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«Южно-Российский онкологический журнал»: профессиональное медицинское издание. В нем публикуются новости медицинского и фармацевтического сообществ, научно-практические статьи для целевой аудитории – врачей-онкологов. Редакция журнала ставит своей задачей популяризацию научно-исследовательских работ и достижений онкологов Южного федерального округа, анализ процесса глубокой реорганизации здравоохранения в России. Редакция приглашает в качестве авторов всех, кто ищет и находит интересные решения многогранных задач, стоящих перед современной медициной, и хочет поделиться своими мыслями и наблюдениями с коллегами.

Цель: способствовать развитию онкологической медицины Юга России и внедрению её достижений в практику.

Задачи: освещать современные достижения онкологической службы Юга России; содействовать обмену опытом и передовыми знаниями между специалистами; информировать читателей об итогах крупных медицинских форумов.

В журнале размещаются публикации различных рубрик: обзоры литературы, мета-анализы, клинические исследования, наблюдения клинических случаев, обсуждения, анонсы и описания новых методов лечения.

Журнал принимает к публикации: оригинальные статьи, организации здравоохранения, лучевой диагностики, обмен опытом, обзоры, клинические наблюдения.

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Purpose: to promote the development of cancer medicine in the South of Russia and the introduction of its achievements into practice.
Tasks: to highlight the current achievements of the oncology service in the South of Russia; to promote the exchange of experience and advanced knowledge between specialists; to inform readers about the results of major medical forums.
The journal contains publications of various categories: literature reviews, meta-analyses, clinical studies, observations of clinical cases, discussions, announcements and descriptions of new treatment methods.
The journal accepts for publication: original articles, health organizations, radiation diagnostics, exchange of experience, reviews, clinical case reviews.

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ORIGINAL ARTICLE

THE NUMBER OF CANCER STEM CELLS IN THE TUMOR TISSUE AND PERIFOCAL TISSUE OF NON-MUSCLE INVASIVE BLADDER CANCER

L. I. Belyakova✉, A. N. Shevchenko, A. B. Sagakyants, E. S. Bondarenko, O. G. Shulgina, E. P. Ulyanova, E. V. Filatova, I. A. Khomutenko

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ABSTRACT

Purpose of the study. Determine the content of cancer stem cells (CSCs) in the tumor tissue (TT) and perifocal tissues (PT) in muscle-non-invasive bladder cancer.

Materials and methods. We've examined fragments of TT and PT of 7 muscle-non-invasive bladder cancer (NMIBC) after surgical intervention – transurethral resection of the urinary bladder (TUR). In tissue samples that were used to obtain cell suspension of TT and PT using the BD Medimachine apparatus (BD, USA) was treated with monoclonal antibodies CD45-APC-Cy7, CD44-FITC, CD133-PE, CD24-PE (BD, USA) and were assessed on flow cytometer FacsCantoII (BD, USA). The percentage of cells with CSC phenotypic markers was determined in the analysis sample: $CD45\text{-}CD44^{+}CD24^{+}$, $CD45\text{-}CD44^{+}$, $CD45\text{-}CD24^{+}$, $CD45\text{-}CD133^{+}$, $CD45\text{-}CD44^{+}CD133^{+}$. The presence of significant differences in the groups was evaluated using the STATISTICA 13 software package and the differences between the samples were considered significant at $p < 0.05$. The percentage of cells of the corresponding phenotype was calculated relative to the total number of cells. The percentage of cells with the corresponding phenotype was calculated relative to the total number of cells.

Results. The relative numbers of cells with CSC phenotypic markers, such as CD24, CD44, were 77 % and 58 % higher in TT than in PT: 18.3 ± 3.5 vs. 4.3 ± 2.1, $p \leq 0.044$ and 15.5 ± 5.3 vs. 6.5 ± 0.8, $p \leq 0.043$, respectively. The number of $CD133^{+}$ cells was 83 % higher in PT compared to TT – 41.6 ± 12.1 vs. 22.7 ± 7.6, $p \leq 0.047$.

Conclusion. The study of CSCs is a promising direction for the study of oncogenesis and can be used to assess the nature of the further development of relapse and / or progression of the disease, as well as various therapeutic approaches that are aimed at eliminating with CSC phenotypic markers and blocking the pathways leading to the emergence and maintenance of this cell population in patients with NMIBC.

Keywords:
non-muscle-invasive bladder cancer, cancer stem cells, perifocal tissues

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ОТНОСИТЕЛЬНОЕ СОДЕРЖАНИЕ ОПУХОЛЕВЫХ СТВОЛОВЫХ КЛЕТОК В ТКАНИ ОПУХОЛИ И ПЕРИТУМОРАЛЬНОЙ ЗОНЕ МЫШЕЧНО-НЕИНВАЗИВНОГО РАКА МОЧЕВОГО ПУЗЫРЯ

Л. И. Белякова✉, А. Н. Шевченко, А. Б. Сагакянц, Е. С. Бондаренко, О. Г. Шульгина, Е. П. Ульянова, Е. В. Филатова, И. А. Хомутенко

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РЕЗЮМЕ

Цель исследования. Определить содержание опухолевых клеток с фенотипом стволовых (ОСК) в ткани опухоли и перитуморальной зоне при мышечно-неинвазивном раке мочевого пузыря (МНИРМП).
Материалы и методы. Исследованы фрагменты опухолевой ткани (ОП) и ткани перитуморальной зоны (ПЗ) 7 пациентов с впервые выявленным мышечно-неинвазивным раком мочевого пузыря (МНИРМП) после проведения оперативного вмешательства в объеме трансуретральной резекции мочевого пузыря (ТУР). В образцах тканей, которые использовались для получения клеточной суспензии ОП и ПЗ с помощью аппарата BD Medimachine (BD, USA), с использованием моноклональных антител CD45-APC-Cy7, CD44-FITC, CD133-PE, CD24-PE (BD, USA), осуществляли определение фенотипических характеристик клеток на проточном цитометре FacsCantoII (BD, USA). В анализируемых образцах определяли процентное содержание клеток с фенотипом стволовых: $CD45\text{-}CD44^{+}CD24^{+}$, $CD45\text{-}CD44^{+}$, $CD45\text{-}CD24^{+}$, $CD45\text{-}CD133^{+}$, $CD45\text{-}CD44^{+}CD133^{+}$. Наличие достоверности различий в группах оценивали при помощи программного пакета Statistica 13, различия между выборками считали достоверными при $p < 0,05$. Расчёт процентного содержание клеток соответствующего фенотипа производился относительно общего числа клеток.
Результаты. Относительное содержание клеток, имеющих фенотипические маркеры ОСК такие как CD24, CD44, в ОП были на 77 % и 58 % больше, чем в ПЗ, соответственно 18,3 ± 3,5 против 4,3 ± 2,1, $p \leq 0,044$ 15,5 ± 5,3 против 6,5 ± 0,8, $p \leq 0,043$. Количество $CD133^{+}$ – клеток оказалось больше на 83 % в ПЗ по сравнению с ОП – 41,6 ± 12,1 против 22,7 ± 7,6, $p \leq 0,047$.
Заключение. Изучение опухолевых стволовых клеток в настоящее время является перспективным направлением для изучения развития злокачественного процесса и может быть использовано для предикции и оценки характера дальнейшего развития рецидива и/или прогрессирования заболевания, а также, в дальнейшем, для применения различных подходов терапии, которые будут направлены на устранение клеток с фенотипом стволовых и блокирования путей, которые приводят к возникновению и поддержанию данной популяции клеток у больных с МНИРМП.

Ключевые слова:
мышечно-неинвазивный рак мочевого пузыря, опухолевые стволовые клетки, перитуморальная зона

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Bladder cancer (BC) is one of the main problems in the structure of the general oncourological morbidity accounts for 4.6 %, inferior to malignant kidney formations [1; 2]. Without appropriate and timely assistance, this malignant neoplasm (MN) can lead to severe disability and a significant deterioration in the quality of life of patients. About 400 thousand new cases of the disease are registered annually in the world [3]. BC is on the 7th place in the structure of cancer incidence in men and 17th place in women in the world [2]. In the structure of the general (both sexes) oncological morbidity in Russia, BC occupies the 13th place (2.7 %), in men this pathology occupies the 9th place (4.6 %), and the 16th in women, thereby forming a fairly significant group of malignant neoplasms of the genitourinary system, accounting for 25.1 % of all MN. The average age of men who became ill in Russia is 66.7 years, women – 68.8 years [4]. In 2020 1,594 people with newly diagnosed BC were registered in the Southern Federal District, and 389 people were registered in the Rostov Region [5].

Muscle-noninvasive BC (NMIBC) at the stages of Ta, T1, q carcinoma (CIS) according to the TNM classification accounts for about 70 % of cases [2], muscle-invasive BC (MIBC), as well as metastatic forms – about 30 % [6]. The metastatic form is characterized by a rather aggressive course and high mortality. The 5-year survival rate for patients with metastatic BC is less than 6 % [7].

Currently, treatment methods and prognosis of the further course of BC are based on the classification of TNM and for NMIBC on prognosis groups, taking into account a number of factors. Despite this, the long-term results of treatment of patients belonging to the same classification groups and receiving identical treatment may vary significantly. In this regard, in order to fully predict the course of BC, it is necessary not only to determine the histological structure of the tumor, the degree of its differentiation, but also to take into account the influence of individual factors that determine the clinical behavior and biological aggressiveness of the tumor [8].

Under the influence of carcinogens in the epithelium of the bladder, the probability of changing the functional state of a heterogeneous cell population increases, the mechanisms of cell cycle control are disrupted, various mutations occur, which leads to changes in the processes of cell proliferation and differentiation. Studies on transgenic mice have shown that epithelial stem cells with HRAS or FGFR3 mutations can transform into tumor stem cells of bladder cancer that develop in NMIBC (local mutations in 12, 13 or 61 codons of the oncogene HRAS1 [9], activating local mutation in 7 and 10 exons of the fibroblast growth factor receptor gene 3 [10], PIK-3CA missense mutations [11]), whereas stem cells with mutations of the p53/Rb/PTEN gene transform into tumor stem cells of the urothelium, which cause NMIBC (deletion of chromosome 9p21, etc.) [9; 12]. The characteristic features of NMIBC are activating mutations and overexpression of proto-oncogenes (FGFR3, HRAS, etc.), in most cases, which are acquired gene abnormalities [9].

Currently, the main method of diagnosis of NMIBC is histological analysis of the material obtained after transurethral resection of the bladder, with which it is possible to determine the depth of invasion and the degree of differentiation of the tumor [13].

Recently, the question of early prediction and prevention of BC development has become acute, on which the course of the disease and it's outcome depend, as well as the possibility of timely qualified care.

Table 1. Bladder cancer biomarkers' characteristics in terms of urine study

Marker	Sensitivity, %	Specificity, %
UroVysion	71	66
BTA assessment test (Bladder Tumor Antigen)	64 for G_1, 92 for G_3	90
Cytokeratin level measurement 19 (CYFRA 21-1)	55.7 for G_1, 91.9 for G_3	85.5
NMP22	55.7	85.7
ImmunoCyt/uCyt+ essay	79.3 for G_1, 92.1 for G_3	80 for G_1, 92 for G_3

The diagnostic spectrum of BC biomarkers is diverse, but the accuracy of the techniques and their prognostic value aren't high enough and have limited use in the clinic, as can be seen from the Table 1, which presents some markers for the diagnosis of BC and their main characteristics, according to various studies published at the moment [14].

Recently, the role of tumor stem cells (CSC) in the diagnosis and evaluation of the effectiveness of cancer treatment has been actively studied. CSC (CSC–Cancer Stem Cells) is a specific tumor cell, which is characterized by the ability to asymmetric division, self–renewal *in vivo*, causes the growth of a tumor identical to the original one. A distinctive feature of CSS is their increased resistance to antitumor effects. It is known that antitumor drugs are aimed at eliminating most of the tumor masses sensitive to the antitumor agent, however, it has been proven that the nucleus of cells in the form of CSC remains in the body, which, in turn, may have the ability to restore, proliferate and progress the disease [15]. In this regard, the identification of CSC is an important aspect in assessing the effectiveness of the methods used to treat cancer pathology.

Despite the experimental and theoretical data accumulated to date, many biological properties of CSC, their involvement in the pathological process and their influence on the processes of recurrence and progression remain poorly understood.

The purpose of the study: was to determine the content of tumor cells with the stem cell phenotype in tumor tissue and peritumoral area in noninvasive muscle BC.

MATERIALS AND METHODS

Fragments of tumor tissue (TT) and tissue of the peritumoral zone (PZ) of 7 patients with newly diagnosed noninvasive muscle bladder cancer (NMIBC), all patients have given written consent to the transfer of biological material and the processing of personal data. Histological structure – papillary urothelial carcinoma of low malignancy (low-grade). In 2 people, the tumor is localized along the back wall of the bladder, in 5 people, the tumor is localized on the side walls of the bladder. 5 patients had 1–2 tumors in the bladder, in 2 patients the tumor had a multifocal character. The 1st patient has a history of MN of a different localization (prostate cancer), 1 patient has a history of chronic viral hepatitis C and HIV of art. III, 1 patient is a convalescent of COVID-19 pneumonia.

All patients underwent transurethral resection of the bladder (TUR), in which material was taken: a fragment of the tumor (up to 1.5 cm in size), a fragment of the perifocal zone (retreating from the tumor by at least 0.8 cm, but not more than 1.5 cm). The obtained tissue fragments immediately after sampling and delivery to the laboratory were used to obtain a cell suspension using BD Medimachine (BD, USA). The cell suspension was treated with a panel of monoclonal antibodies: $CD45^-$APC-Cy7, CD44-FITC, CD133-PE, CD24-PE in accordance with the manufacturer's instructions (BD, USA). The phenotypic characteristics of the cell suspension in order to identify cells with the USC phenotype were evaluated on a FacsCantoII flow cytometer (BD, USA). In the analyzed samples, the percentage of cells with the USC phenotype was determined: $CD45^-CD44^+CD24^+$, $CD45^-CD44^+$, $CD45^-CD24^+$, $CD45^-CD133^+$, $CD45^-CD44^+CD133^+$. The percentage of cells of the corresponding phenotype relative to the total number of cells was calculated.

Patients after the treatment in the volume of the TOUR are under dynamic observation, continue to receive adequate treatment in accordance with the clinical recommendations of the AOR in the volume of intravesical chemotherapy, followed by a control study and, if necessary (the presence of relapse or progression of the disease), a decision on further diagnosis and treatment tactics.

Statistical processing was performed using the STATISTICA 13 package (StatSoft Inc., USA). The nature of the distribution of the obtained data was evaluated using the Shapiro-Wilk criterion. Since the obtained data had a normal distribution, the results were presented in the form of the arithmetic mean and the standard error of the arithmetic mean (M ± s). To compare the average values of quantitative indicators in groups, in the case of a normal distribution law, the parametric Student criterion was used, in another case, the nonparametric Mann-Whitney criterion. The differences were considered significant at $p < 0.05$.

