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Prognostic Value of Lymph Node Number and Ratio Staging System in Stage Ⅲ Rectal Cancer Following Neoadjuvant Radiochemotherapy

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Abstract

Objective: To compare the prognostic value of positive lymph node number (LNN) and lymph node ratio (LNR) in stage III rectal cancer following neoadjuvant radiochemotherapy.

Methods: From 2008 to 2010, 99 rectal cancer cases in our hospital received neoadjuvant radiochemotherapy or radiotherapy. Radical surgery was performed after neoadjuvant therapy. LNN distinguished four stages of lymph node involvement by TNM stage system and LNR divided patients into quartiles. The prognosis value of LNN and LNR to the patients was evaluated by Kaplan-Meier method and Cox regression. We evaluated the prognosis value of LNN and LNR for those with inadequate lymph nodes (<12).

Results: The patients were staged according to lymph node number (LNN=1, 2 ≤ LNN ≤ 3, 4 ≤ LNN ≤ 6 and LNN ≥ 7) and lymph node ratio (LNR<0.075, 0.075 ≤ LNR<0.15, 0.15 ≤ LNR<0.35 and LNR ≥ 0.35). 3 year overall survival rates were different among different LNN groups and different LNR groups. Multivariate analysis showed that LNR ≥ 0.15 was an independent prognostic factor of overall survival (P=0.029). 26 patients with less than 12 lymph nodes harvest were divided into four groups (LNR<0.15, 0.15 ≤ LNR<0.25, 0.25 ≤ LNR<0.50 and LNR ≥ 0.50), LNR was proved to be a better predictor of survival. 3 year overall survival rates were significant different between LNR<0.50 and LNR ≥ 0.50 (P=0.018).

Conclusion: The study showed LNR was an independent prognostic factor for rectal cancer after neoadjuvant radiochemotherapy, LNR 0.15 was a cutoff point for overall survival. LNR might be a better prognostic factor than LNN, especially in patients with less than 12 lymph nodes harvest.

Keywords: Rectal cancer; Neoadjuvant radiochemotherapy; Lymph node ratio; Prognosis

Introduction

The prognosis of patients with rectal cancer is generally assessed using the TNM staging system, which stages lymph node involvement according to the absolute number of involved lymph nodes. Positive lymph nodes affect the prognosis of patients. Some research has indicated that the survival of patients with positive lymph nodes is much poorer. The 7th AJCC staging system divide patients with rectal cancer into four stages (N1a, N1b, N2a, N2b) [1] which is more accurate than the 6th staging system, suggesting patients with more positive lymph nodes have unfavorable prognosis.

TNM staging system suggests more than 12 lymph node harvest is the premise of accurate N stage. However, adequate lymph nodes could be harvested in only approximate 1/3 patients of rectal cancer. Moreover, most of the patients with positive lymph nodes receive neoadjuvant radiotherapy which will reduce the number of lymph nodes harvest [2]. It is difficult for the patients who have received preoperative radiotherapy to get adequate lymph nodes. The reduction of lymph node harvest may decrease patients' prognosis and may not be reflected in TNM staging system [3]. It affects prognosis value of N stage for these patients. Some researchers are searching for a more effective indicator to evaluate the situation of lymph nodes.

The lymph node ratio (LNR), the number of metastatic lymph nodes divided by the total number of examined nodes, might be a suitable staging system. [4] LNR doesn't depend on the absolute number of positive lymph nodes. It treats the ratio of positive lymph node as the indicator of lymph node metastasis. Although it has many drawbacks such as different cutoff values and inconsistent pathological evaluation, researchers focus on it as a valuable prognosis indicator. [5] The aim of present study is to evaluate the prognosis value of TNM system and LNR system. We divide our patients into groups according to these different systems, in order to evaluate which is the more effective one. We also analysis the data of patients with inadequate lymph nodes (<12 nodes) and evaluate the prognosis value of TNM system and LNR system for these patients.

Methods

We performed a retrospective consecutive study of patients with pathologically proven stage III rectal cancer. 99 patients received preoperative chemoradiorherapy and radical resection at the Peking University Cancer Hospital between 2008 and 2010 who were identified from our cancer database. TNM system distinguishes four stages of lymph node involvement according to the AJCC 7th edition of rectal cancer, while LNR divides patients into four groups at the quartiles of all patients.

