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Adequacy of Lymph Node Staging in Colorectal Cancer: Analysis of 250 Patients and Analytical Literature Review

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ABSTRACT

Background: The extent of lymph node involvement is the most important prognostic factor in resected locoregional colorectal cancer. Currently, examination of at least 12 lymph nodes is recommended for adequate colorectal cancer staging.
Objectives: The present study aimed to evaluate the adequacy of lymph node staging in 250 patients with colorectal cancer and analytical literature review.
Patients and Methods: Two hundred fifty patients with histologically proven locoregional invasive colorectal adenocarcinoma from 2005 to 2011 were included. All patients were treated by standard surgical resection for their disease. Twenty-three patients with rectal cancer received neoadjuvant treatment. All potential tumor, patient and treatment variables were evaluated for their impact on the average total number of lymph node examined.
Results: In this study, 147 men and 103 women with a median age of 54 (range 23-84) years were included. The median total number of lymph nodes examined was 7 (mean 9.35). Sixty-nine patients (27.6%) had adequate (≥ 12) lymph nodes examination, and twenty patients (8%) had no nodes examined. In univariate analysis, younger age, colon primary site, larger tumor size, the presence of lymphatic vascular invasion, the lack of neoadjuvant treatments, individual surgeon B and Hospital B were more associated with the average total number of lymph node examined.
Conclusion: This study indicates that only less than a third of patients with colorectal cancer underwent adequate lymph nodes examination. Further investigation using careful pathologic reviewing of specimens with inadequate lymph node examined is suggested for differentiating true inadequate lymph node dissection from inadequate lymph node detection.

Keywords: Colorectal Cancer; Colon; Rectum; Lymph Node Staging; Surgery; Dissection

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▸Implication for health policy/practice/research/medical education:
Inadequate lymph nodes evaluation is a common problem in colorectal cancer. This issue can potentially lead to understaging diseases and insufficient adjuvant treatment. Careful pathologic reviewing of specimens with inadequate lymph node examined was suggested for differentiating true inadequate lymph node dissection from inadequate lymph node detection.

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1. Background

Colorectal cancer is the fifth most frequently diagnosed cancer and the leading cause of cancer death in developing countries (1). In Iran, colorectal cancer is the fourth most commonly diagnosed cancer in males and the second in females (2). Pathologic stage is the most significant prognostic factor determining the use of adjuvant therapy and predicting outcome in patients with this neoplasm (3-6). The American Joint Committee on Cancer (AJCC) The tumor node metastasis (TNM) staging system is widely used for staging colorectal cancer (4). In AJCC TNM staging system, N0 represents no regional lymph node metastasis; N1, metastasis in 1-3 regional lymph nodes and N2, metastasis in four or more regional lymph nodes (4, 7). According to this staging system, the extent lymph node involvement is one of the most important prognostic factors in resected locoregional disease (4, 5, 7). Currently, examination of at least 12 lymph nodes is recommended for adequate colorectal cancer staging (5, 8, 9). Despite this recommendation, inadequate lymph nodes evaluation is common. In the United States, approximately one third of colorectal cancer patients undergo adequate lymph nodes evaluation (10). Inadequate lymph nodes staging in colorectal cancer can potentially lead to understaging patients and insufficient adjuvant treatment (5).

2. Objectives

The present study aimed to investigate the rate of adequacy of lymph node staging in patients with colorectal cancer in Shiraz, Southern Iran, and analytical literature review.