RESEARCH RESULTS

The conducted research revealed a number of features of the relative content and distribution of tumor cells with the stem phenotype. It should be noted that the decisive role in the development of

cancer is played by the environment of the tumor, i.e. those interactions formed between the tumor cell and different types of surrounding cells in the peritumoral zone, changes in which can contribute to further invasion of the process. The number of $CD45^-$cells was analyzed, the pool of which is highly likely to include tumor cells with a stem phenotype. The number of CD45 cells in TT and PZ did not differ significantly, amounting to 61.3 ± 5.8 and 71.8 ± 12.6. The relative content of cells with phenotypic CSC markers such as CD24, CD44 in TT were 77 % and 58 % higher than in PZ, respectively, 18.3 ± 3.5 vs. 4.3 ± 2.1, $p \le 0.044$, 15.5 ± 5.3 vs. 6.5 ± 0.8, $p \le 0.043$. The number of $CD133^+$ cells was 83 % higher in PZ compared to TT – 41.6 ± 12.1 vs. 22.7 ± 7.6, $p \le 0.047$. In tumors of the BC content of the cells with the phenotype $CD44^+CD24^+$ and $CD44^+CD133^+$ exceeded the values in PZ 80 % and 63 %, respectively, of 10.3 ± 4,9 vs 2,1 ± 0,4, $p \le 0.039$ inch, 9,0 ± 4,5 versus 3.3 ± 0,9, $p < 0,046$.

So, cells with the CSC phenotype ($CD45^-CD44^+CD24^+$, $CD45^-CD44^+$, $CD45^-CD44^+CD24^+$ and $CD45^-CD44^+CD133^+$) predominate in the tumor tissue. The peritumoral zone was dominated by cells with the $CD45^-CD133^+$ phenotype (Fig. 1).

DISCUSSION

For the first time, CSCs were isolated by D. Bonnet and Y. E. Dick (1997) in acute myeloid leukemia $CD34^+/CD38^-$, and later in various solid tumors [16].

In BC, USCS were first described in 2009 by K. S. Chan et al., their greater content was found in MIBC than in NMIBS [17]. Markers of CSC in BC are a number of phenotypic determinants CD44, CD133, CD47, CD49, 67LR (67-kD laminin receptor), as well as a characteristic set of cytokeratins (keratin 14, 5 and others) [15]. The use of CD133 for the detection of CSC in MN of the bladder is not often noted, its study continues in terms of informativeness in this pathology.

Based on the sequencing of 59 cells from three bladder cancer samples (including BC stem cells, non-BC stem cells, epithelial bladder stem cells, epithelial non-bladder stem cells) Yangetal. the origin of BC tumor cells from epithelial stem cells of the bladder or epithelial non-stem cells of the bladder has been suggested [18]. Probably, urothelial stem cells are located in the basal cell layer and are able to repair damage to the bladder. Based on the conducted studies of the experimental mod-

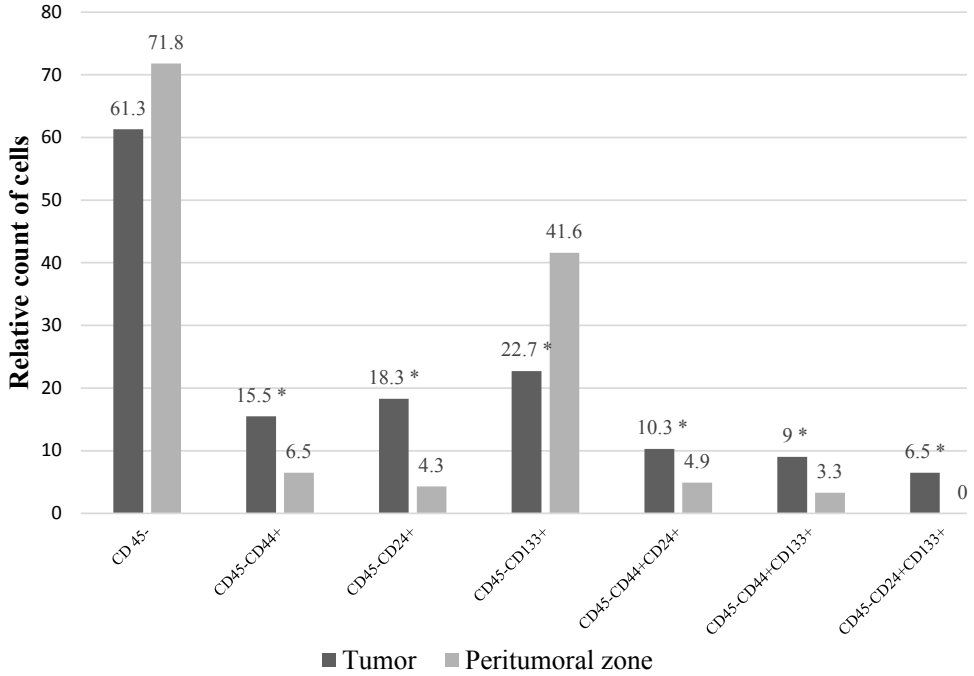

Fig. 1. Relative count of CSC, TT and PZ.

el, the origin of MIBC from urothelial stem cells of the basal cell layer was confirmed. BC tumor stem cells are $CD44^+CK5^+CK20^-$, have phenotypic markers characteristic of basal cells [19]. $CD44^+$ cells were detected in the basal layer of normal urothelium and urothelial carcinoma, in addition, the cells of the intermediate layer also express CD44. It has been shown that due to a mutation in the FGFR3 gene, intermediate layer cells transform into malignant papillary carcinoma of low malignancy and bladder hyperplasia [20].

Experiments to track clones on a mouse tumor model, to which cells isolated *in vivo* were injected intradermally, demonstrated that papillary tumor cells mainly originate from the intermediate layer. In the study of more than 300 samples of patients with transitional cell carcinoma of the bladder, 40 % contained $CD44^+$ cells. Histological analysis showed that the xenografts of the tumor retained a histology similar to that of the patient's original tumor. Cells with the $CD44^+$ phenotype have a high oncogenicity (200 times higher than CD44-tumor cells of BC), and the ability to self-renew. The frequent and significant expression of CD44 in normal tissues and tumors contradicts the idea of the relative rarity of USC, and therefore there is a need to combine CD44 with other markers, for example, CD133 or CD24 to detect CSC [14].

It is known that increased expression in CD44 tumor cells causes metastasis, self-maintenance of these cellular elements, and also contributes to the formation of drug resistance against the background of resistance to apoptosis. A number of studies have revealed a correlation between the presence of CD44 and the degree of prevalence of BC. The presence of $CD44^+$ showed a lower survival rate and incomplete response to previous therapy (chemo and/or radiotherapy), thus, a change in the expression of CD44, which is an adhesive protein and promotes cell migration, can act as one of the mechanisms causing the process of recurrence and progression of BC [21].

Summarizing the data obtained from our work, we found a greater number of $CD44^+$ cells in the tumor tissue, which is consistent with the literature data and may indicate an unfavorable course of the disease, as well as the possibility of using this marker as a marker for predicting disease recurrence after complex treatment.

CD133 (AC133, prominin 1) is a glycoprotein that was first discovered by H. Yu et al. in 1997 as a cell surface protein expressed on $CD34^+$ hematopoietic progenitor cells [22]. Transplantation of tumor stem cells expressing CD133 to mice with immunodeficiency generated histologically similar tumor tissue with self-renewal [23]. In a study by Huang P. and co-author in 2013. It was demonstrated that the $CD133^+$ subpopulation of human bladder cancer cells was characterized by activation of pluripotent stem cell markers – Oct-4 and Sox-2, while demonstrating more aggressive proliferation compared to the CD133-subpopulation. The $CD133^+$ subpopulation also tended to form colonies, which indicates a strong clonogenic ability, i.e. they have phenotypic features associated with CSC [24]. The presence of CD133 on the surface of tumor cells causes the preservation of their stem properties, as well as the launch of the formation of differentiated malignant cells [25].

In our work, CSC with the $CD133^+$ phenotype were found in greater numbers in the peritumoral zone. Based on this, it can be assumed that this marker functions as a modulator of the effects of a wide range of cytokines, affects the activity of various membrane receptors, and an increase in this marker can lead to structural and functional changes in cells with an increase in the probability of their tumor transformation.

Previously published studies have proven the important role of CD24 in the development of oncogenesis and the progression of various types of malignant neoplasms, including renal cell carcinoma (RCC), nasopharyngeal cancer, hepatocellular carcinoma (HCC), ovarian cancer, non-small cell lung cancer (NSCLC), breast cancer and others. This mucin-like cell membrane protein is expressed in many types of tumor tissue. In breast cancer, a correlation was noted between the overexpression of CD24, the prevalence and progression of the disease [26]. CD24 expression was slightly correlated with lymphovascular invasion of the BC tumor, whereas CD133 was associated with distant metastases and aggressiveness of the tumor process. Tumor cells with the phenotype of stem $CD133^+CD24^+$ are characteristic of more aggressive forms, low differentiated (high grade) bladder carcinomas of high malignancy [25].

CONCLUSION

Thus, based on a small sample size, it's possible to assume some phenotypic and quantitative features of

CSC in tumor tissue and peritumoral zone in NMIBC.

The study of CSC is a promising direction for the study of oncogenesis, and with further study, there is a high probability of using these markers to assess the nature of the development of relapse and/or progression of the disease, as well as for new different therapy approaches aimed at eliminating cells with the CSC phenotype by affecting surface markers and corresponding signaling pathways that lead to the emergence and maintenance of this cell population. Despite all the available scientific work related to the search for new effective methods of diagnosis, the study of CSC and their impact on the process of occurrence, metastasis in BC – have not been studied enough, and therefore it is planned to further study these cells with the stem phenotype.

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Bondarenko E. S. – work on a flow cytometer, analysis of the results;
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ORIGINAL ARTICLE

A BENZIMIDAZOLE DERIVATIVE AS AN EFFECTIVE ANTITUMOR AGENT IN TERMS OF SYNGENEIC LUNG TUMORS AND MELANOMA TREATMENT

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ABSTRACT

Purpose of the study. Evaluation of the effect of the benzimidazole derivative dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole (RU-185) on the growth of Lewis lung epidermoid carcinoma and B16-F10 melanoma when administered intragastrically.

Materials and methods. For the experiment, we used female C57Bl/6j mice, which were inoculated subcutaneously with syngeneic tumors: Lewis lung carcinoma (LLC) and B16-F10 melanoma. RU-185 was administered intragastrically to animals in a volume of 0.3 ml for 10 days, 1 time per day. For both tumors, depending on single doses of the substance for administration, groups were divided: 1st and 4th – 50 mg/kg, 2nd and 5th – 220 and 3rd and 6th – 500 mg/kg. The control groups were injected intragastrically with physiological saline in the same volumes and according to the same scheme. The following parameters were assessed: tumor volume, increase in life expectancy (T/S, %) and tumor growth inhibition index (TGI, %).

Results. For animals with LLC in the 2nd group there is an increase in the indicator of life expectancy (T/S 162.3 %), and in the 3rd group there is a tendency to an increase in the T/S indicator. On the 1st day after the end of treatment in the 2nd and 3rd groups TGI was 73.0 % and 30.1 %, respectively ($p < 0.05$). On the 7th and 14th days after the end of the use of RU-185 in the 2nd and 3rd groups the volume of tumors is 3.5 and 1.4 times less (on the 7th day) and 2.3 and 1.3 times (on the 14th day), respectively than in the control group ($p < 0.05$). At a dose of 220 mg/kg, complete regression of LLC tumors was shown in 20 % of animals.

With the growth of B16-F10, the life expectancy of all groups did not differ. Intergroup differences in the dynamics of tumor growth are provided. Highlighted changes were found in the 5th group (on the 14th day after the end of the administration of RU-185, TGI was 48.7 %).

Conclusion. The investigated chemical substance dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole showed antitumor efficacy against syngeneic tumors: Lewis lung epidermoid carcinoma and B16-F10 melanoma when administered intragastrically which leads to further testing of RU-185 as a potential drug for the treatment of malignant neoplasms.

Keywords:
dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole, Lewis lung carcinoma, melanoma B16-F10, antitumor efficacy, intragastric administration

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ПРОИЗВОДНОЕ БЕНЗИМИДАЗОЛА КАК ЭФФЕКТИВНОЕ ПРОТИВООПУХОЛЕВОЕ СРЕДСТВО В ЛЕЧЕНИИ СИНГЕННЫХ ОПУХОЛЕЙ ЛЕГКОГО И МЕЛАНОМЫ

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РЕЗЮМЕ

Цель исследования. Оценка влияния производного бензимидазола дигидробромид-2-(3,4-дигидроксифенил)-9-диэтиламино-этилимидазо-[1,2-a] бензимидазола (РУ-185) на рост эпидермоидной карциномы легкого Льюиса и меланомы B16-F10 при внутрижелудочном применении.

Материалы и методы. Для эксперимента использовали мышей линии C57Bl/6j самок, которым подкожно прививали сингенные опухоли: эпидермоидная карцинома легких Льюис (LLC) и меланома B16-F10. РУ-185 вводили внутрижелудочно животным в объеме 0,3 мл в течении 10 дней 1 раз в сутки. Для обеих опухолей в зависимости от разовых доз субстанции для введения выделены группы: 1-я и 4-я – 50 мг/кг, 2-я и 5-я – 220 и 3-я и 6-я – 500 мг/кг. Контрольным группам внутрижелудочно вводили физиологический раствор в аналогичных объемах и по той же схеме. Оценивали показатели: объем опухоли, увеличение продолжительности жизни (Т/С, %) и индекс торможения роста опухоли (ТРО, %).

Результаты. Для животных с LLC во 2-й группе отмечается увеличение показателя продолжительности жизни (Т/С 162,3 %), а в 3-й показана тенденция к повышению показателя Т/С. В 1-е сутки после окончания лечения во 2-й и 3-й группах ТРО составил 73,0 % и 30,1 % соответственно ($p < 0,05$). На 7-е и 14-е сутки после окончания применения РУ-185 во 2-ей и 3-ей группах объемы опухолей меньше в 3,5 и 1,4 раза (на 7-е сутки) и 2,3 и 1,3 раза (на 14-е сутки) соответственно, чем в контрольной группе ($p < 0,05$). В дозе 220 мг/кг показана полная регрессия опухолей LLC у 20 % животных. При росте B16-F10 продолжительность жизни во всех группах не различалась. Показаны межгрупповые различия динамики роста опухоли. Выраженные изменения обнаружены в 5-й группе (на 14-е сутки после окончания введения РУ-185 ТРО составил 48,7 %).

Заключение. Исследованная химическая субстанция дигидробромид-2-(3,4-дигидроксифенил)-9-диэтиламино-этилимидазо-[1,2-a] бензимидазола показала противоопухолевую эффективность в отношении сингенных опухолей: эпидермоидной карциномы легкого Льюиса и меланомы B16-F10 при внутрижелудочном введении, что обусловливает проведение дальнейших испытаний РУ-185 как потенциального препарата терапии злокачественных новообразований.

Ключевые слова:
дигидробромид-2-(3,4-дигидроксифенил)-9-диэтиламино-этилимидазо-[1,2-a] бензимидазола, эпидермоидная карцинома легких Льюиса, меланома B16-F10, противоопухолевая эффективность, внутрижелудочное введение

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INTRODUCTION

The search for targets for the treatment of malignant neoplasms, despite numerous developments in modern oncology, is still relevant [1–3]. The identified targets require the study of various means of influencing. Chemical substances, in particular benzimidazole derivatives, can be useful and effective for therapeutic purposes in practical oncology.

By it's structure, benzimidazole is a heterocyclic compound in which benzene and imidazole rings are connected. The antitumor efficacy of imidazoles has long been known, some of which, for example, dacarbazine, temozolomide, zoledronic acid, mercaptopurine, nilotinib, tipifarnib, etc., are used in oncological practice in the treatment of various oncological diseases [4]. This antitumor effect of imidazoles is due to their ability to easily bind to protein molecules and destroy them, and in high concentrations directly inhibit the synthesis of the main components of the cell membrane [5].