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Radiotherapy

There were two different neoadjuvant radiotherapy methods. Most of the patients received preoperative radiotherapy which consisted of 50Gy in 25 fractions with capecitabine (825 mg/m^2, twice per day) as radiosensitizer. The other 13 patients received radiotherapy which consisted 30Gy in 10 fractions. It was recommended by Chinese Anti-cancer Association.

Surgery

Total mesorectal excision (TME) performed by an open approach was the standard technique for the surgical treatment of rectal cancer. All 99 patients received laparotomy 6 to 8 weeks after long term radiochemotherapy or 7 to 10 days after short term radiotherapy. Low anterior resection or abdominoperineal resection was performed, depending on the evaluation of surgeons.

LNN groups

There were several cutoff values consistent with TNM staging system. Patients were divided into four groups (LNN=1, 2 ≤ LNN ≤ 3, 4 ≤ LNN ≤ 6 and LNN ≥ 7) according to different positive lymph node number (LNN). These groups represented N1a, N1b N2a and N2b stages, respectively.

LNR groups

Quartiles were always chosen to be the cutoff values of LNR staging system. The three quartiles of all patients in our study were 0.075, 0.15 and 0.35. We divided patients into four groups (LNR<0.075, 0.075 ≤ LNR<0.15, 0.15 ≤ LNR<0.35 and LNR ≥ 0.35). For 26 patients with inadequate lymph nodes, different grouping methods (LNR<0.15, 0.15 ≤ LNR<0.25, 0.25 ≤ LNR<0.50 and LNR ≥ 0.50) were also performed.

Pathological evaluation

Pathological evaluation was carried out by experienced pathologists. They took all surgical specimens seriously and detected all lymph nodes that could be found. Those with inadequate lymph node harvest (<12) would be detected once again.

Follow up

Patients had been followed up for more than 3 years. CEA surveillance was performed every 3 months for 2 years, then every 6 months for a total of 5 years. All patients had a colonoscopy in 1 year after surgery. Chest, abdominal and pelvic computed tomography was performed annually. Diagnosis of tumor recurrence and metastasis depended on these examinations and biopsy if necessary.

Statistical analysis

Nonparametric data were compared using the Wilcoxon rank sum test and categorical data were summarized by frequency within each cohort, and comparisons were performed using the chi square test for proportions. Three-year overall survival (OS) rates were determined by the Kaplan-Meier method, and univariate comparisons were performed using the log-rank test. Cox proportional hazards regression analysis was performed for multivariate comparisons. P values <0.05 were considered significant.

Results

Patient characteristics

Complete data regarding lymph node retrieval and follow-up clinical data were available for all 99 patients (Table 1). There is no description on if there are any age or gender specific effects (P>0.05). The median follow-up time was 37.5 months. The 3 year DFS and OS for all these patients were 62.6% and 79.8%, respectively. Table 2 showed the characteristics of 26 patients with inadequate lymph nodes.

Characteristics	Patients (n)	3 yr DFS	P value	3 yr OS	P value
Gender			0.548		0.847
Male	56	60.7%		78.6%	
Female	43	65.1%		79.1%	
Age			0.296		0.460
<60	56	58.9%		76.8%	
≥60	43	67.4%		81.4%	
Distance to anus			0.085		0.033
≤5 cm	60	56.7%		71.7%	
>5 cm	39	71.1%		89.5%	
Grade			0.062		0.015
G1/2	79	67.1%		83.5%	
G3	20	45.0%		60.0%	
ypT stage			0.004		0.003
ypT1	1	100%		100%	
ypT2	15	100%		100%	
ypT3	66	60.0%		81.5%	
ypT4	17	41.2%		52.9%	
Lymphvascular invasion			0.757		0.719
Yes	88	62.5%		78.4%	
No	11	63.6%		81.8%	
Radiation			0.086		0.005
30Gy/10f	87	65.5%		82.8%	
50. 4Gy/25f	12	41.7%		50.0%	
Surgery			0.931		0.490
LAR	66	62.1%		80.3%	
APR	33	63.6%		75.8%	
Lymph node harvest			0.813		0.910
<12 nodes	26	65.4%		80.8%	
≥12 nodes	73	61.6%		78.1%	

Table 1: Characteristics of patients examined and survival analysis.

