Med. J. Cairo Univ., Vol. 86, No. 7, December: 3625-3632, 2018
www.medicaljournalofcairouniversity.net

Lymphocytic Count and Ratio as Predictive Factors for Pathological Response after Neoadjuvant Therapy in Patients with Rectal Cancer

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Abstract

Background: To evaluate results of pre-operative Complete Blood Count (CBC), with special emphasis on lymphocytic count and ratio as predictive factors for rectal cancer response to neoadjuvant chemoradiotherapy and prediction of complete pathological response.

The Aim of the Study: Is to evaluate results of pre-operative complete blood count, with special emphasis on lymphocytic count and lymphocyte ratio as predictive factors of rectal cancer response to neoadjuvant chemoradiotherapy.

Patients and Methods: This research studied the association between CBC results of patients with stage II or III Locally Advanced Rectal Cancer (LARC) before neoadjuvant therapy and the pathological response found in the specimen after standard surgical management. Patients were divided into two groups; Group I included patients with complete pathological response and Group II included patients with no or partial pathological response to study the predictive factors for complete pathological response.

Results: A total of 36 patients (20 females and 16 males) were included. Mean age was 56.40±11.18 years. 19 patients (52.7%) underwent low anterior resections and 17 patients (47.2%) underwent abdomino-perineal resections. Lymphocytic count and ratio were significant predictive factors for the pathological response of the tumor to neoadjuvant therapy (p=0.011 and 0.048, respectively). Comparison between Group I and Group II showed that lymphocytic count and ratio were significant predictive factors for patients in Group I compared to Group II (p=0.001 and p=0.049, respectively).

Conclusions: Lymphocytic count and ratio can play an important role as predictive factors for pathological response to neoadjuvant therapy in patients with LARC and also as predictive factors for complete pathological response. Further multicenter studies with larger number of patients are needed.

Key Words: *Lymphocytic count – Lymphocytic ratio – Cancer rectum – Neoadjuvant chemoradiotherapy.*

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Introduction

COLORECTAL Cancer (CRC) represents a worldwide major health problem [1]. In western countries, the lifetime risk of developing colorectal cancer is about 4.7% for men and 4.4% for women [2]. In Egypt, it is the fourth most commonly diagnosed cancer representing 6.5% of all cancers [3].

Rectal Carcinoma (RC) represents 30% of all colorectal cancers [4]. Among rectal cancers, Locally Advanced Rectal Cancer (LARC) is a type in which tumors are transmural or with a suspicion of positive lymph nodes on pre-operative imaging (stage II and III) [5]. Treatment of rectal cancer has evolved throughout the past decades. However, management of LARC is especially complex [6].

Neoadjuvant Chemoradiation (nCRT), Total Mesorectal Excision (TME), and new generations of chemotherapeutic agents have decreased recurrence after surgical resection of rectal cancer [7]. They also improved the overall survival [8,9]. However, the local recurrence remains high and seems to be affected by many prognostic factors [10].

The German Rectal Cancer Study focused on prognostic stratification in patients undergoing nCRT and revealed that prognosis was related to the extent of pathological response of the tumor to nCRT [11-16]. Neoadjuvant chemoradiation can achieve clinical down-staging, increase rates of sphincter saving surgery and improve local control [17]. Yet, the type and remission rate to nCRT is considerably variable. While some patients may not respond, other patients experience down-staging, and 15-25% show complete pathological response with no viable tumor cells in surgical specimens [17,18].

Predicting tumor pathological response is an important part of the future monitoring multimodality therapy. The study of either genetic factors or clinical factors may help to change the personalization of treatment strategies for tumors expected to respond from those expected to have poor response [19-21].

Many parameters obtained from the diagnostic workup of primary clinical staging and re-staging in post-treatment interval can be used as predictive factors for pathologic tumor response. Several factors (obtained from demographic data, physical examination, laboratory tests and radiological assessment) have been investigated and found to be more easily collected and much less costly than genetic factors [22,23].

Pre-treatment laboratory values were investigated by a limited number of studies. Hemoglobin level, White Blood Cell (WBC) count and platelet count before nCRT did not show significant differences. However, some of these studies demonstrated that lymphocytic count and ratio may have an impact on the pathologic tumor response after nCRT for LARC [19,20,24].

Although surgery is the standard treatment for rectal cancer patients with complete response after neoadjuvant therapy, wait and see policy has been adopted for a very selected group of those patients in a limited number of studies [25-27]. Therefore, detection of predictive factors for complete pathological response may be useful in future planning for management of this group of patients [28].

