JBUON 2020; 25(4): 1854-1859
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

# Factors associated with lymph node retrieval in surgery for colorectal cancer

Iraklis E. Katsoulis, Lazaros Tzelves, Janneta Lysikatou, Ioannis G.Karaitianos

Department of Surgical Oncology, Saint Savvas Cancer Hospital, Athens, Greece.

## Summary

***Purpose:*** *Accurate staging of cancers of the colon and rectum (CRC) requires adequate lymph node (LN) evaluation, and many studies have demonstrated an association between the number of LNs examined and survival. The number of lymph nodes which are retrieved during resections for CRC may however vary and has been associated with various factors in the literature. The aim of the present study was to identify such factors in our CRC surgical practice.*

***Methods:*** *The study included specimens from 115 male and 177 female patients with a mean age of 69.2±11.9 years (31-94) who were treated for CRC in a Surgical Oncology Department over a 5-year period. The number of LNs harvested per patient was the main endpoint of interested. The analysed parameters were the patient's age and sex, the site of resection, the depth of tumour invasion (T stage), the grade of differentiation, the size of the tumour (maximal diameter) and the length of the resected colon. Neoadjuvant radiotherapy in rectal cancer cases was also taken into consideration. Analysis was applied using the statistical software PASW version 18. A p value<0.05 was considered statistically significant.*

***Results:*** *Female sex, right location of tumour and age younger than 65, were factors associated with significantly higher LN yield in resected specimens of CRC. Furthermore, the length of the resected bowel and the size of the tumour were positively correlated with the LN yield. In patients with rectal cancer, where neoadjuvant radiotherapy was applied, the LN yield was significantly lower. Lastly, the depth of invasion and the grade of tumour's differentiation did not have any impact on the number of harvested LNs.*

***Conclusion:*** *LN harvest in patients with CRC is highly variable and may be determined by multiple factors. Meticulous surgical technique and an adequate length of specimen are required in order to obtain as many LNs as possible.*

***Key words:*** *lymph nodes, colorectal cancer*

## Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of death [1]. The status of lymph nodes (LNs) at the time of surgical resection is the most important prognostic factor in CRC and many studies have demonstrated an association between the number of LNs examined and survival [2,3]. Accurate staging of CRC requires adequate LN evaluation. Retrieval of at least 12 LNs is currently a benchmark in CRC resections [4]. Nevertheless, the number of LNs which are retrieved during resections for CRC has been associated with various factors in the literature [5-11]. The aim of the present study was to identify such factors in our CRC surgical practice.

## Methods

The study included specimens from 115 male and 117 female patients with a mean age of 69.2±11.9 years (31–94) who were treated for CRC in a Surgical Oncology Department over a 5-year period. The operative pro-

*Corresponding author:* Iraklis E. Katsoulis, MD, PhD, FRCS, FEBS. Consultant Surgeon, Saint Savvas Cancer Hospital, 171 Alexandra's Ave, 11522 Athens, Greece.
Tel: +30 6944747226, Email: hrkats@yahoo.co.uk
Received: 28/03/2020; Accepted: 12/04/2020

cedures were 83 right colectomies, 1 transverse colectomy, 16 left colostomies, 36 sigmoid colectomies, 73 low anterior resections (LAR) and 23 abdominoperineal resections (APR). Right-sided colon cancer was defined as a tumour proximal to the splenic flexure, left-sided colon cancer as a tumour between the splenic flexure and rectosigmoid junction and rectal cancer as a tumour distal to the rectosigmoid junction. The number of LNs harvested per patient was the main endpoint of interest. The analysed parameters were the patient's age and sex, the site of resection, the depth of tumour invasion (T stage), the grade of differentiation, the size of the tumour (maximal diameter) and the length of the resected colon. Neoadjuvant radiotherapy in rectal cancer cases was also taken into consideration.

