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ORIGINAL ARTICLE

INDIVIDUAL ORAL HYGIENE QUALITY INFLUENCE ON THE SEVERITY OF POST-RADIATION MUCOSITIS IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE OROPHARYNGEAL REGION

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ABSTRACT

Purpose of the study. Assessment of the quality of individual oral hygiene in patients with squamous cell oropharyngeal cancer before and after radiation therapy.

Materials and methods. Examined 76 patients with squamous cell carcinoma of the oropharyngeal region. For all patients, before and after radiation therapy, evaluated the hygienic state of the oral cavity using indices: index of individual hygiene (Green V.), Silness-Loe index (GI), index of prevalence of periodontal diseases (CPITN).

Results. The number of males was higher than that of females: 52 (68.4%) versus 24 (31.6%). Before radiotherapy, 52 (68.4%) patients had gingivitis, 66 (86.8%) had periodontitis, 43 (56.5%) had metal crowns, and 57 (76%) had destroyed teeth. All patients (100%) had oral mucositis after radiation therapy. We found a significant negative trend: the Green V. index changed by 29.2%, CPITN indicators-by 38%, GI — by 31.2% ($p<0.05$). There was also a direct dependence of the severity of oral mucositis on the total dose of radiation. Thus, patients with squamous cell carcinoma of the oropharyngeal region develop severe oral mucositis with a total radiation dose of 30 Gy and above. The probability of occurrence of oral mucositis of 4 severity is possible in 2/3 cases with a total radiation dose of 40 Gy or higher.

Conclusion. The severity of oral mucositis depends on both the total radiation dose and the initial dental status of the patient. Therefore, quality control of individual oral hygiene and periodontal support for patients with oral malignancies should be carried out throughout the patient's treatment.

Keywords:
head and neck cancer, squamous cell carcinoma of the oropharyngeal region, oral mucositis, index of individual oral hygiene, index of prevalence of periodontal diseases, radiation therapy

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ВЛИЯНИЕ КАЧЕСТВА ИНДИВИДУАЛЬНОЙ ГИГИЕНЫ ПОЛОСТИ РТА НА ТЯЖЕСТЬ ПОСТЛУЧЕВОГО МУКОЗИТА У ПАЦИЕНТОВ С ПЛОСКОКЛЕТОЧНЫМ РАКОМ ОРОФАРИНГЕАЛЬНОЙ ОБЛАСТИ

А.М.Аванесов[1,2], Е.Н.Гвоздикова[1], Т.В.Тарасова[3], Д.А.Хайдар[1]*, А.А.Виноградова[1], И.А.Захаркин[3]

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РЕЗЮМЕ

Цель исследования. Оценка качества индивидуальной гигиены полости рта пациентов с плоскоклеточным раком орофарингеальной области до и после лучевой терапии.

Материалы и методы. Были обследованы 76 пациентов с плоскоклеточным раком орофарингеальной области. У всех пациентов до начала лучевой терапии и после ее завершения оценивали гигиеническое состояние ротовой полости с помощью индексов: индекс индивидуальной гигиены (Green V.), десневой индекс Silness-Loe (GI), индекс распространенности болезней пародонта (CPITN).

Результаты. Количество мужчин было больше по сравнению с лицами женского пола: 52 (68,4%) против 24 (31,6%). До начала лучевой терапии у 52 (68,4%) пациентов был выявлен гингивит, у 66 (86,8%) человек — пародонтит, у 43 (56,5%) — наличие металлических коронок, у 57 (76%) — наличие разрушенных зубов. После окончания лучевой терапии у всех пациентов (100%) был зафиксирован оральный мукозит. Мы выявили достоверную отрицательную динамику: индекс Green V. изменился на 29,2%, показатели CPITN — на 38%, GI — на 31,2% ($p<0,05$). Также была зафиксирована прямая зависимость степени тяжести орального мукозита от суммарной дозы облучения. Так, при суммарной дозе облучения 30 Гр и выше у пациентов со злокачественными новообразованиями (ЗНО) полости рта развивается оральный мукозит тяжелой степени. При суммарной дозе облучения 40 Гр и выше вероятность появления орального мукозита 4 степени тяжести возможна в 2/3 случаев.

Заключение. Степень тяжести орального мукозита зависит и от суммарной дозы облучения, и от исходного стоматологического статуса пациента. Поэтому контроль качества индивидуальной гигиены полости рта и пародонтологическое сопровождение пациентов с ЗНО полости рта должны проводиться на протяжении всего лечения пациента.

Ключевые слова:
рак головы и шеи, плоскоклеточный рак орофарингеальной области, оральный мукозит, индекс индивидуальной гигиены ротовой полости, индекс распространенности болезней пародонта, лучевая терапия

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Oral cancer is the most common malignant disease of the head and neck [1, 2, 3]. This nosology ranks 5–6 among oncological diseases [4]. The prevalence of oral malignancies (OM) in 2018 reached 28.5 cases per 100,000 population, which is 17.5% more than in 2013. The proportion of patients with newly diagnosed malignant tumors of the oral cavity stage 1–2 is 36.9 per cent. The five-year overall survival rate in this group of patients is 40–50% [4]. In 2018 the percentage of patients with overall survival more than 5 years was 51.9% in Russia.

Radiation therapy is most common independent method in the treatment of oral malignancies (17.0%), and in 38% of cases in combination with other methods (Fig. 1). According to various authors, patients have after radiation therapy, in most cases post-radiation complications in the form of edema, hyperemia, wet desquamation of oral tissues, with the formation of ulcers [5, 6].

Most authors believe that smoking, alcohol, and papillomavirus infection are risk factors for developing not only squamous cell carcinoma of the oropharyngeal region, but also for the formation of oral mucositis [7–10]. The researchers also noticed that the severity of post-radiation oral mucositis depends on the initial hygienic state of the oral cavity, the total radiation dose, and the quality of oral care during radiotherapy [11, 12].

Purpose: to estimate the quality of individual oral hygiene in patients with oropharyngeal squamous cell carcinoma before and after radiation therapy.

MATERIALS AND METHODS

We have observed 76 patients with clinically and morphologically confirmed oropharyngeal squamous cell carcinoma. Radiation therapy was performed in all patients included in the study. We registered indicators, during the hygienic state of the oral cavity assessing: the index of individual hygiene (Green V.), the gingival index of Silness-Loe (GI), the index of the prevalence of periodontal diseases (CPITN). We assessed the severity of oral mucositis using the RTOG scale, also taking into account the area of the mucosal lesion, the nature of the discharge (mucosal/hemorrhagic/purulent), the presence of ulcers, etc.

The quality control of individual oral hygiene and periodontal support of patients with oral malignancies (*n*=76) was performed by the dentist both initially (before the start of radiation therapy) and after the end of radiotherapy.

