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DIAGNOSTICS OF LYMPHOGENIC METASTASIS IN PATIENTS WITH RECTAL CANCER BY COMBINING MRI WITH BLOOD CEA ASSESSMENT

Aim: To improve the diagnostics of lymphogenic metastasis in patients with rectal cancer (RCa) by combining magnetic resonance imaging (MRI) with the blood carcinoembryonic antigen (CEA) level assessment. **Materials and Methods:** We have systematized and analyzed the results of the examination and treatment of 77 patients with stage II–III rectal adenocarcinoma ($T_{2-3}N_{0-2}M_0$). Before the start of neoadjuvant treatment as well as 8 weeks after its completion, computed tomography (CT) and MRI were performed. We analyzed such prognostic criteria as the size, shape, and structure of lymph nodes as well as the patterns of contrast accumulation. As a prognostic marker, CEA levels in the blood of patients with RCa before surgical treatment were assessed. **Results:** Radiological exams showed a rounded shape and heterogeneous structure to be the most informative for predicting metastatic lymph node damage, increasing the probability by 4.39 and 4.98 times, respectively. After neoadjuvant treatment, the percentage of positive histopathological reports on lymph node involvement decreased significantly to 21.6% ($p < 0.001$). MRI showed 76% sensitivity and 48% specificity for assessing lymphogenic metastasis. CEA levels differed significantly between stages II and III (N_{1-2}) ($p < 0.032$) with a threshold value of 3.95 ng/ml. **Conclusions:** In order to increase the effectiveness of the diagnosis of lymphogenic metastasis using radiological examination methods in RCa patients, such prognostic criteria as the round shape and heterogeneous structure of the lymph nodes and the threshold level of CEA should be considered.

Keywords: rectum, adenocarcinoma, magnetic resonance imaging, staging, lymph nodes.

Colorectal cancer is the third leading cause of cancer-related deaths worldwide, and its incidence is steadily increasing in developing countries [1]. In recent decades, advances in surgical techniques such as total mesorectal excision, the use of radiation therapy, and perioperative chemotherapy have significantly improved the short-term and long-term outcomes for rectal cancer (RCa) patients [1]. However, overall survival rates are strongly influenced by the stage

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at which the disease is diagnosed. The 5-year survival rates for stage IIA and stage IIB colorectal cancer are 87% and 65%, respectively. For stage III, it is 53%, and for stage IV, or metastatic colorectal cancer, it is only 12% [2].

Notably, the difference in overall survival between RCa patients of stages IIB and III A/B may be due to underestimation of the stage, which can negatively affect the choice of optimal treatment strategies, including adjuvant chemotherapy. This may lead to disease recurrence and lower overall survival rates [2].

The accurate diagnosis and staging based on clinical, laboratory, and radiological exams, especially magnetic resonance imaging (MRI) and computed tomography (CT) scans are crucial for selecting the most effective treatment plan. Characterizing the disease progression using these imaging modalities helps to determine patients who should undergo a total neoadjuvant treatment strategy, neoadjuvant radiotherapy, or surgical treatment first. After neoadjuvant treatment, restaging based on MRI data helps to determine candidate patients for surgical treatment or a "watch and wait" strategy [3].

The TNM staging system is used to stage RCa patients. Patients with affected lymph nodes are assigned to stage III regardless of T and require more aggressive treatment strategies, including long-term neoadjuvant treatment. However, MRI is less sensitive for detecting lymph node involvement [4, 5]. The size of the lymph node is not a reliable prognostic indicator of metastasis as there is an overlap in the sizes of normal and pathologically changed lymph nodes [6]. The old adage that "any palpable pararectal lymph node is metastatic" is no longer true. Patients undergoing MRI have usually preceding colonoscopy or rectoromanoscopy with biopsy, which can cause reactive changes in regional lymph nodes [7].

According to the Society of Abdominal Radiology, a lymph node can be considered metastatic if it has one of the following criteria: the size along the short axis is ≥ 9 mm; a short axis is 5 to 9 mm and has at least two abnormal morphologic features, including heterogeneous signal intensity, irregular border, or rounded shape; short axis < 5 mm, and all three of the abovementioned morphological features are present [8, 9].

The NODE-RADS and RECIST v1.17 systems are commonly used to evaluate lymph node involvement and response to neoadjuvant treatment. NODE-RADS uses a three-level block system to assess the size, structure, and shape of lymph nodes [10]. RECIST, on the other hand, evaluates lymph node status based on the size along the short axis [11].

