Clinical Research Paper

Spread of rectal cancer in the distal mesorectum
A report of 46 cases

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Key words: rectal neoplasm, mesorectum, distal spread, whole-mount section, pathology

Background and Objective: Total mesorectum excision (TME) for rectal cancer may reduce local recurrence by complete eradication of metastatic foci in the distal mesorectum. While the spread regulation of rectal cancer in the distal mesorectum and the ideal length of mesorectum resection are still unclear. This study was to investigate the spread of rectal cancer in the distal mesorectum. Methods: The whole-mount section with HE staining was used to detect tumor spread in the mesorectum of 46 rectal cancer patients. The correlation of tumor spread to clinicopathologic parameters was analyzed by Logistic regression. Results: The occurrence rate of distal tumor spread in rectal cancer was 10.9% with the maximal distance of 1.5 cm; that of distal mesorectum spread was 21.7% with the maximal distance of 4.0 cm, which included metastasis in lymph nodes, solitary tumor foci, vessel and perineural invasion. Multivariate analysis showed that TNM stage was the only significant factor influencing distal spread of rectal cancer. Conclusions: Spread of rectal cancer in the distal mesorectum is common. Resecting at least 5 cm of the mesorectum distal to rectal cancer is recommended.

The local recurrence of rectal cancer, in particular, middle or lower rectal cancer, after sphincter-preserving surgery is still a great threat to long-term survival and life quality of the patients. Total mesorectum excision (TME) can drastically reduce the local recurrence rate of rectal cancer through eradicating metastatic foci in the distal mesorectum. However, TME also could increase the occurrence rate of anastomotic leakage. The regulation of rectal cancer spreading in the distal mesorectum and the ideal length of mesorectum resection are still unclear. This study was to probe into the spread of rectal cancer in the distal mesorectum by pathologic whole-mount sections in order to offer a pathologic reference for determining the length of the distal mesorectum to be resected during sphincter-preserving operation.

Patients and Methods

Clinical data. We enrolled rectal cancer patients who were diagnosed and underwent resection in the Department of Gastrointestinal Surgery, the First People’s Hospital of Guangzhou, from January 2005 to July 2006, pursuant to the following conditions: they had not received radiotherapy or chemotherapy (neoadjuvant treatments) before operation, and a segment of distal rectum or mesorectum of ≥ 5 cm had been resected. Among 46 eligible patients, 25 were men and 21 were women, with a median age of 56 (range, 28–79). The mean tumor size was 4.5 cm (range, 2.0–7.5 cm). The distance from the tumor to the anal margin was less than 5 cm in ten patients, 5–10 cm in 16 patients and 10–15 cm in 20 patients. Of the 46 patients, 36 were diagnosed with adenocarcinoma, and ten with mucous adenocarcinoma or signet ring cell carcinoma; seven were at stage I, 13 at stage II, 22 at stage III and four at stage IV; 38 underwent low anterior resection (LAR) (sphincter-preserving surgery), and eight underwent abdominoperineal resection (APR).

Research methods. Operative procedures. The operative procedures were performed according to the principles of TME.1–3 During operation, the inferior mesenteric vessels were ligated at a high position, and all lymph nodes at the base of blood vessels were excised. The fascia of the splanchnic layer at the inner side of the left and right hypogastric nerves, tumors and the mesorectum were isolated fully to the distal end of tumor (5 cm distant from the tumor, for the patients who did not undergo TME) or to the level of the musculus levator ani at pelvic floor (for the patients who underwent TME). The isolation was performed between the splanchnic layer and the parietal layer of the pelvic cavity with an electric knife under direct visualization, and the fascia of the splanchnic layer was kept intact during the isolation. APR and sigmoidostomy were performed on 8 patients when the distal end of the fully isolated rectum was not long enough (3 cm from the tumor); LAR was performed on 38 patients using two anastomats. No anastomotic leakage occurred.

Collection of specimens. The rectum segment was dissected along its longitudinal axis at the side opposite to the mesorectum as soon as it was excised. The dissected mesorectum and rectum segment were spread out fully, and fixed on a soft wood board with pins. The upper end and lower end of the specimen were marked and the length was...
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measured. Then the specimen along with the board was soaked in 10% formaldehyde; this fixing method eliminated the influences caused by shrinkage of the specimen after fixing.