3. Patients and Methods

In this study, we included 250 patients aged between 23 and 84 years who had locoregional invasive colorectal adenocarcinoma treated at our institution between January 2004 and December 2010. Patients presenting with in situ or metastatic disease, with pathologies other than adenocarcinoma, and with unresectable or inoperable disease were excluded. In addition, we excluded patients with missing or incomplete medical records or who lacked complete pathological reports or who had undergone total colectomy or palliative surgery. All patients were restaged according to the 7th edition of the AJCC TNM staging system (4). The same numbers of primary site (colon, 125 and rectum, 125) were included. All patients with primary colon cancer were initially treated with standard curative surgical resection. In cases with primary rectal cancer; however, 23 patients received neoadjuvant chemoradiation (15 cases) or chemotherapy (8 cases) followed by curative-intent surgery. Concurrent neoadjuvant chemoradiation consisted of conventional external beam radiotherapy using megavoltage telecobalt units or linear accelerator photons. A median dose of 50 (range 45-50.5) Gy was delivered via a daily fraction of 1. 8-2 Gy, with five fractions per week. Concurrent chemotherapy consisted of oral capecitabine 825 mg/m2 twice daily during the whole period of radiotherapy with weekend breaks or intravenous bolus 5-fluorouracil 425 mg/m^2/day and folinic acid 20 mg/m^2/day on days one to five of the first and last week of radiation. Neoadjuvant chemotherapy consisted of capecitabine 1000 mg/m2 twice daily for 14 of every three weeks cycle plus oxaliplatin 85 mg/m^2 intravenously on day one; or 5-fluorouracil 400 mg/m^2 bolus day one, followed by 2400 mg/m2 over 46 hours plus oxaliplatin 85 mg/m2 intravenously on day one, every two weeks. All patients receiving neoadjuvant chemoradiation underwent standard curative surgery with at least 4-6 weeks interval. In this study, we performed a comprehensive literature review of PubMed using the search terms of "node" and "cancer" and "colorectal" or "colon" or "rectum" or "rectal" to find out the major related studies over the last 15 years for discussing the manuscript. Articles in non-English language or with unavailable full text were excluded; however, informative abstracts were included. In all, we selected 55 major series including more than 400000 cases with resected colorectal cancer. The mean and median number of total lymph nodes examined was initially calculated. Subsequently, the percentage of patients who had at least 12 nodes examined and the percentage of patients who had no lymph node in their pathologic report were determined. Using Independent two samples T test and Analysis of Variance (ANOVA) test, the mean number of total lymph nodes examined was compared between groups. All potential tumor (anatomical site, tumor size, grade, surgical margin status, lymphatic-vascular invasion, perineural invasion, bowel obstruction, bowel perforation and the number of involved lymph nodes), patient (age and sex), treatment (surgeon, type of surgery and neoadjuvant treatments) and hospital characteristics were evaluated for their impact on the average total number of lymph node examined. The multivariate analysis using logistic regression modeling method was performed for determining any association between adequate lymph node examined and prognostic factors.

4. Results

There were 147 men and 103 women. The age at presentation was in the range 23–84 years with a median of 54 years. Ninety-six patients were less than or equal to 50 years old and 154 patients were older than 50 years old. The peak incidence was observed in the fifth and sixth decades of life. The age distribution (ages greater or less than 50 years) was not similar in two genders, and men (mean age 56.87 ± 12.97) were significantly older than women (mean age 52.73 ± 12.57) at presentation (P = 0.012). Patients with rectal primary site tended to be presented

Table 1. Patient and Tumor Characteristics by Primary Site

Characteristics	Primary sites			P value
	Rectum	Colon	Total	
Gender, No.				0.797
Male	72	75	147	
Female	53	50	103	
Age, Mean ± SD	57.2 ± 13.01	53.1 ± 12.60	55.16 ± 12.95	0.013
T stage, No.				0.301
0	1	0	1	
I	3	4	7	
II	37	27	64	
III	82	90	172	
IV	1	4	5	
Tumor grade, No.				0.020
Well differentiated	91	81	172	
Moderately differentiated	29	31	60	
Poorly differentiated	2	12	14	
Lymphatic-Vascular invasion, No.				0.725
Negative	65	61	126	
Positive	44	50	94	
Unknown	16	14	30	
Perineural invasion, No.				0.865
Negative	64	60	124	
Positive	16	18	34	
Unknown	45	47	92	
Tumor size, cm, No.				0.019
≤ 5	96	69	155	
> 5	37	56	93	
Obstruction and/or Perforation, No.				0.014
Negative	110	94	204	
Positive	15	31	46	
Total LN[a] examined, Mean ± SD[a]				0.007
Total LN examined	7.78 ± 7.49	10.92 ± 10.38	9.35 ± 9.17	
Adequate LN examined, No.				0.157
Adequate (≤ 12 LN)	96	85	181	
Inadequate (> 12 LN)	29	40	69	
LN involvement, No.				0.501
No	87	81	168	
Yes	38	44	82	
Positive LN[a], Mean ± SD	1.22 ± 2.87	1.12 ± 3.48	1.17 ± 3.18	0.797

