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• COLORECTAL CANCER •

Microscopic spread of low rectal cancer in regions of mesorectum: Pathologic assessment with whole-mount sections

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Abstract

AIM: To assess the microscopic spread of low rectal cancer in mesorectum regions to provide pathological evidence for the necessity of total mesorectal excision (TME).

METHODS: A total of 62 patients with low rectal cancer underwent low anterior resection and TME, surgical specimens were sliced transversely on the serial embedded blocks at 2.5 mm interval, and stained with hematoxylin and eosin (HE). The mesorectum on whole-mount sections was divided into three regions: outer region of mesorectum (ORM), middle region of mesorectum (MRM) and inner region of mesorectum (IRM). Microscopic metastatic foci were investigated microscopically on the sections for the metastatic mesorectal regions, frequency, types, involvement of lymphatic vessels and correlation with the original rectal cancer.

RESULTS: Microscopic spread of the tumor in mesorectum and ORM was observed in 38.7% (24/62) and 25.8% (16/62) of the patients, respectively. Circumferential resection margin (CRM) with involvement of microscopic metastatic foci occurred in 6.5% (4/62) of the patients, and distal mesorectum (DMR) involved was 6.5% (4/62) with the spread extent within 3 cm of low board of the main lesions. Most (20/24) of the patients with microscopic metastasis in mesorectum were in Dukes C stage.

CONCLUSION: Results of the present study support that complete excision of the mesorectum without destruction of the ORM is essential for surgical management of low rectal cancer, an optimal DMR clearance resection margin should be no less than 4 cm, further pathologic assessment of the regions in extramesorectum in the pelvis is needed.

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INTRODUCTION

Local tumor recurrence after surgical resection of rectal cancer remains a major problem. Since Heald *et al*.[1] first reported evidence of isolated tumor deposits in the mesorectum, more authors have demonstrated that residual foci of the tumor within pelvis resulting from inadequate excision of the mesorectum were the cause of such recurrence[2,3]. Further studies revealed that remnant of microscopic tumor nodules in the mesorectum, which cannot easily be detected by imaging preoperatively or by palpation intraoperatively, other than large nodules, contributes to most of local failures[4,5].

Comparison of clinical outcomes between conventional surgery[6,7] and total mesorectal excision (TME)[1,8] showed that a proportion of microscopic tumor nodules of rectal cancer causing local pelvic collapse might settle in the outer region of mesorectum (ORM). Unfortunately, investigations on discrete tumor nodules spread in this region are rare. A comprehensive assessment of ORM in patients with low rectal cancer may provide further pathological evidence for supporting the TME procedure.

Although TME has been extensively employed as a standard procedure for surgical treatment of patients with low rectal cancer in western countries, conventional resection has been dominated in China due to little pathological information standing for TME. The present study investigated the regional spread of microscopic tumor nodules in mesorectum using whole-mount sections.

MATERIALS AND METHODS

Patients

Sixty-two consecutive patients with biopsy-proven adenocarcinoma of the rectum underwent TME at the Division of Gastroenterology Surgery of Affiliated West China Hospital of Sichuan University between November 2001 and June 2002, and specimens were examined prospectively by the same pathologist (Chen DY). Patients (30 males) had a mean age of 58 years (range, 21-78). Lesions were classified as upper or low rectal cancers based on the location of peritoneal reflection, and all diseases from our series were categorized as low rectal cancers with sigmoidoscopy preoperatively. Thirty-two patients had the lower board of primary tumors within 5 cm of anal verge, and another 30 patients had the lower board located not farther than 10 cm from anal verge and above the level of 5 cm from anal verge. None of the patients received any preoperative adjuvant therapy.

Surgical techniques

All patients were operated on by the same chief surgeon (Professor. Zhou ZG) and two assistants according to TME principles[1]. The rectum and mesorectum were mobilized as a package enveloped within the fascia properia with the preservation of autonomic nerves. Under direct vision, electrocautery was used to divide the rectosacral ligament posterior, the peritoneum posterior to the seminal vesicle in the males and the peritoneal reflection in Douglas' pouch in the females anteriorly, lateral ligaments medial to the pelvic plexus laterally. Sharp dissection

was continued down to the pelvic floor in front of Denonvilliers' fascia anteriorly and along the fascia properia posteriorly. Eventually, over 2 cm of distal clearance margin of rectal wall and over 4 cm of mesorectum were attained by transecting the rectum without stretching the bowel wall[9].