Preparation of whole-mount sections. After fixing, consecutive tissue masses about 5 mm thick, including the rectum and its mesentery, were cut transversely from the lower margin of tumor to the distal end of rectum. Upper end and lower end of tissue masses were marked. These tissue masses were also marked consecutively. All tissue masses were embedded routinely in paraffin. Two consecutive tissue slices about 8 μm thick were cut with a whole-mount slicer from the lower end of each tissue mass (Fig. 1), and stained with routine HE dyeing.

Pathologic examination. The slices were observed by an experienced pathologist under a common optical microscope. Cancer cells found in the rectal wall were noted as spread in the wall of distal rectum, and those found in the mesentery were noted as spread in the distal mesorectum.

Calculation of distal spread distance. The spread distance was calculated based on the last tissue mass of the lower end of specimen that containing cancer cells. For example, if cancer cells were found in the first tissue mass of the lower end of specimen, the spread distance was noted as 0.5 cm, those found in the second tissue mass noted as 1.0 cm, those found in the third tissue mass noted as 1.5 cm, and so on.

Statistical methods. The correlations of the distal spread of rectal cancer (in the rectal wall or mesorectum) to the clinicopathologic parameters were analyzed by Logistic regression model using software SPSS 7.0. A p value of < 0.05 was considered significant.

Results

Pathologic findings. Of the 46 patients, five (10.9%) had infiltration in the wall of distal rectum, and ten (21.7%) had distal mesorectum metastasis, among whom three (6.5%) had both infiltration in rectal wall and distal mesorectum metastasis. Therefore, a total of 12 (26.1%) patients had distal spread of rectal cancer.

The distance of infiltration in the wall of distal rectum was 0.5 cm in three patients, 1.0 cm in one patient and 1.5 cm in one patient. The infiltration pattern was direct infiltration of cancer cells to form isolated nests of cancer cells in submucosal or intramuscular layers.

The distance of distal mesorectum metastasis was 1.5 cm in three patients, 1.0 cm in two patients, 1.5 cm in two patients, 2.0 cm in one patient, 3.0 cm in one patient and 4.0 cm in one patient. The metastasis patterns were various, including lymph node metastasis of the mesorectum, formation of isolated cancer nests in the mesorectum (Fig. 2), infiltration of vessels (cancer emboli in blood vessels or lymphatics), and peripheral infiltration of nerves.

The correlations of the distal spread of rectal cancer to the clinicopathologic parameters. Logistic regression was used to analyze the correlations of the distal spread of rectal cancer to the clinicopathologic parameters, including sex, age, serum level of carcinoembryonic antigen (CEA) before operation, tumor location, tumor size, gross type, histological type, cell differentiation, T stage, M stage and TNM stage. Univariate analysis showed that the serum level of CEA before operation, N stage and TNM stage entered the regressive model (Table 1); multivariate analysis showed that only TNM stage entered the model (p = 0.031), indicating that TNM stage was the only factor affecting the distal spread of rectal cancer.

Discussion

As one of the major causes of treatment failure in rectal cancer patients, the local recurrence of rectal cancer after operation is a compelling problem. For a long time, the attention was focused on the length of the distal rectum being excised, based on the consideration that the infiltration and recurrence in the wall of the distal rectum is mainly due to inadequate resection of the rectum. Since Heald proposed the concept of TME for rectal cancer, the spread of rectal cancer in the distal mesorectum has received more and more attention. Heald et al. found that TME may reduce greatly the local recurrence rate of rectal cancer after operation, and this may be attributed to the utmost removal of metastatic foci in the distal
mesorectum by TME which decreases the risk of recurrence; whereas, metastatic foci in the distal mesorectum may not be removed thoroughly by conventional operation due to inadequate resection. In the cases with local recurrent rectal cancer after operation, over a half involve a single recurrence in the pelvic cavity without recurrence on the anastomotic ends, suggesting that the residue in the mesorectum is another major cause of recurrence.