**Table 1.** Summary of the tested variables

| *Variables* | *Number of cases (%)* |
|---|---|
| Sex | |
| Male | 115 (49.6) |
| Female | 117 (50.4) |
| Age, years | |
| Mean (SD) | 69.2 (11.9) |
| <50 | 15 (6.5) |
| ≥50<65 | 53 (22.9) |
| ≥65<80 | 113 (48.7) |
| ≥80 | 51 (21.9) |
| Location of tumour | |
| Right | 83 (35.7) |
| Left | 60 (25.9) |
| Rectum | 89(38.4) |
| Depth of invasion | |
| Tis | 12 (5.2) |
| T1 | 18 (7.7) |
| T2 | 33 (14.2) |
| T3 | 115 (49.6) |
| T4 | 54 (23.3) |
| Grade of differentiation | |
| High | 18 (7.8) |
| Moderate | 187 (80.6) |
| Low | 27 (11.6) |
| Neoadjuvant radiotherapy (rectal cancers) | |
| Yes | 17 (19.1) |
| No | 72 (80.9) |
| Number of harvested LNs | |
| Mean (SD) | 14.98 (8.7) |
| Median | 14 |
| ≥ 12 | 136 (58.6) |
| < 12 | 96 (41.4) |
| Node positive | |
| Yes | 104 (44.8) |
| No | 128 (55.2) |

*Statistics*

Categorical variables were summarised by frequencies and percentages whereas quantitative variables as mean and standard deviation (Table 1). Independent *t*-test was used for comparisons between two groups. Bivariate correlations were performed between continuous variables. All variables were also included in linear regression analysis. The statistical software PASW version18 was used and a p value<0.05 was considered statistically significant.

## Results

As shown in Table 1, the mean number of harvested LNs in this cohort of specimens was 14.98 ±8.7 with a median of 14 lymph nodes. In 58.6% of the cases at least 12 LNs were retrieved.

In females, the mean number of harvested lymph nodes was 15.6±8.9 whereas in males it was

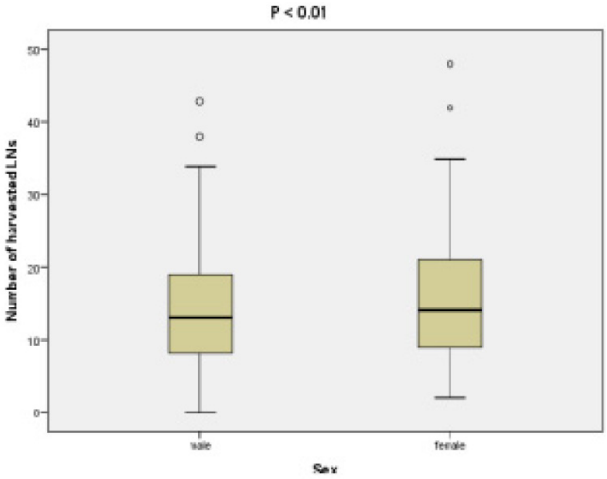


**Figure 1.** Boxplot diagram showing the difference in LN yield between males and females.

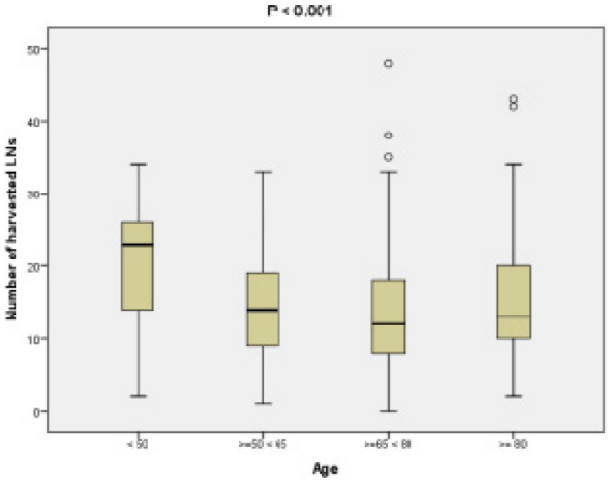


**Figure 2.** Boxplot diagram showing the LN yield in various age groups. The LN yield was significantly higher in younger patients.

14.3±8.6 and this difference was found significant (Figure 1).

In patients younger than 50 years, the mean LN yield was 19.3±9.9, whereas in patients between 50 and 64 years it was 15±7.5, in patients between 65 and 79 years it was 13.9±8.3 and lastly in patients of 80 years and over, the mean number of harvested LNs was 16.5±9.7. This difference in favour of patients younger than 65 years and particularly younger than 50 years was statistically significant (Figure 2).