[a] Abbreviation: LN, lymph node; SD, standard deviation

Table 2. Univariate Analysis of Potential Variables on Total Lymph Node Count in 250 Patients with Colorectal Cancer

Variables, No.	Patients	Mean total L.N	95% CI for means' difference		*P*value
			Lower	Upper	
Gender[a]					
Male	147	9.17			
Female	103	9.61	-2.766	1.883	0.709
Age[a]**, y**					
≤ 50 years	96	11.11			
> 50 years	154	8.27	0.261	5.418	0.031
Primary site[a]					
Rectum	125	7.78			
Colon	125	10.92	-5.392	-0.879	0.007
Type of surgery[a]					
Laparatomy	243	9.50			
Laparoscopy	7	4.14	-1.546	12.265	0.128
Type of rectal surgery[a]					
Low anterior resection	90	7.7			
Abdominoperineal resection	35	8	-3.266	2.666	0.842
Surgeon[a]					
A	58	4.62			
B	192	10.78	-7.894	-4.426	<0.001
Hospital[a]					
A	79	7.70			
B	171	10.11	-4.552	-0.252	0.029
Primary tumor stage[b]					
T0	1	0.0			
T1	7	4.71			
T2	64	8.93			
T3	172	9.59			
T4	5	13.20	8.175	10.466	0.415
Tumor size[a]					
≤ 5 cm	96	11.11			
> 5 cm	153	8.27	0.261	5.418	0.031
Neoadjuvant treatment[a]					
Not received	227	9.85			
Received	23	4.43	5.415	0.993	< 0.001
Surgical margin status[a]					
Negative	241	9.36			
Positive	9	8.22	-5.006	7.287	0.715
Tumor grade[b]					
Well differentiated	172	8.84			
Moderately differentiated	59	9.98			
Poorly differentiated	14	14.92	8.307	10.622	0.051
Lymphatic-vascular invasion[b]					
Negative	126	10.55			
Positive	94	9.20			
Unknown	30	4.76	1.465	10.112	0.007
Perineural invasion[b]					
Negative	124	9.15			
Positive	34	8.61			
Unknown	92	9.89	8.209	10.494	0.744
Obstruction and/or Perforation[a]					
Negative	204	8.76			
Positive	46	1195	-3.191	1.859	0.92
Lymph node involvement[a]					
Negative	168	8.94			
Positive	82	10.19	-1.254	1.235	0.311

* Abbreviations: CI, confidence interval; L.N, lymph node
[a] Independent two samples T test;
[b] ANOVA test

in older age and have well differentiated smaller tumors compared to colon primary site ones. On the other hand, patients with colon primary site presented with higher rate of perforation and/or perforation have higher total number of lymph node examined compared to rectal primary site ones (Table 1).

In whole study population, the median and mean total numbers of examined lymph nodes were 7 and 9.35 respectively. Sixty-nine patients (27.6%) had adequate (≥ 12) lymph nodes examination, and 12 patients (8%) had no examined lymph nodes. Patients with rectal primary site tended to have higher rate of zero lymph node count (17 vs. 3, P = 0.002) compared to colon primary site ones. The majority (64.4%) of patients had 1-10 examined lymph nodes in their pathologic specimen. Figure 1 shows the relative distribution of total lymph node examination in 250 patients with resected colorectal cancer. Eighty-two patients (32.8%) were node positive. There was an association between lymph node positivity and advanced T stages (P = 0.003), the presence of perineural invasion (P = 0.009) and lymphatic vascular invasion (P < 0.001). In univariate analysis, younger age (P = 0.031), colon primary site (P = 0.007), individual surgeon B (P < 0.001), individual hospital B (P = 0.029), larger tumor size (P = 0.31), the presence of lymphatic vascular invasion (P = 0.007) and the lack of neoadjuvant treatments (P < 0.001) were associated with more average number of examined lymph node, (Table 2). Using the stepwise logistic regression modeling method, the independent variables were determined: primary tumor size (P < 0.001, Odds ratio (OR) = 3.141, CI = 1.657-5.953), surgeon (P = 0.001, OR = 7.432, CI = 2.184-25.288), lymphatic vascular invasion (P = 0.001, OR = 0.373, CI = 0.211-0.662), and tumor grade (P = 0.011, OR = 1.984, CI = 1.173-3.355) retained statistical significance in the model.