Statistical processing of the material was carried out with the program “STATISTICA 6.0”. The reliability of differences between quantitative indicators was assessed using the Mann — Whit-

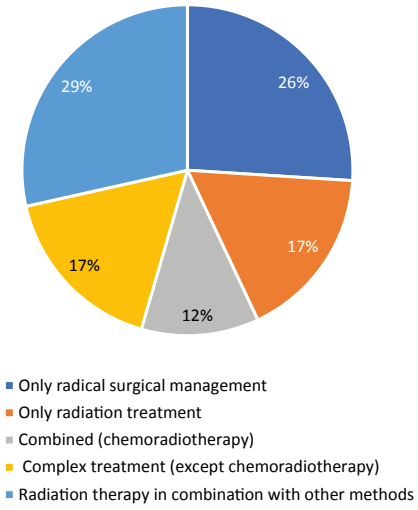

Fig. 1. Treatment types of oral cavity malignant tumors

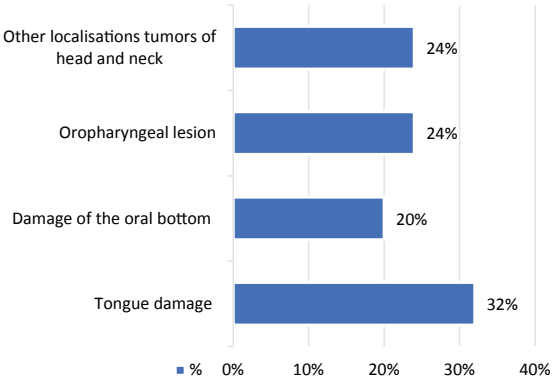

Fig. 2. Distribution of patients by tumor location

ney test. The differences were considered significant at $p<0.05$.

RESULTS

The average age of patients was 52+11 years. The number of males was higher than the number of females: 52 (68.4%) versus 24 (31.6%).

Figure 2 shows the distribution of patients by tumor location. Malignancies of the tongue (32%) prevailed among cancer lesions in other areas. Figure 3 shows a comparison of the number of patients according to the revealed degree of morphological differentiation of the oropharyngeal region of the malignancies. In our study, more than half of the patients were with moderately differentiated oropharyngeal cancer.

Before the radiation therapy, 52 (68.4%) patients had gingivitis, 66 (86.8%) people had periodontitis, 43 (56.5%) had metal crowns, and 57 (76%) had destroyed teeth. Indicators of the Green V index were 1.78+1.12 before the radiation therapy. In most cases, the oral hygiene index was considered satisfactory. The CPITN index before radiotherapy was 2.12+0.43, and the GI index was 2.41+0.39, which indicates the need for professional oral hygiene.

After the end of radiation therapy, oral mucositis was detected in all patients (100%) (table 1).

The Green V., GI, and CPITN indexes have significantly worsened: 2.48+0.29, 3.5+0.40, 3.40+0.38 accordingly. A significant negative dynamics was found for all indicators of the oral hygiene index: the Green V index changed by 29.2%, CPITN indicators — by 38%, GI-by 31.2% ($p<0.05$).

Table 1. Distribution of patients with oral malignancies according to the severity of oral mucositis after the end of radiation therapy

The severity of oral mucositis		Patients with oral malignancies	
		n	%
1	Hyperemia light pain (no need to use painkillers)	1	1.31
2	Focal mucositis, with possible production of serous-hemorrhagic discharge, edema, there may be moderate pain (painkillers re required)	9	11.84
3	Significant fibrinous mucositis, there may be severe pain (narcotic anesthesia is required)	39	51.3
4	Ulcer, necrosis, bleeding	27	35.55

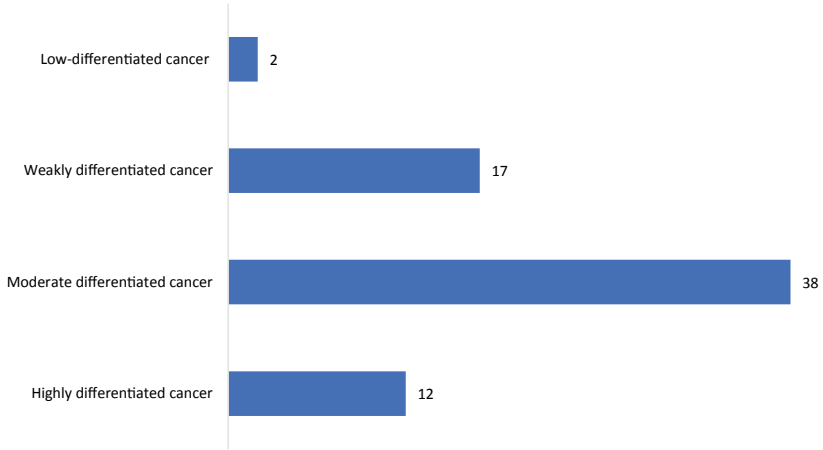

Fig. 3. The number of patients identified by the degree of morphological differentiation of the oropharyngeal malignancies

Green V. and CPITN levels before and after radiotherapy are shown in figures 4 and 5.

We have detected a direct correlation between the severity of oral mucositis and the total radiation dose. Thus, with a total radiation dose of 30 Gr or higher, patients with oral malignancies develop severe oral mucositis. But with a total radiation dose of 40 Gr or higher, the appearance of ulcerative lesions of the oral mucosa was detected in 75% of patients.

DISCUSSION

It is proved that post-radiation oral mucositis begins to manifest at a total radiation dose of 20 Gr or higher [11]. At a cumulative dose of 30 Gr or higher, the ulcerative-necrotic form of mucositis begins to develop [11]. Our study shows that with a total radiation dose of 40 Gr or higher, the probability of oral mucositis of 4 degrees of severity is possible in 2/3 of cases. In oral mucositis, the greatest discomfort is pain, the intensity of which can affect the treatment of the underlying disease and the quality of life of the patient.

Most researchers believe that the rate of development and severity of post-radiation oral mucositis is influenced by the initial dental status of the patient [12, 13, 14, 15]. Some patients already need professional oral hygiene before the start of radiation therapy, which should be continued after the end of radiotherapy [1]. Our study showed that patients had a CPITN index of more than 2 points, and they needed treatment and prevention of oral diseases.

Patients with oral mucositis require special oral care: brushing with a soft toothbrush, regular replacement of the toothbrush, the use of dental floss and rinses with antiseptics and moisturizers [12, 16, 17, 18].

The oral care regimen for patients with oral malignancies should include brushing their teeth with a soft toothbrush, regularly replacing the toothbrush, flossing, and using soft rinses and moisturizers [12, 19].

CONCLUSIONS

The "insidiousness" of post-radiation oral mucositis consists of several factors: the development of damage to the oral mucosa with the addition of necrobiotic processes, intense pain and a decrease in the quality of life. The severity of oral mucositis depends on both the total radiation dose and the initial dental status of the patient. Therefore, the quality control of individual oral hygiene and periodontal support for patients with oral malignancies should be carried out throughout the patient's treatment.