In specimens of right sided tumours, the mean number of harvested LNs was 17.1±8.8, whereas in left sided tumours it was 13.1±7.2 and in rectal tumours it was 13.9±9.1. This difference in favour of right sided tumours was statistically significant (Figure 3).

Furthermore, the length of the resected bowel and the size of the tumour (maximal diameter) positively correlated with the LN yield (Figures 4 and 5).

As shown in Figure 6, in the subgroup of patients with rectal cancer, neoadjuvant radiotherapy was associated with a lower number of harvested LNs (9.38±6.82 vs 14.78±9.15).

Linear regression analysis showed that patient's age and sex, the site of resection, the size of the tumour (maximal diameter) and the length of the resected colon were independent factors significantly associated with the number of the harvested LNs. Lastly, the depth of invasion and the grade of tumour's differentiation did not have any impact on the LN harvest (Table 2).

## Discussion

Accurate staging of cancers of the colon and rectum requires adequate LN evaluation. In order

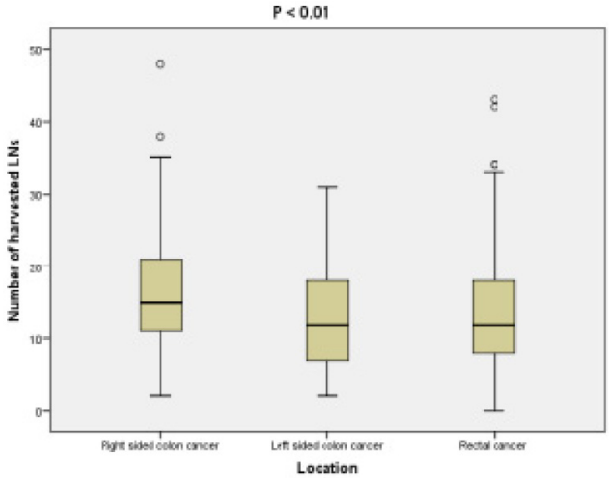


**Figure 3.** Boxplot diagram showing the LN yield according to tumour's location. The LN yield was significantly higher in right sided tumours.

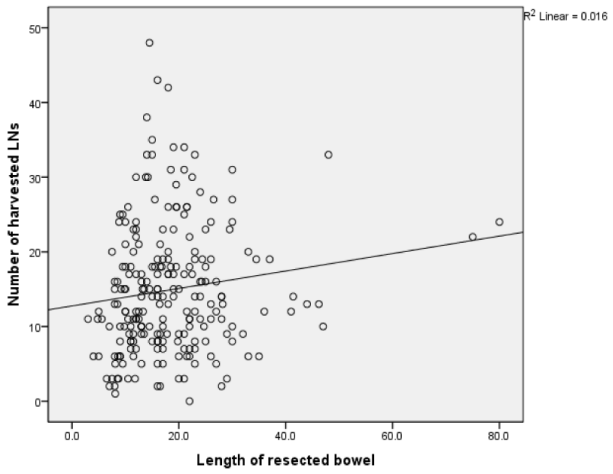


**Figure 5.** Scatter diagram showing a positive linear correlation of the number of harvested LNs with the length of the resected bowel.

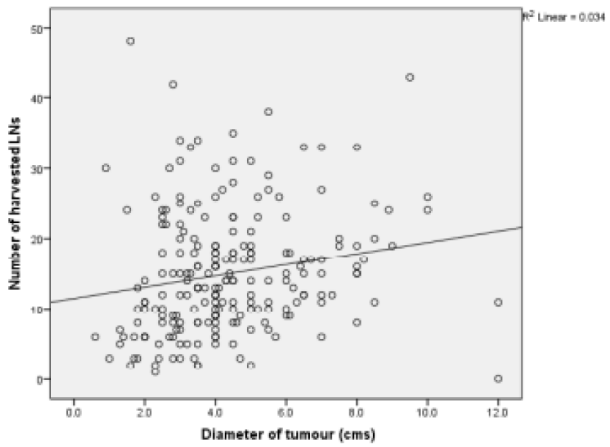


**Figure 4.** Scatter diagram showing a positive linear correlation of the number of harvested LNs with the length of the resected bowel.