Characteristics	Patients(n)	3 yr DFS	P value	3 yr OS	P value
Gender			0.895		0.884
Male	15	66.7%		80.0%	
Female	11	6 3.6%		81.8%	
Age			0.112		0.254
<60	15	53.3%		73.3%	
≥60	11	81.8%		90.9%	
Distance to anus			0.381		0.270
≤5cm	16	75.0%		56.2%	
>5cm	10	90.0%		80.0%	
Grade			0.403		0.231
G1/2	21	61.9%		76.2%	
G3	5	80.0%		100.0%	
ypT stage			0.407		0.401
ypT1-2	3	100%		100.0%	
ypT3	30	60.0%		75.0%	
ypT4	3	66.7%		100.0%	
Lymphvascular invasion			0.139		0.297
Yes	22	59.1%		77.3%	
No	4	100.0%		100.0%	
Surgery			0.948		0.517
LAR	17	64.7%		76.5%	
APR	9	66.7%		88.9%	

Table 2: Characteristics of patients with inadequate lymph nodes and survival analysis.

Lymph node number (LNN)

The patients were staged according to lymph node number (TNM system). At each cutoff value, they were divided into four groups. 3 year overall survival rates were different among different groups (P<0.001) (Figure 1).

Lymph node ratio (LNR)

The patients were staged according to lymph node ratio (LNR system). The patients were divided into four groups. 3 year overall survival rates were significant different from each other. Multivariate analysis showed that LNR was an independent prognostic factor of overall survival (P=0.033) (Figure 2). The results of the multivariate Cox regression analysis had shown that ypT3-4, LNR ≥ 0.15 and distant rectal cancer were independent risk factors (Table 3).

LNR for <12 nodes patients

Among the 99 studied patients, ≥12 lymph nodes were examined from 73 patients (73.7%) and <12 nodes from 26 patients (26.3%). In 26 patients with inadequate lymph node harvest, TNM stage system did not shown significant difference. The survival of patients with more lymph nodes (LNN>7) was not worse. There were no significant differences between different LNN groups (p=0.361) (Figure 3). LNR

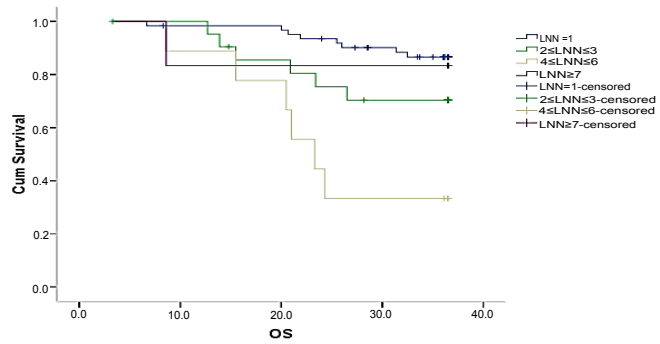

Figure 1: Analysis of overall survival rates of patients based on LNN groups.

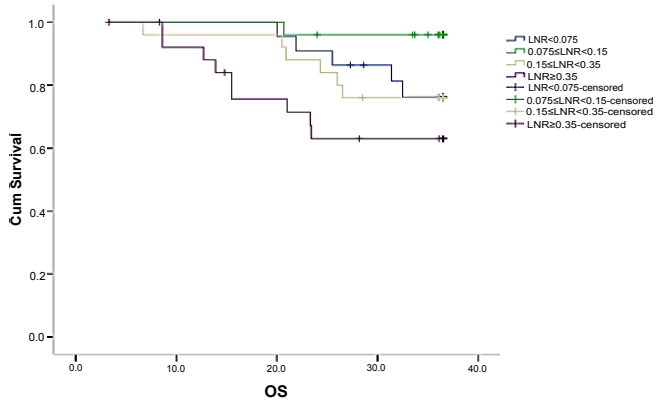

Figure 2: Analysis of overall survival rates of patients based on LNR groups.

Prognosis factors	OR	95% CI	P-value
ypT3-4	3.616	1.660-7.877	0.001
LNR ≥0.15	3.099	1.123-8.553	0.029
Distance to anus <5 cm	0.342	0.113-1.036	0.058

Table 3: Multivariate analysis for prognosis of rectal cancer after neoadjuvant therapy.