The potential antitumor effect of benzimidazole is also due to the similarity of it's structure with natural nucleotides, and therefore cell DNA is an important target for them. Thus, triazolobenzimidazole is able to inhibit check point kinase 2, which plays an important role in the cell's response to DNA damage, and therefore has an antitumor effect [6]. The benzimidazole derivative 2-[(R)-2-Methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide can inhibit DNA repair by inhibiting poly (ADP-ribose) polymerase (PARP)-1 and –2 [7].

The effect of benzimidazole derivatives on the microtubule protein tubulin has been shown, in which it's polymerization and depolymerization are disrupted [8]. The inhibitor of β-tubulin is benzimidazole-2-urea – it's cytotoxic effect against an extensive panel of tumor cells has been shown [9; 10]. The participation of some benzimidazole derivatives benzimidazole-4,7-diones in the activation of caspase-dependent apoptosis on the lung adenocarcinoma cell line was found [11].

The purpose of the study: to evaluate the effect of benzimidazole derivative dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole (RU-185) on the growth of Lewis lung epidermoid carcinoma and melanoma B16-F10 with intragastric use.

MATERIALS AND METHODS

Mice of the C57Bl/6j female line weighing 20–22 grams were used for the experiment. The animals were obtained from the Andreevka vivarium of the FSBIC of biomedical technologies of FMABA Russia (Moscow region) with a veterinary certificate. The study was conducted according to the principles of humane treatment of animals in scientific research in accordance with the European Convention.

Table 1. Study design

	Groups/ Number of animals	Supplement drug	Doses mg/kg	V, ml	Way of supplementation	Duration of supplementation
LLC	1st 12 mice	dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo-[1,2-a] benzimidazole	50	0.3 ml	I/g	10 days
	2nd 12 mice		220			
	3rd 12 mice		500			
	Control 12 mice	Normal saline	-			
B16-F10	4th 12 mice	dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo-[1,2-a] benzimidazole	50			
	5th 12 mice		220			
	6th 12 mice		500			
	Control 1 12 mice	Normal Saline	-			

Note: LLC – Lewis lung epidermoid carcinoma, B16-F10 – melanoma, I/g – intragastric.

Syngenic tumors were used: Lewis epidermoid lung carcinoma (LLC) and melanoma B16-F10. The tumors were inoculated in mice subcutaneously in a standard way.

The design of the experiment is presented in Table 1. The investigated chemical substance dihydrobromide 2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo-[1,2-a] benzimidazole (RU-185) (RF patent No. 2391979) was dissolved in saline solution and administered intragastrically to animals using a nasogastric probe in a volume of 0.3 ml. The mode of administration was 10 days daily, 1 time per day.

The choice of doses to study the antitumor effect is due to the value of the semi-lethal toxicity of LD50, which was determined with a single intragastric administration to outbred mice (LD50 was 1860.4 mg/kg) [12]. For both tumors, depending on single doses of the substance for administration, groups were divided: 1st and 4th – 50 mg/kg, 2nd and 5th – 220 and 3rd and 6th – 500 mg/kg. The control groups, which consisted of animals with transplanted tumors B16-F10 and LLC, were intragastrically injected with saline solution in similar volumes and according to the same scheme. Both the surviving and fallen animals underwent necropsy within 2 hours after death.

The study of the antitumor activity of the substance was carried out in accordance with regulatory documents [13; 14], the following indicators were evaluated: tumor volume, increase in life expectancy (T/S, %), calculated as the ratio of the average life expectancy of animals subjected to therapy to control indicators, and the tumor growth inhibition index (TGI, %) was calculated.

The normality of the distribution of features was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov criteria. Median and interquartile range were calculated for quantitative data. The statistical significance of the differences between the groups was assessed using the Mann-Whitney criterion, and in dynamics using the Wilcoxon criterion. The signifi-

Table 2. The impact of PY-185 on LLC and B16-F10 growth dynamics

Group number (Single dose, mg/kg)	T/S, %	Tumor volume (cm^3), Me [25-75] (TGI, %) The day after treatment termination		
		1	7	14
LLC				
1st (50)	94.3	2.3 [1.9–2.7][2]	8.6 [7.8–9.2][1,2]	10.3 [9.9–10.9][2] (**14.8**)
2nd (220)	162.3	0.4 [0.2–0.7][1,2] (**73.0**)	2.1 [1.9–2.3][1,2] (**70.0**)	4.5 [4.1–5.0][1,2] (**55.0**) – 80 % abdomen 0 (**100**) – 20 % abdomen
3rd (500)	112.9	1.1 [0.8–1.4][1,2] (**30.1**)	5.2 [4.8–5.5][1,2] (**22.1**)	7.4 [6.9–8.0][1,2] (**28.6**)
Control	0	1.6 [1.1–2.1]	6.7 [6.3–7.1]	9.8 [9.3–10.2]
B16-F10 Melanoma				
4th (50)	96. 2	0.4 [0.1–0.9]	2.7 [2.3–3.1]	5.9 [5.3–6.1]
5th (220)	131.1	0.4 [0.2–0.7]	2.6 [2.3–2.9] (**4**)	2.4 [1.9–2.7][1,2] (**48.7**)
6th (500)	103.1	0.4 [0.1–0.9]	2.1 [1.8–2.4][2] (**20.4**)	4.5 [3.9–4.9][2] (**4.5**)
Control		0.3 [0.1–0.7]	2.7 [2.1–3.4]	4.7 [3.9–5.1]

Note: 1 – the differences are significant relative to the control ($p < 0.05$); 2 – the differences are significant relative to the subgroups of the experimental group ($p < 0.05$).

cance level for the methods used was set as $p \leq 0.05$. Statistical data processing was carried out using the STATISTICA 12.0 program.

RESEARCH RESULTS AND DISCUSSION

The use of RU-185 in tumor-bearing animals with LLC caused a change in life expectancy and tumor size in experimental groups (Table 2). Thus, it was found that when a single dose of 220 mg/kg (group 2) was administered, an increase in life expectancy (T/S 162.3 %) was noted. In the group of animals administered a dose of 500 mg/kg (group 3), a tendency to increase the T/S index was shown, which has insignificant differences with the animals of the control group. In group 1, the life expectancy indicator was reduced in comparison with the control.

The study of the growth dynamics of the subcutaneous tumor node LLC with the use of RU-185 revealed differences in the study groups. On the 1st day after the end of treatment in the 2nd and 3rd groups, the tumor growth inhibition index indicated a decrease in the size of the primary focus and amounted to 73.0 % and 30.1 %, respectively ($p < 0.05$) (Table 2). On the 7th and 14th days after the end of the use of RU-185 in the 2nd and 3rd groups, tumor volumes were statistically significantly less by 3.5 and 1.4 times (on the 7th day) and 2.3 and 1.3 times (on the 14th day), respectively, than in the control group ($p < 0.05$). When applying a dose of 220 mg/kg, a complete regression of LLC tumors was shown in 20 % of animals, which was confirmed by the results of necropsy. At the same time, there was a tendency to tumor growth in group 1, but no statistically significant differences were found in comparison with the control group.

When analyzing the study results of the subcutaneous melanoma B16-F10 growth, we've shown that the life expectancy of all experimental groups didn't differ from the control group ($p > 0.05$) (Table 2). The T/S index in tumor-bearing animals with melanoma B16-F10 when using RU-185 was 96.2, 131.1 and 103.1 %, respectively, in groups 4, 5 and 6.

Analysis of the dynamics of tumor growth in 16 showed intergroup differences. In the group with a single dose of RU-185 50 mg/kg, the administration of the substance did not affect the growth of the subcutaneous node, the tumor size indicators at all stages were similar to the control group. The most pronounced changes were shown in the group with a single dose of 220 mg/kg. So, on the 14th day after the end of the administration of RU-185, the TGI index was 48.7 %, which indicates a decrease in tumor size compared to the control group (by 2 times at $p < 0.05$).

CONCLUSION

The studied chemical substance dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole (RU-185) showed antitumor efficacy against syngenic transplantable tumors: Lewis lung epidermoid carcinoma and melanoma B16-F10. It was shown that with intragastric administration of the substance in a single dose of 220 mg/kg for 10 days, a significant decrease in the size of tumors was noted. In animals with melanoma B16-F10, a significant decrease in tumor volume occurs on the 14th day after the end of the administration of the substance. Unlike melanoma, in animals with epidermoid lung carcinoma at a dose of 220 mg/kg, RU-185 has a pronounced inhibition of the growth of the subcutaneous tumor node already on the first day after the end of the use of the substance.

We explain the differences in the effectiveness of the substance under study by the peculiarities of metabolic phenotypes of tumors. Metabolic phenotypes of melanoma demonstrate dynamism between glycolysis and oxidative phosphorylation, which gives an advantage in the survival of tumor cells and in the formation of chemoresistance [15; 16]. Moreover, simultaneous activation of both oxidative phosphorylation and glycolysis (metabolic symbiosis) is vital for the progression of melanoma [15; 16]. At the same time, the metabolism of lung cancer cells is characterized by the activation of glucose oxidation enzymes, which indicates it's glycolytic phenotype [17]. Along with the activation of glycolysis for lung cancer, an increase in the intensity of other glucose-related processes, such as gluconeogenesis, the tricarboxylic acid cycle, has been shown [17].

Thus, the revealed antitumor efficacy of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole determines further testing of RU-185 as a potential drug for the treatment of malignant neoplasms. However, further studies are needed to identify the mechanism of it's antitumor action.

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ORIGINAL ARTICLE

SURGICAL TREATMENT OF RETROPERITONEAL NEUROBLASTOMA IN CHILDREN. CLINICAL EXPERIENCE

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ABSTRACT

Purpose of the study. Was to analyze our experience of surgical treatment of retroperitoneal neuroblastoma in children and the influence of radical surgical treatment on the disease outcomes.
Materials and methods. The study included 35 patients (14 girls and 21 boys, mean age 3.3 years) receiving treatment for retroperitoneal neuroblastoma at the Department of Pediatric Oncology, National Medical Research Centre for Oncology, in 2016–2018. 32 patients underwent surgical treatment. The disease progression during neoadjuvant polychemotherapy was registered in 3 patients. Initially, surgery was performed in 5 patients; the rest of the patients underwent percutaneous trepan biopsy with immunohistochemical testing and subsequent neoadjuvant polychemotherapy. No patients developed complications in the early postoperative period.
In the article, we present our experience in the surgical treatment of pediatric patients with retroperitoneal neuroblastomas.
Results. Patients have been observed during 12 to 24 months. 23 of 28 radically operated patients are alive and have no signs of the disease recurrence or progression. 2 patients developed tumor recurrence and received anti-recurrence PCT and DGT. Currently the patients are in remission. 3 patients showed systemic progression due to primarily advanced disease.
Conclusion. Administration of modern surgical techniques and instrumentation allows radical surgical treatment for a large percentage of patients with locally advanced neuroblastoma.

Keywords:
pediatric patients, retroperitoneal neuroblastomas, surgical treatment, neoadjuvant polychemotherapy, radical tumor removal, progression

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ НЕЙРОБЛАСТОМ ЗАБРЮШИННОЙ ЛОКАЛИЗАЦИИ У ДЕТЕЙ. ОПЫТ КЛИНИКИ

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РЕЗЮМЕ

Цель исследования. Проанализировать собственный опыт хирургического лечения нейробластом забрюшинного пространства у детей и влияние радикальности хирургического лечения на исход заболевания.
Материалы и методы. В исследование включены 35 пациентов, проходивших лечение в отделении детской онкологии ФГБУ «НМИЦ онкологии» Минздрава России с 2016 по 2018 гг. с нейробластомами забрюшинного пространства. Средний возраст пациентов составил 3,3 года. Из них было 14 девочек и 21 мальчик. Хирургическое лечение проведено 32 пациентам. У 3 больных отмечена прогрессия заболевания на фоне проводимой неоадъювантной ПХТ. Изначально оперативное вмешательство было выполнено 5 больным, остальным пациентам проводилась чрескожная трепанбиопсия с иммуногистохимическим исследованием и последующей неоадъювантной полихимиотерапией. В раннем послеоперационном периоде осложнений не отмечено ни у одного пациента.
В статье нами представлен собственный опыт хирургического лечения пациентов детского возраста с нейробластомами забрюшинного пространства.
Результаты. Пациенты наблюдаются в сроках от 12 до 24 мес. Из 28 пациентов, прооперированных радикально, живы без признаков рецидива и прогрессии заболевания 23. У 2 больных возник рецидив опухоли, им проведена противорецидивная ПХТ и ДГТ. В настоящее время пациенты находятся в ремиссии. У 3 пациентов отмечалась системная прогрессия заболевания, связанная с первично-генерализованным процессом
Заключение. Применение современных хирургических техник и инструментария позволяет в большом проценте случаев добиться радикального хирургического лечения при местно-распространенных формах нейробластомы.

Ключевые слова:
пациенты детского возраста, нейробластомы забрюшинного пространства, хирургическое лечение, неоадъювантная полихимиотерапия, радикальное удаление опухоли, прогрессия

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INTRODUCTION

Neuroblastoma is the most common tumor of the peripheral nervous system, occurring in childhood. The incidence of neuroblastoma is 7–8 % of all malignant tumors of childhood [1; 2]. Neuroblastoma is localized mainly in the retroperitoneal space, less often in the mediastinum and on the neck. The source of tumor development in the retroperitoneal space is the adrenal gland in 32 % of cases, sympathetic ganglia located paravertebral in 28 % of cases [3–6]. The biological diversity of neuroblastomas associated with genetic mutations or their absence significantly affects the clinical course of the disease. There are cases of spontaneous tumor regression. This is especially true for children under the age of 1 year. Thus, according to various authors, spontaneous tumor regression in children under 1 year occurs in 50–70 % of cases [7; 8]. At the same time, the presence of N-myc gene amplification, deletions at the 1p36 locus, as well as the age of a child older than 1 year are unfavorable factors, and event-free survival in this group of patients, according to numerous studies, does not exceed 40 % [1; 9].

The diverse course of neuroblastomas in childhood, from spontaneous regression to active progression, dictates the need for different approaches to the treatment of this pathology. Intensification of therapy in high-risk patients makes it possible to achieve more significant results in treatment. Thus, various authors propose the use of systemic radiotherapy using 131I–MIBG, high-dose chemotherapy with autotransplantation of polypotent stem cells [10–13].

Surgical treatment of retroperitoneal neuroblastoma, in particular, locally widespread forms, caused by the involvement of major vessels and adjacent organs in the process, causes particular difficulties [1; 14]. The question of the expediency of radical removal of the tumor with a high risk of surgical

Table 1. Characteristics of patients by the prevalence of the tumor process

Criteria for the characteristics of the tumor process	Patients' quantity			
Primary tumor localisation	Adrenal gland		Paravertebrally	
	12 (34.3 %)		23 (65.7 %)	
Tumour process development	Focal form		Generalised form	
	25 (71.4 %)		10 (28.6 %)	
Risk groups	Middle		High	
	16 (45.8 %)		19 (54.2 %)	
INSS staging	St I	St II	St III	St IV
	2 (5.7 %)	9 (25.7 %)	14 (40 %)	10 (28.6 %)

Table 2. Radiological (CT or MRI) risk factors (IDRFs) for patients with abdominal/retroperitoneal neuroblastoma according to INRG

Group 1	A tumor infiltrating the portal vein and/or hepatoduodenal ligament, including branches of the superior mesenteric artery of the mesentery root, including the ventral trunk and/or trunk of the superior mesenteric artery, infiltrating one or both renal pedicles, including the aorta and/or IVC, including the iliac vessels, pelvic tumor in the area of the sciatic tenderloin
Group 2	A tumor with a spread into the spinal canal (regardless of the level) spread to more than 1/3 of the spinal canal in axial projection and/or the leptomeningeal space is not traced and/or the signal from the spinal cord is pathologically altered
Group 3	Infiltrates the surrounding organs and structures of the pericardium, diaphragm, kidney, liver, pancreatoduodenal zone, mesentery

complications in patients with generalized forms of neuroblastomas that do not allow time to start systemic therapy remains debatable. According to a number of authors, radical removal of the tumor (more than 95 % of the volume) improves the results of treatment of high-risk patients [15–19], other authors say that total removal of neuroblastoma with a high risk of intra- and postoperative complications is inappropriate, since high-risk neuroblastoma is a systemic process with possible metastatic damage to the liver, bone marrow and bones [20–22].