Whole-mount sections

Each specimen was straightened without stretching and pinned to a cork board, different from Quirke's method[2]. The specimens were not opened longitudinally along the antimesenteric border, and fixed in 40 g/L buffered formaldehyde for 48 h. Serial longitudinal tissue blocks were cut at 5 mm intervals from the distal portion. Each block, consisting of the full thickness of the rectal wall with the mesorectum, was fixed in 40 g/L buffered formaldehyde for another 48 h, and then embedded in paraffin. Whole-mount sections of the bowel wall and mesorectum were sliced transversely on the embedded tissue blocks in 4 μm at 2.5 mm intervals, stained with hematoxylin and eosin (HE), and examined for discrete tumor nodules microscopically (Figure 1). Circumferential resection margin (CRM) involvement was assessed in the conventional manner[10].

Parameters

The following pathological parameters were used for analysis, namely Dukes stage, differentiation grade, presence of microscopic tumor nodules, local metastasis of lymph nodes, outer region of mesorectum (ORM), distal mesorectum (DMR), CRM (involved ⩽1 mm, or clear >1 mm), and distant metastases. Microscopic metastatic nodules of rectal cancer were defined as tumor nodules ⩽1 mm in diameter, which could not be detected either preoperatively or intraoperatively. Large metastatic nodules of rectal cancer were defined as tumor nodules >5 mm in diameter, most of which could be easily detected by palpation during operation. The mesorectum on the transverse whole-mount section was divided into three regions (Figure 2).

Discrete tumor nodule spread in the mesorectum 1 mm or less away from the outermost board of CRM was recorded as involvement of CRM, and discrete tumor nodule spread in the mesorectum blow the lowest board of primary tumor was defined as involvement of DMR.

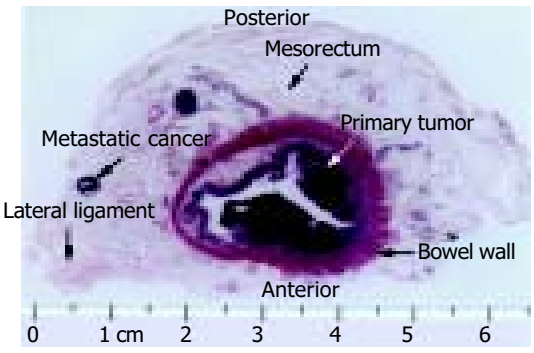

Figure 1 Illustration for regions of mesorectum.

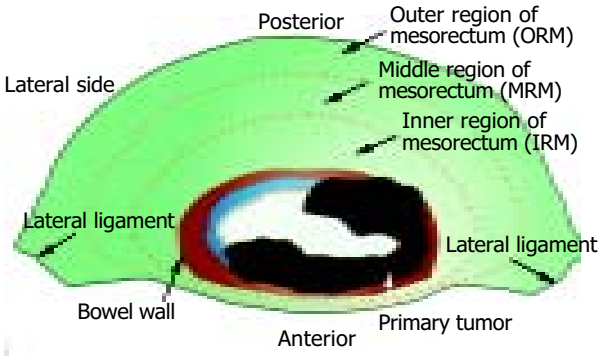

Figure 2 Transverse whole-mount sections of the specimen, HE staining, macroscopic view.

RESULTS

The clinicopathologic characteristics of the patients are summarized in Table 1. All the 62 patients underwent low anterior resection. In 52 patients (83.9%) the operation was potentially curative, while residual tumors in 2 patients (3.3%) were noticed to remain in pelvis on operation and distant metastases were observed in 8 patients (12.9%).

