·Colerectal Cancer-related Research·

Risk factors related to lymph node metastases after neoadjuvant therapy for locally advanced rectal cancer

Zhi-Fan Zeng,[1,2] Pei-Rong Ding,[1,3] Zhi-Zhong Pan,[1,3] Jun-Zhong Lin,[1,3] Li-Ren Li,[1,3] Zhen-Hai Lu,[1,3] Xiao-Jun Wu,[1,3] Ling-Heng Kong,[1,3] Zhong-Guo Zhou[1,3] and De-Sen Wan[1,3]

1. State Key Laboratory of Oncology in South China, Guangzhou, Guangdong, 510060, P. R. China
2. Department of Radiotherapy, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, 510060, P. R. China
3. Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, 510060, P. R. China

Correspondence to: De-Sen Wan
Tel.: 86.20.87343124
Email: wds@medmail.com.cn

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[**Abstract**] **Background and Objective**: Neoadjuvant therapy (radiotherapy, RT or chemoradiotherapy,CRT) could change status of the invasion and lymph node metastasis of rectal cancer. The risk factors of lymph node metastasis in rectal cancers without neoadjuvant therapy have been well known, but those in rectal cancers treated with preoperative RT or CRT remain unclear. This study was to investigate the risk factors of lymph node metastasis in patients who underwent preoperative RT or CRT for rectal cancers. **Methods**: Clinical data of 93 patients underwent preoperative RT or CRT followed by total mesorectal exesion (TME) for locally advanced rectal adenocarcinoma from August, 2003 to February, 2008 were reviewed. Twelve clinicopathologic factors and treatment-related factors were studied with univariate and multivariate analyses. **Results**: Univariate analysis showed that post-RT or post-CRT serum carcinoembryonic antigen (CEA) level, radiation dose, time interval from RT or CRT to TME, concurrent chemotherapy with oxaliplatin-containing regimens, and infiltration extent to bowel wall after RT or CRT (ypT stage) were significantly associated with lymph node status after RT or CRT (ypN stage). Multivariate analysis showed that concurrent chemotherapy with oxaliplatin-containing regimens (r=−0.481, P<0.01) and ypT stage (r=0.503, P<0.01) were independent risk factors of ypN stage. **Conclusions**: Pathologic T stage is the most reliable predictor of lymph node stage in rectal cancer patients received preoperative RT or CRT. Oxaliplatin-containing regimens could significantly reduce the risks of lymph node metastases and potentially improve the prognosis.

Key words: rectal neopalsm, neoadjuvant therapy, lymph node metastases, multivariate analysis

Surgical operation is the mainstay treatment of rectal cancer but with a high postoperative recurrence rate. Although total mesorectal excision (TME) can significantly reduce the recurrence rate, the local recurrence rate after TME alone is as high as 9.7% -12%.[1-3] The application of neoadjuvant therapy (radiotherapy or chemoradiotherapy) significantly improve the resection rate, local control rate and sphincter-preserving rate,[3-6] which is the mainstay approach to the patient with middle-to-low rectal cancer and brings fundamental changes of rectal cancer treatment. Due to the effects of neoadjuvant therapy, the status of infiltration depth and lymph node metastases are changed. Thus it is instructive to understand the behavior of lymph node metastases after radiotherapy for the

choice of neoadjuvant therapy and subsequent therapies. The present study aimed to explore the risk factors related to the lymph node metastases after neoadjuvant therapy, providing references for the individualized treatment of rectal cancer.

Data and method

Clinical data. Clinical data of 93 patients with moderate-to-low rectal cancer that underwent neoadjuvant therapy and TME operation in Cancer Center of Sun Yat-Sen University from August 2003 to February 2008 were reviewed. Inclusion criteria: 1. Adenocarcinoma was pathologically confirmed; 2. Lower margin of the tumor was within 8 cm to the anal verge; 3. Endorectal ultrasonography and pelvic CT (or MRI) revealed that the tumor infiltrated out of the intestinal muscularis (cT3) or to the perirectal tissues, the mass was adhered and fixed (cT4), or there were peripheral lymph node metastases (N+), and distant metastases were ruled out with pelvic B-mode ultrasound and CT and chest X-ray; 4. No past history of rectal operation or pelvic radiotherapy and chemotherapy; 5. Multiple primary colorectal cancers were ruled out preoperatively with colonoscopy. The age of the group was ranged from 22 to 85 (median, 54). All patients were pathologically confirmed to be the adenocarcinoma.

