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Clinicopathological features of colon cancer depending on the dMMR status of the tumor

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ABSTRACT

Aim. To conduct a clinical and morphological assessment of the characteristics of colon cancer depending on the dMMR / pMMR status of the tumor.

Materials and methods. A retrospective study included 66 patients with operable colorectal cancer (CRC) ($T_{1-4b}N_{0-2b}M_1$), who were treated at Cancer Research Institute of Tomsk National Research Medical Center (NRMC). The average age of the patients was 64.4 ± 12.8 years. All patients underwent hemicolectomy or colon resection, as well as intraoperative resection of distant metastases, if present.

Results. We determined that in CRC patients with pMMR tumors, hematogenous metastases were detected in 27.3% of cases, while in patients with dMMR tumors, hematogenous metastases were detected only in 6.1% of cases ($p = 0.021$). A comparative analysis of dMMR and pMMR tumors also allowed to establish higher frequency of perineural invasion among the pMMR subgroup of carcinomas ($p = 0.039$). The sign of tumor budding was found both in dMMR carcinomas (36%) and in pMMR tumors (45%). This sign was associated with damage to regional lymph nodes ($p = 0.0017$). A more detailed analysis of the tumor budding phenomenon showed that in dMMR tumors, Bd1 low-grade budding (83%) predominated. In pMMR tumors, Bd2 intermediate-grade budding (33%) and Bd3 high-grade budding (26.7%) prevailed. Bd2 and Bd3 tumor budding types were associated with hematogenous metastasis ($p < 0.001$).

Conclusion. The obtained data demonstrate the differences in such pathomorphological parameters as perineural invasion and the degree of tumor budding depending on the dMMR / pMMR status of the tumor. These histologic parameters in tumor tissue are also associated with higher incidence of distant metastasis in patients with pMMR carcinomas as opposed to patients with dMMR tumors.

Keywords: mismatch repair system proteins, dMMR / pMMR status, colon cancer

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Клинико-патологические особенности рака толстой кишки в зависимости от dMMR статуса опухоли

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РЕЗЮМЕ

Цель. Провести клинико-морфологическую оценку особенностей рака толстой кишки (РТК) в зависимости от dMMR/pMMR статуса.

Материалы и методы. В исследование ретроспективно включено 66 пациентов с операбельным РТК T1-4bN0-2bM1, прошедших лечение в НИИ онкологии Томского НИМЦ. Средний возраст больных составил 64,4 ± 12,8 года. Всем пациентам выполнено оперативное лечение в объеме гемиколэктомии или резекции кишки, а также интраоперационная резекция отдаленных метастазов при их наличии.

Результаты. Установлено, что у пациентов с РТК и pMMR статусом гематогенные метастазы определялись в 27,3% случаев, в то время как у пациентов с dMMR статусом гематогенные метастазы были обнаружены лишь в 6,1% случаев (p = 0,021). Сравнительный анализ опухолей с dMMR и pMMR статусом также позволил установить большую частоту наличия периневральной опухолевой инвазии среди pMMR подгруппы карцином (p = 0,039). Признак «опухолевого почкования» был обнаружен как в карциномах с дефицитом белков мисматч репарации (36%), так и в профицитных опухолях (45%). Данный признак был сопряжен с поражением регионарных лимфатических узлов (p = 0,0017). Более детальный анализ феномена «опухолевого почкования» показал, что в опухолях с дефицитом белков мисматч репарации преобладал первый тип почкования (Bd1) low grade – низкой степени – (83%), в то время как профицитные опухоли характеризовались преобладанием почкования второго типа (Bd2) – intermediate grade – умеренной степени (33%) и (Bd3) – high grade – высокой степени (26,7%). Феномен «опухолевого почкования» Bd2 и Bd3 был сопряжен с гематогенным метастазированием (p < 0,001).

Заключение. Полученные данные демонстрируют различия по таким патоморфологическим параметрам, как периневральная инвазия и степень «опухолевого почкования» в зависимости от dMMR/pMMR статуса карциномы. Данные гистологические параметры в опухолевой ткани также связаны с большей частотой встречаемости отдаленных метастазов у пациентов с карциномами со статусом pMMR в отличие от пациентов с dMMR статусом опухоли.