The current research proves that the distal spread route of rectal cancer includes direct infiltration in the rectal wall and distal mesorectum metastasis, and the occurrence rate and the metastatic distance for the former are greater than those for the latter. Of the 46 patients, ten (21.7%) had tumor spread in the distal mesorectum. This result is accordant to those reported in literature. In this study, the occurrence rate of infiltration in the distal rectal wall is 10.9% (5/46) with the longest distance of infiltration being 1.5 cm, and the overall occurrence rate of the distal spread of rectal cancer is 26.1% (12/46), indicating that distal spread is not an event of small probability and should be paid due attention. In particular, rectal cancer may spread in the distal mesorectum for 4 cm or more, therefore, it may recur if the distal mesorectum has not been resected thoroughly. Our results also confirm the pathologic basis of TME, that is, the spread of rectal cancer exists in the distal mesorectum to different extents. Based on these results, we suggest to resect the distal mesorectum of 5 cm or longer from the lower end of tumor in the patients with upper rectal cancer, and perform TME on the patients with middle or lower rectal cancer according to the standard and principles proposed by Heald in order to reduce the local recurrence rate of rectal cancer to utmost extent.

Besides lymph node metastasis, the spread patterns in the mesorectum also include isolated cancer foci and infiltration in vessels and nerves. This may be attributed to the fact that cancer cells may spread through ample intercommunicating vessels in loose mesorectal tissue, or cancer cells may penetrate the rectal wall to enter the mesorectum, and then implant in the mesorectal space to form metastatic foci. It has been reported that tumor location, the infiltration depth in the rectal wall (T stage) and clinical stage are factors affecting the spread of rectal cancer in the distal mesorectum. In our research, multivariate analysis revealed that only clinical stage affects the spread of rectal cancer in the distal mesorectum, indicating a poor prognosis for the patients with spread in the distal mesorectum and suggesting the need for enhancement of surgical quality and postoperative adjuvant treatment.

As to the problem how far the distal rectum should be resected, Goligher et al. had suggested that a segment of the distal rectum of 5 cm long should be regarded as the limit of safe resection considering the existence of cancer infiltration in the wall of distal rectum; this is the so-called classic “5 cm rule”. However, recent clinicopathologic studies rose doubts on the validity of this conclusion; the results of multiple researches revealed that the spread distance of rectal cancer in the wall of distal rectum does not exceed 2 cm in general, and our own observations support this viewpoint. Therefore, we suggest resection of 2–3 cm of the distal rectum to guarantee the success of sphincter-preserving surgery.

In summary, in contrast with the spread of rectal cancer in the wall of distal rectum, its spread in the distal mesorectum is more common with a longer distance. When performing radical operation of rectal cancer, adequate resection of both distal rectum and distal mesorectum is important for reducing the local recurrence rate of rectal cancer. Our results need to be proved by a larger scale clinical research with clinical follow-up.

Table 1 Univariate logistic regression analysis of influencing factors of spread of rectal cancer in the distal mesorectum

<table>
<thead>
<tr>
<th>Variate</th>
<th>Coefficient β</th>
<th>S.E.</th>
<th>Wald value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.284</td>
<td>0.854</td>
<td>0.100</td>
<td>0.700</td>
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<td>Age</td>
<td>20.013</td>
<td>40193.151</td>
<td>0.000</td>
<td>1.000</td>
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<td>Serum CEA level</td>
<td>2.010</td>
<td>0.980</td>
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<td>0.900</td>
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<td>Tumor size</td>
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<td>0.946</td>
<td>1.868</td>
<td>0.203</td>
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<td>Gross type</td>
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<td>0.846</td>
<td>0.220</td>
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<td>Histology</td>
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<td>1.120</td>
<td>1.803</td>
<td>0.186</td>
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<td>0.875</td>
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<td>M stage</td>
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<td>26412.624</td>
<td>0.000</td>
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<td>TNM stage</td>
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<td>4.426</td>
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Table 2 Multivariate logistic regression analysis of influencing factors of spread of rectal cancer in the distal mesorectum

<table>
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<tr>
<th>Variate</th>
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<th>S.E.</th>
<th>Wald value</th>
<th>p value</th>
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<tr>
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<tr>
<td>TNM stage</td>
<td>2.027</td>
<td>0.994</td>
<td>4.426</td>
<td>0.031</td>
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References