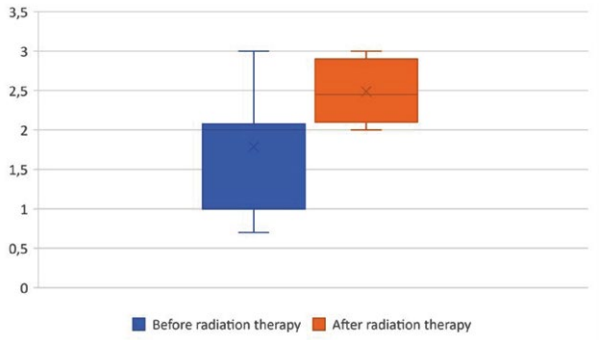

Fig. 4. Individual hygiene index (Green V.) before and after radiation therapy (p<0.05)

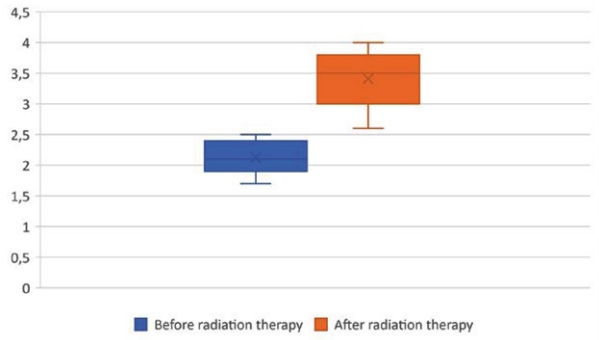

Fig. 5. The index of periodontal diseases spread (CPITN) before radiation therapy and after its termination (p<0.05)

Authors contribution:
Avanesov A.M. – concept and design of the study.
Gvozdikova E.N. – writing the text, interpretation of data, processing of the material.
Tarasova T.V. – scientific editing.
Haidar D.A. – data collection, analysis, technical editing.
Vinogradova A.A. – design of the references.
Zakharkin I.A. – preparation of illustrations.

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ORIGINAL ARTICLE

THE ULTRASOUND DIAGNOSTICS POTENTIAL OF THE SMALL PELVIS TUMORS IN CHILDREN

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ABSTRACT

Purpose of the study. To assess the potential of sonography in the diagnosis of pelvic tumors in children.
Patients and methods. We retrospectively analyzed results of ultrasound examination of the small pelvis, abdominal cavity and retroperitoneal space in 110 children with pelvic cancer referred for examination and treatment to National Medical Research Centre for Oncology of the Ministry of Health of Russia, distinguishing the most significant ultrasound parameters regardless of the tumor histological structure. 69.1% of patients were diagnosed with germ cell tumors, including 72.4% with gonadal and 27.6% with extragonadal tumors, 85.8% with sacrococcygeal tumors, 9.5% — uterine and 4.7% — vaginal tumors. Rhabdomyosarcoma was detected in 25.4%, neuroblastoma in 4.5% and a primitive neuroectodermal tumor in 1%. Standard ultrasound examination was performed using scanners Philips IU22 (USA) and Logic 400 MD (GE, USA) with convex transducers (3.5–5.5 MHz) in grayscale, color Doppler and power Doppler modes.
Results. The first stage of diagnostics showed that malignant pelvic tumors were characterized with an irregular shape registered in 97 (88.2%; $p<0.0001$), uneven, fuzzy contours — 94 (85.5%; $p<0.0001$), heterogeneous echostructure — 102 (92.7%; $p<0.0001$), in 70 people (63.6%; $p=0.001$) due to cystic inclusions, calcified inclusions were found in 37 (33.6%; $p>0.05$); tumor echodensity was reduced in 75 children (68.2%; $p=0.001$). Dopplerography in most patients — 100 (90.9%) — registered a hyperintense intratumoral blood flow, mainly of an arterial type, with maximum arterial velocities (MAV) ranging from 12.5 to 45 cm/s, average MAV = 30±2.7 cm/s. The specificity of the method was 86.3% ($p=0.001$), sensitivity 85.2% ($p=0.011$), accuracy 87.5% ($p=0.014$). Ultrasound monitoring was performed during treatment after each polychemotherapy cycle; we assessed changes in the size of tumors, their structure and neovascularization, allowing evaluation of the antitumor treatment effectiveness.
Conclusion. A complex sonography is an important method in the primary diagnostics of pelvic tumors in children, as well as a priority method in antitumor treatment monitoring, which allows detection of the tumor extent and helps to avoid multiple radiation exposure of the growing child's body.

Keywords:
pelvic tumors, children, germ cell tumors, neuroblastoma, rhabdomyosarcoma, ultrasound examination

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ВОЗМОЖНОСТИ УЛЬТРАЗВУКОВОЙ ДИАГНОСТИКИ ОПУХОЛЕЙ МАЛОГО ТАЗА У ДЕТЕЙ

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РЕЗЮМЕ

Цель исследования. Оценить возможность сонографии в диагностике опухолей малого таза у детей.
Пациенты и методы. Нами были ретроспективно проанализированы протоколы ультразвуковых исследований малого таза, брюшной полости и забрюшинного пространства 110 детей со злокачественными опухолями полости таза, проходивших обследование и лечение в ФГБУ «НМИЦ онкологии» Минздрава России, с выделением наиболее значимых ультразвуковых параметров независимо от гистологической структуры. Выявлено 69,1% человек с герминогенными опухолями, среди которых 72,4% пациентов с гонадной формой и 27,6% пациентов с экстрагонадной формой новообразований, 85,8% человек с крестцово-копчиковой локализацией, 9,5% пациенток с расположением в матке и 4,7% – во влагалище. Рабдомиосаркома выявлена у 25,4%, нейробластома – у 4,5% и примитивная нейроэктодермальная опухоль – у 1%. УЗИ выполнены на сканерах Philips IU22 (USA), Logic 400 MD (GE, USA) конвексными датчиками (3,5–5,5 МГц) по стандартной методике в серошкальном режиме, в режимах цветового и энергетического допплеровского картирования.
Результаты. На первом этапе диагностики установлено, что для злокачественных новообразований малого таза характерны неправильная форма, которая встречалась у 97 (88,2%; $p<0,0001$), неровные, нечеткие контуры – 94 (85,5%; $p<0,0001$), неоднородная эхоструктура – 102 (92,7%; $p<0,0001$), у 70 человек (63,6; $p=0,001$) за счет кистозных включений, у 37 (33,6%; $p>0,05$) наблюдались кальцинированные включения, акустическая плотность опухолей у 75 детей (68,2%) $p=0,001$ была пониженной. При допплерографии у наибольшего количества пациентов (100 (90,9%)) регистрировался гиперинтенсивный внутриопухолевый кровоток преимущественно артериального типа с диапазоном максимальных артериальных скоростей (МАС) от 12,5 до 45 см/с, среднее значение МАС – 30±2,7 см/с. Специфичность метода составила 86,3% ($p=0,001$), чувствительность – 85,2% ($p=0,011$), точность – 87,5% ($p=0,014$). В ходе лечения, после каждого курса полихимиотерапии, осуществлялся ультразвуковой контроль, мы оценивали изменения в размерах, структуре и неоваскуляризации новообразований, что позволяло оценить эффективность противоопухолевого лечения.
Заключение. Комплексная сонография является важным методом в первичной диагностике злокачественных тазовых опухолей в детском возрасте и приоритетным методом на этапах мониторинга противоопухолевого лечения, позволяющим определить степень распространенности опухолевого процесса и избежать многократной лучевой нагрузки на растущий детский организм.