Ключевые слова: белки системы мисматч репарации, dMMR/pMMR статус, колоректальный рак

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

According to the World Health Organization (WHO), colorectal cancer (CRC) is one of the most common malignant neoplasms in the world. It is the 5th most common cancer. Over one million newly diagnosed tumors are reported among both sexes annually. The number of deaths exceeds 570,000 per year [1]. In 2021, over 18,000 new cases of CRC were registered in the Russian Federation, which accounts for 7.1% of all

malignant neoplasms. The increase in the incidence in 2011–2021 was 25.3% [2]. In 2021, more than 23,000 deaths from CRC were registered, making this disease the third leading cause of mortality from malignant neoplasms in the Russian Federation [2].

Only 30–50% of CRC patients achieve 5-year survival, since the disease in most cases is detected at late clinical stages [3]. Despite this, if the tumor is diagnosed at an early stage (T_{1-} T_2N_0), the 5-year survival rate is more than 90%. It is worth noting that among stage II CRC patients, the 5-year relapse rate is extremely variable, ranging from 12 to 38%. Moreover, in stage III CRC patients, the 5-year relapse-free survival rate does not exceed 50% [3].

The key stage in the diagnosis of CRC is morphological verification of the diagnosis followed by the assessment of pathomorphological signs. Currently, the main parameters are: the size of the primary tumor, histologic grade, degree of malignancy, pT and pN criteria, the condition of the resection margins and lymph nodes, extramural and peritumoral vascular invasion, perineural invasion, as well as the assessment of the invasive tumor front area for the presence of morphological manifestations of tumor budding [3]. This phenomenon is detected when there are clusters of single tumor cells at the invasive margin of the tumor (from 2 to 4 cells in one tumor bud).

Currently, depending on the number of tumor cell clusters at the invasive margin per 1 field of view, three budding grades are distinguished: 0–4 buds indicate low-grade budding (Bd1); 5–9 buds indicate intermediate-grade budding (Bd2): ≥ 10 buds indicate high-grade budding (Bd3) [4]. This phenomenon is based on epithelial – mesenchymal transition (EMT) [5]. EMT is the process by which the cell changes its phenotype from epithelial to mesenchymal, which ultimately leads to the possibility of tumor invasion, as well as to lymphogenous and hematogenous metastasis, which correlates with an unfavorable prognosis for the disease course in the presence of this morphological sign in the tumor tissue [6].

Despite the existing pathohistological criteria used in diagnosing surgical material to assess the objective prognosis of the disease course and elaborate an individual approach to treatment, morphological studies should be supplemented with the results of molecular genetic methods. To date, the most common and recommended methods are determination of mismatch repair deficiency proteins (dMMR status of the tumor – mismatch repair deficient status) or microsatellite instability (MSI) by immunohistochemistry using polymerase chain reaction [7, 8]. According to clinical guidelines, including the Russian Society of Clinical Oncology RUSSCO, these techniques can be mutually exclusive, since their concordance in CRC is more than 95% [9].

It should be noted that dMMR / MSI status of the tumor depending on the clinical stage of the disease can serve as both a prognostic and a predictive factor for the response to drugs, such as checkpoint inhibitors [9], as well as to the effectiveness of fluoropyrimidines [10], which are the main therapeutic drugs in both postoperative treatment and subsequent lines. This significantly influences the treatment strategy of a patient for both local and diffuse tumor processes.

Despite widespread testing of dMMR / MSI in clinical practice, studying the clinical and pathological characteristics of the primary tumor and their relationship with parameters of regional and distant metastasis is of interest in CRC.

MATERIALS AND METHODS

The study included 66 patients diagnosed with stage $T_{1-4b}N_{0-2b}M_{1a}$ CRC. The inclusion criterion for the study was histologically verified CRC. The exclusion criterion was preoperative chemotherapy. The scope of surgical treatment corresponded to hemicolonectomy (right / left) or radical resection of the colon with simultaneous removal of distant metastases, if present. A morphological study of the surgical material was carried out, assessing the following parameters: histologic tumor grade, density of immune cell infiltrate in the tumor stroma (in 10 fields of view at × 400), signs of lymphovascular and perineural invasion, the presence and number of tumor buds at the invasive tumor margin, presence / absence of metastases in the lymph nodes (at least 12 regional lymph nodes).