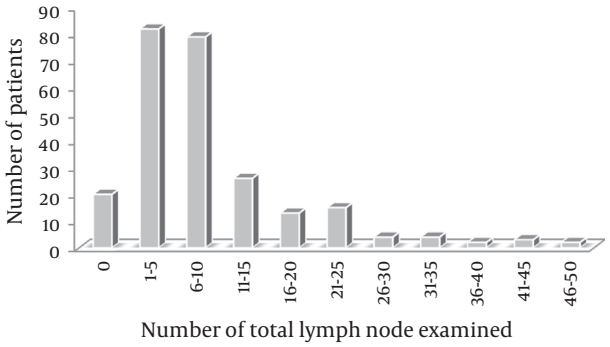

Figure 1. Relative Distribution of Total Lymph Node Examination in 250 Patients with Resected Colorectal Cancer

5. Discussion

Inadequate lymph node examination is a common pitfall in pathologic staging of colorectal cancer. This staging defect causes a great clinical challenge for predicting the prognosis and determining adjuvant treatments (8). Currently, standard management approach for patients with stage III colorectal cancers includes curative surgery combined with adjuvant treatments. In the case of inadequate lymph node examination, patients with actual stage III disease may be classified as stage I or II disease; therefore, they will be divested of optimal treatment (5). Pheby et al. concluded that an increased lymph node harvest was associated with higher rate of stage III disease detection in colorectal cancer patients (11). Despite many reports regarding the adequacy of lymph node staging in resected colorectal cancer in the literature, there is no data regarding this topic in Iran. Colorectal cancers usually occur in the seventh and eighth decades of life (10, 12-15). In the present study, the median age of our patients was 54 years old, which was remarkably lower than that of the results of the literature review in which the average median age of 303632 patients in 15 reported series was 70.7 (range 58-71) years old. To the contrary of the literature, in this study, patients with rectal cancer were found to be older than that of colon ones (13-17). Colorectal cancer is generally more common in women in the literature and in the 11 large studies including 217906 patients, men accounted for 47.4% (range 43%-58%) of all cases (12-15, 18-24); however, in our study, this value was 58.8% for male patients. The mean total number of lymph node examined was 10.9 (range 8.1-19.1) for 72102 patients in 16 studies (11, 12, 16-18, 23, 25-34). In the present study, the mean total number of lymph node examined was 9.3. Likewise, the average median total number of lymph node examined was 9.5 (range 6-20) for 396460 patients in 21 studies (9, 10, 13-15, 17-20, 23, 25, 26, 32-40). In this study, the median total number of lymph node examined was 7. In addition, in our study, the percent of patients with stage III (the ratio of patients with positive lymph node to all population study) was 32.8% which was consistent with that of the literature review in which this value was 30.4% (range 15% - 44.5%) for 32286 patients in 9 studies (12, 16, 17, 20, 22, 26, 34, 38, 40). Inadequate lymph node evaluation is common in the literature. By analyzing a pooled data of 23 large series including 379084 patients, only 41.2% (range 13% - 79%) of all patients had adequate (≥ 12) lymph node evaluation (10, 12-14, 17-20, 22, 25, 26, 28-32, 34, 35, 37-39, 41, 42). In the present study, 27.6% of patients had an adequate lymph node evaluation which is significantly lower than that of mean value in the literature. Likewise, in this study, we found 8% of patients having no lymph nodes for examination which was significantly higher than 5.4% (range 1.4% - 12.7%) among 350701 patients in 11 reported series (10, 13-15, 18, 25, 26, 28, 33, 41, 42), (Table 3).

