Pathological Features of Lymph Nodes Around Inferior Mesenteric Artery in Rectal Cancer: A Retrospective Study

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Research

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Abstract

Objective: To explore the pathological characteristics of lymph nodes around inferior mesenteric artery in rectal cancer, and to explore its risk factors and its impact on tumor staging.

Methods: Cases of rectal cancer patients underwent proctectomy surgery were collected in this study. Clinical features of patients, including gender, age, BMI, tumor size, pathological type, differentiation, nerve invasion, lymph nodes, tumor marker and pathological examinations were analyzed.

Results: A total of 485 cases were included in this study. There were 29 cases with IMA-LN metastasis, the metastasis rate was 5.98% (29/485). Positive IMA-LNs were associated with distance from anal verge, CEA, pathological type, differentiation, nerve invasion, T stage and N stage. Multivariate analysis showed that distance from anal verge, CEA level, differentiation, and T stage were independent risk factors for positive IMA-LNs.

Conclusion: Distance from anal verge, CEA level, differentiation, and T stage were independent risk factors for positive IMA-LNs. No skip metastasis occurred in IMA-LNs. We should choose the appropriate surgical methods to achieve better oncological results and reduce the incidence of postoperative complications.

Introduction

In the treatment principle of colorectal cancer, there are great differences between the East and the West. For locally advanced rectal tumors, the US guidelines recommend TME surgery on sequence of neoadjuvant chemotherapy, while for resectable colon tumors, neoadjuvant chemotherapy plus intestinal resection and full dissection of regional lymph nodes are recommended. However, Asian doctors represented by China, Japan and South Korea advocated D3 lymphadenectomy based on Japanese guidelines. Therefore, whether to perform the third station lymph node dissection is controversial. As the core of the third station lymph nodes, the one around the root of Inferior mesenteric artery (IMA-LNs), its impact on prognosis and the way of dissection have been the focus of research.

Materials And Methods

Clinical samples

From Jan. 2018 to Dec. 2020, we performed a retrospective analysis of patients who were eligible to receive proctectomy surgery in the Department of Gastrointestinal Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine. Inclusive criteria: no distant metastasis; no obstruction; no emergency surgery; no radiotherapy or chemotherapy and other anti-tumor treatment; no history of other malignant tumors; no colorectal multiple primary cancer.
The study was approved by the Research Ethics Committee of Renji Hospital and carried out in accordance with the ethical standards formulated in the Helsinki Declaration.

**Pathological Analysis**

The specimens were dissected by the surgeon after operation, and all the accessible lymph nodes were routinely submitted for examination. Pathological examination was performed by pathology department of our hospital. Routine examination included HE stained of tumor sections and lymph nodes and microsatellite instability (expression of mismatch repair protein MLH1, MSH2, MSH6 and PMS2) and ras gene mutation (K-ras, N-ras and BRAF gene mutations). Pathological staging was performed according to American Joint Committee on Cancer (AJCC) 8th Edition TNM staging system.

**Statistical analysis**

All categorical data were counted as cases or percentages, and continuous data were expressed as mean ± SD. The software IBM SPSS 22.0 was used for statistical analysis. Categorical data were analyzed using the Chi-squared ($\chi^2$) test or Fisher's exact test. Statistical significance was reached at a value of (P < 0.05).

**Results**

**Positive rate of IMA-LN**

According to the above inclusion criteria, a total of 485 cases were enrolled in this study. All patients successfully completed IMA-LN dissection. In this study, IMA-LN metastasis (positive) was defined as at least one positive lymph node was found in this area. In IMA-LNs, a total of 1043 lymph nodes were found, of which 38 were positive (3.6%). The rate of IMA-LNs Lymph node metastasis rate was defined as IMA-LN metastasis cases/ total number of cases. Among all the included cases, there were 29 cases with IMA-LN metastasis, the metastasis rate was 5.98% (29/485).

**Ima-In And Clinical Characters**

In this study, we found that positive IMA-LNs were not associated with gender, age or body mass index (BMI), but related to the distance from anal verge. All patients were routinely examined for tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 19 – 9 (CA19-9) and carbohydrate antigen 72 – 4 (CA72-4). We found that positive IMA-LNs were not associated with CA19-9 or CA72-4, but related to CEA (Table 1).
### Table 1
IMA-LN and clinical characters