The microscopic examination was carried out using the Eclipse Ci-L upright microscope (Nikon, Japan). The histotype and stage of the disease were determined according to the 2019 WHO Classification of Tumors of the Digestive System. The density of the immune cell infiltrate in the tumor stroma was quantified. The results were converted into a point scale (1 point – mild infiltration, up to 300 immune cells; 2 points – moderate infiltration, 300–600 cells; 3 points – pronounced infiltration, more than 600 cells).

The assessment of tumor budding was carried out as follows: counting of tumor buds in hotspots at the invasive tumor margin per unit area of

0.785 mm^2 (corresponding to a ×20 eyepiece lens with a field of view diameter of 20 mm). The obtained quantitative values were also converted into a point scale, where 0–4 buds corresponded to Bd1 (low-grade budding); 5–9 buds corresponded to Bd2 (intermediate-grade budding); ≥10 buds and more corresponded to Bd3 (high-grade budding). The dMMR status of carcinoma was assessed on paraffin sections of the tumor tissue (surgical material) by immunohistochemistry. Staining was performed on the Bond RX Fully Automated IHC and ISH Staining System (Leica Biosystem) using such antibodies as MLH1 (Clone ES05, RTU, Dako An Agilent Technologies Company, RTU); MSH2 (Clone FE1, RTU, Dako An Agilent Technologies Company), MSH6 (Clone EP49, RTU, Dako An Agilent Technologies Company); and PMS2 (Clone EP51, RTU, Dako An Agilent Technologies Company) (Fig. 1–3). In the absence of nuclear IHC staining of at least one marker, mismatch repair protein deficiency was diagnosed (tumor with microsatellite instability – dMMR status). In the study group, distant metastases were detected in 16.67% of cases (n = 11 / 66). The presence of metastatic lesions and the number of metastatic lymph nodes (N) are presented in Table.

Statistical data analysis was performed using the SPSS 23.0 software package (IBM SPSS Statistics, USA). Quantitative variables were presented as the median and the interquartile range Me (Q_{25}; Q_{75}). Qualitative variables were described by absolute and relative frequencies n (%). The quantitative and qualitative variables in independent samples were compared using the Mann – Whitney U test and the $\chi 2$ criterion. The results were considered statistically significant at a $p < 0.05$.

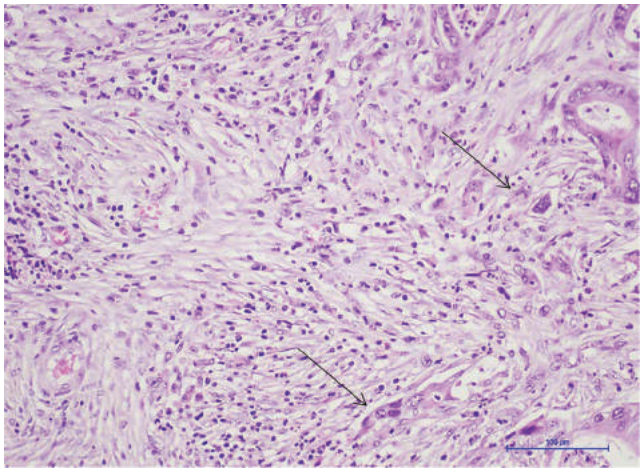


Fig. 1. Tumor budding at the invasive tumor front margin (marked by arrows) in colorectal adenocarcinoma. Here and in Fig.2 – H&E staining, × 200