Despite the advances in imaging technologies, there is still no reliable system for accurately detecting metastatic lymph nodes. Accumulating and systematizing data on the clinical and morphological characteristics of the disease will help improve and individualize the approach to diagnosing lymphogenic metastasis. The aim of the study was to assess the improvement of diagnosing lymphogenic metastasis in RCa patients by combining MRI with the blood CEA level assessment.

Materials and Methods

In the study, the results of examinations of 77 patients with stage II—III rectal adenocarcinoma (T2-3N0-2M0) who received treatment at the KNP "Prykarpattia Clinical Oncology Center of the Ivano-Frankivsk Regional Council" in the period from 2019 to 2021 were systematized and analyzed. The study included patients with an uncomplicated course of RCa and the absence of other oncological diseases. All patients received combined treatment according to NCCN recommendations, which included TGT, perioperative or adjuvant chemotherapy as indicated, and surgical treatment. Rectal resection or extirpation was performed in a standard volume in accordance with the principles of TME and CVL [12]. The research program was approved by the

Bioethics Commission of the Ivano-Frankivsk National Medical University. All patients gave informed written consent to participate in the study.

In order to determine the disease stage, before the start of neoadjuvant treatment and 8 weeks after its completion, CT of the chest, abdominal cavity, and pelvis was performed using IV contrast with the Tomohexol solution (Farmak, Ukraine) on a Somatom Emotion tomograph 16-slice (Siemens, Germany) and MRI of the pelvic organs on a Magnetom Espree (Siemens, Germany) with a magnetic field strength of 1.5 T. We have analyzed such prognostic criteria as the size, shape, structure of lymph nodes as well as patterns of contrast accumulation. A lymph node was considered metastatic if its largest short axis size was >9 mm or 5—9 mm and 2 criteria for lymph node involvement (round shape, heterogeneous structure, or uneven edges) or <5 mm and 3 criteria for lymph node involvement.

After the operation, a histological examination of at least 12 lymph nodes from the removed macropreparation was performed. Based on the results of the morphological assessment, the patients were distributed into 2 groups: with the absence (group A) or the presence (group B) of metastatic lesions in regional lymph nodes. As a prognostic marker, CEA levels in the blood of patients before surgical treatment were assessed.

Statistical processing of data was carried out using author's computer programs based on Microsoft Excel (calculation of relative values, errors, *t*-test). The licensed IBM SPSS 26.0 for Windows statistical analysis packages including descriptive statistics and graphics programs were used. The reliability of the obtained indices was confirmed by calculating the error (±m) for relative values. The probability of the data difference in the compared groups, taking into account a large number of observations and the resulted approximation to the normal distribution, was proved on the basis of Student's *t*-test. Additionally, non-parametric methods (Mann — Whitney test) were used for a series with a non-normal distribution. To determine the metastatic lesion of the lymph nodes during the histopathological examination, depending on the result of CT scan/MRI, a prognostic model was developed using the method of binary logistic regression. A ROC curve was plotted to determine the optimal threshold of the CEA level.

Student's *t*-test was used to assess the significance of the difference in the dynamic quantitative indicators at different stages of treatment, and McNemar's test was used for frequency indicators. The differences were considered statistically significant at $p < 0.05$. Cochran's test was used to analyze the statistical hypothesis about the effect of neoadjuvant treatment on the frequency of lymph node involvement. The differences in the indicators were considered statistically significant at $p < 0.05$.

Results

According to the results of the histopathological examination, the patients with RCa (n = 77) were divided into group A (n = 60) and group B (n = 17). By the data of examination of the postoperative macro-preparation in the vast majority of cases (85%), G2 adenocarcinoma was diagnosed in patients of both groups (Table 1).

According to the results of CT, in group A, lymph nodes were up to 10 mm in size, oval in shape, and actively accumulating contrast in 60% of cases (Table 2). Lymph nodes with a size ≥10 mm were detected twice more rarely. According to the MRI data, the ratio was somewhat different, in particular, lymph nodes up to 10 mm in

Table 1. **Differentiation grade of rectal adenocarcinoma**

Differentiation grade	Group A	Group B
G1	2 (3.33%)	0
G2	54 (85%)	16 (94.12%)
G3	4 (6.67%)	1 (5.88%)

size were found in 76.47% of patients of group A, while larger — only in one case.

According to CT scan data, in 40% of patients from group B, the size of lymph nodes did not exceed 10 mm (40%), they were of a round shape with a heterogeneous structure and/or accumulated contrast. At the same time, MRI showed the maximum size of lymph nodes up to 10 mm in 80% of cases, their oval shape in 68.75% of cases, and a homogeneous structure in half of the cases (Table 2).