Patients and Methods

This prospective study included 36 patients who were diagnosed as stage II or stage III rectal cancer (LARC) in middle and lower thirds of the rectum. They were admitted to Alexandria Main University Hospital, Egypt, during the period from January to December 2017. All patients were treated with neoadjuvant chemoradiotherapy prior to standard surgical management. Patients with early, metastatic or complicated cancer rectum were excluded from the study.

Forty-five patients were enrolled in this study. However, nine patients were excluded from the study (two patients refused the neoadjuvant therapy, two patients did not complete the neoadjuvant therapy because of complications that necessitated urgent surgical intervention, two patients had their surgical management after more than 12 weeks because of associated co-morbidity and three patients were missed after they finished the neoadjuvant therapy).

The study protocol was approved by the Ethical Committee of Faculty of Medicine, Alexandria University (IRB 00007555). Informed consent was obtained from each participant patient.

Demographic data of all patients were collected. Patients were subjected to thorough history taking, physical examination, and Digital Rectal Examination (DRE). All patients were investigated by laboratory investigations (including CBC and CEA), colonoscopy and biopsy, CT scan of chest, abdomen and pelvis and pelvic MRI.

Peripheral venous blood samples were collected 0-7 days before starting neoadjuvant chemoradiotherapy to obtain blood data. Two ml of blood were collected in sterile EDTA vacutainer tube; the blood cell counts in the samples were analyzed by automated hematology analyzer.

All patients received neoadjuvant chemoradiotherapy consisting of 50.4Gy divided into 28 fractions, with infusional 5-fluorouracil (1000mg/m^2 per day for 5 days in the first and fifth weeks of radiation) [7]. After 6 weeks from completing the neoadjuvant chemoradiotherapy, the patients underwent DRE, proctoscopy, CT scan of chest, CT of abdomen and pelvis, and pelvic MRI with evaluation of rectal cancer response to nCRT using Response Evaluation Criteria in SolidTumors (RECIST) [29,30]. After completing the nCRT by 6-8 weeks, all patients underwent Low Anterior Resection (LAR) or Abdominoperineal Resections (APR) according to the rules of TME via either open or laparoscopic surgery [31]. All specimens were sent for pathology examination and evaluation oftumor response using Mandard Tumor Regression Grade (TRG) which is a 5-stage system defined by Mandard et al., [32].

After pathological examination, patients were divided into two groups; Group I included patients with a complete pathological response (TRG 1) and Group II included patients with no or partial pathological response (TRG 2-5), in order to detect the predictive factors for complete pathological response in comparison to partial or no pathological response.

Outcomes:

Primary endpoint:

Pre-treatment circulating lymphocytic count and ratio, as predictive factors of rectal cancer response to neoadjuvant therapy.

Secondary endpoint:

Comparison between Group I (patients with complete tissue response) and Group II (patients with partial or no tissue response) regarding pre-treatment circulating lymphocytic count,ratio and other clinical, laboratory and radiological findings as predictive factors for tissue response of rectal cancer to neoadjuvant therapy.

Statistical analysis:

Collected data were entered into a computer, using the Statistical Package for Social Sciences (SPSS, Version 23). Descriptive statistics (i.e., frequency, percentage, range, mean and standard deviation) were calculated. Significance of differences between study groups were tested using appropriate tests of significance, i.e., independent sample *t*-test, F-test (ANOVA), Chi square test (with Fisher exact and Monte Carlo tests), Mann Whitney U-test and Kruskal Wallis H-test. *p*-values less than 0.05 were considered as statistically significant.

Results

This study included 36 patients with cancer of the lower two-thirds of the rectum (20 females and 16 males). Age of our patients ranged from 23 to 65 years with a mean of 56.40 ± 11.18 years. The mean interval between completion of nCRT and surgery was 7.67 ± 0.59 weeks. Nineteen patients (52.7%) underwent Low Anterior Resections (LAR) and seventeen patients (47.3%) underwent Abdominoperineal Resections (APR).

Results of CBC parameters as predictive factors for pathological response are shown in (Table 1). Hemoglobin, platelet count and total leukocytic count showed insignificant associations with pathological response. On the other hand, both lymphocytic count and ratio were significant predictive factors for the pathological response of the tumor to neoadjuvant therapy (p=0.011 and 0.048, respectively).