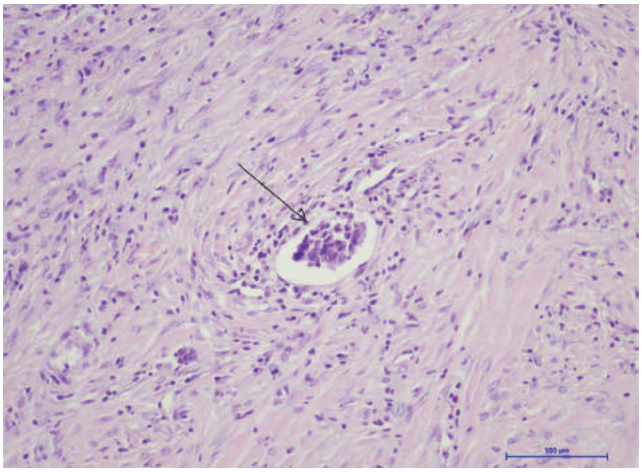
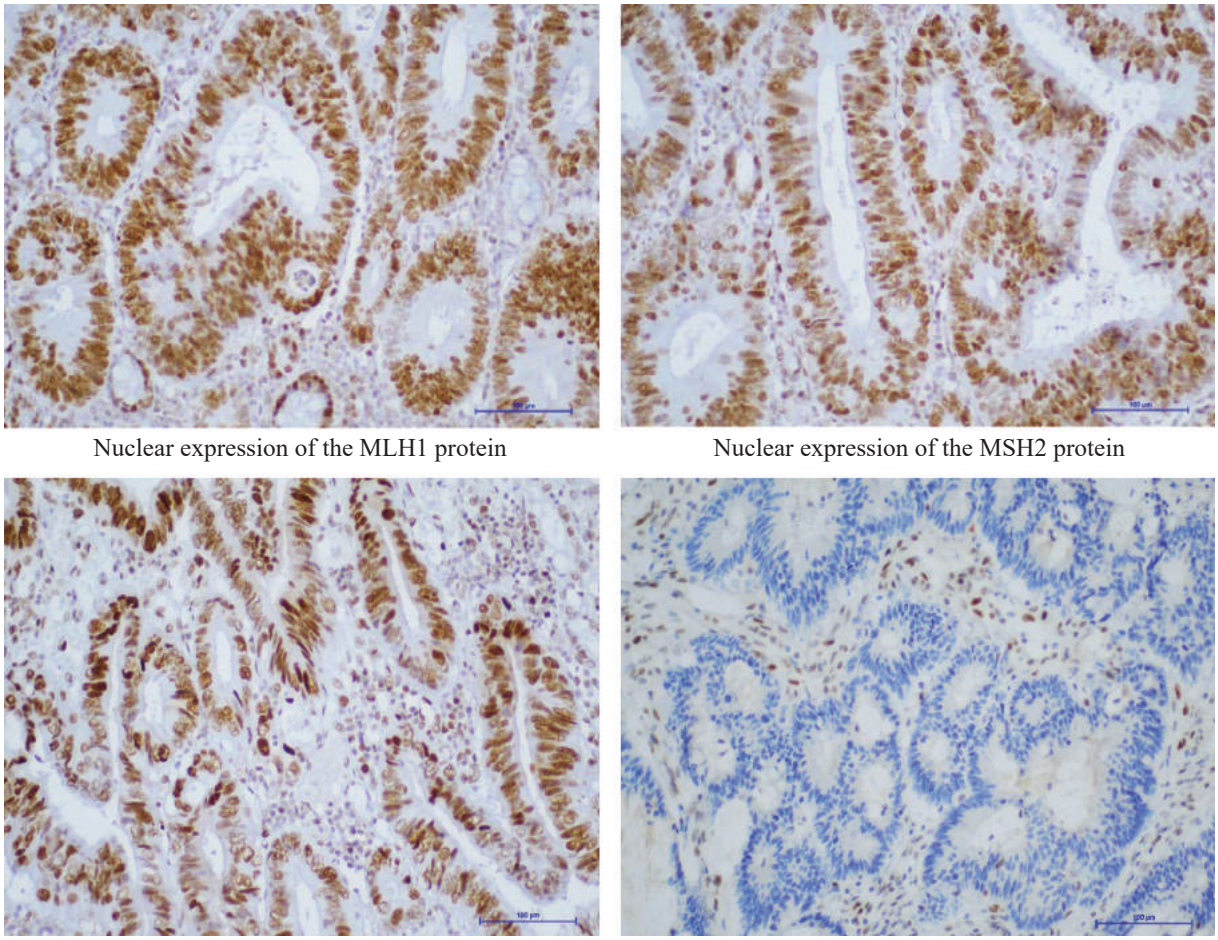


Fig. 2. Lymphovascular invasion (the arrow indicates a tumor embolus in the lumen of the vessel)