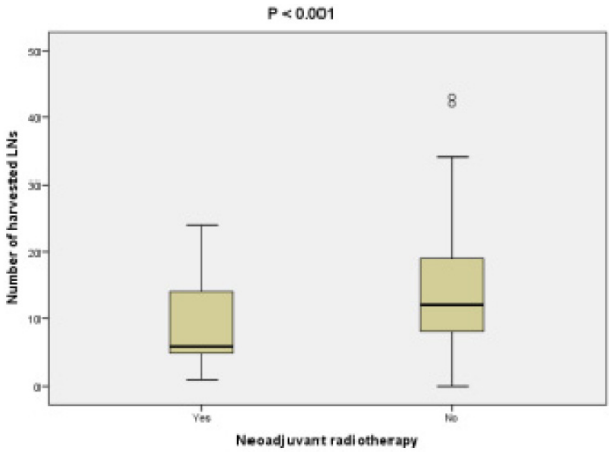


**Figure 6.** Boxplot diagram showing the LN yield in rectal specimens. Neoadjuvant radiotherapy was associated with a lower number of harvested LNs.

**Table 2.** Output of regression analysis

| *Model* | *Unstandardised Coefficients* | | *Standardised Coefficients* | *t* | *Sig.* | *95.0% Confidence Interval for B* | |
|---|---|---|---|---|---|---|---|
| | *B* | *Std. error* | *Beta* | | | *Lower bound* | *Upper bound* |
| (Constant) | 12.296 | 0.681 | | 18.058 | 0.000 | 10.962 | 13.631 |
| Age | -0.023 | 0.006 | -0.029 | -3.541 | 0.000 | -0.035 | -0.010 |
| Sex | 0.481 | 0.140 | 0.028 | 3.432 | 0.001 | 0.206 | 0.755 |
| Length of resected colon | 0.088 | 0.007 | 0.100 | 11.920 | 0.000 | 0.073 | 0.102 |
| Diameter of tumour | 0.623 | 0.037 | 0.147 | 17.064 | 0.000 | 0.551 | 0.694 |
| Grade of differentiation (G) | 0.234 | 0.172 | 0.012 | 1.362 | 0.173 | -0.103 | 0.571 |
| Depth (T) | 0.100 | 0.073 | 0.012 | 1.373 | 0.170 | -0.043 | 0.243 |
| Site of resection | -0.696 | 0.081 | -0.072 | -8.544 | 0.000 | -0.856 | -0.537 |

to define pathological N staging in CRC, current guidelines recommend retrieval of at least 12 LNs in the surgical specimen. In clinical practice, however, there is a wide variation regarding the number of LNs that are retrieved in resected specimens of colon and rectum. This reflects variability both in surgical and pathological performance. Surgical factors include operator's experience and adequacy of the *en bloc* resection [12]. Pathological factors include the use of fat clearing or LN revealing solutions and the experience of the pathologist in finding LNs [13]. It has been shown that with accumulation of experience and colorectal workload the number of retrieved LNs increases with time [14]. Furthermore, the number of LNs which are retrieved during resections for CRC has been associated with various other factors in the literature [5-11].

The present study found that the number of LNs harvested in surgery for CRC tends to be higher in females. This is consistent with other studies in the literature [5,14,15].

The number of lymph nodes harvested is associated with the age of the patients [16-18]. Other studies have also reported a reduction in the number of LNs with advancing age in colon cancer independently of sex and AJCC stage. A plausible explanation is that in older patients, LNs may be more difficult to be identified and retrieved due to reduced immunological response. Another explanation which needs to be considered is that in older patients, surgeons are often reluctant to perform extensive resections. In patients younger than 65 years and particularly younger than 50 years, the LN yield was significantly higher in the present study.

Several studies have shown that tumour location is significantly associated with the number of LNs in resection specimens; specifically, more LNs are usually obtained from right-sided colon cancers than from left-sided colon cancers, and the lowest number is from rectal cancers [19-22]. The reasons for this difference are still not fully understood. The literature indicates that more numerous intermediate nodes can be found in and around the ileocaecal region than in the mid-, left, and sigmoid colon. This may partially explain generally higher LN yield in right-sided specimens than in left-sided specimens. In addition, difficulties in LN recovery from rectal resection specimens are well known. Cawthorn et al [23] found that LN metastases in the supralevator part of the mesorectum may be difficult to identify by manual dissection. One theory to explain the higher LN yield in right colon cancers is that right hemicolectomy specimens are generally longer and therefore have a larger mesocolon but the evidence for this hypothesis is conflicting [8,24,25]. It is still not known whether the right colon mesentery contains more LNs than the left colon mesentery in normal subjects and this is currently under investigation [9].