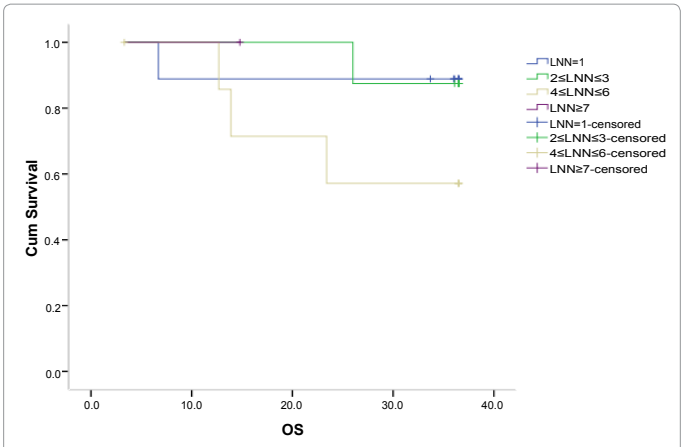

Figure 3: Analysis of overall survival rates of patients with inadequate lymph nodes based on LNN groups.

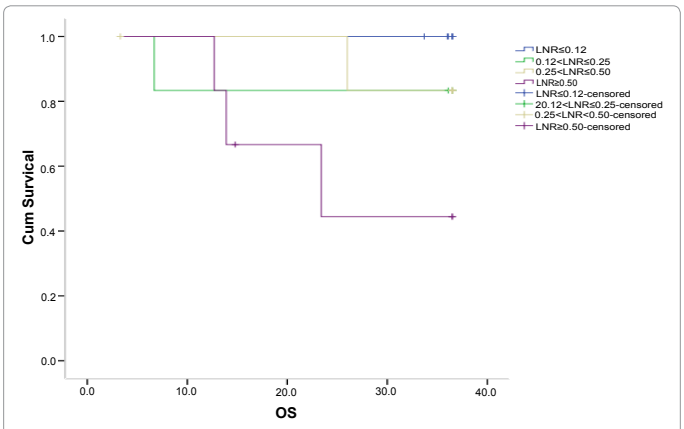

Figure 4: Analysis of overall survival rates of patients with inadequate lymph nodes based on LNR groups.

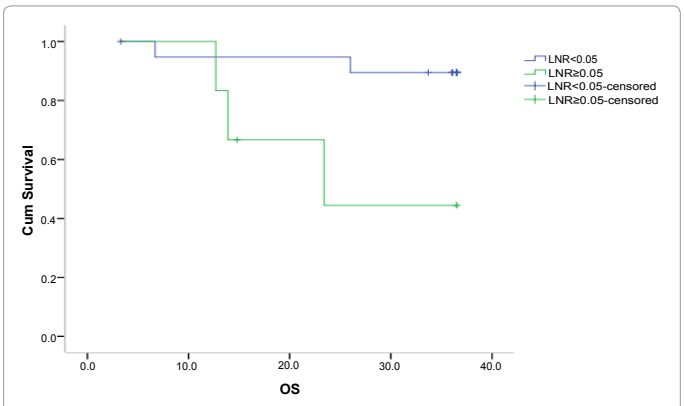

Figure 5: Analysis of overall survival rates of patients with inadequate lymph nodes based on classification at 3/4 quartile of LNR (LNR <0.50 and LNR ≥0.50).

was proved to be a better predictor of survival although differences among groups were not significant (p=0.102) (Figure 4). At 3/4 quartile of LNR, 3 year overall survival rates were significant different between LNR<0.50 and LNR ≥ 0.50 (P=0.018) (Figure 5).

Discussion

Nowadays, TNM stage system has become the principle method

for assessing the prognosis of rectal cancer patients. The AJCC seventh edition for rectal cancer has been released based on the recent medical evidence. N stage is an important part. The postoperative survival of patients who have metastatic lymph nodes is significantly worse. Accurate analysis of lymph node involvement is important to evaluate the prognosis for rectal cancer. With the progress of researches, the lymph node staging system has been modified. According to the seventh TNM classification, the sixth edition N1 classification was sub-classified into N1a/b (1 involved regional lymph node (LN)) and N1b (2-3 involved LNs), T2 classification was subclassified into N2a (4-6 involved regional LNs) and N2b (>6 involved regional LNs). Accurate N stage requires more than 12 lymph nodes to validate pN0 status [6]. Some researchers suggested that adequate lymph nodes improve survival of rectal cancer [7]. Patients with 12 or more lymph nodes examined have better survival than those with less than 12 lymph nodes [8]. It required surgeons did their best to get more lymph nodes, nevertheless it was sometimes difficult.