We developed a prognostic model for determining the probability of metastatic damage to lymph nodes based on the results of CT scan and MRI among patients with RCa using the binary logistic regression method. Such a dependence is described by the equation:

$$P = 1/(1 + e) \cdot 100\%,$$

$$z = -3.02 + 0.02X_s + 1.50X_{sh} + 1.42X_{str} + 0.37X_{con},$$

where P is the probability of lymph node damage (%), X_s — size (mm), X_{sh} — shape (0 — oval, 1 — round), X_{str} — structure (0 — homogeneous, 1 — heterogeneous), X_{con} — contrast (0 — does not accumulate, 1 — accumulates), e — Euler number, z — standard regression equation.

The obtained regression models are statistically significant ($p = 0.004$).

According to the value of the Nigelkirk coefficient, the model takes into account 30.6% of the factors that determine the variance of the probability of detecting a lymph node lesion in the groups of RCa patients. According to the values of the regression coefficients, the parameters had a direct relationship with the probability of establishing a metastatic lesion of the lymph node. The characteristics of the criteria for the lymph node involvement, the influence of which can be considered significant ($p < 0.05$), have the following predictors: round shape — 4.39 (CI 1.133—

Table 2. **Survival of GC patients differing in BMI and prognostic NLR values**

Criterion	**CT (n = 25)** n (%), group A	**MRI (n = 51)** n (%) group A	**CT (n = 5)** n (%) group B	**MRI (n = 16)** n (%) group B
Size, mm				
3—5	4 (16.00)	15 (29.41)	1 (20.00)	3 (18.75)
6—9	11 (44.00)	24 (47.06)	1 (20.00)	10 (62.50)
10—14	6 (24.00)	1 (1.96)	1 (20.00)	1 (6.25)
≥15	2 (8.00)	0	0	0
Not detected	2 (8.00)	11 (21.57)	2 (40.00)	2 (12.50)
Shape				
Oval	17 (68.00)	21 (41.18)	1 (20.00)	1 (68.75)
Round	6 (24.00)	19 (37.25)	2 (40.00)	3 (18.75)
Not detected	2 (8.00)	11 (21.57)	2 (40.00)	2 (12.50)
Structure				
Homogeneous	18 (72.00)	24 (47.06)	1 (20.00)	8 (50.00)
Heterogeneous	5 (20.00)	16 (31.37)	2 (40.00)	6 (37.50)
Not detected	2 (8.00)	11 (21.57)	2 (40.00)	2 (12.50)
Contrast				
Accumulated	14 (56.00)	26 (50.98)	2 (40.00)	10 (62.50)
Not accumulated	9 (36.00)	14 (27.45)	1 (20.00)	4 (25.00)
Not detected	2 (8.00)	11 (21.57)	2 (40.00)	2 (12.50)

17.13, $p < 0.03$), and heterogeneous structure — 4.98 (CI 1.28—19.32, $p < 0.03$). Thus, the round shape and heterogeneous structure increase the probability of metastatic damage to the lymph node by 4.39 and 4.98 times, respectively.

The threshold value of the logistic function P was 77.0% when using the given criteria for lymph node involvement (structure, shape). The specificity and sensitivity of this model were 84.4% and 56.3%, respectively.

We analyzed the dynamics of lymph node involvement indices based on MRI data in 37 patients before neoadjuvant treatment and 8 weeks after its completion (Table 3). After the course of neoadjuvant treatment in all cases, the size of the lymph node decreased from 8.16 ± 2.72 to 5.26 ± 3.79, and in some cases, the other criteria (rounded shape, heterogeneous structure, and contrast accumulation) also improved.

We compared the percentage of patients with affected lymph nodes before and after neoadjuvant treatment comparing the number of positive pathohistological conclusions (PHC), which was reduced to 21.6%. According to MRI imaging, the percentage of lymph node involvement indices after neoadjuvant treatment decreased from 70.3 to 48.6% (Table 3). The difference was significant by Cochrane test.

In order to increase the accuracy of the diagnosis of lymphogenic metastasis at the preoperative

Table 3. **Assessment of the criteria for lymph node status in patients from groups A and B according to CT and MRI data 8 weeks after the completion of neoadjuvant treatment**

Index	Treatment stage		*p*
	Before neoadjuvant treatment (n = 37)	After neoadjuvant treatment (n = 37)	
Diagnosis of metastatic lymph node lesion according to MRI data	26/37 (70.3%)	18/37 (48.6%) *	0.022
Size, mm	8.16 ± 2.72	5.26 ± 3.79 *	<0.001
Round shape	13/37 (35.1%)	10/37 (27.0%)	0.42
Heterogeneous structure	13/37 (35.1%)	9/37 (24.3%)	0.18
Accumulation of contrast	28/37 (75.6%)	17/37 (45.9%) *	0.002

Note: *change in the index is significant ($p < 0.05$).