Ключевые слова:
опухоли полости таза, дети, герминогенные опухоли, нейробластома, рабдомиосаркома, ультразвуковое исследование

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INTRODUCTION

Neoplasms in the projection of the small pelvis in children are a rare pathology, which accounts around 0.5–2% of the total structure of childhood cancer incidence [1, 2]. The early diagnosis of these neoplasms is an urgent problem. Parents seek medical care only at stages III–IV due to the long preclinical phase of the disease, the appearance of the first symptoms associated with pelvic organ dysfunction only when reaching large tumor sizes, and the inability to get reliable information about complaints from small patients [3, 4].

The updated topical diagnosis and assessment of the prevalence of the tumor process in the pelvic cavity in children allows us to determine the feasibility and scope of surgical intervention. Radiation diagnostics (ultrasound, spiral x-ray computed tomography, magnetic resonance imaging) plays a leading role in the whole set of laboratory and instrumental methods for diagnosing pelvic tumors in children [5, 6]. Among all instrumental diagnostic methods, ultrasound diagnostics is the most accessible, non-invasive method of visualization of pelvic cavity tumors, a method of primary, differential, screening diagnostics that does not have a radiation effect on the growing body and does not require anesthesia during the study. After establishing the fact of the presence of a mass lesion in the pelvic cavity, computer tomography and other methods of instrumental diagnostics are performed in order to confirm the diagnosis and clarify the prevalence of the tumor process [7].

Purpose of the study: to assess the potential of sonography in the diagnosis of pelvic tumors in children.

PATIENTS AND METHODS

We retrospectively analyzed the protocols of ultrasound examinations of the pelvis, abdominal cavity and retroperitoneal space of 110 children with malignant tumors of the pelvic cavity who were examined and treated at the National Medical Research Centre for Oncology of the Ministry of Health of Russia, with the identification of the most significant parameters of neoplasms, such as: shape, size, volume, contours, echodensity, echo structure, prevalence of the process, neovascularization. For retrospective analysis we used statistical data of organizational-methodical Department, National Medical Research Centre for Oncology of the Ministry of Health of Russia, notifications about newly diagnosed patients, control charts of dispensary monitoring, inpatient and outpatient charts, surgical operating logs, results of histological and laboratory tests. All parents of children with pelvic tumors gave their voluntary informed consent for the use of the material removed during surgery for scientific purposes.

76 (69.1%) people with germ cell tumors were observed, including 55 (72.4%) patients with gonadal and 21 (27.6%) patients with extragonadal tumors, 18 (85.8%) people with sacrococcygeal tumors, 2 (9.5%) patients with tumors in the uterus and 1 (4.7%) in the vagina. Rhabdomyosarcoma was detected in 28 children (25.4%), neuroblastoma in 5 children (4.5%) and a primitive neuroectodermal tumor in 1 (1%) child.

By gender, the children were distributed as follows: germ cell tumors in 70 (92.1%) girls and 6 (7.9%) boys, rhabdomyosarcoma in 8 (28.5%) girls and 20 (71.5%) boys, neuroblastoma in 2 (40%) girls and 3 (60%) boys, primitive neuroectodermal tumor (PNET) in 1 boy.

The age composition of patients included in the study ranged from 1.5 months to 14 years.

Ultrasonography was performed on ultrasound devices Philips IU22 (USA), Logic 400 MD (GE, USA) with broadband convex transducers (3.5–5.5 MHz).

Abdominal gray-scale ultrasound imaging was used for ultrasound biometry and evaluation of the status and echostructure of the pelvic organs: the uterus and appendages in girls, prostate gland area in boys, bladder, bowel loops, sacrococcygeal region; the existence of the tumor was stated. The next step included measuring the volume of the tumor and evaluation of its echostructure, shape, contours, and extent. During dopplerography (DG) in the modes of color Doppler and power Doppler imaging (CDI, PDI),

the condition of the main vessels was evaluated, and a qualitative assessment of neovascularization was performed: the number and form of pathological vascular loci, the type of blood supply and its intensity. Dopplerometry (DM) measured the rate of intra-tumor blood flow.

Transabdominal ultrasound with retrograde bladder filling was performed in 2 (1.8%) children to clarify the degree of prevalence of the process [8].

Ultrasound monitoring during treatment is one of the most popular branches in oncopediatrics. We performed pelvic and abdominal ultrasound after each cycle of PCT.

Statistical processing was performed using the program STATISTICA 12.0 (StatSoft, USA). In this case, we used a frequency analysis module, which calculated the absolute and relative (in%) frequency of features, the confidence probability p for the difference of alternative states in the group. Diagnostic accuracy, sensitivity and specificity of ultrasound methods were determined according to standard principles of evidence-based medicine. The range of values was used and the average trend was estimated in the form of an average sample and its error, while assessing the variability of quantitative characteristics.

THE RESULTS OF THE STUDY AND DISCUSSION

In the studied group of children diagnosed with germ cell tumors, the abnormal form of neoplasms prevailed in 71 patients (93.5%), uneven, indistinct contours in 70 children (92.2%), solid-cystic echo structure in 56 cases (73.7%) with calcified inclusions in 21 (27.6%) patients. The echodensity of neoplasms in 40 people (52.6%) was hypoechoic and in 36 (47.4%) mixed.

The ultrasound picture of rhabdomyosarcoma was characterized mainly by an irregular shape in 22 patients (78.6%) with uneven, indistinct contours in 19 (67.8%), solid echo structure in 17 (60.7%), mixed echogenicity of 17 (60.7%) with anechogenic zones of necrosis and hemorrhage in 11 (39.3%) and calcified inclusions in 12 (42.9%).

Neuroblastomas had an irregular shape 4 (80%), bumpy, indistinct contours 4 (80%), solid echo structure with calcified inclusions 4 (80%), reduced echo density in 3 (60%) patients, mixed echo density in 2 (40%) patients.

We observed one child with PNET. The B-mode located a tumor of an oval shape, with bumpy, indistinct contours, mixed echo density, solid-cystic echo structure.

In the examined group of children, the minimum linear size of the tumor according to ultrasound was 2.0 cm, the maximum size 14.5 cm.

We did not detect pathognomonic sonographic differences between pelvic malignancies in children and considered it possible to combine them into a single group.