The purpose of the study: to analyze our own experience of surgical treatment of retroperitoneal neuroblastoma in children and the effect of radical surgical treatment on the outcome of the disease.

MATERIALS AND METHODS

The study included 35 patients who were treated at the Department of Pediatric Oncology of the National Medical Research Centre for Oncology from 2016 to 2018. The average age of patients was 3.3 years. Of these, there were 14 girls and 21 boys. The staging of the tumor process was carried out according to the INSS criteria. All patients were treated in accordance with the NB 2004 protocol. According to the localization of the tumor in 12 patients (34.3 %), the primary tumor was localized in the projection of one of the adrenal glands, in 23 (65.7 %) there was a paravertebral spread of the tumor along the main vessels. 10 patients (28.6 %) had primary generalization of the tumor process with metastases to the liver, bones and bone marrow, and 25 patients (71.4 %) had localized stages of the disease. The largest number of patients were with stage 3 of the disease – 14 patients (40 %), with stage 4–10 patients (28.6 %), with stage 2–9 patients (25.7 %), and with stage 1–2 patients (5.7 %). The high risk group was determined in 54.2 % of patients, the average risk group in 44.8 % of patients. The characteristics of patients by the prevalence of the process are presented in Table 1.

Surgical treatment was performed in 32 patients. In 3 patients, the progression of the disease was noted against the background of neoadjuvant PCT.

Initial surgical intervention was performed in 5 patients, the remaining patients underwent percutaneous trepan biopsy with immunohistochemical examination and subsequent neoadjuvant polychemotherapy.

When planning a surgical intervention, we used data from spiral computed tomography with angiography, magnetic resonance imaging data and ultrasound examination of the abdominal cavity and retroperitoneal space. The risk factors for surgical intervention in imaging (IDRF) described in the International Neuroblastoma Risk Group (INRG) guidelines for imaging and staging neuroblastoma [23] and characterizing the involvement of major vessels and other adjacent organs in the tumor process were taken into account. Figure 1 schematically shows the relationship between the tumor and the main vessels in the absence of risk factors during imaging (IDRF) and in their presence.

Table 2 presents detailed radiological criteria for inclusion of patients in the group with risk factors for imaging according to INRG.

Among the operated patients, 12 had no risk factors during imaging and 19 had. Figure 2 shows the frequency of involvement of the main vessels

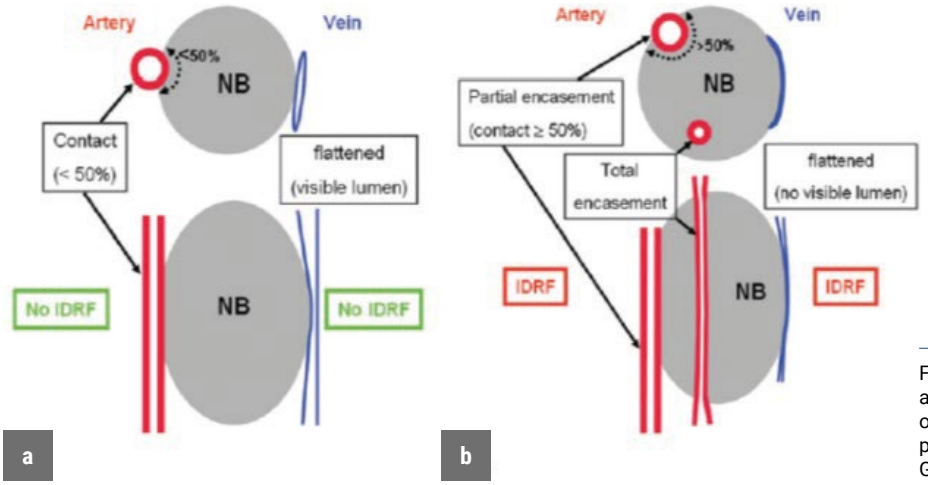

Fig. 1. Diagram of the ratio of tumor and major vessels in the absence of risk factors (DFR) (a) and their presence (b) (Monclair T, Brodeur G.M., 2009).

and adjacent organs in the tumor process. More often, the vessels of the renal pedicle, the aorta, and the superior mesenteric artery were involved in the process.

As illustrative examples of risk factors assessment during visualization, we give 2 clinical examples.

Clinical example 1. Patient K. 5 years old with the diagnosis: undifferentiated retroperitoneal neuroblastoma with bone metastases. StIV. A high-risk group. The presented CT scans (Fig. 3, 4) show a reduction in tumor mass in the retroperitoneal space after neoadjuvant polychemotherapy. The residual tumor involves the aorta and the renal arteries on both sides in a process with a muff-like covering. The tumor also covered the lower mesenteric artery, flattened the left renal vein on itself.

Figure 5 shows an intraoperative image after removal of a tumor with skeletonized main vessels of the retroperitoneal space. The tumor was removed completely in this case.

Clinical report 2. Patient B. 4 years old with a diagnosis of retroperitoneal ganglioneuroblastoma. An accidental finding during ultrasound examination of the abdominal cavity. According to the MRI study,

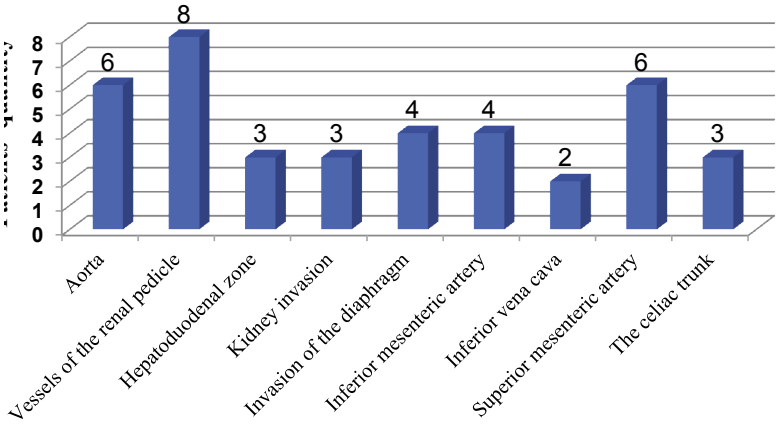

Fig. 2. The frequency of involvement of the main vessels and adjacent organs in the tumor process.

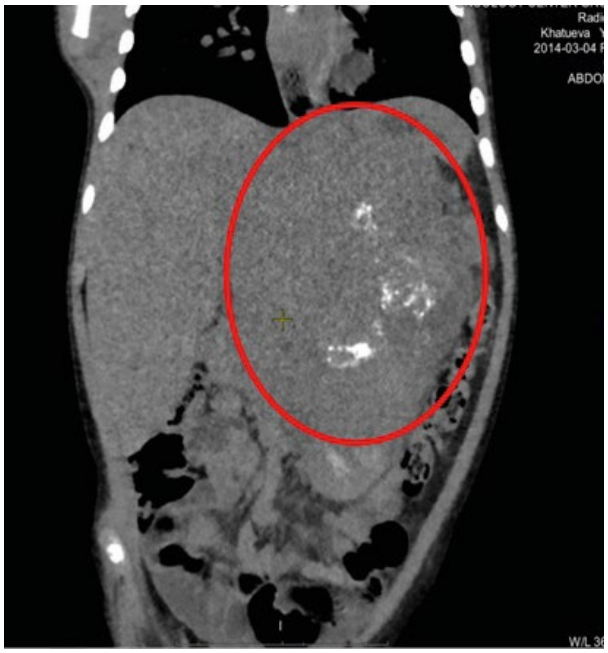

Fig. 3. CT scans before 6 courses of polychemotherapy of patient K. The primary prevalence of the tumor before induction polychemotherapy.

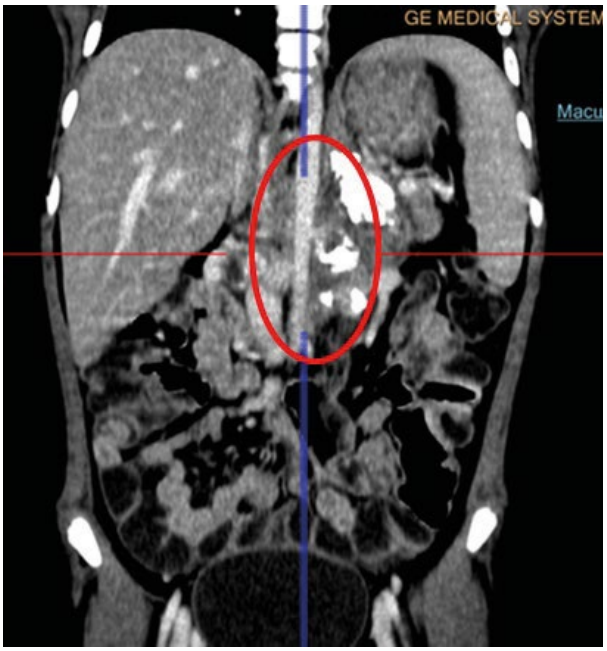

Fig. 4. CT scans (tumor prevalence) after 6 courses of polychemotherapy of patient K.

we did not find classical risk factors in imaging. The computed tomography images shown in Figure 6 show that all the main vessels only adhere to the tumor, without their muff-like covering, however, the area of location between the vessels is the inferior vena cava, renal vessels, elements of the hepatoduodenal ligament, aorta, superior mesenteric artery causes no less difficulties than during operations in patients with risk factors during visualization. In order to get to this tumor, it was necessary to isolate all the elements of the hepatoduodenal ligament, separate from the inferior vena cava, and isolate the superior mesenteric artery (Fig. 7). Therefore, risk factors in imaging are very conditional, but they help the surgeon to adequately assess the possibilities of radical surgical treatment.

The use of high-tech surgical equipment during surgical interventions (ultrasonic scalpel, modern bipolar electrocoagulating instruments) allowed to minimize the amount of blood loss and traumatization of healthy tissues.

RESEARCH RESULTS

According to the results of the operations performed, in 25 cases (78.3 %) we performed total removal of the tumor, in 3 cases (9.3 %) removal of more than 95 % of the tumor and in 4 cases (12.4 %) subtotal removal of the tumor from 50 to 95 % of the tumor mass was performed. Less than 50 % of the tumor was not removed in any case.

Complications include the development of intraoperative bleeding in 7 patients who developed from non-arterial vessels and were stopped by ligation or electrocoagulation. The volume of blood loss in these cases did not exceed 20 % of the CBV.

Also, according to many authors, complications of the operation include nephrectomy. Of the 32 operated patients, nephrectomy was performed in two due to the muff-like covering of the kidney by the tumor. In preparation for the operation, these patients were planned to perform a nephrectomy in advance.

In the early postoperative period, no complications were noted in any patient. In the late postoperative period, 2 months after the operation, one patient was found to have impaired blood supply to the contralateral kidney. The cause of this complication is not related to the technical stage of the surgical intervention, since during the operation they worked on the kidney vessels on the affected side, and the contralateral kidney and its vessels remained intact.

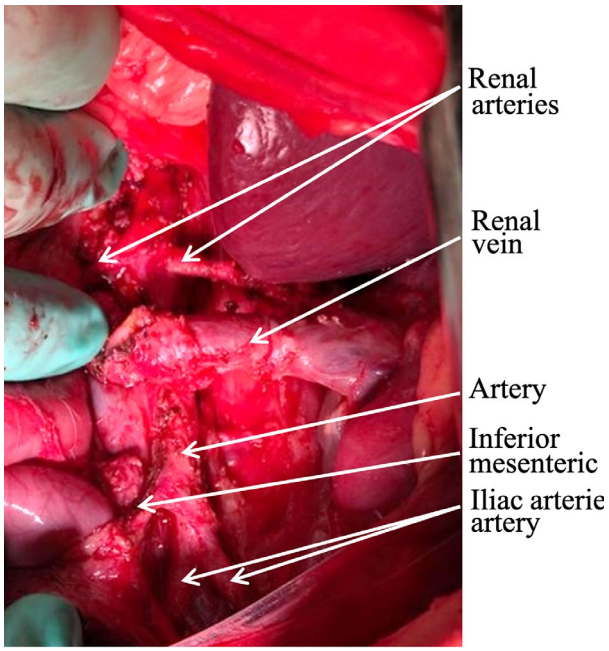

Fig. 5. Intraoperative image after removal of the tumor.

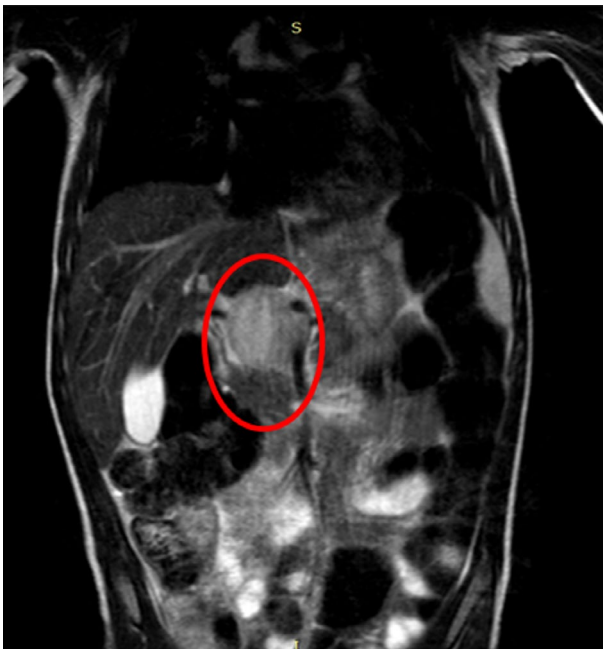

Fig. 6. Magnetic resonance imaging image of patient B. before surgical treatment.

Patients are observed for periods from 12 to 24 months. Of the 28 patients who underwent radical surgery, 23 are alive without signs of relapse and progression of the disease. 2 patients had a relapse of the tumor, they underwent anti-relapse PCT and DHT. Currently, the patients are in remission. Systemic disease progression was observed in 3 patients.

Of the 4 patients operated non-radially, only 2 are observed without signs of continued tumor growth and generalization.

All patients who had a recurrence or progression of the tumor process – 9 patients – belonged to the high-risk group.

