received laparoscopy-assisted radical colectomy or proctectomy (with CME or TME) with R0 dissection. All participants signed informed written consents in this research. This study was approved by the Tongji Hospital Ethics Committee.

Clinical samples of CRC were obtained from the resected colorectal tissue. The location and size of the primary lesions were recorded immediately after the tumor was removed, and then the mesentery was completely separated from the intestinal wall along with the anterior edge. All specimens were fixed in 10% formaldehyde before processing. The lymph nodes were obtained from the mesentery. Next, the mesentery was cut into strip-shape with a width of 2 cm in an outward-to-inward manner, vertical to the intestinal wall. The strip-shaped samples were cut into cube samples with a mean length of 2 cm.

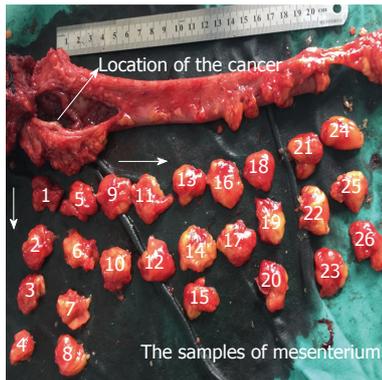


Figure 1 Samples of mesenterium from colorectal cancer patients. Analysis of large cross sectional tissue samples of mesentery of colorectum from surgically resected specimens.

Table 1 Data in 63 colorectal cancer patients

Parameters	Results
Gender	
Female	25
Male	38
Age (yr, mean, range)	55.5 (28-86)
Location of cancer	
Colon	11
Rectum	52
Differentiated grade	
Well	6
Moderately	46
Poorly	11
Affected lymph nodes	
N0	35
N1	14
N2	14
Invasive depth	
T1	1
T2	12
T3	39
T4	11

All of the small samples were numbered from inside (proximal end of the cancer) to outside (Figure 1). These samples were embedded in 10% formaldehyde. Demographic characteristics of the 63 patients are described in Table 1. The clinicopathological stage was determined by the 7th edition of the AJCC Cancer Staging Manual.

Immunohistochemical analysis of Metastasis V

Immunohistochemistry was performed using the cytokeratin 19 antibody. Cytokeratin 19 is specifically expressed in intestine epithelia cells and CRC cells^[9]. Hence, it has been proven to be a highly sensitive marker for CRCs.

Immunostaining was performed by the standard streptavidin-biotin method. First, the slices were deparaffinized and rehydrated. To retrieve antigenicity, the slices were boiled in 0.01 mol/L, pH 6.0 sodium citrate buffer for approximately 15 min. Endogenous peroxidase was restrained with 0.3% hydrogen

peroxide for roughly 25 min. After blocking with 3% BSA for 30 min, the anti-cytokeratin 19 monoclonal antibody was arranged in blocking buffers and the slices were incubated at 4 °C overnight. After being washed in pH 7.4 PBS 3 times (5 min each time), the corresponding secondary antibody, retained at room temperature for approximately 50 min and marked by HRP was added. After one more wash with pH 7.4 PBS for 15 min, the chromogenic reagent DAB was added to the colorate. The slices were counterstained with Harris hematoxylin, dehydrated in a graded alcohol series (75% alcohol for 6 min, 85% alcohol for 6 min, absolute ethyl alcohol I for 6 min, and absolute ethyl alcohol II for 6 min), cleared in xylene for 5 min, and mounted. Individual tumor cells in mesenteries, separated from primary lesion and lymph nodes, were identified to be Metastasis V.

Immunohistochemistry image analysis

Image Pro Plus Software 6.0 (Media Cybernetics, CA, United States) was used to semi-quantitatively measure the concentration of the cytokeratin 19 immunohistochemistry. This procedure, was split into six steps: (1) discovering and surveying the section of interest; (2) adjusting the optical densities; (3) obtaining, transforming and preserving images; (4) amending the background and background staining; (5) configuration of the section of interest to determine the optical density; and (6) examining optical densities.

Statistical analysis

The Fisher's exact test, χ^2 test, and Mann-Whitney *U* test were used to inspect the significance of the differences between the covariates. We considered a *P* value of less than 0.05 statistically significant. Standard statistical analyses were performed by SPSS version 20.0.

RESULTS

Detection of Metastasis V in mesenterium of CRC patients

Metastasis V was detected in 14 of the 63 (22.2%) patients by immunohistochemistry staining. These isolated cancer cells separated from the primary lesion and lymph nodes were observed in the same slice (Figure 2). In terms of "T" stage, only one case showed limited muscular layer invasion, seven cases had sub-serosal invasion, and the rest had serosal invasion. In these patients, there were three lymph node negative patients with different invasive depths (Table 2).