Table 3. The Status of Lymph Nodes Evaluation in Resected Colorectal Cancer in the Major Reported Series and the Present Study

Authors [ref]	Patients, No.	Primary Site	Stage	Median Age	TLNE[a], Mean	TLNE, Median	Stage III, Mean %	ALNE[a], %	Zero TLNE, %
Barbas (12)	371	Colon	I-III	67	19.1	-	39.9	77.9	-
Baxter (10)	116995	Colorectal	I-III	71	-	9	-	37	6.5
Baxter (13)	5647	Rectum	I-III	66	-	9	-	30.5	9
Bernhoff (25)	3536	Colon	I-IV	-	13	12	-	50.3	1.4
Bilimoria(14)	142009	Colon	I-IV	72	-	10	-	44.5	3.4
Chang (15)	23809	Rectum	I-IV	65	-	9	-	-	12.7
de la Fuente (16)	286	Rectum	I-IV	58	15.4	-	33	-	-
Dejardin (41)	4197	Colorectal	II-III	-	-	-	-	45.2	2
Elferink (35)	30682	Colon	I-III	-	-	8	-	49	-
Elferink (26)	10788	Rectum	I-III	-	8.9	7	40	22.6	5.8
Gelos (36)	341	Colorectal	I-III	-	-	15	-	-	-
Govindarajan (27)	708	Rectum	I-III	-	12.6	-	-	-	-
Hsieh(42)	10460	Colon	I-III	-	-	-	-	43.9	3.7
Kanemitsu (9)	4538	Colorectal	I-III	-	-	19	-	-	-
Joseph (33)	1585	Colon	II-III	-	18.5	16	81	-	4.1
Lagoudianakis (37)	454	Colorectal	I-III	-	-	13	-	58.4	-
Lee (17)	4538	Colon	I-III	64	12.5	11	34.6	51	-
Lemmens(20)	2168	Colon	I-III	70	-	6	36.8	13	-
Lindboe (28)	1050	Colorectal	I-III	-	8.1	-	-	22.3	4
Mitchell (38)	444	Colorectal	I-IV	70	-	11	47	49.1	-
Moore (34)	11399	Colon	I-III	-	11.6	10	15	41	-
Pheby (11)	1547	Colorectal	I-III	-	11.5	-	-	-	-
Shaw (22)	1194	Colorectal	I-IV	63	-	-	44.5	45.5	-
Shimomura (39)	266	Colorectal	III	64	-	14	100	65.8	-
Stocchi (19)	901	Colon	II	71	-	20	0	79	-
Thomas (40)	1098	Colorectal	I-III	-	-	11	41	-	-
Tsai (29)	366	Colorectal	I-II	69	12	-	0	50	-
Tsikitis (30)	329	Colon	III	70	14.7	-	100	51	-
Valsecchi (31)	337	Colorectal	I-III	-	12.7	-	-	51	-
Vather (32)	328	Colon	II	-	16	14	0	-	-
Vather (23)	4309	Colon	II-III	70	13.8	11	54.8	-	-
Wong SL (18)	30625	Colon	0-III	-	9.4	10	9.1	38.5	2
Present study	250	Colorectal	I-III	54	9.3	7	32.8	27.6	8

[a] Abbreviations: ALNE, adequate lymph node examine; TLNE, total lymph node examined

The cause of inadequate lymph node yield is multifactorial. Several potential patients, tumor, treatment, and hospital factors can cause lymph node yield in resected colorectal cancer (8). In the literature review, among patient's factors, younger age (10, 14, 16, 17, 19, 20, 23, 25, 26, 35, 37, 38, 41, 43, 44) and female gender (10, 14, 16, 17, 20, 23, 25, 26, 35, 43-45) had the most common association with higher examined lymph node.