Table 1 Clinicopathologic characteristics of the 62 patients

Parameters	Results
Age (yr, range, mean)	20-78, 58
Sex (No. of patients)	
Male	30
Female	32
Dukes stage (No. of patients)	
A	2
B	10
C	42
D	8
Differentiation grade (No. of patients)	
High	4
Medium	34
Low	24
Distance of the primary tumor from anal verge (No. of patients)	
⩽5 cm	32
>5 cm	30
Diameter of the primary tumor (No. of patients)	
<5 cm	24
⩾5 cm	38

Microscopic spread types and involvement of mesorectum

Four types of microscopic spread of the tumor were observed in mesorectum: discrete microscopic tumor nodules, blood vessel invasion, lymphatic vessel invasion and perineural invasion (Figure 3). Microscopic spread in mesorectum was observed in 38.7% (24 of 62) of the patients (Table 2).

Table 2 Mesorectal regions with involvement of discrete tumor nodules (%)

	Involved mesorectal regions					
	MR	ORM	MRM	IRM	DMR	CRM
Tumor nodules	58.1 (36/62)	45.2 (28/62)	35.5 (22/62)	41.9 (26/62)	6.5 (4/62)	6.5 (4/62)
Microscopic tumor nodules	38.7 (24/62)	25.8 (16/62)	25.8 (16/62)	29.0 (18/62)	6.5 (4/62)	6.5 (4/62)

MR: mesorectum; ORM: outer region of mesorectum; MRM: middle region of mesorectum; IRM: inner region of mesorectum; DMR: distal mesorectum; CRM: circumferential resection margin.

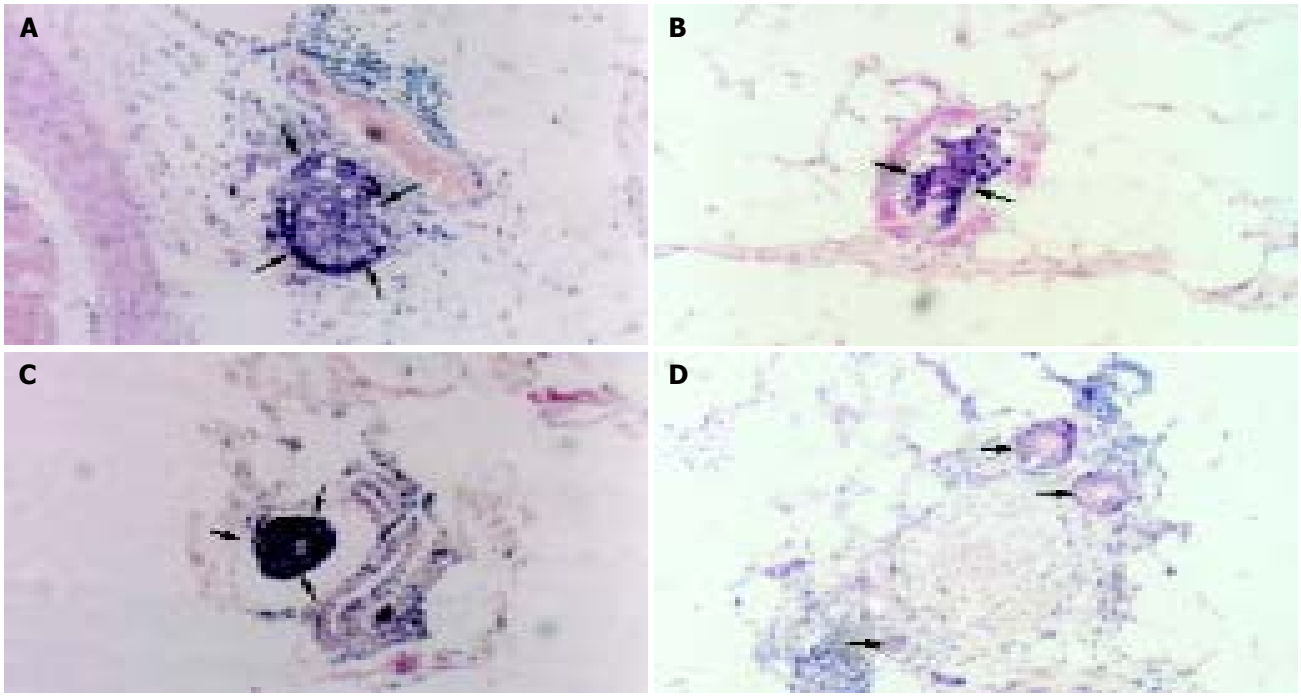

Figure 3 Spread types of microscopic tumor nodules (→) in the mesorectum, HE, ×100. A: Discrete microscopic tumor nodules; B: Blood vessel invasion; C: Lymphatic vessel invasion; D: Perineural invasion.

