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PARENCHYMATOUS-STROMAL RATIO IN COLORECTAL CANCER TUMORS AS AN INDICATOR OF METASTASIS

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ABSTRACT

Relevance: *Colorectal cancer (CRC) is one of the five most common cancers worldwide and is characterized by trends in incidence, disabi lity, and mortality. A significant recurrence rate and early metastasis characterize CRC. Many meta-analyses in the world literature are aimed at finding factors that determine the probable outcome of the disease.*

The study aimed to *evaluate the role of the parenchymal-stromal ratio in the progression of colorectal cancer.*

Methods: *When microcopying at 40x magnification, the parenchyma (Sp) and stroma (Sm) area were measured in superficial tumor growth and deep invasion. The parenchymal-stromal ratio (PSR) was calculated using the formula PSS=Sp/Sm, and the correlation with tumor metastasis was determined.*

Results: *With an increase in the depth of tumor invasion, the frequency of metastasis to the liver also increased. The metastasis rate for invasion into the muco-submucosal layer (T1) and the muscular layer (T2) was 4%, respectively. The rate increased to 80% with the involvement of the subserous membrane (T3). Metastases in regional lymph nodes worsened the outcome of the disease threefold. With locally widespread and locally regional in the zone of deep invasion, the parenchymal component predominates over the stroma. PSS is 2.5:1.0 and 1.6:1.0. With CRC disseminated growth in the zone of deep tumor invasion, PSS was 1.0:1.4 with a predominance of the stromal component up to 57%.*

Conclusion: *There is a decrease in PSS in superficial growth zones in disseminated forms of colorectal cancer compared with local and local-regional types of cancer. The predominance of the stromal component in the zone of deep invasion is directly proportional to the high adverse outcome.*

Keywords: *colorectal cancer (CRC), tumor microenvironment, parenchymal-stromal ratio (PSR).*

Introduction: Colorectal cancer (CRC) ranks 3rd among all malignancies globally. The CRC incidence is more than 1 million patients annually, and the mortality rate is about 700 thousand. According to data from several authors, the progression of CRC depends on the stromal microenvironment of the tumor: the extracellular matrix, blood vessels, inflammatory infiltrate cells, and fibroblasts. Dysregulation between the parenchyma and stroma leads to a change in normal stromal cells with the acquisition of abnormal phenotypes that promote neoplasm growth and progression.

There are relevant publications on determining the new morphological signs of the tumor progression risk, characterizing the internal properties of parenchymal cells, and interaction of the tumor microenvironment components. The AJCC study (1996-2015 years) of tumors in five locations (lung cancer, CRC, melanoma, breast, and prostate cancer) identified 176 prognostic tools (formulas, risk scores, calculators, nomograms, etc.) to establish additional independent prognostic markers that compensate the shortcomings of the system for determination of adverse outcomes risks [1].

In order to predict the survival of patients with CRC, 53 models have been identified [2]. These techniques combine clinical data and information from the pathology report of the tumor characteristics to assess the probability of a particular outcome occurring at a specific time [3, 4]. However, these models do not consider the tumor microenvironment's components. The analysis of the scientific publications showed the absence of universal systems for pathomorphological assessment of the probable outcomes of the disease. We could not find the model of pathomorphological characteristics of the primary tumor, which enabled us to predict the development of metastases in patients with localized CRC. The personification of the prognosis of adverse outcomes is required at disease stages I and II since the frequency of distant metastases after radical surgery can reach up to 10%. The permits above set the goal of the study.

The study aimed to evaluate the role of the parenchymal-stromal ratio in the progression of colorectal cancer**.**

Materials and methods: The clinical data of the medical records of 50 patients of the age range of 30-75 years old who were treated at the "Marat Ospanov West Kazakhstan Medical University" NCJSC from 2021 to 2022 have been studied—male and female patients composed 26 (52%) and 24 (48%), respectively. Of them, 21 patients had a tumor in the sigmoid colon, 11 (22%) – in the rectosigmoid region, 9 (18%) – in the colon, 6 (12%) – in the rectum, and 3 – in the cecum gut. Depending on the degree of tumor growth form, all patients have been divided into three groups: 1 – with locally advanced CRC, 2 – with local-regional CRC, and 3 – with disseminated growth of CRC. The patients were divided into groups: Group 1 included 17 people (9 men and eight women; 12 had CRC in the sigmoid colon, and 5 – in

the colon), Group 2 of 18 people (9 men and nine women; 3 had CRC in the cecum, 9 – in the sigmoid colon, 4 – in the colon, and 2 – in the rectosigmoid region), and Group 3 of 15 people (8 men and seven women; 6 had CRC in the rectum, and 9 – in the rectosigmoid region).

In order to check the normality of the distribution of the studied quantitative indicators in the groups, the KS test has been used. The statistical processing has been done using the Mann-Whitney U test of the Statistica 8.0 software package.