Treatment procedures. All patients underwent radiotherapy or chemotherapy+ surgery.Radiotherapy regimens: the lesion was radiated by X-ray produced by linear accelerator, target area included the primary site and lymph nodes drainage areas; mono-isocentric 3-field radiotherapy, posterior field: left field: right field=2:1:1, the upper margin of radiation field was L5/S1 level, and the lower margin was 3 cm below the mass lower margin. The total radiation dose was 30 Gy/10 times or 46 Gy/23 times.

Chemotherapy strategies:patients underwent combined radiotherapy and chemotherapy received concurrent FOLFOX4 chemotherapy at day 1 and day 22, that is, Oxaliplatin, 85 mg/m^2 for day 1; intravenous injection of Leucovorin at the dose of 200 mg/m^2 for day 1 and day 2; bolus injection of 5-FU at the dose of 400 mg/m^2 at day 1 and day 2, or continuous intravenous injection for 22 h at the dose of 600 mg/m^2 for day 1 and day 2. Or the patient received concurrent XELOX chemotherapy at day 1 and 22, that is, Oxaliplatin (130 mg/m^2, day 1) and capecitabine (2000 mg/m^2, day 2-15).

Surgical procedures:the patient received operation four to ten weeks after radiotherapy, which was performed by senior surgeons who had received strict TME training program. Lymph nodes were dissected by the surgeons and sent for pathological examination. There was no case died because of surgical procedures (died within three months after operation), 34 cases (36.6%) underwent anterior resection, three cases (3.2%) underwent anterior resection plus preventive colostomy, 52 cases (55.9%) underwent abdomino-perineal resection and four cases (4.3%) underwent other procedures (one with posterior pelvic radical resection, two cases with total pelvic dissection and one case with Hartmann procedure).

Pathologic Complete Response (pCR) refers to the condition that no tumor tissue is identifiable at all under microscopy after thorough examination of the potential tumor-existing sites.

Observational parameters. Twelve clinical data were collected for analysis, including age, sex, distance of the tumor to anal verge, histological type, layer of infiltration to the intestinal wall, pre and post-radiotherapy serum CEA and CA19-9 levels, radiation dose, whether underwent concurrent chemotherapy, and time interval between radiotherapy and operation.

Statistical analysis. Data were analyzed with STATA8.0 software, quantitative data were expressed as ± s. Logistic regression for ordinal response model was established to analyze the related factors with lymph node metastases (N stage). The univariate Logistic regression was firstly performed, and the significant variables were introduced into the ordinal Logistic regression model for multivariate analysis. The correlations of ordinal variables were analyzed with Spearman correlation analysis. The significance level was defined to be 0.05.

Results

Lymph node metastasis. There were 20 cases (21.5%) with pathologic complete response. The number of sent lymph nodes was from 0 to 37 (mean, 8.4; median, 7). Patients were divided into groups according to T stages after neoadjuvant therapy (ypT stage), the proportions of patients with lymph node metastases in ypT0-1, ypT2 and ypT3-4 were 5%, 11.8%, 39.5% and 76.9%, respectively

Results of the univariate analysis. The results of univariate analysis showed that the post-radiotherapy serum CEA level, radiation dose, time interval between radiotherapy and operation, concurrent chemotherapy with oxaliplatin-containing regimen and ypT stage was associated with lymph node metastases status (see Tab. 1).

Results of the multivariate analysis. The results of multivariate analysis showed that the postoperative T stage and concurrent chemotherapy with oxaliplatin-containing regimen were the risk factors of lymph nodes metastases (Tab. 2). And the Spearman correlation analysis showed that the correlation of ypT and ypN stage is statistically significant ($r=0.503$, $P<0.01$, Tab. 3); and concurrent chemotherapy with oxaliplatin-containing regimen was also correlated to the ypN stage ($P<0.01$, $r=-0.481$).