Neoadjuvant chemoradiotherapy has become standard treatment for local advanced rectal cancer. It reduces pelvic recurrence of rectal cancer [9]. While not increase the incidence of postoperative complications [10]. Patients can benefit from preoperative radiotherapy, [11] especially for the ones who get an early stage from neo-adjuvant RCT [12]. However, along with the development of radiotherapy, surgeons have found it difficult to get enough lymph nodes for accurate N stage, especially for patients which are sensitive to radiation [13]. More than 12 lymph nodes can be found in only 1/3 patients who receive neoadjuvant chemoradiotherapy. For these patients, N stage cannot reflect the real value of lymph nodes [14]. Other authors suggest the number of negative lymph nodes examined may be also a prognostic factor in patients with rectal cancer who receive preoperative chemoradiation [15]. As a consequence, researchers concentrate their attentions on finding another indicator which can accurately evaluate the status of metastatic lymph nodes after neoadjuvant chemoradiotherapy. Several researches have proved that metastatic lymph nodes ratio (LNR) is an independent prognostic factor for local advanced rectal cancer, [16,17] whether or not they received neoadjuvant chemoradiotherapy [4]. LNR is a better indicator especially for patients with less than 12 lymph nodes when the value of N stage decrease [18,19]. These researches always use different cutoff values. It is still unable to reach a consistent cutoff value because of the difference of these researches' samples. It stops LNR from being an accepted prognostic staging system [20].

Some of our patients received short term radiotherapy (30Gy/10f) which was recommended by China Anticancer Association [21]. Its biological equivalent dose was 36Gy, close to the dose of 5 × 5Gy (BED: 37.5Gy). We divide the patients into two groups by all the quartiles. We find that LNR is an independent prognosis factor for rectal cancer after neoadjuvant chemoradiotherapy, whether or not lymph nodes are adequate [22]. However, LNR cannot form a better staging system when we get more than 12 lymph nodes, because it is consistent with N stage [23]. However, for some of patients who are sensitive to neoadjuvant chemoradiotherapy, the number of lymph node harvest decreases. N stage cannot reflect the prognostic value of lymph nodes metastasis. The value of LNR will be demonstrated [24].

Other authors' works have shown that LNR is an important prognostic factor for colorectal cancer. Compared with others' work, our work has several differences. Some reports discuss the prognostic value of LNR in colorectal cancer. But our study doesn't include patients with colon cancer, because the prognosis of colon cancer and rectal cancer is quite different from each other. Patients who received radiotherapy sometimes get less than 12 lymph nodes. Pathologists search the specimen again carefully for these with inadequate lymph nodes. It ensures these patients are ones with real inadequate lymph nodes, rather than the bias of pathologists. Besides, different from other reports, patients without lymph node metastasis after neoadjuvant radiotherapy (ypN0) have been expelled, who have better survivals than patients with lymph node metastasis. Perhaps it causes the smaller samples, but it decreases the influence of ypN0 patients.

Conclusion

For rectal cancer after neoadjuvant radiochemotherapy, both LNN and LNR were effective indicator to evaluate lymph node involvement. However, when lymph node was inadequate (<12), LNN could not reflect the prognosis accurately. LNR staging system might be a better prognostic factor than N stage.