|           | Case(n) | IMA-LN | $\chi^2$ value | P value |
|-----------|---------|--------|----------------|---------|
|           |         | Metastasis (n) | Metastasis rate (%) |         |
| Gender    |         |                |                  |         |
| Male      | 296     | 16 | 5.4 | 0.445 | 0.505 |
| Female    | 189     | 13 | 6.9 |       |       |
| Age (year)|         |        |                  |         |
| ≤ 60      | 171     | 10 | 5.8 | 0.008 | 0.929 |
| >60       | 314     | 19 | 6.1 |       |       |
| BMI (kg/m²)|         |        |                  |         |
| ≤ 25      | 298     | 19 | 6.4 | 0.216 | 0.642 |
| >25       | 187     | 10 | 5.3 |       |       |
| Distance from anal verge(cm) |         |        |                  |         |
| ≤ 10      | 322     | 13 | 3.7 | 6.428 | 0.011*|
| >10       | 163     | 16 | 9.2 |       |       |
| CEA (ng/ml)|         |        |                  |         |
| ≤ 5       | 202     | 5  | 2.5 | 7.561 | 0.006*|
| >5        | 283     | 24 | 8.5 |       |       |
| CA19-9 (U/ml) |         |        |                  |         |
| ≤ 27      | 213     | 10 | 4.7 | 1.115 | 0.291 |
| >27       | 272     | 19 | 7.0 |       |       |
| CA72-4 (U/ml) |         |        |                  |         |
| ≤ 6.9     | 304     | 17 | 5.6 | 0.217 | 0.641 |
| >6.9      | 181     | 12 | 6.6 |       |       |

*P<0.05, the difference was statistically significant

**Ima-In And Pathological Parameters**
Positive IMA-LNs were not associated with tumor size, lymph nodes harvest number, microsatellite status or ras phenotype, but related to pathological type, differentiation and nerve invasion. And positive IMA-LNs were related to T stage and N stage, as shown in Table 2. Interestingly, there was no case of IMA-LN positive without paracancerous lymph node metastasis, means no case of skip metastasis.
| Case(n) | IMA-LN | χ² value | P value |
|---------|--------|----------|---------|
| Tumor size(cm) |        |          |         |
| ≤ 4 | 262 | 11 | 4.2 | 3.215 | 0.073 |
| >4 | 223 | 18 | 8.1 |        |        |
| Pathological type |        |          |         |
| ADC | 408 | 20 | 4.9 | 5.306 | 0.021* |
| MC/SRCC | 77 | 9 | 11.7 |        |        |
| Differentiation |        |          |         |
| High/Middle | 384 | 12 | 3.1 | 26.724 | <0.0001* |
| Low | 101 | 17 | 15.9 |        |        |
| Nerve invasion |        |          |         |
| No | 381 | 11 | 2.9 | 30.22 | <0.0001* |
| Yes | 104 | 18 | 17.3 |        |        |
| LN harvest number |        |          |         |
| <12 | 138 | 7 | 5.1 | 0.282 | 0.595 |
| ≥ 12 | 347 | 22 | 6.3 |        |        |
| Microsatellite status |        |          |         |
| stable | 440 | 25 | 5.7 | 0.747 | 0.387 |
| unstable | 45 | 4 | 8.9 |        |        |
| Ras phenotype |        |          |         |
| Wild | 289 | 17 | 5.8 | 0.012 | 0.918 |
| mutant | 196 | 12 | 6.1 |        |        |
| T stage |        |          |         |
| Tis or 1 | 16 | 0 | 0 | 35.72 | <0.0001* |
| 2 | 40 | 1 | 2.5 |        |        |
| 3 | 286 | 12 | 4.2 |        |        |

ADC: Adenocarcinoma; MC: Mucinous Carcinoma; SRCC: Signet Ring Cell Carcinoma
| Case(n)          | IMA-LN | $\chi^2$ value | P value |
|-----------------|--------|----------------|---------|
| Metastasis(n)   | Metastasis rate (%) |         |         |
| 4\(^a\)        | 143    | 16             | 11.2    |
| N stage         |        |                |         |
| 0               | 206    | 0              | 0       | 10.43  | 0.015* |
| 1               | 162    | 13             | 8.0     |
| 2               | 117    | 16             | 13.7    |

ADC: Adenocarcinoma; MC: Mucinous Carcinoma; SRCC: Signet Ring Cell Carcinoma

\(a\): Including high rectal cancer and preoperative MRI prompt T3

\(*P<0.05\), the difference was statistically significant

Further, eight variables with $P<0.05$.

Table 3
Multivariate Logistic regression analysis for risk factors on IMA-LN metastasis

| Regression Coefficients | Standard error | Wald value | OR     | 95% CI            | P value |
|-------------------------|----------------|------------|--------|-------------------|---------|
| distance from anal verge| -1.545         | 0.718      | 4.633  | 0.052–0.871       | 0.031*  |
| CEA level               | -2.721         | 0.980      | 7.710  | 0.010–0.049       | 0.005*  |
| tumor size              | -0.481         | 0.777      | 0.383  | 0.135–2.835       | 0.536   |
| pathological type       | 0.003          | 0.806      | 0.000  | 1.003             | 0.997   |
| differentiation         | -3.913         | 0.714      | 30.050 | 0.005–0.081       | 0.000*  |
| nerve invasion          | -1.484         | 0.845      | 3.084  | 0.043–1.118       | 0.079   |
| T stage                 | -2.169         | 1.078      | 3.883  | 0.015–1.045       | 0.048*  |
| N stage                 | -0.672         | 0.586      | 1.316  | 1.958             | 0.621–6.167 | 0.251 |

\(*P<0.05\), the difference was statistically significant

Discussion
Lymph node metastasis is the most common and main metastasis pathway of colorectal cancer, and it is also an important indicator of staging and prognosis of colorectal cancer [1]. The value of lymph node dissection around root of IMA is still disputed. Many studies have reported that D3 dissection can reduce paraaortic recurrence and systemic metastasis [2], and improve the prognosis [3, 4]. On the other side, some studies believe that the lymph node metastasis rate of IMA-LNs is relatively low, even after resection this kind of patients suggest poor prognosis, so it is of less significance to be resected [5–7].