Correlation between Metastasis V and clinical factors

The demographic characteristics of patients and the pathologic features of tumors with Metastasis V are shown in Table 3. There was no significant difference

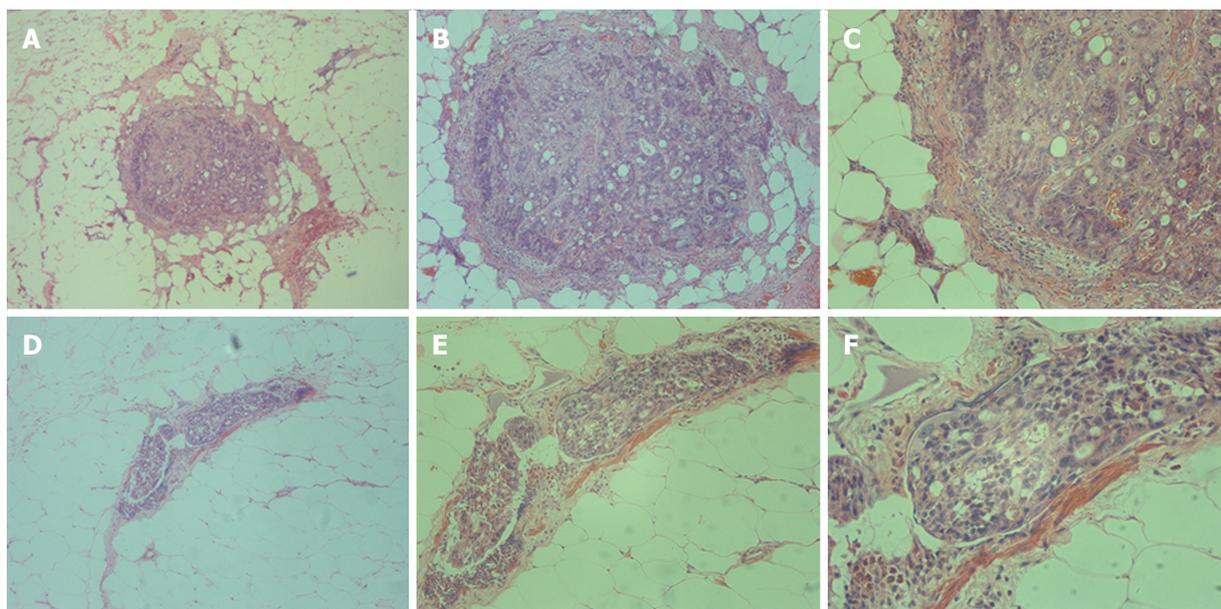


Figure 2 Detection of Metastasis V in colorectal cancer patients. Isolated cancer cells were detected in the mesentery of colorectum by HE staining. A ($\times 10$), B ($\times 20$) and C ($\times 40$) represent the same slide; D ($\times 10$), E ($\times 20$) and F ($\times 40$) represent the same slide.

Table 2 Data in Metastasis V-positive patients

Patients	Sex	Age (yr)	Cancer size (cm)	Cancer location	Differentiated grade	Invasive depth	Affected lymph nodes	TNM
1	F	37	2.5	Rectum	Poorly	Serosal	8/15	pT4N2M0
2	F	42	3	Rectum	Moderately	Subserosal	5/17	pT3N2M0
3	M	33	2	Rectum	Moderately	Serosal	5/15	pT4N2M0
4	M	48	6	Sigmoid	Well	Serosal	12/21	pT4N2M0
5	F	63	3	Rectum	Poorly	Muscularis	0/15	pT2N2M0
6	F	45	3	Rectum	Moderately	Serosal	5/28	pT4N2M0
7	M	58	3	Rectum	Poorly	Subserosal	8/12	pT3N2M0
8	M	64	4	Rectum	Poorly	Subserosal	7/15	pT3N2M1
9	M	54	6	Rectum	Moderately	Subserosal	2/13	pT3N1M0
10	F	60	2	Descending colon	Moderately	Subserosal	0/17	pT3NxM0
11	M	54	3	Rectum	Moderately	Serosal	5/12	pT4N2M0
12	M	58	3	Rectum	Moderately	Subserosal	0/16	pT3N0M0
13	F	57	3	Rectum	Poorly	Serosal	2/21	pT4N1M1
14	M	47	4	Rectum	Moderately	Subserosal	24/32	pT3N2M0

in age, gender, tumor size, and tumor location ($P > 0.05$). Metastasis V was more likely to occur in poorly differentiated tumor (5/11; 45.5%) than moderately (8/46; 17.4%) and well-differentiated one (1/6; 16.7%). The Metastasis V in N2 stage (9/14; 64.3%) was more frequent than that in the N0 stage (3/35; 8.6%) or N1 stages (2/14; 14.3%). In addition, Metastasis V was positively related to the tumor invasive depth (T1: 0/1, 0%; T2: 1/12, 8.3%; T3: 7/39, 17.9%; T4: 6/11, 54.5%).

Correlation between Metastasis V and preoperative CEA levels

Previous studies have demonstrated the correlation between increased preoperative CEA and the poor prognosis of rectal cancer patients^[10,11]. Here, we further determined the correlation between Metastasis

V and preoperative CEA levels. Totally 42 CRC patients who underwent operations in our department were retrospectively studied. Metastasis V was detected in nine patients according to the pathological reports. Six patients were excluded because their preoperative CEA data was missed. The CEA levels were divided into two grades. The CEA levels more than 3 times of normal range (15.00 ng/mL) were classified as high grade, while those less than that were designated as low grade. Our data indicated that preoperative serum CEA levels in Metastasis V-positive patients were significantly higher than in Metastasis V-negative patients (4.27 ng/mL vs 3.00 ng/mL) (Table 4).