In agreement with the literature, younger age was significantly associated with higher examined lymph node in our study; however, gender was not a significant factor for lymph node yield. Regarding the tumor factors, the average number of evaluated lymph nodes was correlated with specimen length (19, 31, 36, 43, 46), tumor size (16, 29, 31, 37, 43, 45-47), primary tumor stage (10, 14, 17, 20, 25, 26, 29, 31, 35-38, 41, 43, 44), tumor grade (10, 14, 17,

34, 45), lymphatic invasion (6, 36) site of primary tumor (14, 19, 23, 26, 31, 35-37, 41, 43, 44, 46, 47) and the presence of lymph node metastases (10, 17, 20, 22, 25, 26, 34, 35, 38, 41). In our research, larger tumor size, colon primary site, high grade tumors and the presence of lymphatic invasion were associated with higher average number of examined lymph nodes. According to our results, several reports confirmed the impact of surgeon (19, 22, 26, 35, 41, 48, 49), neoadjuvant treatments (13, 16, 27, 35, 44, 50-53) and pathologist (9, 11, 14, 18, 26, 35, 38, 41, 42, 54) on lymph node yield in resected colorectal cancer. Chang et al. concluded that preoperative radiotherapy was associated with an increased likelihood of zero lymph node in resected rectal specimen compared to postoperative therapy (18.6% vs. 6.2%) (15). There are conflicting reports regarding the impact of other potential factors such as body mass index (BMI) and the type of surgery on examined lymph node. Damadi et al. demonstrated no correlation between the number of lymph nodes and body mass index (BMI) among patients undergoing colectomy for colon cancer (55). In addition, Wu et al., in a meta-analysis investigated the impact of surgical approach on the number of total lymph nodes harvested colorectal cancer. They found no difference in the number of lymph nodes harvested in laparoscopic surgery compared to open surgery in colorectal cancer patients (56). There are some studies indicating significant improvement of lymph node yield over time (10, 22, 53, 57-59). Baxter et al., in a population-based study, found the fraction of patients with adequate (≥ 12) lymph node examination increased from 32% in 1988 to 44% in 2001 (10). In another study, Reese et al. showed the percentage of specimens achieving adequate lymph node examined increased from 50 to 67% between 1999 and 2006, and also increased from 83 to 87% between 2003 and 2006. In addition, they demonstrated the important role of pathology assistant training in harvesting the lymph nodes in colorectal cancer (57). Likewise, Sjo et al. found an increase in the number of examined lymph nodes and the proportion of patients with stage III disease from 1993 to 2009 (58). In the present study, we did not find an improvement in the number of examined lymph nodes over the study period (P = 0.138). Retrieval and detection of lymph nodes is clearly an essential component in evaluation of colorectal cancer pathologic specimen. Following curative surgery, the retrieval of at least 12 lymph nodes for each pathologic specimen can be achieved in vast majority of patients who had not received neoadjuvant. Therefore, in cases with insufficient lymph nodes examined, re-examination of the pathologic specimen with more accurate method such as fat-clearance or lymphatic staining techniques is highly recommended (6). Frasson et al. introduced another technique named mesocolon quality pathological evaluation protocol and the arterial ex vivo injection of methylene blue for improving pathologic lymph node detection in colorectal cancer specimens. They demonstrated this protocol along with the arterial ex vivo injection of methylene blue can drastically increase the number of nodes detection in colorectal cancer specimens (60). Moreover, some authors suggest different pathologic and lymphatic staining methods that can enhance the further and the smaller lymph node detection and improve the lymph node harvest of resected colorectal specimens (61-63).

This study indicates that only less than a third of patients with colorectal cancer underwent adequate lymph nodes examination in Shiraz, southern Iran. Further investigation using careful pathologic reviewing of specimens with inadequate lymph node examined is suggested for differentiating true inadequate lymph node dissection from inadequate lymph node detection.

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Authors' Contribution

Leila Ghahramani involved in design, writing, revising the manuscript, and approval of final version. Samira Razzaghi involved in conception, design, data collection, literature review, writing the manuscript and approval of final version. Mohammad Mohammadianpanah, involved in design, data collection, literature review, writing, revising the manuscript, and approval of final version of the manuscript. Saeedeh Pourahmad involved in data analysing, interpretation, writing, revising the manuscript, and approval of final manuscript.

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