1. Risk factors of IMA-LN

Our study showed that the positive rate of IMA-LN was related to distance from anal verge, CEA level, tumor size, pathological type, differentiation, nerve invasion, T stage and N stage. The result is similar to the previous reports [8]. Sun et al. [9] pointed out that for rectal cancer, neoadjuvant chemoradiotherapy can reduce the lymph node metastasis rate of IMA-LNs. For the patients who received neoadjuvant chemoradiotherapy, the location of the lesion above peritoneal reflexes, low degree of tumor differentiation and high preoperative serum CEA level were the risk factors of positive IMA-LNs. Nagasaki et al. [10] found that for patients with stage III colon cancer, serum CEA level, T stage, number of lymph node dissection will significantly affect the positive situation of the third station lymph nodes (including IMA-LNs). Multivariate Logistic regression analysis showed that only four factors (distance from anal verge, CEA level, differentiation, and T stage) were independent risk factors for positive IMA-LNs. There is no clear evidence that different locations of the lesion in the rectum affect the lymph node metastasis rate. It is worth noting that the lymph node metastasis rate of sigmoid colon tumor is significantly higher than that of rectal tumor [6, 11].

2. The influence of IMA-LN on TNM staging

The AJCC staging is determined by the number of lymph nodes rather than the distance from the tumor [12, 13]. There are few studies and reports about the effect of IMA-LNs on TNM staging [14]. The positive IMA-LNs can aggravate the severity of the original stage III patients [15, 16]. Some surgeons believe that IMA-LNs metastasis can occur in T2, 3, 4 colorectal tumors, and there may be skip metastasis. Therefore, IMA-LNs should be routinely removed for colorectal tumors beyond T1 [17, 18]. But in this study, we did not find N positive was caused by only IMA-LN, that means no skip metastasis. It also means that if IMA-LNs turns negative, TNM staging will not be reduced. Does it mean that IMA-LN is not the origination of metastasis, but just the destination or interchange station?

3. Benefits of high ligation

Whether lymph node dissection around IMA can benefit patients is still uncertain, which may be the reason why the guidelines differ in this respect. Since there is no clear evidence that D3 lymph node dissection can benefit patients, the European and American guidelines do not consider it necessary to perform routine third station lymph node dissection [19]. High ligation has been reported to be effective in oncology, it can reduce paraaortic recurrence and systemic metastasis, and improve the prognosis of some patients [20]. But from the point of view of complications such as anastomosis leakage and
postoperative physiological dysfunction, it seems that high ligation is slightly worse than low ligation [21, 22]. For laparoscopic or robotic assisted radical surgery for colorectal cancer, the guidelines are conservative and not recommended as a routine recommendation. Only doctors with relevant experience should be recommended. At the same time, tumor staging, lymph node metastasis and surgical difficulty should be considered comprehensively [23]. Many studies think that there is no significant difference between high and low ligation [24–26]. In our study, from the pathological features, the benefit of high ligation with low tumor location is limited.

4. The area to be resected in high ligation

Although the range of lymphadenectomy is controversial in different guidelines, the importance of lymphadenectomy is consistent. According to Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines for the treatment of colorectal cancer, IMA-LNs are defined as the lymph nodes from the root of IMA to the beginning of LCA and along the IMA [27]. Similarly, follow the principles of CME, the scope of dissection is around the root of IMA, but it often goes beyond the boundary in real operation. It is possible that part of the retroperitoneal tissue may be removed due to excessive traction. So we need further research to define such a region.

Conclusion

Distance from anal verge, CEA level, differentiation, and T stage were independent risk factors for positive IMA-LNs. No skip metastasis occurred in IMA-LNs. Surgeons should fully evaluate the above related factors and choose the appropriate surgical methods in order to achieve better oncological results and reduce the incidence of postoperative complications. At present, there is no strong evidence of evidence-based medicine that IMA-LNs dissection can improve patients the prognosis of patients, but IMA-LN metastasis is a risk factor for poor prognosis. With the development of precision medicine, it is expected that new diagnostic techniques can accurately evaluate the status of lymph node metastasis before operation, and more high-quality multicenter randomized controlled trial is expected to guide clinical decision-making.

Abbreviations

IMA: Inferior mesenteric artery; LN: Lymph node; LCA: Left colonic artery; BMI: body mass index.

Declarations

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Not applicable.

Authors’ contributions
CHJ and YL wrote the main manuscript and participated in the study design and data analysis. CJX and YYS analyzed and interpreted the patient data. QX and LG modified the article. LG was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

All patients provided written informed consent before the operation, and this study was approved by the ethics committee of our hospital (number of ethics approval: KY2019-014).

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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