DISCUSSION

A number of authors indicate that there was no significant difference in 5-year relapse-free survival among patients who underwent complete or incomplete resection [24–26]. At the same time, there are publications proving that surgical treatment should be in the form of complete resection of the tumor, and cases of partial resection are associated with a high risk of relapse of the disease, the need for careful monitoring and the possible use of radiation therapy [27]. According to our data, the development of relapse and progression of the disease occurred only in high-risk patients, which speaks in favor of the systemic nature of the disease and the influence on the progression of factors such as the prevalence of the primary process and the presence of genetic mutations, namely, amplification of MYC-N, deletion 1p36, allowing stratification of the patient into a high risk group. The development of relapses and progression of the disease in radically operated patients speaks in favor of the lack of significance of radicalism of surgical intervention. However, we can reliably say this by conducting a randomized study on a much larger amount of material. And yet, after a radical operation, there are fewer questions about the further tactics of treatment and management of patients with neuroblastoma, especially since the use of modern surgical techniques makes it possible to achieve radicalism of surgical treatment while minimizing the risks of complications.

CONCLUSION

Thus, the following conclusions can be made:

1. The use of modern surgical techniques and tools allows a large percentage of cases to achieve radical surgical treatment for locally common forms of neuroblastoma without the threat of serious complications.

2. Proper planning of surgical intervention taking into account risk factors during visualization allows minimizing intraoperative and postoperative complications.

3. Given the systemic nature of the lesion in neuroblastoma, it is impractical to conduct a radical operation with total removal of the tumor, accompanied by the development of complications that do not allow time to start systemic therapy.

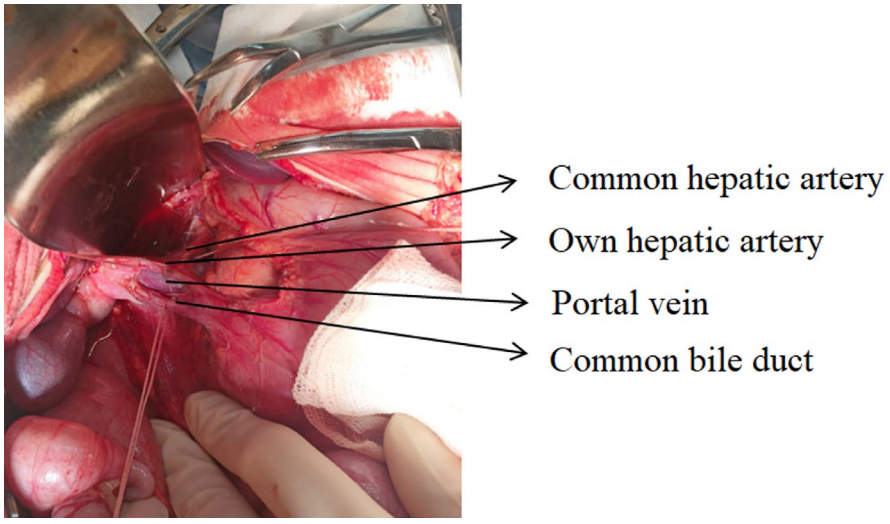

Fig. 7. Intraoperative image after removal of the tumor. Patient B.

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Shevchenko A. N. – surgical treatment, analysis and critical assessment of the work;
Kozel Yu. Yu. – manuscript analysis, critical revision with valuable intellectual content;
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ORIGINAL ARTICLE

MARKERS OF STRUCTURAL AND CELLULAR RENAL DAMAGE IN LOCALIZED RENAL CELL CARCINOMA BEFORE TREATMENT

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ABSTRACT

Purpose of the study. The purpose of the study was to analyze parameters of molecular markers of structural and cellular renal damage in localized renal cell carcinoma (RCC) with determining the nature of the initial abnormalities in the kidney functional state before the treatment.

Patients and methods. The study included 46 patients receiving elective surgical treatment for localized renal cancer in the Department of Oncourology, National Medical Research Centre for Oncology. The comparison group included the clinical and laboratory data of 13 healthy people comparable with the RCC patients in terms of age and gender. Cystatin C, IL-18, KIM-1, L-FABP, NGAL were determined in blood and urine in all patients.

Results. Evaluation of the kidney functional state of RCC patients showed that the initial values of serum creatinine and the glomerular filtration rate were similar to the reference levels in healthy people, but statistically significant differences were found in the ratios of cystatin C concentrations in the blood and urine in all patients, compared with normal values. Determination of L-FABP indices in RCC patients showed that their levels were 2.5 times higher than normal values, and the urine concentration of IL-18 was 1.7 times higher than normal values ($p < 0.05$). Blood and urine levels of NGAL and KIM-1 did not differ significantly from the comparison group.

Conclusions. The development of localized RCC is accompanied by the formation of tubulointerstitial dysfunction with impaired renal filtration capacity. All RCC patients showed elevated endogenous markers of structural and cellular renal damage – cystatin C, L-FABP, and IL-18.

Keywords:
localized renal cell carcinoma, acute renal injury, cystatin C, interleukin-18, NGAL, L-FABP

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ОРИГИНАЛЬНАЯ СТАТЬЯ

МАРКЕРЫ СТРУКТУРНОГО И КЛЕТОЧНОГО ПОЧЕЧНОГО ПОВРЕЖДЕНИЯ ПРИ ЛОКАЛИЗОВАННОМ ПОЧЕЧНО-КЛЕТОЧНОМ РАКЕ ДО НАЧАЛА ЛЕЧЕНИЯ

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РЕЗЮМЕ

Цель исследования. Провести анализ показателей молекулярных маркеров структурного и клеточного почечного повреждения при локализованном почечно-клеточном раке (ПКР) с определением характера исходного уровня нарушений функционального состояния почек до начала лечения.

Пациенты и методы. В исследование включено 46 больных, находившихся на плановом хирургическом лечение по поводу локализованного рака почки в онкоурологическом отделении ФГБУ «НМИЦ онкологии» Минздрава России. В качестве группы сравнения использовали клинико-лабораторные данные 13 относительно здоровых людей, сопоставимых с группой больных ПКР по возрасту и полу. Изучали: цистатин С, ИЛ-18 (интерлейкин-18), КИМ-1 (молекула-1 повреждения почек (Kidney Injury Molecule-1)), L-FABP (жировой кислотный связывающий белок печени (Fatty Acid Binding Protein)), NGAL (нейтрофильный желатиназо-ассоциированный липокалин-2 (Neutrophil Gelatinase Associated Lipocalin)) в крови и моче.

Результаты. Оценка функционального состояния почек больных ПКР показала, что при исходных значениях креатинина сыворотки крови и скорости клубочковой фильтрации соответствующих референтным показателям здоровых людей имели место статистически значимые отличия в соотношении концентрации цистатина С в крови и моче у всех больных по сравнению с нормальными показателями. Исследование показателей L-FABP у больных ПКР в сравнении с группой здоровых людей показало, что концентрация данного показателя плазмы крови была в 2,5 раза выше нормальных значений, а концентрация IL-18 в моче превышала нормальные значения в 1,7 раза ($p < 0,05$). Показатели концентрации NGAL и KIM-1 в крови и моче не имели значимых различий с группой сравнения.

Заключение. Развитие локализованного ПКР сопровождается формированием тубулоинтерстициальной дисфункции с нарушением фильтрационной способности почек. У всех больных ПКР были выявлены повышенные показатели эндогенных маркеров структурного и клеточного почечного повреждения – цистатина С, L-FABP и ИЛ-18.

Ключевые слова:
локализованный рак почки, острое почечное повреждение, цистатин С, интерлейкин 18, NGAL, L-FABP

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RELEVANCE

According to world statistics, kidney cancer (RP) is registered annually in 403.3 thousand people, which corresponds to the 15th place among the standardized indicators of the incidence rate. In the Russian Federation, a similar trend is observed, renal cell carcinoma (RCC) is diagnosed in 4 % of patients of both sexes, and among men it is detected in 4.7 %, ranking 3rd among tumors of the genitourinary system with an increase in incidence to 6.9 % among men of socially active age 30–59 years [1; 2]. The growth of malignant kidney diseases dictates the need for a more detailed approach to the study of the pathogenesis of the disease with the possibility of early diagnosis and the necessary correction of the resulting disorders.

Modern targeted drugs and current immunotherapy regimens, as well as new oncosurgery technologies, serve as a guarantee of successful treatment of RCC patients. The standard of surgical treatment of this category of patients is the performance of organ-preserving operations with radical removal of the tumor, which definitely helps to reduce the risk of cardiovascular complications and chronic kidney disease. According to a number of clinical studies, overall survival is comparable in patients after radical nephrectomy and kidney resection. At the same time, it should be noted that the frequency of acute renal injury (AKI) in the postoperative period is 30 % [3; 4]. This is due to factors related to changes in the patient population, the widespread use of potentially nephrotoxic drugs, contrast research methods and an increase in combined surgical interventions. Acute renal dysfunction leads to the formation of nephrosclerosis with the subsequent development and progression of chronic kidney disease (CKD), which has a clear tendency to increase morbidity rates [5]. As is known, AKI is characterized by a complex, morphofunctional state, which is formed both as a result of external factors and due to a number of reasons that cause primary organ damage. In case of a tumor lesion, the formation of renal dysfunction is due to a combination of several pathological processes: firstly, mechanical invasion of the tumor with an anatomical defect in the structure of the renal tissue and destruction of nephrons; secondly, a change in the functional state of the organ due to the influence of biologically active components secreted by the tumor [6; 7]. In other words, the manifestation of AKI in RCC patients may be due not only to a decrease in the number of normally functioning nephrons after organ-preserving operations and surgical trauma, but also be directly related to concomitant somatic diseases and the presence of initial kidney dysfunctions due to the development of a tumor process in the organ [8].

Of course, the detection of AKI triggers in the perioperative period in patients with localized RP during organ-preserving surgical interventions dictates the need for a more detailed approach to the study of the pathogenesis of the disease with the possibility of timely correction of functional disorders [9].

It would seem that the modern capabilities of computed tomography, renoscintigraphy and excretory urography make it possible to register violations of the structural and functional state of the kidney as much as possible, however, the standard approach in diagnosis does not always form a complete picture of the nature of the disease and the reserve capabilities of the body in the conditions of the development of the tumor process. In order to determine the choice of the optimal volume of surgical intervention, the criteria of the nephrometric diagnostic system R.E.N.A.L. are used. (Radius, Exophytic/endophytic, Proximity, Anterior/posterior, Location), which is based on the analysis of the complex morphometric characteristics of the tumor process with the determination of the level of complexity of the planned operation. The evaluation of the parameters takes into account the endophytic or exophytic growth of the tumor, the diameter of the tumor node with the determination of the anatomical features of the tumor and its location relative to the collecting system of the kidney [10].

The generally recognized use of this scale orients the surgeon in choosing the volume of the planned operation, but does not allow to fully assess the functional state of the renal parenchyma with the determination of the prognosis of renal failure in the postoperative period. According to Kidney Disease Improving Global Outcomes – "Initiative to Improve Global Outcomes of Kidney Diseases" (KDIGO) [11], AKI is diagnosed with a persistent, for 48 hours or more, maximum change in serum creatinine level and/or its increase by 1.5 times within 7 days compared to the baseline level. In this regard, it should be noted that at the present stage of RCC therapy, the assessment of the dynamics of indicators of

markers of functional-structural and cellular renal damage in the process of antitumor treatment is of particular relevance. Thus, the identification of preclinical signs of metabolic dysfunction of the kidney, as a result, may be an important predictor in the development of acute renal failure during radical surgical treatment [5; 12]. Early diagnosis of the imbalance of molecular markers determines the final effect of therapy and the course of the disease in patients with RCC.

In this regard, in order to predict the development and early diagnosis of AKI, our attention was drawn to the use of markers of damage to the structure of the kidneys. Specific markers cystatin C, interleukin-18 (IL-18), fatty Acid Binding protein of the liver/Fatty Acid Binding Protein (L-FABP), neutrophil gelatinase-associated lipocalin-2/Neutrophil Gelatinase Associated Lipocalin (NGAL), Kidney Injury Molecule-1/Kidney Injury Molecule-1 (KIM-1) are of great practical importance, determining the tactics of treatment of patients with impaired function kidneys. It should be noted that cystatin C is the main and most accurate marker in the diagnosis of renal damage and assessment of glomerular filtration rate (GFR) [9]. Interleukin-18 refers to proinflammatory cytokines. This marker is secreted in the distal tubules of the kidneys when exposed to various nephrotoxic factors on the human body, as well as after an episode of ischemia. The active form of IL-18 enters the urine during the development of AKI. However, it should be borne in mind that an increased level of plasma IL-18 is characteristic not only for AKI, but also for autoimmune and inflammatory diseases, including sepsis [5]. Neutrophilic lipocalin-2 (NGAL) is one of the most studied markers of structural kidney damage. This protein is secreted by various tissues of the body, including epithelial cells of the proximal tubules of the kidneys as a result of organ damage. It is a proven fact that an increase in the concentration of NGAL in urine and blood is recorded in cases of renal dysfunction and the development of CKD [13; 14]. Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein with a molecular weight of 90 kDa. Normally, with unchanged kidney tissues, KIM-1 molecules are not detected in blood and urine. High protein expression is detected in cells of regenerating proximal renal tubules after toxic or ischemic damage and is not specific to other damaging agents [14–16]. Detection of L-FABP in the patient's blood and urine is recorded in response to damage to renal structures. An increase in the excretion of L-FABP in the urine indicates the progression of kidney damage [14]. Taking into account the problem of AKI formation in the early postoperative period in patients with RCC, the study of markers of structural and cellular renal damage before treatment will optimize early diagnosis, determine the timing and tactics of nephroprotective therapy.

The purpose of the study: to analyze the indicators of molecular markers of structural and cellular renal damage in localized renal cell carcinoma with determination of the nature of the initial level of violations of the functional state of the kidneys before the start of treatment.

MATERIALS AND METHODS

This study was conducted at the National Medical Research Centre for Oncology with the approval of the Ethical Committee of the institution and voluntary consent to the participation and processing of personal data in accordance with the standards of the Helsinki Declaration (1964) as amended in 2013. 59 patients were examined. Inclusion criteria: age over 18 years, documented consent of the patient to conduct the study, normal blood creatinine levels. Exclusion criteria: age less than 18 years, refusal of the patient to participate in the study, elevated blood creatinine levels. In all patients, the following parameters were studied in this study: cystatin C, interleukin-18 (IL-18), Kidney Injury Molecule-1 (KIM-1), fatty Acid binding protein of the liver/Fatty Acid Binding Protein (L-FABP), neutrophil gelatinase-associated lipocalin-2/Neutrophil Gelatinase Associated Lipocalin (NGAL) in blood plasma and urine.

The main group included 46 patients with RCC who were treated in the oncourological department. The age criteria of patients with RP at the time of the study were presented: men 30–44 years – 2 patients (6.6 %), 45–59 years – 6 patients (20.3 %), 60–74 years – 15 patients (49.7 %), 75 years and older – 7 patients (23.4 %); women 30–44 years – 1 patient (6.2 %), 45–59 years – 5 patients (31.3 %), 60–74 years – 9 patients (55.8 %), 75 years and older – 1 patient (6.2 %). The median age was 58 (29–76) years. It should be noted that males prevailed in the cohort of patients – 30 out of 46 people (65.3 %). Our data

are consistent with literature data indicating that the incidence of RCC among men is 1.5–2 times higher than in women [17]. According to the preoperative examination, the distribution by stages of the oncological process is represented by T1aN0M0 in 25 patients (54.3 %), T1bN0M0 in 21 patients (45.7 %). Morphological characteristics of the tumor are presented: RCC light-cell variant of the structure in 19 of 46 (41.3 %), papillary in 16 (34.8 %) chromophobic in 11 (23.9 %) patients, with the prevalence of highly differentiated processes in 23 patients (50.0 %). Concomitant diseases in patients with RCC are presented in the Table 1.

It should be noted that according to general clinical and anamnestic examinations, the vast majority of patients – 91.3 % had concomitant diseases, which are classified as modifiable risk factors for the development and progression of chronic kidney disease [11].