In fragments of the removed large intestine, a standard pathomorphological study assessed the degree of differentiation of the tumor, depth of invasion into the intestinal wall, and presence or absence of lymphogenous and hematogenous metastases. Using a Nikon Eclipse E200 microscope (Japan) with the application of Genesis software (Genesis Software, India) to assess the quantitative and qualitative microenvironment in 5 fields of view at 40-fold magnification, the area of superficial growth and deep tumor invasion was scanned, followed by measurement of the area of the parenchyma (Sp) and stroma (Sm). The parenchymal-stromal ratio (PSR) was calculated using the formula PSR=*Sp/Sm*.

Results: In analyzing clinical data, it was found that adenocarcinoma progression did not depend on gender, age, and the degree of tumor differentiation. However, the number of hematogenous metastases proportionally depended on the tumor's location, depth of invasion, and presence of lymphogenous metastases. When the tumor was localized in the sigmoid colon, hematogenous metastases reached 48%. The degree of depth of tumor invasion into the intestinal wall is directly proportional to the frequency of metastasis to the liver. The metastasis rate for invasion into the muco-submucosal layer (T1) and the muscular layer (T2) was 4%, respectively. The rate increased to 80% with the involvement of the subserous membrane (T3). Metastases in regional lymph nodes worsened the outcome of the disease threefold.

With locally advanced and locally regional in the zone of deep invasion, the parenchymal component predominates over the stroma. PSS is composed of 2.5:1.0 and 1.6:1.0.

With disseminated growth of CRC in the zone of deep tumor invasion, the PSR is 1.0:1.4 with a predominance of the stromal component up to 57% [5].

Discussion: For colorectal cancer, "degree of differentiation" is often used rather than the "degree of histological malignancy." There is no explicit link between the degree of differentiation and invasiveness or metastasis. The degree of differentiation does not mean the tumor aggressiveness in CRC. The ability to lead to an unfavorable outcome relatively quickly is based on the whole complex of properties of neoplastic cells and their microenvironment. Researchers describe the transition probability from one type to another depending on the tumor microenvironment [6-8]. The individual type of invasion is developed according to the epithelial-mesenchymal transition (EMT) mechanism. The morphological manifestation of the EMT phenomenon is considered to be so-called "budding," that is, the appearance of individual tumor cells in the invasive front of the tumor. "Budding" shows the degree of readiness for the separation of tumor cells at an early stage of the metastatic process and is one of the high-risk factors. "Budding" has a higher prognostic value compared to the degree of tumor differentiation [9-11].

Colorectal adenocarcinomas are characterized by a "kaleidoscope" of stromal-parenchymal elements. Many cell cooperation and collaboration variants, established during each tumor morphotype's development, determine the tumor's further behavior and the disease outcome. With maximum approaching of characteristics of the tumor parenchyma and stroma to the structure of normal mucous membrane of the colon and with retention of the "protective" function of the immune system, the CRC tumor is characterized by slow progression and a tendency to metastatic spread.

Conclusion: In summary, we have established the difference in PSR depending on the degree of tumor invasion. There is a decline of PSR in superficial growth zones in disseminated forms of CRC compared to local and local-regional distribution.

The predominance of the stromal component over the parenchyma in areas of deep invasion characterizes a high degree of metastasis.

The modern approach to cancer epidemiology and carcinogenesis qualifies malignant tumors as an invasive parasite. It occupies an appropriate place in the ecosystem of primary organs. Then, it spreads, forming regional and distant communities around metastases, forming a single system of interconnected ecosystems throughout the body. During metastatic spread, the tumor cells are exposed to certain risks [12, 13]. They acquire a metastatic phenotype, alter metabolism, lose their proliferative advantage, and transform from an epithelial to a mesenchymal cell. When the cell initiates an invasion, successfully evading the immune surveillance and infiltrating the blood vessels, it is exposed to a high risk of death during circulation in the bloodstream. The risks associated with metastatic spread explain the need for an external signal to start metastasis. Thus, the acquisition of metastatic capacity does not mean that the tumor cell necessarily has to leave the ecosystem of the maternal tumor. The metastatic migrants respond to the signal for the invasion to start. The existing angiogenic process does not provide rapid local cell proliferation, so the tumor outgrows the vascular network. Anabolically, the process entails local hypoxia and dystrophy, accumulation of metabolic decay products, and decreased pH, leading to an unproductive toxic swamp – tumor swamping [14, 15]. All of the above becomes a signal for the initiation of metastatic spread.

Considering that, according to several authors, the progression of colorectal cancer also depends on the stromal microenvironment of the tumor (extracellular matrix, blood vessels, inflammatory infiltrate cells, and fibroblasts), we will highlight that issue in the subsequent scientific publication.