Table 4. **Diagnostic value of MRI and CT examination in patients with adenocarcinoma of the rectum in relation to the verification of metastatic lesions of regional lymph nodes**

Index	PHC MRI		PHC CT	
	Positive test	Negative test	Positive test	Negative test
Positive test	13	29	3	23
Negative test	4	31	2	2
Sensitivity		0.76		0.60
Specificity		0.48		0.92
Positive predictive value		0.31		0.12
Negative predictive value		0.89		0.50
Positive likelihood ratio		2.0		7.5
Negative likelihood ratio		0.68		0.43
Diagnostic accuracy of the test		0.57		0.17

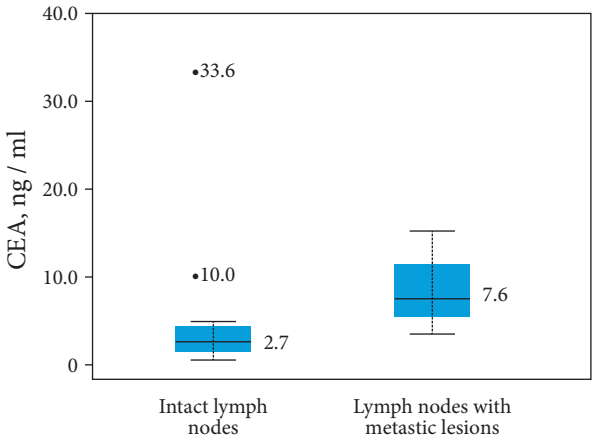

Fig. 1. Dependence of CEA on the presence of metastatic lymph nodes

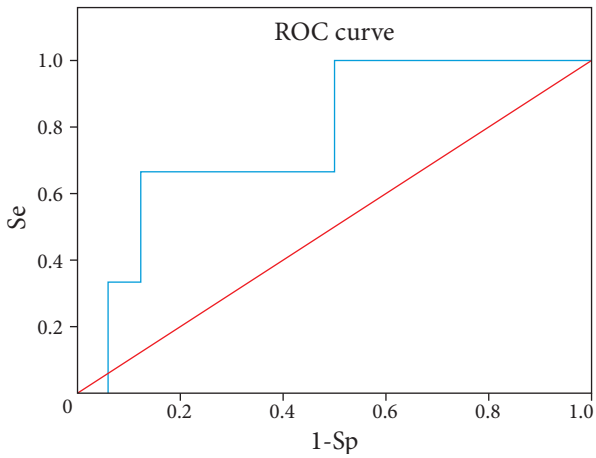

Fig. 2. ROC-curve for the relationship between predictive lymph node involvement and blood CEA level

stage in patients with RCa, we analyzed the levels of CEA in the blood of patients of both groups.

The non-parametric Mann — Whitney test was used to compare independent groups. The levels of CEA in patients with metastatic lesions and patients with intact lymph nodes differ significantly ($p < 0.032$). At the same time, the presence of two "outliers" (atypical values) of the CEA level in group A (10.0 ng/ml and 33.6 ng/ml) were found among the patients who were not included in the study (Fig. 1).

We constructed a ROC curve to detect the threshold value of CEA (Fig. 2). The area under the ROC curve that corresponded to the relationship between the prognosis of metastatic lesion in lymph nodes and the CEA index in patients with RCa was 0.77 ± 0.13 with a 95% CI: 0.50—0.99. The threshold value of CEA at the cut-off point was 3.95 ng/ml. Therefore, the CEA level >3.95 ng/ml in RCa patients increases the probability of metastatic lesions in regional lymph nodes (Table 4).

According to our data, the sensitivity of MRI for detecting metastatic lymph nodes was 76%, but the specificity was only 48%, while the sensitivity of CT was 60%, but the specificity was much higher than that of MRI and reached 92%.