Nuclear expression of the MLH1 protein

Nuclear expression of the MSH2 protein

Nuclear expression of the MSH6 protein

Absence of PMS2 protein expression

Fig. 3. Immunohistochemical determination of the dMMR status of the tumor

RESULTS

Two groups of patients were formed depending on the immunohistochemically verified dMMR / pMMR status of the tumor. Group 1 included 50% of cases (n = 33 / 66) with mismatch repair protein deficiency (dMMR status) in the tumor. An equal number of cases (50%; n = 33 / 66) were included in the control group: tumors with mismatch repair protein proficiency (pMMR status). The assessment of existing correlations in the selected groups with tumor histotype, localization of the tumor in the colon, and the stage of the disease did not show significant differences (Table). The comparative analysis of cases with lymphogenous metastases in the groups of dMMR / pMMR tumors did not reveal significant differences. We did not find any differences in the number of metastatic lymph nodes.

Next, we assessed the relationship between the dMMR / pMMR status of carcinoma and the presence of hematogenous metastases. The results of the analysis allowed to establish that in the group of patients with dMMR tumors, hematogenous metastases were detected in 6.1% of cases (n = 2 / 11). Moreover, in cases with pMMR tumors, distant metastases were detected in 27.3% of cases (n = 9 / 11) (χ^2 = 5.3; p = 0.02) (Fig.4). As a result of this work, we did not see any significant differences between the dMMR / pMMR status and the density of immune cell infiltrate in the tumors (Table).

The assessment of tumor budding at the invasive tumor margin showed its presence in both groups. However, significant differences were found between tumor budding grades (χ^2 = 6.0; p < 0.04). Thus, we observed Bd1 (n = 10) and Bd2 (n = 2) in dMMR tumors, with the presence of morphological manifestations of tumor budding at the invasive margin. No morphological manifestations of this phenomenon were found in other dMMR tumors (n = 21).

In the group of pMMR tumors, we identified Bd3 (n = 4) along with Bd1 (n = 6) and Bd2 (n = 5). No manifestations of this phenomenon were found at the

invasive margins of other tumors ($n = 18$). The additional analysis of the results obtained allowed to establish that tumors with Bd2 and Bd3 budding were characterized by the presence of hematogenous metastases ($\chi^2 = 17.2$; $p < 0.001$). The assessment of perineural tumor invasion revealed that in dMMR tumors this morphological feature was detected less frequently compared to pMMR carcinomas ($\chi^2 = 4.2$; $p = 0.03$).

Table

Clinical data and morphological parameters of the tumor in CRC patients

Parameter		dMMR		pMMR		Criterion value	*p*
		n	%	*n*	%		
Sex	male	23	69.7	19	57.6	1.048	0.433
	female	10	30.3	14	42.4		
Age, years, *Me* (Q_{25}; Q_{75})		63 (54.5; 63) 63.3±13.5		66 (59.5; 74) 65.6±12.1		481.5	0.419
Tumor histotype	high-grade adenocarcinoma	10	30.3	9	27.3	0.635	0.728
	low-grade adenocarcinoma	14	42.4	12	36.4		
	mucinous adenocarcinoma	9	27.3	12	36.4		
Tumor localization	cecum	5	15.2	3	9.1	10.094	0.183
	ascending colon	6	18.2	3	9.1		
	hepatic flexure	4	12.1	4	12.1		
	transverse colon	2	6.1	2	6.1		
	splenic flexure	4	12.1	2	6.1		
	descending colon	5	15.2	1	3.0		
	sigmoid colon	6	18.2	17	51.5		
	rectosigmoid colon	1	3.0	1	3.0		
Cancer stage (T)	T2	5	15.2	1	3.0	4.333	0.228
	T3	6	18.2	8	24.2		
	T4a	19	57.6	23	69.7		
	T4b	3	9.1	1	3.0		
Lymphogenous metastasis (N)	N0	17	51.5	15	45.5	3.869	0.568
	N1a	6	18.2	3	9.1		
	N1b	2	6.1	1	3.0		
	N1c	1	3.0	4	12.1		
	N2a	3	9.1	5	15.2		
	N2b	4	12.1	5	15.2		
Density of the immune cell infiltrate	mild	6	18.2	3	9.1	1.310	0.519
	moderate	13	39.4	16	48.5		
	pronounced	14	42.4	14	42.4		
Lesion side	right	17	51.5	13	39.4	0.978	0.459
	left	16	48.5	20	60.6		