The comparisons between Groups I and II regarding different clinical, laboratory, radiological and pathological findings are shown in (Tables 2,3). Comparison between Group I and Group II regarding different demographic, clinical, laboratory and radiological data revealed that age, RECIST, and pre-treatment CEA showed significant differences as predictive factors for complete pathological response (p=0.035, p=0.041, and p=0.032, respectively).

Regarding CBC results, only lymphocytic count and ratio were significant predictive factors for patients in Group I compared to Group II (p=0.001 and p=0.049, respectively), as shown in (Table 4).

Table (1): Evaluation of CBC parameters as predictive factor for pathological response.

	TRG					Test of significance	*p*-value
	Complete response (n=7)	Fibrosis >tumor (good response) (n=7)	Fibrosis <tumor (partial response) (n=8)	Dominant tumor (poor response) (n=2)	No response (n=12)		
Hemoglobin (gm/dl):							
Min.-max.	9.84-14.75	9.10-11.90	9.10-14.10	10.90-13.90	10.90-13.90	F=	0.689
Mean ± SD.	11.70±1.79	11.58±1.46	10.90±1.49	12.40±2.12	12.40±2.12	0.566	
Platelet count (X1000/dl):							
Min.-max.	173.0-331.0	121.0-324.0	176.0-378.0	288.0-304.0	288.0-304.0	F=	0.695
Mean ± SD.	290.0±70.7	296.0±83.9	290.0±79.8	296.0±11.3	296.0±11.3	0.560	
WBCs (X1000/d):							
Min.-max.	5.40-9.00	5.70-9.10	4.90-8.00	4.80-5.90	4.80-5.90	F=	0.440
Mean ± SD.	7.87±2.21	7.07±2.28	6.60±2.19	5.35±0.78	5.35±0.78	0.970	
Lymphocyte count (X1000/dl):							
Min.-max.	1.70-3.70	0.70-3.80	1.30-3.30	1.00-1.60	1.00-1.60	F=	0.011 *
Mean ± SD.	2.95±0.77	2.42±1.17	2.32±0.61	1.30±0.42	1.30±0.42	4.07*	
Lymphocyte ratio %:							
Min.-max.	24.0-46.0	6.70-50.0	16.0-48.0	18.0-29.0	18.0-29.0	F=	0.048*
Mean ± SD.	35.19±8.45	32.82±13.77	30.98±10.90	23.5±7.78	23.5±7.78	2.795	

F : F-value for ANOVA test.
KW : Kruskal Wallis H-test.
* : Statistically significant at $p \leq 0.05$.

Table (2): Comparing between Group I and Group II regarding radiological finding.

	Pathological response				Test of sig.	*p*
	Complete response (TRG1) (n=7)		Non complete response (TRG2-5) (n=29)			
	No.	%	No.	%		
Pre-treatment max. tumor length by MRI (cm):						
≤4cm	2	28.6	6	20.7	χ^2=0.048	p_{FE}=1.000
>4cm	5	71.4	23	79.3.0		
Mean ± SD.	5.0± 1.26		5.16± 1.14		*t*=0.330	0.746
Recist on MRI:						
cCR	4	57.2	4	13.77	χ^2=6.000*	p_{FE}=0.041*
Non-CR	3	42.8	25	86.3		
Radiological involvement of CRM:						
Negative involvement	7	100.0	22	75.9	χ^2=1 .500	p_{FE}=0.553
Positive involvement	0	0.0	7	24.1		
cT:	3 (3.0-3.0)		3 (3.0-4.0)		Z=0.644	0.520
3	7	100.0	26	89.7		
4	0	0.0	3	10.3	χ^2=0.429	p_{FE}=1.000
cN:	1 (1.0-1.0)		1 (0.0-2.0)		Z=0.866	0.386
0	1	14.2	2	7.0		
1	6	85.8	18	62.0		
2	0	0.0	9	31.0	χ^2=2.571	p_{MC}=0.507

χ^2 : Chi square test.
t : Student *t*-test.
Z : Z-value for Mann Whitney test.
FE : Fisher Exact for Chi square test.
MC : Monte Carlo for Chi square test.
* : Statistically significant at $p \leq 0.05$.

Table (3): Comparison between Group I and Group II regarding different clinical, laboratory and pathological finding.