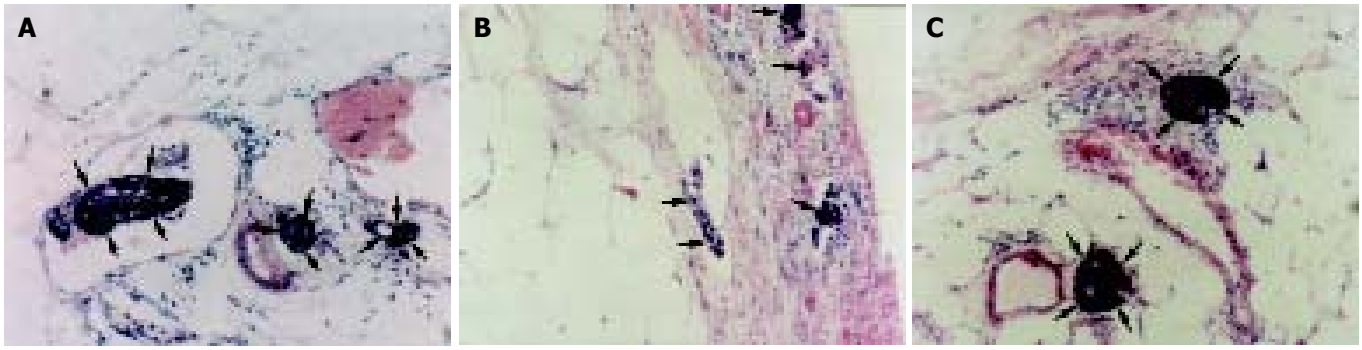

Figure 4 Microscopic tumor nodule spread (→) in outer region of the mesorectum (ORM) (4a), CRM (4b) and DMR(4c) , HE, ×100.

Microscopic spread of the tumor in outer region of mesorectum

Microscopic spread in ORM (Figure 4) occurred in 25.8% (16 of 62) of the patients (Table 2).

Microscopic spread of the tumor in circumferential resection margin

Four of 36 patients with tumor involvement of mesorectum and 2 of the 52 patients having potentially curative resections had microscopic spread in CRM.

Table 3 Mesorectal regional discrete microscopic tumor nodules involving lymph nodes or lymphatic vessels

	Involvement of MR	Involvement of ORM
L type (No. of patients)	16	14
NL type (No. of patients)	18	13

MR: mesorectum; ORM: outer region of mesorectum; L type: involving lymph nodes or lymphatic vessel; NL type: without involving lymph nodes or lymphatic vessels.

Microscopic spread of the tumor in distal mesorectum

DMR with involvement of microscopic tumor nodules was observed in 4 patients. The utmost spread was 3.0 cm or less from the low edge of primary carcinoma. The most extensive distal infiltration was seen in two cases of Dukes stage C.

Table 4 Correlation between mesorectal microscopic spread and primary tumors

Primary tumor	Spread in MR (No. of patients)	Spread in ORM (No. of patients)
Diameter: <5 cm / ⩾5 cm	10 / 14	8 / 8
Differentiation grade: high / medium / low	0 / 10 / 14	0 / 8 / 8
Dukes stage: A / B / C / D	0 / 2 / 20 / 2	0 / 2 / 12 / 2
From anal verge: ⩽5 cm / >5 cm	12 / 12	8 / 8

MR: mesorectum; ORM: outer region of mesorectum.

Microscopic spread of the tumor in mesorectal lymph nodes or lymphatic vessels

Microscopic spread nodules without involvement of lymph nodes or lymphatic vessels in mesorectum were observed in 18 patients, and such a spread in ORM was found in 13 patients (Table 3).

Correlation between regional mesorectal microscopic spread and primary tumors

Most patients (20 of 24) with mesorectal microscopic spread in

MR and 12 of 16 microscopic spreads in ORM were Dukes C stage (Table 4).