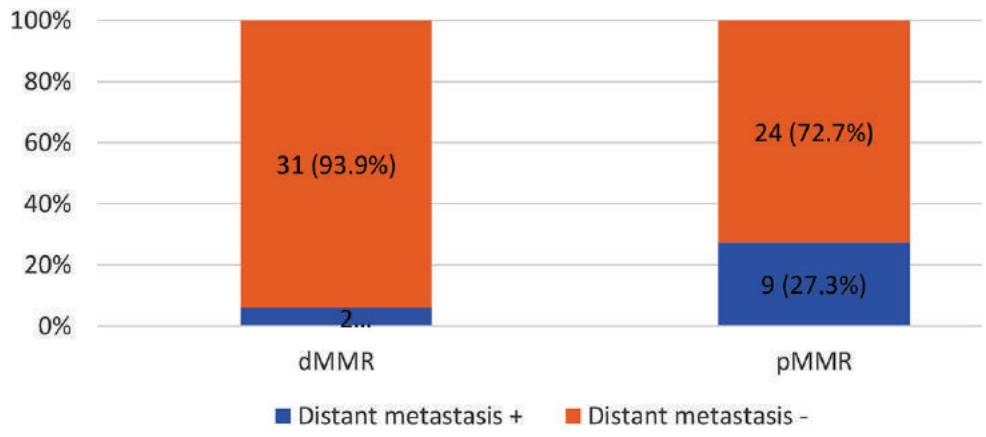


Fig.4. Frequency of distant metastasis in CRC patients depending on the dMMR / pMMR status of the primary tumor

DISCUSSION

Our research showed that in CRC, various clinical and morphological features can be simultaneously characteristic of both dMMR and pMMR tumors. In this work, we identified a number of differences that may determine the nature of the disease course. Thus, the comparative analysis of dMMR and pMMR tumors depending on tumor morphology and its localization did not show significant differences. The most important morphological features that were characteristic of dMMR carcinomas were lower frequency of perineural invasion and predominance of Bd1 and Bd2 tumor budding grades.

In the analyzed literature, there was no description of similar morphological characteristics depending on the molecular status of the tumor in CRC. The most indicative parameter that we detected was low hematogenous metastatic potential of dMMR tumors compared to pMMR carcinomas. One of the reasons explaining the discovered relationship may be different biological behavior of tumors due to differences in the volume of mutational load [10]. This hypothesis is also supported by the fact that no significant differences in the density of the immune cell infiltrate (which, according to one of the existing hypotheses, has a tumor suppressive effect) were found between dMMR and pMMR carcinomas [11, 12].

It may be assumed that the dMMR status of the tumor and associated morphological parameters, such as low frequency of perineural invasion and predominance of the Bd1 tumor budding, are interrelated and explain lower metastatic potential. It should be noted that the absence in the tumor tissue of signs of perineural invasion, manifestations of Bd3 tumor budding at the invasive margin, and signs of hematogenous metastasis can be considered as indirect morphological parameters that may indicate the dMMR status of a colonic tumor.

CONCLUSION

Our data demonstrate the presence of morphological differences in the primary tumor tissue in colonic tumors depending on the dMMR / pMMR status of the tumor. Based on the obtained results, it can be assumed that certain histologic parameters, such as the presence of perineural invasion and the predominance of various tumor budding grades at the invasive tumor margin, can be associated with the frequency of hematogenous metastasis and, therefore, can serve as a prognostic criterion for CRC with immunohistochemically verified dMMR or pMMR molecular status of colorectal carcinoma.

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Authors' contribution

Naumov S.S., Krakhmal N.V. – conception and design, analysis and interpretation of the data, carrying out of immunohistochemistry. Tarasov M.N., Taranenko M.I., Kolobovnikova Yu.V. – collection of the material, work with archives, literary review. Udut E.V. – critical revision of the manuscript for important intellectual content. Vtorushin S.V. – critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

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