References

1. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, et al. (2010) AJCC cancer staging handbook. Springer, New York.
2. Baxter NN, Morris AM, Rothenberger DA, Tepper JE (2005) Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: A population-based analysis. Int J Radiat Oncol Biol Phys 61: 426-431.
3. Joseph NE, Sigurdson ER, Hanlon AL, Wang H, Mayer RJ, et al. (2003) Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. Ann Surg Oncol 10: 213-218.
4. Manilich EA, Kiran RP, Radivoyevitch T, Lavery I, Fazio VW, et al. (2011) A novel data-driven prognostic model for staging of colorectal cancer. J Am Coll Surg 213: 579-588.
5. Ceelen W, van Nieuwenhove Y, Pattyn P (2010) Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. Ann Surg Oncol 17: 2847-2855.
6. Sobin LH (2001) TNM classification: clarification of number of regional lymph nodes for pN0. Br J Cancer 85: 780.
7. Onitilo AA, Stankowski RV, Engel JM, Doi SA (2013) Adequate lymph node recovery improves survival in colorectal cancer patients. J Surg Oncol 107: 828-834.
8. Kanemitsu Y, Komori K, Ishiguro S, Watanabe T, Sugihara K (2012) The relationship of lymph node evaluation and colorectal cancer survival after curative resection: a multi-institutional study. Ann Surg Oncol 9: 2169-2177.
9. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, et al. (2012) Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 30: 1926-1933.
10. Sauer R, Fietkau R, Wittekind C, Rödel C, Martus P, et al. (2003) Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. Colorectal Dis 5: 406-415.
11. Park JH, Yoon SM, Yu CS, Kim JH, Kim TW, et al. (2011) Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer 117: 3703-3712.
12. Du CZ, Li J, Cai Y, Sun YS, Xue WC, et al. (2011) Effect of multidisciplinary team treatment on outcomes of patients with gastrointestinal malignancy. World J Gastroenterol 17: 2013-2018.
13. La Torre M, Mazzuca F, Ferri M, Mari FS, Botticelli A, et al. (2013) The importance of lymph node retrieval and lymph node ratio following preoperative chemoradiation of rectal cancer. Colorectal Dis 15: e382-e388.
14. Wang H, Safar B, Wexner SD, Denoya P, Berho M (2009) The clinical significance of fat clearance lymph node harvest for invasive rectal adenocarcinoma following neoadjuvant therapy. Dis Colon Rectum 52: 1767-1773.
15. Tsai CJ, Crane CH, Skibber JM, Rodriguez-Bigas MA, Chang GJ, et al. (2011) Number of lymph nodes examined and prognosis among pathologically lymph node- negative patients after preoperative chemoradiation therapy for rectal adenocarcinoma. Cancer 117: 3713-3722.

16. Allaix ME, Arezzo A, Cassoni P, Mistrangelo M, Giraudo G, et al. (2013) Metastatic lymph node ratio as a prognostic factor after laparoscopic total mesorectal excision for extraperitoneal rectal cancer. Surg Endosc 27: 1957-1967.

17. Tayyab M, Sharma A, Macdonald AW, Gunn J, Hartley JE, et al. (2012) Prognostic significance of lymph node ratio in patients undergoing abdominoperineal resection of rectum. Langenbeck's Archives of Surgery 397: 1053-1057.

18. Junginger T, Goenner U, Lollert A, Hollemann D, Berres M, et al. (2014) The prognostic value of lymph node ratio and updated TNM classification in rectal cancer patients with adequate versus inadequate lymph node dissection. Tech Coloproctol 18: 805-811.

19. Klos CL, Bordeianou LG, Sylla P, Chang Y, Berger DL (2011) The prognostic value of lymph node ratio after neoadjuvant chemoradiation and rectal cancer surgery. Dis Colon Rectum 54: 171-175.

20. Medani M, Kelly N, Samaha G, Duff G, Healy V, et al. (2013) An appraisal of lymph node ratio in colon and rectal cancer: not one size fits all. Int J Colorectal Dis 28: 1377-1384.

21. Zhan T, Gu J, Li M (2013) Intermediate-Fraction Neoadjuvant Radiotherapy for Rectal Cancer. Dis Colon Rectum 56: 422-432.

22. Lee SD, Kim TH, Kim DY, Baek JY, Kim SY, et al. (2012) Lymph node ratio is an independent prognostic factor in patients with rectal cancer treated with preoperative chemoradiotherapy and curative resection. Eur J Surg Oncol 38: 478-483.

23. Vather R, Sammour T, Kahokehr A, Connolly A, Hill A (2011) Quantitative lymph node evaluation as an independent marker of long-term prognosis in stage III rectal cancer. ANZ journal of surgery 81: 883-888.

24. Huebner M, Therneau T, Larson D (2012) Estimating underreported N2 disease in rectal cancer patients with low lymph node counts. Journal of surgical oncology 106: 248-253.