Discussion

Lymph node metastasis is a poor prognostic factor for RCa patients [13]. Accurate staging is essential for choosing the optimal treatment program [14]. Imaging modalities such as endorectal ultrasound, CT, and MRI are used for preoperative assessment of the lymph node status [15]. However, there are significant differences in the accuracy, sensitivity, and specificity of CT and MRI for determining metastatic lymph node involvement in RCa patients [16—18]. In a study comparing CT and MRI accuracy for assessing primary tumors, MRI had similar accuracy to CT (92—98%), but even with 3.0 T MRI, specificity and accuracy for examining lymph nodes could not be significantly improved (62—67%) [19]. In our study, MRI sensitivity and specificity for detecting metastatic lymph node involvement using standard lesion criteria were 76 and 48%, respectively, and those of CT were 60 and 92%, respectively. Continuous improvement in imaging technology and resolution allows for the detection of the smallest foci and lymph nodes up to 5 mm in size, but the lack of a single concept for evaluating lymph nodes often leads to false-positive or false-negative conclusions [20]. A predictive model for metastatic lymph node lesions was developed on the basis

of separate criteria, such as round shape and heterogeneous structure, which increased the probability by 4.39 and 4.98 times, respectively. The sensitivity and specificity of this model were 56.3% and 84.4%, respectively [21]. CEA indices were significantly different ($p < 0.032$) in patients with stages II (N_0) and III (N_{1-2}) of the disease, and the threshold value of CEA (3.95 ng/ml) was determined as a risk factor for the presence of metastatic lesions in the lymph nodes.

This study has found that the level of CEA in the blood of RCa patients can be a useful risk factor for lymph node involvement. There was a significant difference ($p < 0.032$) in the CEA levels between patients with stage II (N_0) and stage III (N_{1-2}) disease, which suggests the use of this marker to improve the accuracy of preoperative diagnosis of lymph node involvement. A threshold value of CEA (3.95 ng/mL) was determined, above which we propose to consider the risk of metastatic involvement in lymph nodes.

To sum up, the study has shown that the standard diagnostic program using only MRI is not accurate enough for detecting lymph node metastasis in RCa patients. Instead, the level of CEA in the blood of patients can be a useful risk factor for lymph node involvement, which can be used to improve diagnosis accuracy. This can help in selecting the optimal treatment program for RCa patients.

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ДІАГНОСТИКА ЛІМФОГЕННОГО МЕТАСТАЗУВАННЯ У ХВОРИХ НА РАК ПРЯМОЇ КИШКИ ЗА ДАНИМИ МРТ З УРАХУВАННЯМ РЕА

Мета. Покращити діагностику лімфогенного метастазування у хворих на рак прямої кишки променевими методами обстеження з урахуванням рівнів РЕА у крові пацієнтів. **Матеріали та методи.** Систематизовано та проаналізовано результати обстежень та лікування 77 хворих з аденокарциномою прямої кишки II—III стадій ($T_{2-3}N_{0-2}M_0$) на базі КНП «Прикарпатський клінічний онкологічний центр Івано-Франківської обласної ради» в період з 2019 по 2021 рік. З метою визначення стадії захворювання до початку неоад'ювантного лікування, а також через 8 тижнів після його завершення виконували комп'ютерну томографію та магнітно-резонансну томографію. Аналізували такі прогностичні критерії, як розмір, форму, структуру лімфатичних вузлів, а також особливості накопичення ними контрасту. В якості прогностичного маркера досліджували рівні РЕА в крові пацієнтів перед хірургічним лікування. **Результати.** При використанні променевих методів обстеження для доопераційного стадіювання лімфогенного метастазування у хворих на рак прямої кишки найбільш інформативною, згідно отриманих даних, є візуалізація їхньої округлої форми та неоднорідної структури, що збільшує ймовірність метастатичного ураження лімфатичних вузлів відповідно в 4,39 та 4,98 рази. При оцінці зміни частоти встановлення висновку про ураження лімфатичних вузлів на різних етапах лікування хворих було виявлено статистично значуще зниження показника з 70,3 до 21,6 % ($p < 0{,}001$). Враховуючи, що чутливість магнітно-резонансної томографії для оцінки лімфогенного метастазування становить 76 %, а специфічність лише 48 %, з метою підвищення ефективності доопераційного стадіювання ми пропонуємо враховувати рівень онкомаркера РЕА в крові, встановлено статистично значиму різницю ($p < 0{,}032$) при порівнянні показників між II (N_0) та III стадіями (N_{1-2}). Порогове значення РЕА склало 3,95 нг/мл. **Висновки.** Для підвищення ефективності діагностики лімфогенного метастазування за допомогою променевих методів обстеження у хворих на рак прямої кишки слід враховувати такі прогностичні критерії, як наявність круглої форми та неоднорідної структури лімфатичного вузла з урахуванням порогового рівня РЕА, яке становить 3,95 нг/мл.

Ключові слова: пряма кишка, аденокарцинома, магнітно-резонансна томографія, стадіювання, лімфатичні вузли.