Another hypothesis is that right-sided colon cancers are biologically distinct from left-sided colonic and rectal cancers [26,27]. Sporadic CRCs with microsatellite instability or CpG island methylator phenotype are more common in the right colon and tend to occur at an older age [28-31].

Furthermore, these right-sided tumours show a greater lymphocyte infiltration [29,31,32]. It is hypothesized that this reflects the host's anti-tumour immune response, which may explain the improved prognosis associated with microsatellite instability and why right-sided colonic cancers have a higher lymph node yield [31].

The length of resected bowel specimen is a strong predictor of the harvested LNs. A longer segment of resected bowel will have more pericolic and mesenteric LNs. This is consistent with the principle that the surgeon must perform a surgical resection, including removal of an adequate seg-

ment of bowel and the main lymphovascular supply to the resected segment.

In the present study, a positive correlation was also found between the number of harvested LNs and the maximal diameter of the tumour. The size of the tumour is a parameter that has not been addressed in previous studies.

The present study also found that the number of harvested LNs increased with increasing T stage, which is consistent with several other studies [4,16]. It is possible that the locoregional immune response to the tumour is stimulated in proportion to the depth of tumour invasion [4]. Reactive changes in the draining LNs lead to enlargement and this in turn makes them easier to detect.

Lastly, the grade of tumour's cellular differentiation was not associated with the LN yield in the present study.

Patients with rectal cancer receiving neoadjuvant radiotherapy were found to have a lower LN number in this study. Previous reports have identified significantly decreased LN yield in patients treated with neoadjuvant radiation [33,34]. The diligence and accuracy of the pathologist and the correct high-quality total mesorectal excision by surgeon are essential in order to detect the majority of LNs and to achieve a valid nodal staging after preoperative radio (chemo) therapy [35].

In conclusion, LN harvest in patients with CRC is highly variable and may be determined by multiple factors. Meticulous surgical technique and an adequate length of specimen are required in order to obtain as many LNs as possible.

## Conflict of interests

The authors declare no conflict of interests.

## References


1. Cunningham D, Atkin W, Lenz HJ et al. Colorectal cancer. Lancet 2010; 375:1030-47.
2. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99:433-41.
3. McDonald JR, Andrew G, Renehan AG, Dwyer ST, Haboubi NY. Lymph node harvest in colon and rectal cancer: Current considerations. World J Gastrointest Surg 2012;4:9-19.
4. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FI, Troti A. AJCC cancer staging manual (7th Edn). New York: Springer; 2010.
5. Gonsalves WI, Kanuri S, Tashi T et al. Clinicopathologic factors associated with lymph node retrieval in resectable colon cancer: a Veterans' Affairs Central Cancer Registry (VACCR) database analysis. J Surg Oncol 2011;104:667-71.
6. Bilimoria KY, Stewart AK, Palis BE, Bentrem DJ. Talamonti MS. Ko CY. Adequacy and importance of lymph node evaluation for colon cancer in the elderly. J Am Coll Surg 2008;206:247-54.
7. Hong KD, Lee SI, Moon HY. Lymph node ratio as determined by the 7th edition of the American Joint Committee on Cancer staging system predicts survival in stage III colon cancer. J Surg Oncol 2011;103:406-10.
8. Shen SS, Haupt BX, Ro JY, Zhu J, Bailey HR, Schwartz MR. Number of lymph nodes examined and associated clinicopathologic factors in colorectal carcinoma. Arch Pathol Lab Med 2009;133:781-6.
9. Ahmadi O, Stringer MD, Black MA, McCall JL. Influence of age and site of disease on lymph node yield in colorectal cancer. NZMJ 2014;127: 31-40.
10. Stocchi L, Fazio VW, Lavery I, Hammel J. Individual surgeon, pathologist, and other factors affecting lymph node harvest in stage II colon carcinoma. Is a minimum of 12 examined lymph nodes sufficient? Ann Surg Oncol 2011;18:405-12.
11. Evans MD, Barton K, Rees A, Stamatakis JD, Karandikar SS. The impact of surgeon and pathologist on lymph node retrieval in colorectal cancer and its impact on survival for patients with Dukes' stage B disease. Colorectal Dis 2008;10:157-64.
12. Wright FC, Law CH, Berry S, Smith AJ. Clinically important aspects of lymph node assessment in colon cancer. J Surg Oncol 2009;99:248-55.
13. Khalifa MA, Smith A. Lymph node assessment: issues in pathology. J Surg Oncol 2009;99:260-4.
14. Parsons HM, Tuttle TM, Kuntz KM, Begun JW, McGovern PM, Virnig BA. Association between lymph node evaluation for colon cancer and node positivity over the past 20 years. JAMA 2011;306:1089-97.
15. Chou JF, Row D, Gonen M, Liu YH, Schrag D, Weiser MR. Clinical and pathologic factors that predict lymph node yield from surgical specimens in colorectal cancer: a population-based study. Cancer 2010;116:2560-70.
16. Wang L, Hollenbeak CS, Stewart DB. Node yield and node involvement in young colon cancer patients: is there a difference in cancer survival based on age? J Gastrointest Surg 2010;14:1355-61.
17. Steele SR, Chen SL, Stojadinovic A et al. The impact of age on quality measure adherence in colon cancer. J Am Coll Surg 2011;213:95-103.
18. Patel SS, Nelson R, Sanchez J et al. Elderly patients with colon cancer have unique tumor characteristics and poor survival. Cancer 2013;119:739-47.
19. Canessa CE, Badia F, Fierro S, Fiol V, Hayek G. Ana-