Thus, at the first stage of diagnosis, it was found that malignancies of the pelvis were characterized by an irregular shape observed in 97 (88.2%; $p<0.0001$), uneven, indistinct contours — 94 (85.5%; $p<0.0001$), heterogeneous echostruc-

Table 1. The distribution of the sonographic features of malignant tumors of the pelvis in children

The sign	abs. number	%	*p*
the irregular shape	97	88.2	$p<0.0001$
Heterogeneous structure of the tumor	102	92.7	$p<0.0001$
The contours of the tumor are rough and indistinct	94	85.5	$p<0.0001$
Cystic inclusions in tumors	70	63.6	$p=0.001$
Calcified inclusions in tumors	37	33.6	$p>0.05$
Hypoechoic acoustic echodensity	75	68.2	$p=0.001$

ture 102 (92.7%; $p<0.0001$), in 70 people (63.6%; $p=0.001$) due to cystic inclusions, in 37 (33.6%; p>0.05) calcified inclusions were observed, and the echodensity of tumors in 75 children (68.2%) $p=0.001$ was reduced (table 1).

CDI in the majority of patients — 100 (90.9%) registered hyperintensive intra-tumor blood flow of mainly arterial type with a range of maximum arterial velocities (MAV) from 12.5 to 45 cm/s, the average value of MAV = 30±2.7 cm/s.

The accuracy of the method was 87.5% ($p=0.014$), sensitivity 85.2% ($p=0.011$), specificity 86.3% ($p=0.001$).

All children included in the study were given polychemotherapy as the first stage of treatment. Before each subsequent cycle of PCT, a comprehensive ultrasound of the pelvic organs was performed. Based on changes in the echographic picture of neoplasms, we concluded that induction therapy was effective.

Thus, in 78 children (71%) with a significant and partial effect of treatment, we observed a decrease in the volume of the tumor by 55–90%, a change in the contours of neoplasms, they became smoother and clearer in 52 patients (66.6%) of 78. However, in 26 (33.4%) with a

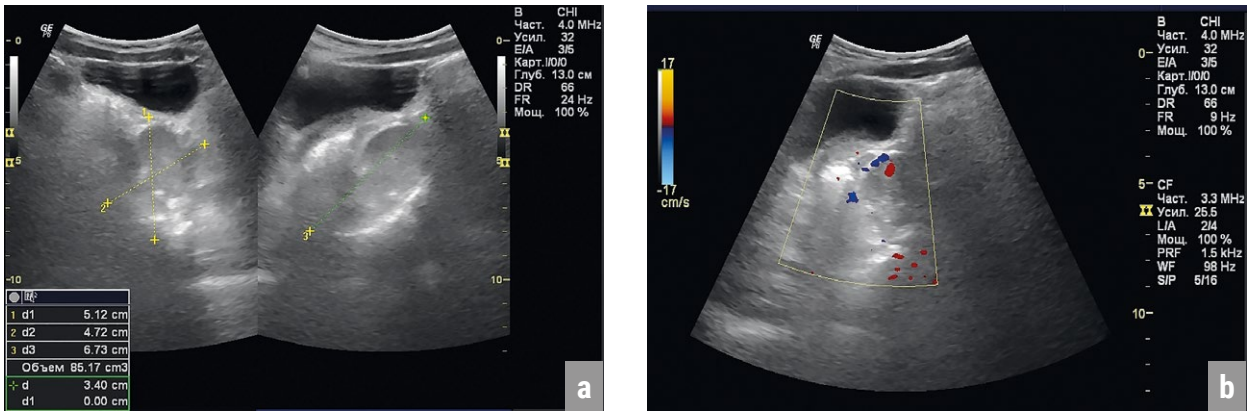

Fig. 1. Patient M., 1 year and 5 months old. Echogram of a germ cell tumor before treatment
a) B-mode – solid hypoechoic neoplasm, irregular shape, heterogeneous echostructure with single hyperechoic, calcified inclusions, the contours of the tumor are fuzzy, rough, sized 4.7x5.1x6.7 cm, the volume of the neoplasm is 85.17 cm^3
b) The CDI mode – isointensive intranodular bloodstream

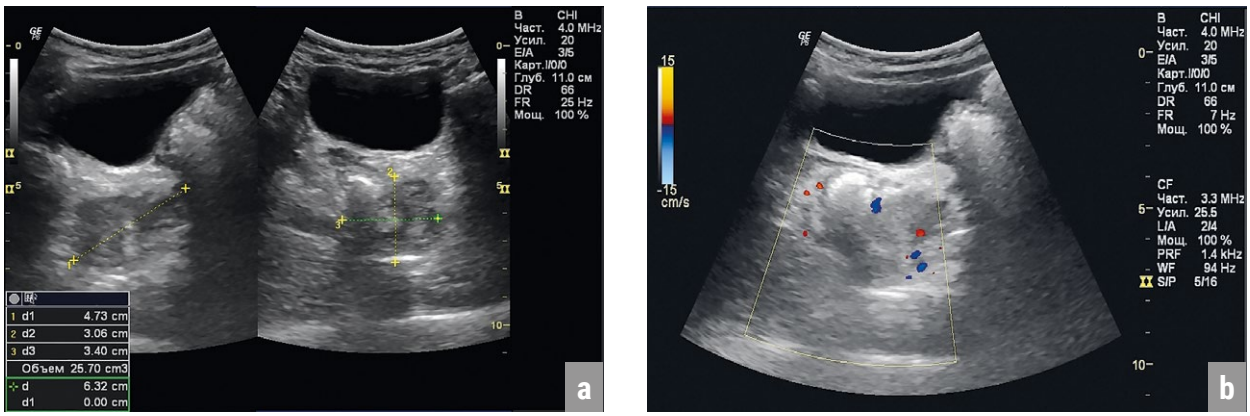

Fig. 2. Patient M., 1 year and 5 months old. Echogram of a germ cell tumor after 1 cycle of polychemotherapy:
a) B-mode – solid volume, hypoechoic neoplasm, irregular shape, size 3.0×3.4×4.7 cm, volume 25.7 cm^3, contours are fuzzy, uneven, inhomogeneous echo structure with single calcified, hyperechoic inclusions
b) CDI mode – hypointensive intranodular blood flow, MAV is 12 cm/s

significantly (by over 85%) decreased tumor volumes, contour visualization deteriorated sharply. The echo structure of tumors became more homogeneous in 40 patients (51.3%). In 31 patients (39.7%), an increase in the echodensity of tumors was observed during treatment. Also, the degree of vascularization of tumors decreased with a decrease in blood flow parameters, up to its complete disappearance in 9 children (11.5%).

To illustrate the effectiveness of ultrasound in antitumor treatment monitoring, here we present clinical cases.

Clinical case № 1.

Patient M., 1 year and 5 months old. Clinical diagnosis: Pelvic germ cell tumor with spread to the soft tissues of the sacro-coccygeal region, with metastatic lesions of the coccygeal vertebrae, lungs, stage IV, clinical group 2.