Table 1 Univariate analysis of lymph node metastasis-related factors

Variate	Stage ypN0	Stage ypN1	Stage ypN2	*P* value
Case number	63	20	10	
Median age (years)	54	51.5	58.5	0.358
Sex (number)				0.477
Man	48	14	10	
Woman	15	6	0	
Distance from the anal verge (cm)	42.0±16.4	42.3±14.0	46.0±17.1	0.580
pre-CRT CEA (number)				0.521
≤5 μg/L	32	8	6	
>5 μg/L	29	11	3	
pre-CRT CA19-9 (number)				0.519
$\leq 3.5\times10^4$ u/L	51	16	7	
$>3.5\times10^4$ u/L	10	3	2	
Post-CRT CA19-9 (number)				0.153
$\leq 3.5\times10^4$ u/L	57	14	7	
$>3.5\times10^4$ u/L	3	3	3	
Post-CRT CEA (number)				0.038
≤5 μg/L	50	10	8	
>5 μg/L	10	7	2	
Pathologic type (number)				0.376
Adenocarcinoma	61	19	9	
Mucinous or signet cell carcinoma	2	1	1	
Dose of irradiation (number)				0.001
30 Gy	9	8	6	
46 Gy	54	12	4	
Time interval from CRT to resection (days)	44.9±17.3	37.2±10.4	34.2±10.1	0.003
Chemotherapy (number)				<0.001
Without	10	12	7	
With	53	8	3	
ypT classification (number)				0.001
T0	19	1	0	
T1	0	0	0	
T2	15	2	0	
T3	26	11	6	
T4	3	6	4	

The data of some patients are imcomplete. ypN, N stage after neoadjuvant therapy; pre-CRT, pre-neoadjuvant chemoradiotherapy; Post-CRT, post-neoadjuvant chemoradiotherapy; CEA, carcinoembryonic antigen; CRT, chemoradiotherapy. All values of distance from the anal verge and time interval from CRT to resection are presented as mean ± SD of relevant groups.

Table 2 Multivariate analysis of lymph node metastasis-related factors

Variate	β	Std. Err	*P* value	OR	95% CI
ypT classification (0/1/2/3/4)	8.12	4.66	<0.001	8.12	2.64–25.00
Post-CRT CEA(−/+)	1.44	0.97	0.585	1.44	0.39– 5.35
Dose of irradiation	0.94	0.04	0.166	0.94	0.87– 1.02
Time interval from CRT to resection	0.57	0.19	0.088	0.57	0.30– 1.08
Chemotherapy (without/with)	0.22	0.16	0.036	0.22	0.05– 0.91

OR, odds ratio; CI, confidence interval. Other abbreviations as in Table 1.

Table 3 Correlation of ypN stage to ypT stage

	ypN0	ypN1	ypN2	ypN+(%)
ypT0	19	1	0	1/20 (5.0)
YpT1	0	0	0	0/0 (0)
ypT2	15	2	0	2/17(11.8)
ypT3	26	11	6	17/43(39.5)
ypT4	3	6	4	10/13(76.9)

ypN stage, N stage after neoadjuvant therapy; ypT stage, T stage after neoadjuvant therapy. $r=0.503$, $P<0.001$.

Discussion

Neoadjuvant therapy can degrade the primary stage to ypT0-1 in 5-42% patients.[5,7,8] Because these patients require to preserve sphincter muscles or they cannot tolerate the surgical procedure, the proportion of transanal endoscopic microsurgery (TEM) is increasing. Therefore, deep understanding of the relationship between infiltration depth and lymph node metastases after neoadjuvant therapy is fundamental to the choice of TEM operation. For patients underwent surgery alone, the lymph node metastases is closely associated with infiltration depth,[9,10] while for those underwent neoadjuvant chemotherapy, the relationship between infiltration depth and lymph node metastases is controversial. Read et al.[8] demonstrated that lymph node metastasis rate for ypT0-1 patients was 3.4%, which increased up to 23% and 51.5% for those with ypT2 and ypT3-4, respectively. Kim et al.[11] also obtained similar results that the rate of ypT0-1 was less than 5%. Because the ypT stage can accurately predict the lymph node metastasis, the authors proposed that ypT stage could screen appropriate candidates to receive local resection procedures. However, Zmora et al.[12] showed that the lymph node metastatic risk of ypT0-1 patients was as high as 12.1%, and 97.5% ypT0 patients showed lymph node metastasis. And Medich et al.[5] also showed that ypT stage cannot predict lymph node metastasis reliably, and the ypT0-1 cannot screen appropriate candidates to receive TEM. The present study showed that lymph node metastatic rate of ypT0-1 was 5%, while the ypT2 and ypT3-4 were 11.8%, 39.5% and 76.9%, respectively. With the progress of primary lesion infiltration, lymph node metastases rate (N+) increased as well. Moreover, Spearman rank correlation analysis showed that ypT was closely associated with ypN stage (N0-2), further indicating that the ypT stage is predictive factor of lymph node metastasis. We analyzed the differences of ypT and ypN relationship and found that it was probably due to the differences of radiation dose, dividing method, concurrent chemotherapy, time interval between radiotherapy and operation and the pathologic complete response evaluation, particularly the evaluation criteria of pathologic complete response, the section thicknesses of different studies are quiet different, as well as the judgment of residual tumor tissue.[11,13,14] Many studies do not specify the criteria of ypT0, for instance, studies with 5 mm thickness section is more likely to omit residual tumor tissues than