Correlation between microscopic tumor nodules and large tumor nodules

Microscopic tumor nodules coexisting with large tumor nodules were observed in 14 of 24 (58.3%) patients with microscopic spread in mesorectum.

DISCUSSION

Whole-mount sections were used to facilitate the precise and effective assessment of rectal cancer, especially in mesorectal regional spread of discontinuous microscopic tumor nodules. All whole-mount sections showed that whole morphological features of the surgical specimen enclosing the primary tumor, bowel wall and the mesorectum, could be directly observed with naked eyes and by microscopy, which enabled the investigators to obtain valuable pathological outcomes on rectal cancer[2,11].

The present study showed the incidence of discrete microscopic tumor nodules was 38.7% (24 of 62) of patients in mesorectum and 25.8% (16 of 62) of patients in ORM. The high frequency of microscopic tumor nodules in mesorectum (especial ORM) highlighted the importance of complete excision of mesorectum with fascia propria circumferentially intact for low rectal cancer. Disturbance of ORM during operation would predispose local recurrence because the undetected microscopic foci in the mesorectum, especially in ORM were easily left behind in pelvis[4,12,13]. Frequency of CRM involvement after conventional resection was reported up to 27%[2,11,14,15], compared with 6.5% after TME[16,17], which is consistent with our findings. The decrease of CRM involvement rates after TME justified the theory: the frequency of microscopic spread in ORM could be very high, and destruction of ORM which often occurred in conventional resection, could easily lead to positive CRM.

Distal mesorectal spread can be evaluated pathologically after TME, after standard resection of the rectal cancer, the DMR remained inside pelvis[18]. Frequency of discrete tumor cancer spread 3 cm or more from the primary lesions in DMR varied from 0 to 10% of the cases[4,17,19-22], and discontinuous spread in DMR could be found even up to 5 cm beyond the lower margin of the primary tumor[1,6], some patients with DMR spread had poor prognosis[21-23]. The present study showed that four cases with tumor involvement of DMR had the spread within 3 cm of primary mural tumors, with a maximum of 3.0 cm. Therefore, we support a safe DMR resection margin of no less than 4 cm for lower rectal cancer, and consider that failure to adequate excision of the involved DRM would risk in leaving behind residual microscopic cancer foci in a significant percentage of patients. The most common pattern of pelvic recurrence is extramural diseases emanating from the sacral hollow or pelvic floor, which is entirely compatible with this hypothesis[24]. But others argued that pathological evidence of DMR spread in itself did not necessarily justify total removal of DMR in all cases because the local recurrence rate and survival rate were not improved significantly even after TME[4,17].

Cawthorn[25] reported that mesorectal involvement of large tumor nodules (greater than 4 mm) was associated with significant poorer prognosis than that of small ones (less than 4 mm). However, the author cautioned that the poor prognosis might result from residual microscopic tumor nodules, which coexist with large nodules and can easily be overlooked and left behind during operation. Ueno *et al*.[13] demonstrated that large tumor nodules and microscopic tumor nodules correlated closely, and that large tumor nodules had a predicting value for existence of microscopic tumor nodules. The present study showed that 58.3% (14/24) patients with microscopic tumor foci involvement of the mesorectum had large tumor nodules (greater than 5 mm) in the mesorectum, which was lower than that reported by Ueno *et al*.

Kapiteijn *et al*. recently reported that standardized TME in combination with preoperative radiotherapy could significantly decrease the local recurrence rate in patients with rectal cancer, though its benefits in survival were not demonstrated because of a relatively short time of follow-up[26]. Other authors also concluded that preoperative radiotherapy could improve the prognosis of patients with rectal cancer[27]. In our series, no patients were treated with adjuvant therapy due to the high frequency of postoperative complications and its controversial impact on prognosis.

Extended lateral dissection beyond the extent of TME has been widely accepted in Japan as the improvement in survival rates was reported[28,29], but some argued that it had a limited advantage in prognosis and the functional problems were considerable[30,31]. Microscopic tumor nodule involvement of CRM after TME in our series suggested that a proportion of the patients had microscopic tumor spread in the extramesorectal regions in the pelvis. Further comprehensive pathological assessment of the extramesorectum is required to evaluate the curative value of TME in rectal cancer.

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