	Pathological response				Test of sig.	*p*
	Complete response (TRG1) (n=7)		Non complete response (TRG2-5) (n=29)			
	No.	%	No.	%		
• *Sex:*						
Male	4	57.2	12	41.3	χ^2=1.000	p_{FE}=0.364
Female	3	42.8	17	58.7		
• Age (years)	53.10±6.65		47.34±6.15		*t*=2.19*	0.035*
• Interval (weeks)	7.20±0.54		7.30±0.71		*t*=0.0	1.000
• Pre-treatment distance from anal verge by DRE/rigid Proctoscopy (cm)	7 (1.0-9.5)		6.5 (2.5-10.0)		Z=0.225	0.822
• *Histological type:*						
Mucinous	0	0.0	10	34.5	χ^2=2.571	p_{FE}=0.286
Adenocarcinoma	7	100.0	19	65.5		
• *Histological grade:*						
Well differentiated	2	28.6	8	27.6	χ^2=4.500	p_{MC}=0.105
Moderately differentiated	5	71.4	9	31.0		
Poorly differentiated or mucinous	0	0.0	12	41.4		
• Pre-treatment CEA (ng/dl)	1.70 (1.50-3.77)		3.12 (1.45-284.0)		Z=2.143*	0.032*

χ^2 : Chi square test.
t : Student *t*-test.
Z : Z-value for Mann Whitney test.
FE : Fisher Exact for Chi square test.
MC : Monte Carlo for Chi square test.
* : Statistically significant at $p \leq 0.05$.

Table (4): Comparison of CBC parameters as predictive factor between patients with complete and incomplete response.

CBC before nCRT	Pathological response		Test of sig.	*p*
	Complete response (TRG1) (n=7)	Non complete response (TRG2-5) (n=29)		
HB	11.70±1.79	11.21±0.78	*t*=1.341	0.191
Platelet (X1000/dl)	290.0±70.7	281.0±68.5	*t*=0.310	0.758
WBCs (X1000/d)	7.87±1.21	6.45±1.23	*t*=2.027	0.052
Lymphocyte count	2.95±0.77	1.50±0.69	*t*=4.890*	<0.001*
Lymphocyte ratio	35.19±8.45	25.94±11.09	*t*=1.947	0.049*

t: Student *t*-test.
Z-value for Mann Whitney test.
*: Statistically significant at $p \leq 0.05$.

Discussion

Response of LARC to neoadjuvant therapy is variable. There is no model to predict this response until now. However, this model is important for future planning of management of LARC **[17,18,33]**.

It has been proposed since 1979 that tumor shrinkage is related to both direct damage to tumor cells and patients' immune response. There is some evidence that peripheral blood lymphocytes level and its ratioare correlated with the recurrence and survival in many tumors **[34-37]**.

Therefore, in the current study, relation between pre-treatment CBC parameters and pathological response of LARC to nCRT was investigated. However, no significant association between any of CBC parameters and the response of LARC to nCRT was noted, except the lymphocytic count and ratio, which proved to be significant predictive factors for pathological response.

These findings are in agreement with those reported by several researchers. Kitayama et al., **[38]**, reported similar results regarding the circulating lymphocytic count in peripheral blood. Choi et al., **[24]**, also reported that lymphocytic ratio is a significant factor for predicting tumor regression. Moreover, Tada et al., concluded that both lymphocytic count and ratio are independent factors for predict tumor response **[39]**.

These findings may be explained by the concept that tumor microenvironment is an important factor that affects the response of the tumor to radiotherapy, and as part of the microenvironment peripheral blood lymphocytes count and ratio have same effect and can be an available simple and cheap predictive factor of response of locally advanced rectal cancer to neoadjuvant therapy **[33,40]**. Another explanation is the potential role of circulating T lymphocytes in predicting the response to nCRT and enhancing host immunological response **[33,38,40]**.

Xue Dou et al., **[41]** found similar results to those revealed in our study.However, they considered that different blood cell ratiosconstitute more powerful factors than blood cell count, since the absolute counts of blood cells varyamong different persons. Furthermore, the subsets of blood cells show change in the count between daytime and night.

In the current study, age, RECIST, pre-treatment CEA, lymphocyte count and lymphocyte ratio were found to be significant predictive factorsfor complete pathological response after neo-adjuvant chemoradiotherapy.