Ultrasound examination determined a bulk solid hypoechogenic lesion in the pelvic cavity posterior to the uterine body, with an irregular shape, heterogeneous echo-structure with single hyperechogenic, calcified inclusions, the tumor contours fuzzy, rough, size 4.7×5.1×6.7 cm, tumor volume 85.17 cm³; DG recorded iso-

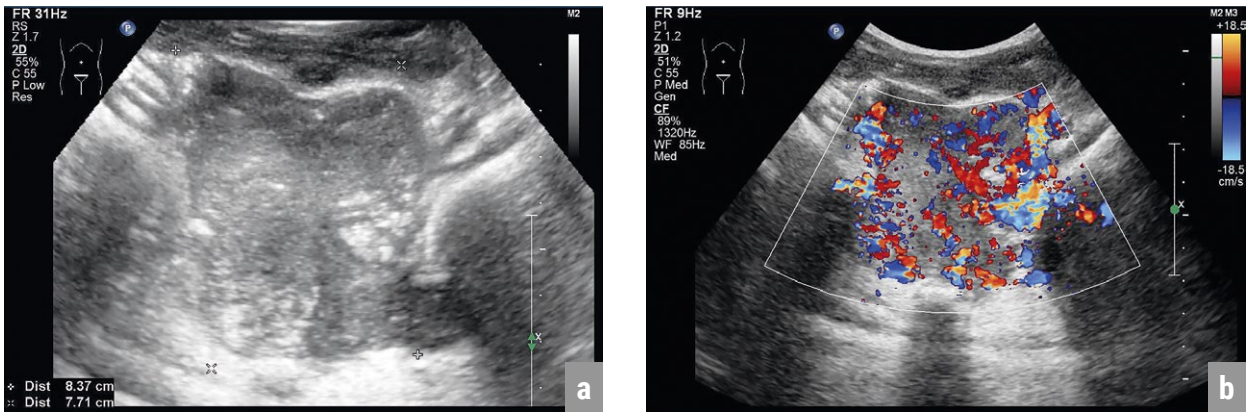

Fig. 3. Patient M., 1 year old. Neuroblastoma echogram before treatment
a) B-mode – volume hypoechoic nodular solid neoplasm with the size of 8.37×7.7×7.0 cm, volume of 451 cm³ with uneven, fuzzy contours, multiple hyperechoic calcified inclusions
b) CDI mode – hyperintensive intra-tumor blood flow in the central and peripheral zones

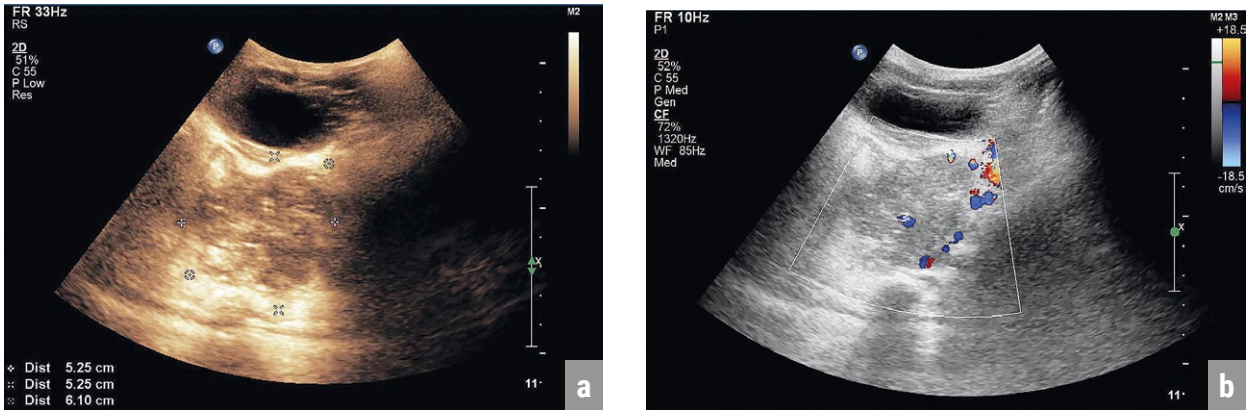

Fig. 4. Patient M., 1 year old. Neuroblastoma echograms after the 2nd cycle of PCT:
a) B-mode – hypoechoic nodular neoplasm, solid, heterogeneous echostructure with single calcified inclusions, with rough, indistinct contours, size 5.25×5.25×6.1 cm, volume 168 cm³
b) CDI mode – hypointensive intratumor bloodstream

intense intratumoral blood flow, arterial type, MAV=25 cm/s. (Fig. 1 a, b).

After the first cycle of polychemotherapy, ultrasound determined a solid, hypoechoic neoplasm of irregular shape in the projection of the pelvis posterior to the uterine body, size 3.0×3.4×4.7 cm, volume 25.7 cm³, with fuzzy, uneven contours, heterogenous echo structure with single calcified, hyperechoic inclusions; DG recorded intra-tumor blood flow of low intensity, MAV 12 cm/s. (Fig. 2 a, b).

We regarded this example as a positive dynamics of the disease — the effective sensitivity of tumors to PCT, the volume of the tumor after the first cycle decreased by 70%, and the tumor hypovascularization was noted.

Clinical case № 2.

Patient M., 1 year old. Clinical diagnosis: Retroperitoneal neuroblastoma, stage III, clinical group 2.

Ultrasound examination determined a volumetric hypoechoic nodular solid neoplasm centrally in the pelvic cavity, with the size of 8.37x7.7x7.0 cm, volume of 451 cm³ with rough, indistinct contours, multiple hyperechoic calcified inclusions. DG reg-

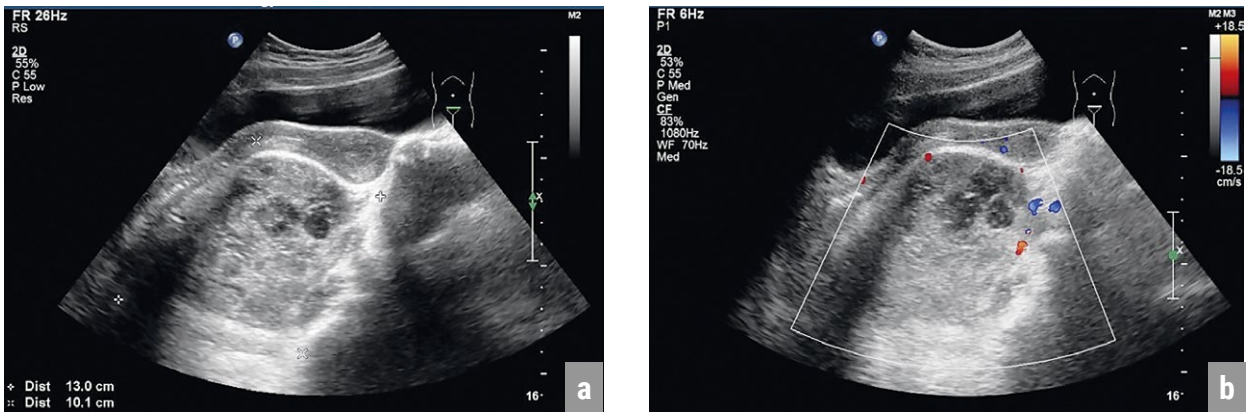

Fig. 5. Patient H., 12 years old. Echogram of PNET before treatment
a) B-mode – solid neoplasm, oval shape, size 13.0×10.0×9.5 cm, volume 617.5 cm³, contours are fuzzy, uneven, heterogeneous, solid-cystic echo structure, mixed echo density.
b) the CDI mode – isointensive peripheral arterio-venous bloodstream