As a comparison group, clinical and laboratory data of 13 relatively healthy people, comparable to the group of patients with RCC by age and gender, were used.

Indicators of markers of renal damage were carried out before treatment and determined by enzyme immunoassay using standard test kits: cystatin C (BioVendor, Czech Republic), IL-18 (Bender Medsystems, USA), NGAL (BCM Diagnostics, USA), KIM-1 (BCM Diagnostics, USA), L-FABP (Hycultbiotech, Netherlands).

Statistical support was carried out using a package of certified application programs Statistica 6.0. (StatSoft, USA). The significance of the differences in the average values of the indicator was carried out according to the Student-Fisher t-criterion for independent samples with reliable indicators at a significance level of $p < 0.05$.

RESEARCH RESULTS AND DISCUSSION

A comprehensive assessment of the functional state of the kidneys of patients with RCC showed that the initial values of serum creatinine corresponded to the reference values of healthy people – from 50 to 110 mmol/l and amounted to 63.9 ± 26.8 mmol/l (41.1–101.8) ($p < 0.05$). The calculation of the initial GFR was performed according to the formula Modification of Diet in Renal Disease study with classification according to the National Kidney Foundation/ Kidney Disease Outcomes Quality Initiative classification National Kidney Foundation [18]. The median GFR was 73 (55–103) ml/min/1.73 m^2. These indicators, at first

Table 1. Concomitant diseases in the group of patients with RCC

Concomitant disease	RCC patients (n = 46)	
	Abs. n.	%
Not detected	4	5.3
Diseases, that don't impact the RCC flow		
COPD	3	3.9
Bronchial Asthma	1	1.3
Hepatobiliary system chronic diseases	7	9.2
Lower limb veins varices	14	19.4
Peptic ulcer of the stomach and duodenum 12	2	2.6
Diseases, that impact the RCC flow		
Diabetes mellitus	7	9.2
Arterial hypertension	13	17.6
Cardiovascular diseases	9	11.8
Kidney stones	3	3.9
Chronic urinary tract infections	2	2.6
Obesity/metabolic syndrome	5	6.6

glance, create an idea of the normal functioning of the organ during the development of a malignant tumor in a patient. However, according to the modern concept of AKI development, the concentration of creatinine and GFR in blood plasma during the development of renal dysfunction are not sufficiently informative criteria. Thus, the variability of creatinine concentration depends on many factors such as gender, weight, age, composition of the diet, body mass index, etc. [19–21].

The most accurate and promising endogenous marker in the assessment of renal damage is cystatin C, which is produced by the body's nuclear cells and enters the bloodstream evenly, maintaining a constant level of concentration in blood plasma. Cystatin C is an inhibitor of lysosomal proteinases, the main function of which is aimed at protecting the body from uncontrolled activation of proteolysis of its own proteins. Low affinity to other serum proteins and small molecular weight allows cystatin C to be freely excreted in the renal glomeruli. Due to megalin-kubulin-mediated endocytosis, cystatin C is able to be maximally metabolized in the epithelial cells of the proximal tubules of the kidneys [22]. An increase in the excretion of cystatin C and an increase in its concentration in urine indicates a violation of reabsorption in the proximal tubules and the formation of tubular dysfunction [23].

In our study, the determination of the concentration of cystatin C before the start of treatment showed that in 21 patients (45.7 %) in blood plasma, this indicator varied within normal values, in 25 patients (54.3 %) the content of cystatin C exceeded 1000 ng/ml. Subsequently, all patients of the main group were divided into 2 subgroups: 1st – cystatin with 1000 ng/ml and below, 2nd – cystatin With above 1000 ng/ml. The results of the study of cystatin C in the blood showed that in all patients with normal values of cystatin C, the glomerular filtration rate corresponded to physiological values, with an increased concentration of cystatin C, GFR was almost 1.5 times lower compared to healthy people ($p < 0.05$) (Table 2).

When evaluating the data, it was determined that statistically significant differences occurred in the ratio of the concentration of cystatin C in the blood and urine of all patients compared with normal indicators. So, in subgroup 1, the concentration of cystatin C in the blood was 1.8 times lower, and in subgroup 2–1.4 times higher ($p < 0.05$) compared to healthy. The content of cystatin C in urine in subgroup 1, with normal GFR and serum creatinine values was increased almost 2 times ($p < 0.05$) In subgroup 2, with elevated plasma cystatin C with reduced GFR, indicators within normal values were recorded. The

Таблица 2. Показатели маркеров почечного повреждения в плазме крови у больных ПКР до начала лечения и здоровых пациентов (M ± m)

Indicator	Study group		
	Healthy people (n = 13)	RCC patients	
		1st subgroup (n = 21)	2nd subgroup (n = 25)
Cystatin C in blood (ng/mg)	877.1 ± 81.9	787.4 ± 110.3 (638.9–919.3)	1284.0 ± 113.7[1] (1196.8–1335.7)
Cystatin C in urine (ng/mg)	1068.7 ± 83.4	2154.1 ± 223.6[1] (194.8–4086.4)	1088.2 ± 86.4 (510.5–2035)
Blood L-FABP (ng/ml)	0.42 ± 0.03	0.37 ± 0.07 (0.21–0.6)	0.92 ± 0.09[1] (0.7–0.33)
Urine L-FABP (ng/ml)	0.34 ± 0.21	0.28 ± 0.03 (0.15–0.49)	0.69 ± 0.05[1] (2.04–0.018)
Blood IL-18 (pg/ml)	33.7 ± 2.7	20.0 ± 1.8 (8.7–44.4)	90.7 ± 8.6[1] (18.7–259)
Urine IL-18 (pg/ml)	19.8 ± 2.2	18.0 ± 2.4 (6.3–32.2)	28.6 ± 2.4[1] (3.4–56.3)
Blood NGAL (ng/ml)	3.06 ± 0.30	2.65 ± 1.00 (1.7–4.1)	3.57 ± 0.80 (2.2–6.3)
Urine NGAL (ng/ml)	1.11 ± 0.21	0.23 ± 0.05 (0.06–0.17)	0.31 ± 0.05 (0.02–0.46)
Blood KIM-1 (ng/ml)	0.21 ± 0.01	0.18 ± 0.02 (0.07–0.36)	0.14 ± 0.01 (0.06–0.27)
Urine KIM-1 (ng/ml)	0.55 ± 0.21	1.30 ± 0.10 (0.09–2.6)	1.50 ± 0.20 (0.4–2.8)

Note: [1] – the significance of differences in comparison with healthy ($p < 0.05$). IL-18 – interleukin-18; L-FABP – fatty acid binding protein of the liver; KIM-1 – kidney damage molecule-1; NGAL – neutrophil lipocalin-2.

results obtained indicate the diagnostic value of determining the concentration of cystatin C as the most accurate and early indicator of the development of renal damage at the preclinical stage. The nature of these changes in the concentration of cystatin C can be associated with the presence of renal dysfunction caused by a tumor lesion of the kidney [23].

In order to predict the development of AKI in patients who were scheduled for surgical treatment in the volume of kidney resection, a more detailed study of the levels of markers was conducted: L-FABP, IL-18. The data is given in Table 2.

When studying the concentrations of L-FABP and proinflammatory cytokine IL-18 in blood plasma and urine in patients with RCC before the start of surgical treatment, significant differences were revealed compared with healthy people (Table 2). L-FABP is a fatty acid binding protein of the liver, which belongs to the markers of the cytoplasmic protein family with a molecular weight of 15 kDa and participates in intracellular transport of long-chain fatty acid with expression by liver cells in response to the damaging factor. It is known that L-FABP is also expressed in the straight and convoluted parts of the renal tubules in acute interstitial tissue damage and is not detected in urine in healthy people. A number of researchers have noted the important role of L-FABP in the development of oxidative stress as an effective cytoprotector [24]. Analysis of clinical data showed that in the preoperative period, L-FABP plasma values were 1.9 times higher than those in the comparison group ($p < 0.05$). The concentration of L-FABP in urine was increased 2.3-fold ($p < 0.05$) only in patients of subgroup 2, who previously had an increased concentration of cystatin C and a decrease in GFR with a diagnosed preclinical stage of CKD. Probably, this increase in the level of L-FABP in patients with RCC compared to a group of healthy individuals indicates functional disorders with damage to the epithelium of the proximal tubules of the kidneys, which can be regarded as a preclinical change in the functional and structural components of the kidneys. The results obtained can be compared with the studies conducted by Kamijo-Ikemori A. in patients at an early stage of nondiabetic CKD, in which the level of L-FABP concentration in urine was significantly higher than the reference values [18; 21]. When assessing the IL-18 indicators, it was revealed that in comparison with the group of healthy patients in patients with RCC, the concentration of this indicator of blood plasma was 2.5 times higher than normal values, and the concentration of IL-18 in urine exceeded normal values by 1.7 times ($p < 0.05$). According to the literature, an increase in the concentration of IL-18 and L-FABP in urine is observed with the development of renal insufficiency [24–26]. The simultaneous increase of IL-18 and L-FABP markers in the blood of patients with RCC before treatment was regarded by us as a sign associated with the development of a malignant process in the kidney. Additionally, in order to assess the full picture of changes in the structural and functional state of the kidneys during the malignant process, we studied and analyzed NGAL and KIM-1 markers. As can be seen from Table 2, the concentration of NGAL and KIM-1 in blood and urine had no significant differences with the comparison group. Accordingly, these markers are not advisable to use in order to determine renal dysfunction in the early stages of the disease. However, at the present stage of development of oncology, the dynamics of indicators of molecular markers of renal damage KIM-1 and NGAL should be considered as a predictor of effective antitumor treatment of patients with RCC.

CONCLUSION

As a result of this study, it was found that the development of localized kidney cancer is accompanied by the formation of tubulointerstitial dysfunction with impaired filtration capacity of the kidneys. Thus, elevated indicators of endogenous markers of structural and cellular renal damage – cystatin C, L-FABP and IL-18 were detected in all patients with RCC. At the same time, there were no clinical manifestations of renal dysfunction in these patients, and the initial values of GFR and creatinine were within the reference values. Thus, routine determination of creatinine and glomerular filtration rate cannot guarantee the normal functioning of the kidneys. Probably, the severity of changes in the markers of cellular renal damage of cystatin C, L-FABP and IL-18 is the most prognostically significant in determining the degree of damage to the renal tubules and the risk of acute renal damage before surgical treatment. It should be borne in mind that early diagnosis of initial functional disorders is a necessary condition in choosing a rational tactics of nephroprotective therapy with the predestination of the development of undesirable complications, including acute renal injury at the stage of surgical treatment.

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ORIGINAL ARTICLE

POTENTIAL OF SONOGRAPHY IN DIAGNOSIS OF TONGUE TUMORS

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ABSTRACT

Purpose of the study. An analysis of sonography potential in the primary diagnosis and clinical staging of tongue cancer.
Patients and methods. The study included 18 patients aged 40–70 years with tongue tumors. The majority accounted males – 14 (77.7 %). Women were represented by 4 (22.2 %) examinees. Ultrasound examinations were performed using expert-class ultrasound systems with broadband linear multifrequency transducers.
Transoral examination with linear transducers required tumor location in the anterior and lateral parts of the oral tongue. During ultrasound examinations we evaluated: tumor shape, tumor invasion depth; tumor sizes – width and thickness; tumor echogenicity and structure; tumor vascularization in Doppler modes.
The results were compared with the data of histological examination.
Results. Transoral ultrasound examination of patients with tongue cancer allows clear visualization of the tumor and assessment of it's spread.
The study showed that the round shape of tongue tumors prevailed in 13 (72.2 %) patients, the tumor echo structure in 10 (55.5 %) was heterogeneous, the contours were even and clear in the majority of patients – 13 (72.2 %), all tumors showed a reduced acoustic density, the depth of invasion ranged from 2 to 6 mm in 8 (44.4 %) patients and exceeded 6 mm in 6 (33.3 %) patients, which corresponded to stages III and IV of the diseas. Doppler ultrasonography recorded intense intratumoral blood flow in 100 % of cases. In 8 (44.4 %) cases, metastatic lesions of the cervical lymph nodes were observed.
Conclusion. Transoral ultrasound diagnosis of tongue cancer is a highly informative, safe and modern method providing surgeons with information that helps in choosing the scope of surgical treatment and in determining the disease prognosis at the preoperative stage. The accuracy of the method was 87 %, the sensitivity was 85 %, and the specificity was 86.2 %.

Keywords:
tongue cancer, ultrasound examination, transoral access

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ВОЗМОЖНОСТИ СОНОГРАФИИ В ДИАГНОСТИКЕ ОПУХОЛЕЙ ЯЗЫКА

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РЕЗЮМЕ

Цель исследования. Изучить возможности ультразвукового исследования в первичной диагностике и клиническом стадировании рака языка.
Пациенты и методы. В исследование вошло 18 больных с опухолью языка в возрасте от 40 до 70 лет. Большинство пациентов – мужчины – 14 (77,7 %). Женщины были представлены 4 (22,2 %) наблюдениями. Ультразвуковые исследования выполнялись на аппаратах экспертного класса, широкополосными линейными мультичастотными датчиками. Необходимым условием для трансорального исследования являлось расположение опухоли в передних и боковых отделах подвижной части языка.
При УЗИ первичного очага мы оценивали: форму, размеры, глубину инвазии опухоли; эхогенность и структуру образования, васкуляризацию в режимах допплерографии.
Полученные результаты сравнивались с данными гистологического исследования.
Результаты. При обследовании больных раком языка с применением трансоральной методики ультразвукового исследования удается четко визуализировать опухоль, определить распространенность процесса.
В результате исследования превалировала округлая форма опухолей языка у 13 (72,2 %), пациентов, эхо-структура новообразования у 10 (55,5 %) была неоднородная, контуры у большинства ровные, четкие – 13 (72,2 %), все новообразования имели пониженную акустическую плотность, глубина инвазии у 8 (44,4 %) пациентов составляла от 2 до 6 мм и у 6 (33,3 %) больше 6 мм, что соответствует III, IVстадиям заболевания. В 100 % наблюдений при допплерографии регистрировался интенсивный внутриопухолевый кровоток. В 8 (44,4 %) случаях наблюдалось метастатическое поражение шейных лимфоузлов.
Заключение. УЗ-диагностика трансоральным доступом рака языка – высокоинформативный, безопасный, современный метод, дающий информацию врачам-хирургам, помогающую в выборе объема хирургического лечения и в определении на дооперационном этапе прогноза заболевания. Точность метода составила 87 %, чувствительность – 85 %, специфичность – 86,2 %.

Ключевые слова:
рак языка, ультразвуковое исследование, трансоральный доступ

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INTRODUCTION

Tongue cancer accounts for 65 % of the incidence of malignant neoplasms of the oral cavity and develops from elements of the squamous epithelium. Men get sick 5–7 times more often than women, as a rule, in adulthood, after 50 years [1; 2]. The incidence of malignant neoplasms of the tongue is steadily increasing [3]. Despite the fact that tongue cancer is a localization available for examination, up to 80 % of patients do not consult a doctor for a long time and at the time of initial treatment, the stage of the disease is III–IV. All this confirms the relevance of the topic of diagnosis and treatment of tongue cancer.

Systematic interaction of the tongue mucosa with various chewing mixtures, cigarette smoke, strong alcohol, as well as chronic diseases of the tongue, such as ulcers, infection in the oral cavity, traumatization, erythroplakia, leukoplakia, are etiological factors of the development of tongue cancer [1–5].