DISCUSSION

In this study, we have shown that metastatic cancer

Table 3 Comparison between Metastasis V-positive patients and Metastasis V-negative patients

Parameters	Metastasis V		P value
	Negative	Positive	
Age (yr)			NS
< 45	8	3	
≥ 45 and ≤ 59	19	8	
≥ 60	22	3	
Cancer size (cm)			NS
≤ 3	24	10	
> 3 and < 5	14	2	
≥ 5	11	2	
Gender			NS
Female	19	6	
Male	30	8	
Cancer location			NS
Colon	9	2	
Rectum	40	12	
Differentiated grade			NS
Well	5	1	
Moderately	38	8	
Poorly	6	5	
Affected lymph nodes			< 0.05
N0	32	3	
N1	12	2	
N2	5	9	
Invasive depth			< 0.05
T1	1	0	
T2	11	1	
T3	32	7	
T4	5	6	

Table 4 Comparison of preoperative CEA levels between Metastasis V-positive and Metastasis V-negative patients

Parameters	Metastasis V		P value
	Negative	Positive	
Median (ng/mL)	3	4.27	< 0.05
Grade			< 0.05
High (> 15.00 ng/mL)	5	5	
Low (≤ 15.00 ng/mL)	73	16	

cells can reside in the mesentery of the colorectum of CRC patients. These tumor cells showed no direct attachment to the primary lesions, with no involvement of vessel-lymphatic drainage system, and are confined to the fatty tissues enveloped by the fascia proper (Figure 1). In our previous study, we proposed a novel type of tumor metastasis designated as Metastasis V in gastric cancer patients^[8]. Thus, we believe that Metastasis V could be detected in the mesenteries of both gastric and CRC patients. Similar to our previous studies, the incidence of Metastasis V was closely related to the tumor invasion of CRC patients, which was mainly detected in the T3 and T4 tumors (Table 2). Metastasis V was also correlated with lymphatic metastasis. Lymphatic nodes staging N1-N3 had larger percentages of Metastasis V than N0 (Table 2). Therefore, immunohistochemical analysis of Metastasis V in these patients is strongly recommended in clinical

practice.

More interestingly, the preoperative serum CEA levels in Metastasis V-positive patients were significantly higher than in Metastasis V-negative patients (4.27 ng/mL vs 3.00 ng/mL) (Table 4). These data indicated that the prognosis of the patients with Metastasis V-positive tumors was worse than that of patients with Metastasis V-negative tumors. Due to the limited number of patients in the current study, a larger sample of cohort study should be enrolled for further analysis.

Little is known about the exact route or mechanism of Metastasis V. It was hypothesized that primary tumor lesions penetrates the intestinal wall, and then the cancer cells could probably scatter into the fatty tissues enveloped by proper fascia. In this way, Metastasis V occurs not only in CRC and gastric cancers, but also in oral head-neck, pancreas and papilla of Vater tumors^[12-20].

It has been well known in practice that radical surgery for cancers should include *en bloc* resections of the primary tumor and neighboring tissues. However, it is difficult to determine the exact boundaries of *en bloc* resection within gastrointestinal tumors. "TME" or "CME" can reduce the tumor recurrence and increase patient survival, however, the possible reason is still unknown. In our opinion, the mesenteries of colorectum enveloped by the proper fascia not only propose a precise boundary for resection, but also function as pathologic barriers of Metastasis V spreading. Thus, our findings are clinically significant because TME or CME should be a useful choice for surgical excision of Metastasis V. Further studies on the efficiency of Metastasis V excision *via* TME or CME will be investigated.

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COMMENTS

Background

Local-regional recurrence of colorectal cancer (CRC) is still often noted in the patients who received radical R0-resection with no lymph-node metastasis.

Research frontiers

In addition to the classical four metastatic patterns, the existence of metastatic cancer cells in the mesentery of colorectum has also been reported, and this type of metastasis was named as "extra-capsular spreads" or "extra-nodal metastasis". Examination of the clinical and oncological significance of isolated tumor cells found in mesentery of colorectum in CRC patients is one of the main frontiers in surgical oncology.

Innovations and breakthroughs

Metastasis V is defined as the appearance of cancer cells in the mesogastrium, and may be a risk factor for the poor prognosis after radical surgery. This study demonstrated that Metastasis V was also detected in the mesentery of colorectum, and it might be associated with the poor prognosis of CRC.

Applications

It is clinically useful to be assisted in evaluation of prognosis of CRC patients.

Peer-review

In this paper, the authors well described an interesting study about isolated cancer cells in the mesentery of colorectum (named as Metastasis V). This is an interesting point, and the issue of metastasis in patients with CRC is of main importance.

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