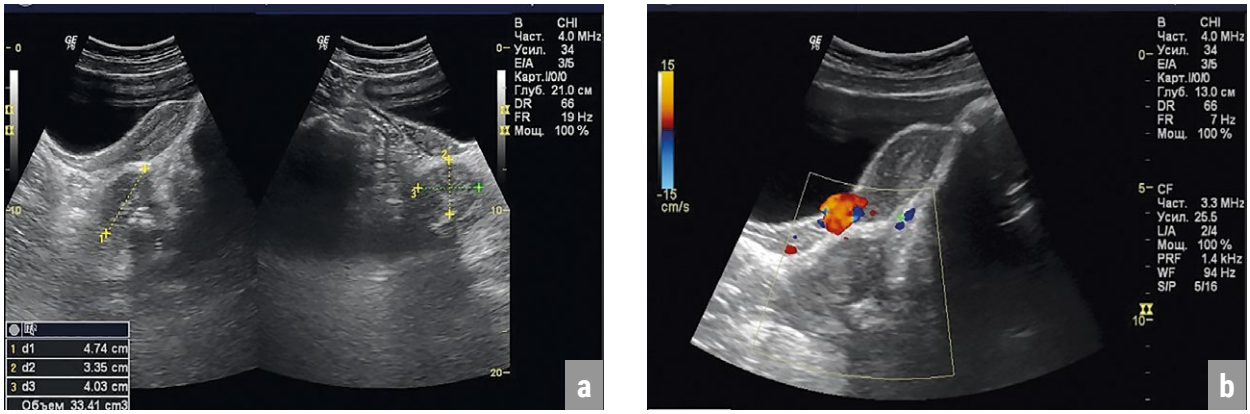

Fig. 6. Patient H., 12 years old. Echogram of PNET after 3 cycles of PCT
a) B-mode – solid neoplasm size 4.7×3.3×4.0 cm, V=33.4 cm³, contours are fuzzy, uneven, solid-cystic, heterogeneous echo structure, reduced echo density
b) CDI mode – single vascular loci on the periphery

istered hypervascularization of neoplasms in the central and peripheral zones, arterial type throughout, MAV was up to 67 cm/s. (Fig. 3 a, b).

After two cycles of polychemotherapy, ultrasound determined a hypoechoic nodular neoplasm centrally in the pelvic cavity, solid, heterogeneous echo structure with single calcified inclusions, with rough, indistinct contours, size 5.25×5.25×6.1 cm, volume 168 cm³. In DG, hypointensive intra-tumor blood flow was registered mainly in the peripheral parts, MAV was up to 18 cm/s (Fig. 4 a, b).

We regarded this example as a positive dynamics of the disease — the effective sensitivity of the tumor to PCT, because the volume of the tumor decreased by 63%, tumor echostructure became more homogenous, the number of calcified inclusions decreased; the tumor hypovascularization was noted, and parameters of arterial intratumoral hemodynamics decreased by 70%.

Clinical case № 3.

Patient H., 12 years old. Diagnosis: Primitive neuroectodermal pelvic tumor spreading to the soft tissues of the left gluteal region, destruction of the sacrum and left iliac bone, lung metastases, stage IV, high-risk group, clinical group 2.

Ultrasound examination determined an oval solid mass in the pelvic cavity behind the uterus and close to the sacrum, with the size of 13.0x10.0x9.5 cm, volume of 617.5 cm³ with indistinct uneven contours, solid and cystic echostructure, mixed echodensity. DG registered isointense intratumoral arterial venous blood flow, MAV = 15 cm/s. (Fig. 5 a, b).

After three cycles of polychemotherapy, the ultrasound determined a solid volume neoplasm in the pelvic cavity with dimensions of 4.7x3.3x4.0 cm, V=33.4 cm³, with fuzzy, uneven contours, heterogeneous echo structure with single cystic inclusions, reduced echo density; DG recorded single vascular loci along the periphery (Fig. 6 a, b), MAV= 7 cm/s

We regarded this example as a positive dynamics as well, effective sensitivity to the treatment of the tumor process, since the volume of the tumor decreased by 94.5%, the echo structure became more homogenous, the number of cystic inclusions decreased, and significant hypovascularization of the tumor was noted.

CONCLUSION

1. Complex sonography is an important method in the primary diagnosis of pelvic tumors in childhood. The accuracy of the method was 87.5% (p=0.014), sensitivity 85.2% (p=0.011), specificity 86.3% (p=0.001).

2. Ultrasound is a sensitive and priority diagnostic method in monitoring the dynamics of the tumor process during the ongoing treatment, which allows avoiding multiple radiation loads on the growing body and planning the surgical stage.

Authors contribution:
Maksimova N.A. – research concept and design, scientific editing, ultrasound examinations, preparation of illustrations.
Kozel Yu.Yu. – scientific editing, treatment of patients.
Ilchenko M.G. – data collection, analysis and interpretation, ultrasound examinations, technical editing, article preparation.
Mkrtchyan G.A. – data collection, treatment of patients.

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ORIGINAL ARTICLE

MINIMALLY INVASIVE SURGERY IN TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

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ABSTRACT

Purpose of the study. Was to improve the results of treatment for metastatic colorectal cancer using laparoscopic surgical technologies.

Patients and methods. We analyzed the data on 311 patients aged 44–78 years with colorectal cancer and liver metastases; in 2005–2015, all patients received treatment at National Medical Research Centre for Oncology of the Ministry of Health of Russia. The main group included 161 patients with metastatic colon cancer and resectable liver metastases receiving laparoscopic surgery; 150 patients with the same disease receiving open surgery were controls.

Results. The study demonstrated that laparoscopy with a combination of developed surgical techniques significantly (p<0.05) reduced the number of surgical complications in the main group (1.8%) compared to controls (12.8%). Patients with metastatic colorectal cancer receiving laparoscopy demonstrated higher, compared to patients with standard open surgery, relative risks of cardiovascular and respiratory complications (HR=4.7, p=0.001), thrombohemorrhagic complications (HR=2.8, p=0.05) and arrhythmia (HR=3.73, p=0.07), but lower risks of surgical complications (HR=0.13, p=0.001). Survival of patients with metastatic colorectal patients was statistically significantly higher in the main group compared to controls: log-rank test = 2.11 at p=0.035.

Conclusions. Laparoscopy reduced the number of surgical complications, compared to open surgery. However, patients with comorbid pathologies showed higher relative risks of other complications.