studies with 4 mm thickness sections, which degrades the ypT stage, thereby influencing the analysis of the relationship between ypT stage and lymph node metastasis. Meanwhile, neoadjuvant therapy, especially the neoadjuvant chemotherapy and radiotherapy, can not only reduce the size of primary tumor, but also reduce the lymph node size and lead to mesenteric fibrosis, thus, the detection of lymph node can be affected and the judgment of lymph node status is variable.[15] Similarly, whether the findings of mucus lake without malignant cells should be judged as complete response or not also influences the results.[11,13,14] Therefore, the investigation of relationship of ypT and lymph node metastasis should based on strict pathologic evaluation system.

The application of neoadjuvant has changed the treatment failure of rectal cancer. In the era of neoadjuvant radiotherapy, the postoperative local recurrence rate has dropped from 10%-20% to 2-3% with TME,[2,3,6,16] while the distant metastasis rate is three times of the local recurrence rate. Therefore, adding systemic chemotherapy to the neoadjuvant radiotherapy can not only induce desirable degradation, but also control the micrometastasis to improve clinical outcome. Several studies showed that concurrent chemotherapy on the basis of radiotherapy can further degrade the T stage and increase the proportion of ypT0. However, the impact of concurrent chemotherapy on the lymph node metastasis is unknown currently. Bosset et al.[15] demonstrated that although the ypT0 of the concurrent chemotherapy (5-FU based) group was 2.5 times higher than the chemotherapy alone group, the difference of lymph node metastasis rate was not significant, indicating that although neoadjuvant chemotherapy with 5-FU could degrade the T stage of the primary site, the lymph node was not degraded. In contrast to the study by Bosset, multivariate analysis of our study showed that lymph node metastasis of the concurrent chemotherapy (containing oxaliplatin) was significantly lower than radiotherapy alone group, the difference of the two studies is likely due to that the oxaliplatin-containing regimen can strengthen the cytotoxic effect of radiotherapy, whereby enhancing the lymph node metastasis control rate. For instance, in the patient with metastatic colorectal cancer, oxaliplatin-containing regimen can significantly prolong the disease-free survival rate and total survival rate as compared with 5-FU based regimen. Meanwhile, oxaliplatin is a potent radiation sensitizer that can enhance tumor cell DNA damage, inhibit DNA repairing and tumor cell proliferation, and in vitro and in vivo experiments has proved its radiation sensitizer effects.[4,17] Because the ypN stage is the independent determinant of prognosis after neoadjuvant therapy,[18,19] besides the short term benefit of low lymph node metastatic rate achieved by oxaliplatin-containing regimen, the clinical outcome can be potentially improved. However, further deduction requires evidences from long term follow up.

Parameters of radiation dose, time interval between operation and radiotherapy, CEA level after neoadjuvant therapy and concurrent chemotherapy that have been included in the univariate analysis were not introduced into the multivariate regression model. Because these factors are closely associated with the ypT stage of the primary lesion,[15,16,20,21] their impact on the ypN stage was reduced with the introduction of ypT stage.

In conclusion, ypT stage of rectal cancer after neoadjuvant therapy is related to the ypN stage, for instance, ypT0 patients have low lymph node metastatic rate (5%). This relationship is conducive to the screening of appropriate patients to undergo anal local resection operation. Concurrent chemotherapy with oxaliplatin-containing regimen can significantly reduce the risk of lymph node metastasis rate, and can potentially improve the clinical outcome. Because the study is retrospective in nature, prospective study is mandatory to provide cogent evidence.

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