In 65 % of cases, the tumor is located on the lateral surfaces of the tongue and in 90–95 % of cases it is squamous cell carcinoma. According to the form, there are: papillary, ulcerative, infiltrative and infiltrative- ulcerative forms of tongue cancer.

By development and growth: exophytic tumor protruding into the oral cavity and endophytic, diffuse tumor that grows into the deep layers of the tongue, oral cavity.

Metastatic lesion of the cervical lymph nodes in cancer of the tongue occurs in 40–80 %. Hematogenous metastases are rare, they can affect the liver, lungs, skeletal bones, and brain [6].

Accurate information about the extent of the tumor process at the preoperative stage allows you to choose the necessary treatment strategy [7–8].

Ultrasound examination (ultrasound) is a non-invasive, easy-to-use method for detecting changes in the free part of the tongue and lymph nodes of the neck [9; 10]. However, the use of ultrasound in the primary diagnosis of tongue cancer has not been sufficiently studied and requires special consideration of all possible aspects.

The purpose of the study: to study the possibilities of ultrasound examination in the primary diagnosis and clinical staging of tongue cancer.

PATIENTS AND METHODS

The study included ultrasound data of 18 patients, aged 40 to 70 years, with malignant tumor processes of the tongue. By gender, the patients were distributed as follows: men – 14 (77.7 %), women – 4 (22.2 %).

Ultrasound was performed on the devices "IU 22 PHILIPS", broadband multi-frequency linear sensors, 5–17 MHz.

To assess the shape, size, echogenicity, echo structure, depth of invasion this is the distance from the surface of the neoplasm to the lower border of the tumor, deep into the muscles of the tongue, vascularization in the modes of DH, EDC of the primary tumor located in the lateral and anterior sections of the movable part of the tongue, we performed ultrasound with transoral access.

The obtained results of the depth of invasion of the neoplasm were compared with the data of histological examination.

RESEARCH RESULTS AND DISCUSSION

In the study of patients with tongue cancer using ultrasound transoral access, it is possible to visualize the tumor and determine the prevalence of the process. Table 1 presents the main sonographic criteria for tumors of the tongue of patients included in our study.

As a result of the study, the shape of the tumors of the tongue prevailed rounded in 13 (72.2 %), the oblong form was registered in 5 (27.7 %) patients, the echo structure in 10 (55.5 %) was heterogeneous, the contours of the majority were smooth, clear – 13 (72.2 %), all neoplasms had a reduced acoustic density, the depth of invasion was in 8 (44.4 %) from 2 to 6 mm and in 6 (33.3 %) more than 6 mm, which corresponds to the III, IV stages of the disease and confirms the literature data on late the appeal of patients. Intense intra-tumor blood flow was recorded in DH. Metastatic lesion of cervical lymph nodes was observed in 8 (44.4 %) cases.

The accuracy of the method was 87 %, sensitivity 85 %, specificity 86.2 %.

A clinical case.

Patient M., born in 1960, applied for an appointment with complaints about the presence of a tumor on the tongue, considers herself ill for three months when she discovered a nodular formation on the left side of her neck. Not treated.

When examined, a dense, limited movable node up to 25 mm is determined in the carotid triangle of the neck on the left. On the lateral surface of the

free part of the tongue on the left, a tumor infiltrate measuring 45 × 25 mm is determined.

A CT scan of the brain and soft tissues of the neck was performed on the patient – no pathological changes in the brain substance were detected. Infiltrative lesion of the tongue, mts in the left side of the neck.

In the projection of the lateral surface of the free part of the tongue on the left, a hypoechoic formation, irregular shape, uneven contours, fuzzy, 1.3 × 3.0 cm in size, the depth of invasion is 13 mm (Fig. 1), with DH – hyperintensive intranodular blood flow (Fig. 2).

The cervical lymph nodes on the right are not enlarged, on the left in the upper third 1.3–2.3 cm (Fig. 3).

A biopsy of the tongue tumor was performed – layers of squamous cell carcinoma with a tendency to keratinization. Minor leukocyte infiltration. A puncture biopsy of the specified lymph node was performed. The cytogram is characteristic of metastasis of squamous cell carcinoma with keratinization.

Based on the clinical diagnostic study, the diagnosis was made: tongue cancer with metastases to the lymph nodes of the neck on the left St III (T3N1M0), cl. gr. 2.

The patient underwent surgical treatment in the volume of combined resection of the floor of the oral cavity with microsurgical plastic surgery, cervical lymphadenectomy on the left. G.A: Metastasis of

Table 1. Sonographic criteria for tumors of the tongue

Diagnostic criteria		Abs. numb.	%
Shape	Rounded	10	55.5
	Oblong	4	22.2
	Irregular	4	22.2
Size	Up to 20 cm	7	38.9
	20–40 cm	8	44.4
	Above 40 cm	3	16.7
Contours	Smooth/distinct	13	72.2
	Smooth/not distinct	-	-
	Rough/distinct	3	16.7
	Rough/not distinct	2	11.1
Echogenisity	Homogenous	6	33.3
	Non homogenous	12	66.7
Acoustic density	Isoechgenic	-	-
	Hypoechogenic	18	100
	Anechogenic	-	-
Invasion depth	Up to 5 mm	4	22.2
	4–10 mm	8	44.4
	Above 10 mm	6	33.3
L.n. lesion	Present	8	44.4
L.n. lesion	Absent	10	55.5
Vascularization	Central	5	27.8
	Peripheral	0	0
	Mixed	13	72.2
Blood flow intensity	Isointensive	5	27.8
	Hypeintensive	10	55.5
	Hypointensive	3	16.7

squamous cell carcinoma with keratinization; squamous cell carcinoma with keratinization, infiltrative growth. Invasion of the deep muscle layer. Invasion – 10 mm. The next stage, after topometric preparation on a Simens Somatom computed tomograph (Effective dose per study 4.5 mSv) using radiopaque labels and dosimetric planning, a course of remote gamma therapy was conducted on the bed of the removed tumor and a lymphocollector, irradiation was carried out on a TERATRON device, 2.4 G, 5 fractions per week, 17 fractions, SOD 40.8 G (42izoGr). Final diagnosis. Cancer of the tongue with metastases in the l/nodes of the neck on the left, stIII, pT3N1M0, condition after surgical treatment, radiation treatment SOD 42 Gr, cl. gr. 2

CONCLUSION

Based on the conducted studies, it is safe to say that determining the depth of tumor invasion with transoral ultrasound of the tongue, as well as examining the soft tissues of the neck to identify metastatic regional lymph nodes helps to establish the stage of the disease. Thus, ultrasound diagnosis of tongue cancer is a highly informative, safe, modern method that provides information to surgeons, helps in choosing the scope of surgical treatment and at the preoperative stage to determine the prognosis of the disease. The accuracy of the method was 87 %, sensitivity 85 %, specificity 86.2 %.

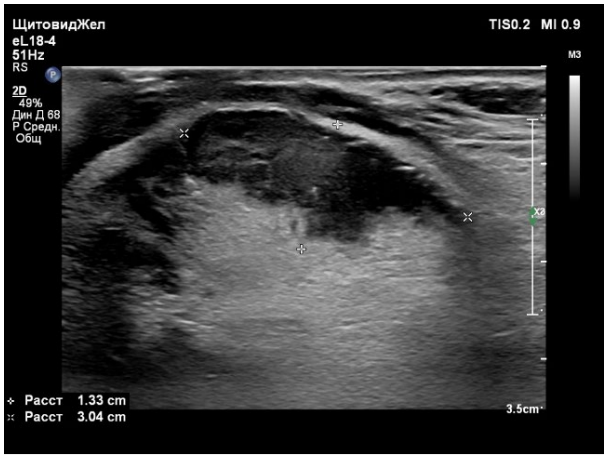


Fig. 1. B-mode ultrasound image of a tongue tumor: hypoechoic neoplasm, irregular shape, uneven, indistinct contours, heterogeneous echostructure, 1.3 × 3.0 cm in size.

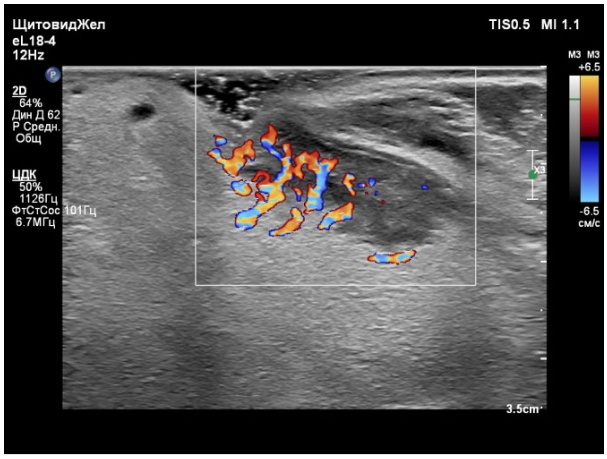
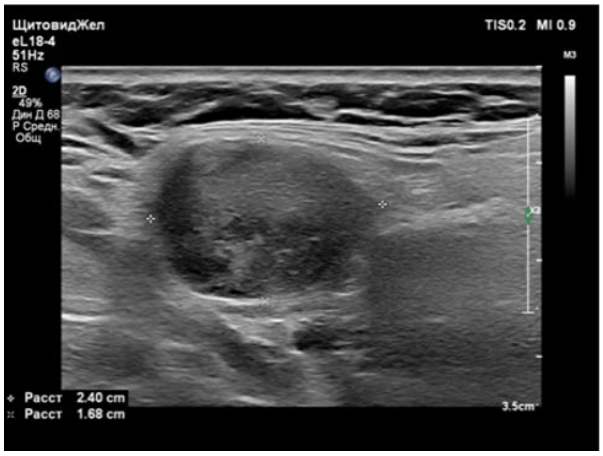


Fig. 2. Color Doppler ultrasound image of a tongue tumor: hyperintense intra- and perinodular blood flow.



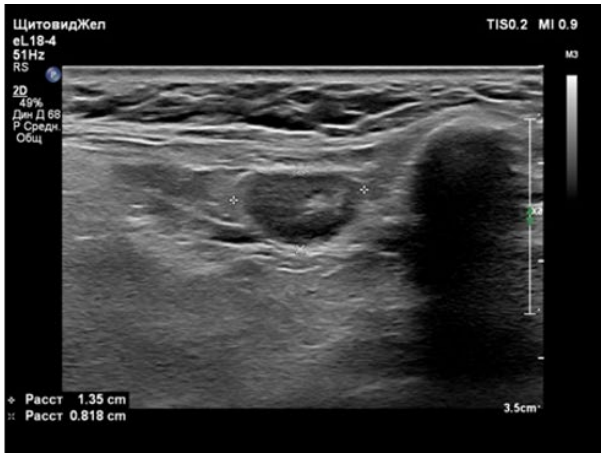


Fig. 3. B-mode ultrasound image of lateral surfaces of the neck – hypoechoic lymph nodes, heterogeneous echostructure, 1.3–2.4 cm in size.

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REVIEW

LEIOMYOSARCOMA OF THE SCALP AND LOWER LEG SKIN. CLINICAL CASES AND LITERATURE REVIEW

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ABSTRACT

Malignant soft tissue tumors localized in the skin, particularly leiomyosarcoma, are rare. Cutaneous leiomyosarcomas could have superficial and deep forms, while subcutaneous leiomyosarcomas are usually nodular. The tumor can spread to the underlying muscle fascia. The immunophenotype of leiomyosarcoma is determined by the following antibodies: ASMA, desmin, and N-caldeston; expression of PanCK is also possible. Researchers do not have any common opinion on the clinical course and biological behavior of cutaneous leiomyosarcomas. This is probably due to the tumor heterogeneity and the carcinogenesis specificity associated with molecular genetic changes. We detected these tumors at the histological examination which resulted in an analysis of the literature and our own material. We analyzed cutaneous tumors diagnosed in 2522 patients during 5 years (2016–2020). Squamous cell and basal cell histotypes were the most common ones. We did not diagnosed cutaneous leiomyosarcoma in our material during this period. This article presents two cases of cutaneous leiomyosarcoma localized in the scalp and calf skin. Morphological and immunohistochemical profiles of the tumors are described. The immunohistochemical analysis confirmed the morphological diagnosis and established the tumor immunophenotypes. The morphological diagnosis in one case was complicated due to the rarity of this pathology and the ambiguity of the interpretation of histological changes. Analysis of histological preparations and immunohistochemical study allowed verification of the tumor as leiomyosarcoma with its characteristic immunophenotype. All of the above demonstrate the need to perform morphological and immunohistochemical tests in specialized research cancer centers.

Keywords:
sarcoma, scalp skin, soft tissues, immunohistochemical study, clinical data, literature review

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ОБЗОР

ЛЕЙОМИОСАРКОМА КОЖИ ВОЛОСИСТОЙ ЧАСТИ КОЖИ ГОЛОВЫ И КОЖИ ГОЛЕНИ. ОПИСАНИЕ НАБЛЮДЕНИЙ И ОБЗОР ЛИТЕРАТУРЫ

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РЕЗЮМЕ

Мягкотканые злокачественные опухоли и, в частности, лейомиосаркомы, локализующиеся в коже, встречаются редко. В кожных лейомиосаркомах выделяют поверхностные и глубокие формы. Для первичных подкожных лейомиосарком характерна узловая форма. Опухоль может распространяться на подлежащую мышечную фасцию. Иммунофенотип лейомиосарком определяется следующими антителами: ASMA, desmin, N-caldeston. Возможна экспрессия PanCK. В литературе существуют противоречивые суждения о клиническом течении и биологическом поведении кожных лейомиосарком. Вероятно, это обусловлено гетерогенностью опухоли и особенностями канцерогенеза, связанного с молекулярно-генетическими изменениями. Обнаружение этих опухолей при гистологическом исследовании операционного материала побудило к анализу литературы и собственного материала. Проведен анализ опухолей кожи за 5 лет (2016–2020 гг.). За этот период опухоли были диагностированы у 2522 пациентов. Основным гистотипом были плоскоклеточные и базальноклеточные раки. Лейомиосарком кожи за этот период на нашем материале диагностировано не было. Приведены два наблюдения лейомиосаркомы кожи: волосистой части кожи головы и кожи голени. Описана морфологическая и иммуногистохимическая картина опухолей. Выполненное иммуногистохимическое исследование позволило подтвердить морфологический диагноз и установить иммунофенотип опухолей. При установлении морфологического диагноза в одном наблюдении возникли трудности, обусловленные редкостью данной патологии и неоднозначностью трактовки гистологических изменений. Анализ гистологических препаратов, проведение иммуногистохимического исследования позволили верифицировать опухоль как лейомиосаркому с характерным для нее иммунофенотипом. Все вышеизложенное свидетельствует о необходимости проведения морфологического и иммуногистохимического исследования в специализированных научных онкологических центрах.

Ключевые слова:
саркома, кожа головы, мягкие ткани, иммуногистохимическое исследование, клинические данные, обзор литературы

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RELEVANCE

Cutaneous malignant tumors are divided into epithelial and mesenchymal. Skin cancer is one of the most common types of cancer, which in most cases appears on areas of the skin exposed to the sun. Skin cancer develops from cells that, as a result of mutations, have acquired the ability to multiply uncontrollably and have ceased to obey the general mechanisms of regulation. Malignant skin tumors can develop from different tissues [1].

One of the variants of stromal malignant tumors is tumors of muscular origin. Primary subcutaneous leiomyosarcomas are manifested by a node or a focus of diffuse compaction. The tumor can spread to the underlying muscle fascia, as well as along the subcutaneous veins [2–4]. The frequency of cutaneous sarcomas is 2–3 % of the number of all cutaneous soft tissue sarcomas.