tomic study of the lymph nodes of the mesorectum. Dis Colon Rectum 2001;44:1333-36.

20. Topor B, Acland R, Kolodko V, Galandiuk S. Mesorectal lymph nodes: their location and distribution within the mesorectum. Dis Colon Rectum 2003;46:779-85.
21. Leibl S, Tsybrovskyy O, Denk H. How many lymph nodes are necessary to stage early and advanced adenocarcinoma of the sigmoid colon and upper rectum? Virchows Arch 2003; 443:133-8.
22. Prandi M, Lionetto R, Bini A et al. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: results of a secondary analysis of a large scale adjuvant trial. Ann Surg 2002;235:458-63.
23. Cawthorn SJ, Gibbs NM, Marks CG. Clearance technique for the detection of lymph nodes in colorectal cancer. Br J Surg 1986; 73:58-60.
24. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA. Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 2005;97:219-25.
25. Morikawa T, Tanaka N, Kuchiba A et al. Predictors of lymph node count in colorectal cancer resections: data from US nationwide prospective cohort studies. Arch Surg 2012;147:715-23.
26. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol 2004; 88:261-6.
27. Snaebjornsson P, Jonasson L, Jonsson T, Möller PH, Theodors A, Jonasson JG. Colon cancer in Iceland--a nationwide comparative study on various pathology parameters with respect to right and left tumor location and patients age. Int J Cancer 2010;127:2645-53.
28. Yamaji Y, Mitsushima T, Ikuma H et al. Right-side shift of colorectal adenomas with aging. Gastrointest Endosc 2006;63:453-8.
29. Hawkins N, Norrie M, Cheong K et al. CpG island methylation in sporadic colorectal cancers and its relationship to microsatellite instability. Gastroenterology 2002;122:1376-87.
30. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol 2010;7:153-62.
31. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 2005;23:609-18.
32. Guidoboni M, Gafa R, Viel A et al. Microsatellite instability and high content of activated cytotoxic lymphocytes identify colon cancer patients with a favorable prognosis. Am J Pathol 2001;159:297-304.
33. Rullier A, Laurent C, Capdepont M et al. Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. Am J Surg Pathol 2008;32:45-50.
34. Leibold T, Shia J, Ruo L et al. Prognostic implications of the distribution of lymph node metastases in rectal cancer after neoadjuvant chemoradiotherapy. J Clin Oncol 2008;26:2106-11.
35. Scabini S, Ferrando V. Number of lymph nodes after neoadjuvant therapy for rectal cancer: How many are needed? World J Gastrointest Surg 2012;4:32-5.