In a study by Perez et al., **[42]**, 99 patients were prospectively examined after 12 weeks from completion of nCRT. Sixteen patients had cCR, of them 13 were confirmed pCR and 3 had residual tumor cells. On the contrary, Hiotis et al., **[43]** concluded that even if clinical parameters may predict tumor response, they are unable to distinguish pCR and to predict which patient does not require surgical excision following CRT. Regarding CEA, while Zeng et al., **[44]** and Kitayama et al., **[38]**, reported CEA level ≤5ng/dl as a cut-off to predict pCR, Park et al., **[45]** and Das et al., **[11]**, reported a level of≤2.5ng/dl as a cut-off value. We think that further studies may be required to determine the accurate cut-off value of CEA level for proper planning of the management of LARC.

Kitayama et al., **[38]** reported that, in patients with LARC, there is a strong correlation between lymphocytic ratio before and during neoadjuvant radiotherpy and complete pathological response, suggesting that lymphocyte-mediated immune response plays an important role in the eradication of tumor cells by preoperative radiotherapy.

Neoadjuvant chemoradiotherapy for patients with low cancer rectum delays the surgical treatment in some patients especially those with no pathological response. In addition, it may be associated with complications in some patients **[41]**. Since the present study showed that lymphocytic count and ratio were significant predictive factors for pathological response of LARC, customization of treatment plans for patients with LARC could be achieved.

Limitations:

The current study is single-center, that comprised relatively limited number of patients with LARC (n=30) that fulfilled the inclusion criteria.

Conclusions:

Lymphocytic count and ratio can play an important role as predictive factors for pathological response to neoadjuvant therapy in patients with LARC and also as predictive factors forcomplete pathological response. However, further multicenter studies with larger number of patients are needed.

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العد الليمفاوى والنسبة الليمفاوية كعوامل تنبؤية للإستجابة النسيجية بعد العلاج الكيماوى والإشعاعى المساعد قبل العملية لمرضى سرطان المستقيم

\الهدف: إستهدفت الدراسة تقييم عد الدم الكامل قبل العملية، خاصة العد الليمفاوى والنسبة الليمفاوية، كعوامل تنبؤية للإستجابة النسيجية بعد العلاج الكيماوى والإشعاعى المساعد قبل العملية لمرضى سرطان المستقيم وللتنبؤ بالإستجابة النسيجية الكاملة.

\المنهجية: تم دراسة العلاقة بين نتائج عد الدم الكامل لمرضى سرطان المستقيم المصنفين بالمرحلة الثانية والثالثة (منتشر موضعى) قبل إعطاء العلاج الكيماوى والإشعاعى المساعد قبل العملية والإستجابة النسيجية الموجودة فى العينة المستآصلة بعد إجراء العملية. تم تقسيم المرضى إلى مجموعتين، ضمت المجموعة الآولى ذوى الاستجابة النسيجية الكاملة وضمت المجموعة الثانية المرضى ذوى الإستجابة الجزيئية آو عدم الإستجابة، وذلك لدراسة العوامل التى تنبئ بالإستجابة الكاملة.

\النتائج: تضمنت الدراسة ٣٦ مريضا (٢٠ آنثى و١٦ ذكرا)، وكان متوسط آعمارهم هو ٥٦.٤٠±١١.١٨ عاما. وقد تم إجراء إستئصال للمستقيم مع الحفاظ على الشرج لتسعة عشر مريضا (٥٢.٧٪) بينما تم إستئصال المستقيم والشرج لسبعة عشر مريضا (٤٧.٢٪). وآظهرت الدراسة آن العد الليمفاوى والنسبة الليمفاوية هى عوامل تنبؤية ذات دلالة إحصائية للإستجابة النسيجية بعد العلاج الكيماوى والإشعاعى المساعد قبل العملية لمرضى سرطان المستقيم. كما آظهرت المقارنة بين المجموعة الآولى والثانية آن العد الليمفاوى والنسبة الليمفاوية هى عوامل تنبؤية ذات دلالات إحصائية للإستجابة النسيجية الكاملة.

\الإستنتاجات: يمكن آن يكون للعد الليمفاوى والنسبة الليمفاوية دور مهم كعوامل تنبؤية ذات للإستجابة النسيجية بعد العلاج الكيماوى والإشعاعى المساعد قبل العملية لمرضى سرطان المستقيم، وكذلك للتنبؤ بالإستجابة النسيجية الكاملة. ولا يزال الآمر يحتاج إلى دراسات مستقبلية متعددة المراكز، وبعدد آكبر من المرضى لتآييد نتائج هذه الدراسة.