Leiomyosarcomas of the skin, like all soft-tissue leiomyosarcomas, have characteristic cytological and histological signs. Smooth muscle cells in highly differentiated tumors look oblong, with cigar-shaped, centrally located nuclei and eosinophilic cytoplasm. Sometimes the cells are arranged in the form of a palisade. In low-grade tumors, there are anaplastic bizarre multinucleated giant cells. The number of mitoses varies, including atypical forms [5–8].

There is evidence that subcutaneous leiomyosarcomas metastasize with a frequency of 30 to 60 %, and the recurrence rate is 80 % of cases and recur within 5 years [7].

There are conflicting opinions about the clinical course and biological behavior of cutaneous leiomyosarcomas. There is evidence that dermal leiomyosarcomas are associated with Li-Fraumeni syndrome [9]. It is suggested that EBV-associated leiomyosarcomas may be observed in immunosuppressive patients [5].

The issues of carcinogenesis, including soft tissue sarcomas, have been considered at the molecular genetic level in recent years, which makes it possible to approach their interpretation and therapy in a new way [10]. A germinal FH mutation has been described in a number of observations [11].

The immunophenotype of soft tissue leiomyosarcoma is characterized by overexpression of ASMA, desmin, N-caldeston, MSA In 45 % of cases, keratin expression occurs [9; 12].

Clinical manifestations and severity of symptoms depend on the primary localization and size of the tumor. Most often, soft tissue sarcomas of the head and neck have an asymptomatic course.

Preoperative verification of the pathological process is established on the basis of histological examination of the tissue of the formation. There are two methods of obtaining the material for the study:

- thick-needle biopsy;
- open biopsy.

The biopsy should be performed in the localization that will enter the excision zone of the tumor formation during the operation.

The treatment of a patient with soft tissue sarcomas of the head and neck requires a comprehensive approach involving a number of specialists: a surgeon, a radiation diagnostician, a pathologist, a chemotherapist, a radiologist. Surgical intervention is the main method of treating patients with this pathology. The growth of soft tissue sarcomas occurs in a capsule, which subsequently pushes away nearby tissues. This shell is called a pseudocapsule. Surgical intervention involves removing the pseudocapsule in a single block with negative resection edges without damaging it, since violation of the integrity of this formation increases the risk of tumor recurrence. In the postoperative period, radiation therapy can be performed to ensure local control. Additional methods of treatment include chemotherapy and radiation therapy.

The prognosis for soft tissue sarcomas of the head and neck largely depends on the size of the tumor, the primary localization. With early diagnostic measures and adequate timely therapy, the prognosis is favorable.

Isolated observations of cutaneous leiomyosarcomas are given in the literature. They concern tumors with a predominant localization on the proximal parts of the extremities.

The treatment of dermal sarcoma consists in the correct surgical removal of the primary tumor with a wide capture of the surrounding tissues. Relapses of leiomyosarcoma are characterized by an aggressive course [1; 6].

Clinical data

Clinical data, results of morphological and immunohistochemical studies are presented. The analysis of skin tumors for 5 years (2016–2020) was carried out.

For 5 years (2016–2020), 2522 patients with epithelial skin tumors were operated on at National Medical Research Centre for Oncology. The average age is 50–59 years. The distribution by age and gender was approximately the same.

The main malignant epithelial tumors were basal cell (2200, 88 %) and squamous cell (284, 11 %) skin cancer. All other malignant tumors – metatypical cancer, cancer of the sweat and sebaceous glands, cancer from Merkel cells) were represented by single observations (< 1 %).

Non-epithelial malignant skin tumors were found in 648 patients. The main age group is 60–69 years old. Basically, tumors occurred in patients after 50 years. The distribution by gender and age was also approximately the same.

The distribution by nosological forms was as follows. Malignant melanoma – 593 (91.5 %), fibrosarcoma – 32 (5 %), non-Hodgkin's lymphoma, skin lymphomas – 23 cases (3.5 %).

Clinical observations

Leiomyosarcoma was not diagnosed on our material for the period 2016–2020. Due to the rarity of this malignant tumor of soft tissue sarcoma of the skin, we present our observations.

Observation 1. Patient Zh., 71 years old, was admitted to the department of head and neck tumors of National Medical Research Centre for Oncology on 11.05.2021 with the diagnosis: malignant neoplasm of the scalp, cl. gr. 2.

After a bruise, a pinkish spot appeared on the scalp, which gradually increased in size and a tumor formed in its place.

In the skin under the epidermis of the scalp, the formation of 2.0 × 1.5 cm of a soft consistency. The skin above the formation is not changed.

Puncture of the formation of the scalp skin was performed – during cytological examination, the cellular composition is represented by sharply polymorphic spindle-shaped tumor cells, with large oval

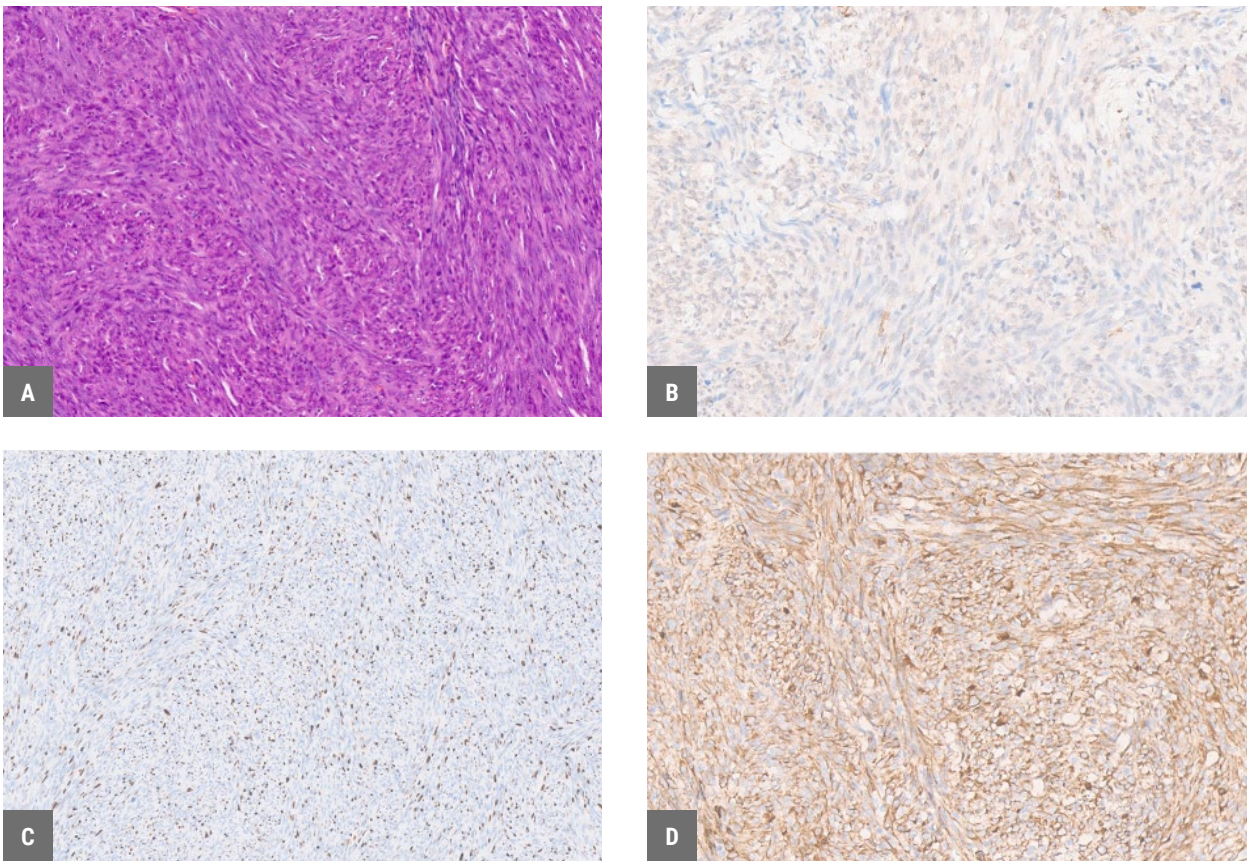

Fig. 1. Microarchitectonics of leiomyosarcoma of the skin, A-D – leiomyosarcoma of the skin, A – leiomyosarcoma G3, B – positive reaction with SMA, G – positive reaction with caldeston, C – proliferative activity of Ki-67, A – staining with hematoxin and eosin, B, C, D – immunohistochemical reaction, A, B, C, D – × 200.

nuclei with nucleoli, with abundant, partially vacuolized light cytoplasm, single multinucleated cells, elements of pronounced inflammation (neutrophilic leukocytes in abundance), single vascular elements. Cytogram of malignant neoplasm of sarcomatous nature. SRCT of the head: no pathological changes in the substance of the brain were detected, the tumor of the parietal region is 2 × 2.1 cm without invasion into bone structures. Ultrasound of the l/nodes of the neck – Cervical / above /subclavian l/y from 2 sides are not enlarged.

Pathology of the thoracic and abdominal organs was not revealed. The formation was removed.

A skin flap with a tumor node measuring 1.8 × 1.4 cm was delivered for morphological examination. The node protrudes above the surface of the epidermis by 0.5 cm, gray, dense, coarse-grained.

Histological examination revealed the following changes. In the flap of skin under the epidermis – G3 fusiform cell sarcoma with infiltrative growth, invasion of level IV, in some drugs – the invasion spreads to adipose tissue. High mitotic activity is detected in the tumor. Extensive hemorrhages are noted. The epidermis is ulcerated. Outside the tumor, there is a slight leukocyte infiltration. The tumor was removed within healthy tissues. The edges of the resection have the usual structure. The histological picture most closely corresponds to leiomyosarcoma; pT1. An immunohistochemical study was conducted. A positive reaction was detected in tumor cells with Caldesmon, SMA antibodies. Proliferative activity (Ki-67) positive reaction in 30 % of tumor cell nuclei. There is no expression in tumor cells with the myogenin antibody. Thus, the conducted immunohistochemical study made it possible to establish the immunophenotype of the tumor – leiomyosarcoma (Fig. 1).

In the future, the patient is under observation.

Observation 2. An 87-year-old patient was admitted with complaints of the presence of a skin tumor of the right shin. In a non-core medical institution, the formation was removed. Dermatofibroma was

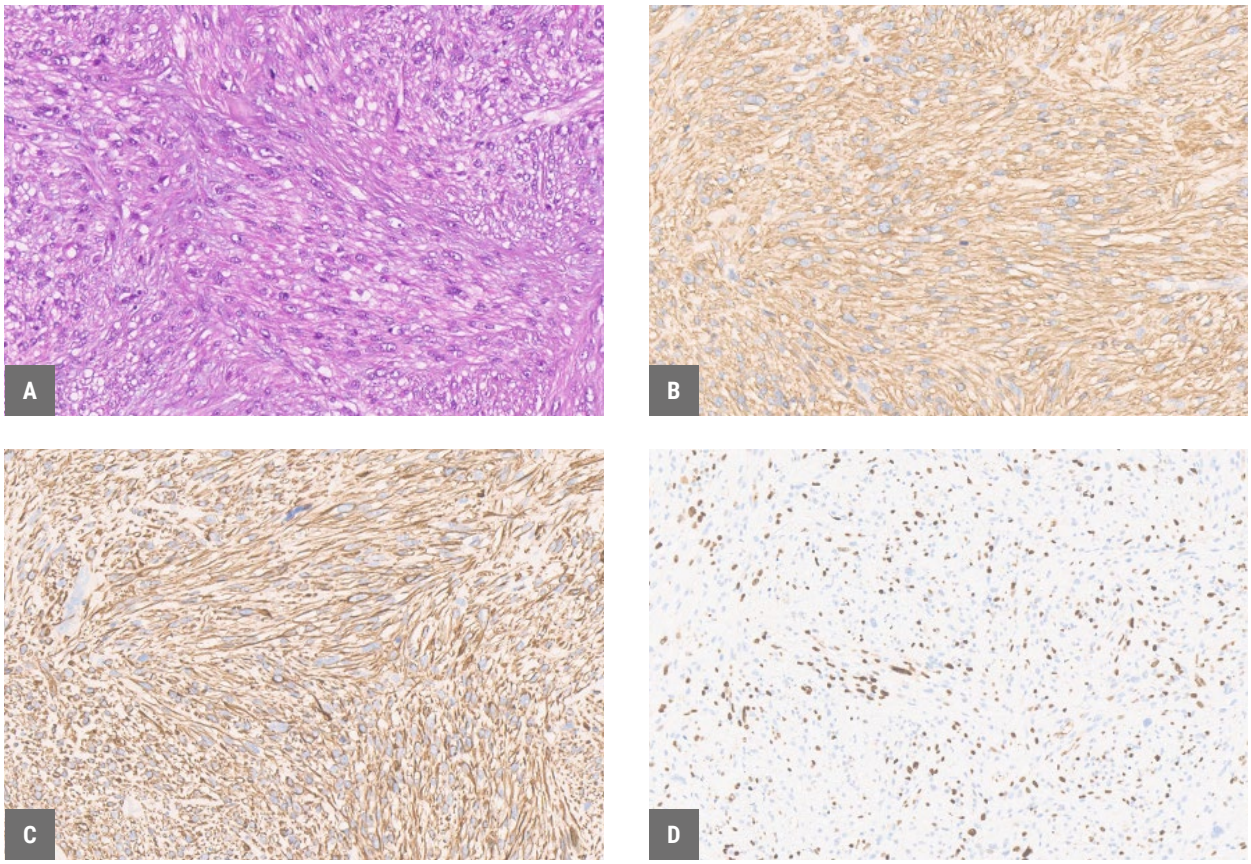

Fig. 2. Microstructure of deep leiomyosarcoma of the shin skin, A-D – leiomyosarcoma of the shin skin, A – leiomyosarcoma G1, B – positive reaction with SMA, C – positive reaction with caldesmon, D – proliferative activity of Ki-67, A – staining with hematoxylin and eosin, B, C, D – immunohistochemical reaction, A, B, C, D – × 200.

diagnosed. In the future, the patient turned to the National Medical Research Centre for Oncology for consultation.

When reviewing histopreparations, the following changes were found. In the skin flap, in the dermis, there is a tumor node that spreads into adipose tissue. The tumor is represented by elongated cells with signs of smooth muscle differentiation. There are large cells with hyperchromic, polymorphic nuclei. Few mitoses are determined. The opinion is expressed about cutaneous leiomyosarcoma (atypical smooth muscle tumor).

To determine the immunophetotype, an IHC study was performed. The IHC study revealed the following changes: a positive reaction with antibodies SMA, caldesmon. The marker of proliferative activity was 30 % of the nuclei of tumor cells. Expression with the CD34 marker was absent.

Thus, the morphological picture and immunophenotype of tumor cells were characteristic of cutaneous leiomyosarcoma (atypical smooth muscle tumor) (Fig. 2).

CONCLUSION

The article analyzes skin tumors according to National Medical Research Centre for Oncology, which amounted to 2,522 patients over 5 years (2016–2021). It was found that soft tissue skin tumors are rare. Leiomyosarcoma of the skin during this period was not detected on our material, which prompted the description of our observations.

Two observations of leiomyosarcoma of the skin are given: the scalp and the shin skin. The morphological and immunohistochemical picture of these tumors is described. It is noted that there are difficulties of morphological diagnostics in verification. All of the above indicates the need for morphological research in specialized oncological research centers.

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