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АНДАТПА

ҚОЛОРЕКТАЛЫҚ РАКТЫҢ ІСІКТЕРІНДЕГІ ПАРЕНХИМАТАЛЫҚ-СТРОМАЛДЫҚ ҚАТЫНАСЫ МЕТАСТАЗДАРДЫҢ КӨРСЕТКІШІ РЕТІНДЕ

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Өзектілігі: *Колоректальды қатерлі ісік әлемдегі ең көп таралған бес ісіктің бірі болып табылады және ауру, мүгедектік және өлім тенденцияларымен сипатталады. ККІ елеулі қайталану жылдамдығымен және ерте метастазбен сипатталады. Әлемдік әдебиеттердегі көптеген мета-талдаулар аурудың ықтимал нәтижесін анықтайтын факторларды табуға бағытталған.*

Зерттеудің мақсаты *– колоректальды қатерлі ісіктің өршуіндегі паренхимальды-стромальды қатынастың рөлін бағалау.*

Әдістері: *40 есе үлкейту кезінде микрокөшіру кезінде паренхиманың (Sp) және строманың (Sm) ауданы ісіктердің үстіңгі өсу және терең инвазия аймақтарында өлшенді. Паренхималық-стромальды қатынас PSS=Sp/Sm формуласы арқылы есептелді және ісік метастазымен корреляция анықталды.*

Нәтижелері: *Ісік инвазиясының тереңдігінің жоғарылауымен бауырға метастаздың жиілігінің жоғарылауы байқалады. Шырышты-су асты қабатына (T1) және бұлшықет қабатына (T2) инвазия үшін метастаздың жылдамдығы сәйкесінше 4% құрады. Субсерозды мембрананың (T3) қатысуы кезінде көрсеткіш 80%-ға дейін өсті. Аймақтық лимфа түйіндеріндегі метастаздар ауырудың нәтижесін 3 есе нашарлатты. Терең инвазия аймағында жергілікті кең таралған және жергілікті аймақтық болғандықтан, паренхималық компонент стромадан басым болады. PSS 2,5:1,0 және 1,6:1,0. Ісіктердің терең инвазиясы аймағындағы CRC диссеминирленген өсуімен PSS стромальды компоненттің 57%-ға дейін басым болуымен 1,0:1,4 құрайды.*

Қорытынды: *ісіктің жергілікті және жергілікті-аймақтық түрлерімен салыстырғанда колоректальды обырдың диссемирленген түрлерінде үстіңгі өсу аймақтарында PSS төмендеуі байқалады. Терең инвазия аймағында стромальды компоненттің басым болуы жоғары қолайсыз нәтижеге тікелей пропорционалды.*

Түйінді сөздер: *колоректальды қатерлі ісік, ісік микроортасы, паренхимальды-стромальды қатынас.*

АННОТАЦИЯ

ПАРЕНХИМАТОЗНО-СТРОМАЛЬНОЕ СООТНОШЕНИЕ В ОПУХОЛЯХ КОЛОРЕКТАЛЬНОГО РАКА КАК ИНДИКАТОР МЕТАСТАЗИРОВАНИЯ

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Актуальность: *Колоректальный рак (КРР) входит в пятерку самых распространённых раков во всем мире и характеризуется трендами заболеваемости, инвалидизации и смертности. КРР характеризуется значительной частотой рецидива и ранним мета-*

стазированием. Множество метаанализов в мировой литературе направлены на поиск факторов определения вероятного исхода заболевания.

***Цель исследования** – оценить роль паренхиматозно-стромального соотношения в прогрессировании колоректального рака.*

***Методы:** при микрокопировании в 40-кратном увеличении измеряли площадь паренхимы (Sp) и стромы (Sm) в зонах поверхностного роста опухоли и глубокой инвазии. Рассчитывали показатель паренхиматозно-стромального соотношения (ПСС) по формуле ПСС=Sp/Sm и определяли корреляционную взаимосвязь с метастазированием опухоли.*

***Результаты:** С увеличением глубины инвазии опухоли отмечается повышение частоты метастазирования в печень. Показатель метастазирования при инвазии в слизисто-подслизистый слой (Т1) и мышечную оболочку (Т2) составил 4% соответственно. Показатель возрастал до 80% при вовлечении субсерозной оболочки (Т3). Метастазы в регионарные лимфатические узлы ухудшали исход заболевания в 3 раза. При местно-распространённом и локально-регионарным в зоне глубокой инвазии преобладает паренхиматозный компонент над стромой. ПСС составляет 2,5:1,0 и 1,6:1,0. При диссеминированном росте КРР в зоне глубокой инвазии опухоли ПСС равен 1,0:1,4 с преобладанием стромального компонента до 57%.*

***Заключение:** отмечается снижение ПСС в поверхностных зонах роста при диссеминированных формах КРР по сравнению с местным и локально-регионарном типах рака. Преобладание стромального компонента в зоне глубокой инвазии прямо пропорционально с высоким неблагоприятным исходом.*

***Ключевые слова:** колоректальный рак, микроокружение опухоли, паренхиматозно-стромальное соотношение (ПСС).*

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