Keywords:
colorectal cancer, surgical treatment, laparoscopic surgery, liver metastasis, comorbid disease, surgical complications

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ОРИГИНАЛЬНАЯ СТАТЬЯ

МАЛОИНВАЗИВНЫЕ ХИРУРГИЧЕСКИЕ ВМЕШАТЕЛЬСТВА В ЛЕЧЕНИИ БОЛЬНЫХ МЕТАСТАТИЧЕСКИМ КОЛОРЕКТАЛЬНЫМ РАКОМ

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РЕЗЮМЕ

Цель исследования. Улучшение результатов лечения метастатического колоректального рака с использованием лапароскопического метода.

Пациенты и методы. Проводился анализ историй 311 пациентов с раком ободочной и прямой кишки, имеющих метастатические очаги в печени, которые проходили лечение в ФГБУ «НМИЦ онкологии» Минздрава России в период с 2005 по 2015 гг. Возраст больных от 44 до 78 лет. В основную группу вошел 161 пациент с резектабельными очагами в печени, которым были выполнены лапароскопические оперативные вмешательства. Контрольную группу составили 150 человек, перенесших открытые операции.

Результаты. Было доказано, что лапароскопический доступ с применением разработанных хирургических методик позволил достоверно снизить частоту послеоперационных хирургических осложнений у пациентов в основной группе (1,8%) по сравнению с контрольной (12,8%; $p<0,05$).

Использование лапароскопического доступа по сравнению с открытым позволило снизить риск хирургических осложнений (ОР=0,13; $p=0,001$), однако привело к увеличению развития осложнений со стороны сердечно-сосудистой и дыхательных систем (ОР=4,7; $p=0,001$), аритмий (ОР=3,73; $p=0,07$), тромбогеморрагических осложнений (ОР=2,8; $p=0,05$). Выживаемость в основной группе была статистически значимо выше, логарифмический ранговый критерий составил 2,11 при $p=0,035$.

Заключение. Лапароскопический доступ позволил сократить число хирургических осложнений по сравнению с открытыми операциями. Однако у больных, имеющих коморбидную патологию, выше относительный риск развития осложнений со стороны других органов и систем.

Ключевые слова:
колоректальный рак, хирургическое лечение, лапароскопическая хирургия, метастатическое поражение печени, коморбидная патология, хирургические осложнения.

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Colorectal cancer ranks third in the structure of overall cancer incidence [1]. However, despite the entire Arsenal of modern diagnostic methods, 25% of the initial examination have stage IV of the process, with the presence of metastatic foci in the liver [2]. The standard therapy for such patients is combined and complex treatment using both surgical and medicinal methods [3]. The use of drug therapy contributes to the transition of unresectable tumors to resectable ones [4,5,6].

The best way to obtain satisfactory treatment results for such patients is to resect liver tumors [7,8,9]. Recently, laparoscopic access has become the main method of surgery for metastatic colorectal cancer [10,11]. In the literature, there is more information about synchronous resections of the primary focus and liver metastases [12,13]. The advantages of this method are confirmed by randomized studies [14,15,16]. Low trauma is the main advantage in laparoscopy, but despite this, this access for individual patients remains an alternative to open interventions.

Objective: to improve the results of treatment of metastatic colorectal cancer by using laparoscopic techniques.

PATIENTS AND METHODS

We studied data on 311 patients with colon and rectal cancer who have metastatic foci in the liver. The age of patients was 44–78 years. The main group included 161 patients who underwent laparoscopic access, and the control group included 150 patients who underwent open operations. All patients received the treatment at National Medical Research Centre for Oncology of the Ministry of Health of Russia the period from 2005 to 2015. Inclusion criteria: the patient's consent to participate in this study, the absence of concomitant pathology in the stage of exacerbation or decompensation, the presence of verification of processes, resectability of metastases. In the main group of patients with sigmoid colon cancer and liver metastases, a retractor was used to mobilize the sigmoid colon (RF patent for utility model no. 2489150 of 10.08.2013, bul. no. 22: "Retractor for sigmoid colon mobilization"). In all groups, when selecting a linear cross-linking device, the method of measuring the wall thickness of the organs being stitched using a special reusable meter was used (received a patent for a utility model No. 186083 from 28.12.2018 "Device for measuring during minimally invasive endoscopic interventions").

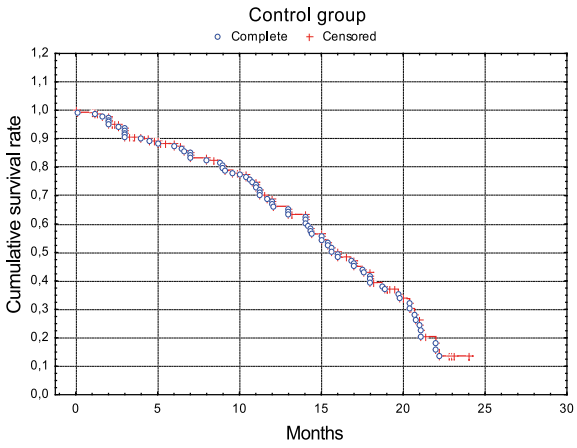

Fig. 1. Overall survival of patients in the control group for two years after the operation. Complete – fatal outcome, Censored – pending case

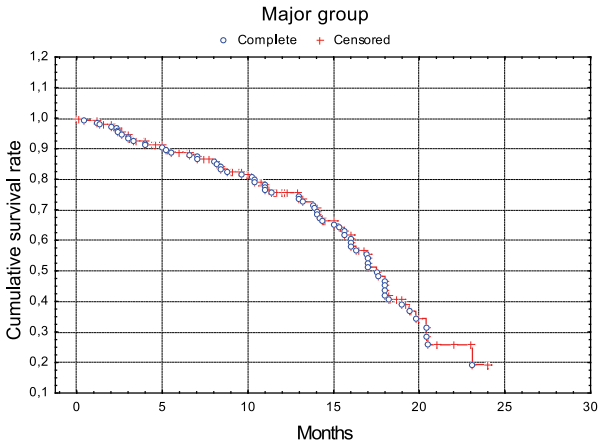

Fig. 2. Overall survival of patients in the main group for two years after the operation. Complete – fatal outcome, Censored – pending case

In the main and control groups of the study, women (52.7 and 54.3%, respectively) were more numerous than men (47.3% and 45.7).

Both in the main and control groups, patients with rectal pathology were more common (35.3% and 32.7%, respectively). All patients had adenocarcinoma, but the majority were patients with low-grade adenocarcinoma (65.3% in the main group and 71.8% in the control group). All patients in the groups had stage IV disease (T2–4N1M1). Often performed surgical intervention, both in the main and control groups were: sigmoid colon resection (31.1 and 33.3%), anterior rectal resection (23.4% and 22.5%, respectively). Anatomic liver resections were performed more often in the main group, and atypical liver resections were performed in the control group. Statistical data processing was performed using the software Statsoft Statistica 10.0. The Shapiro-Wilk W-test is used to estimate the normality of the distribution.

THE RESULTS OF THE STUDY AND DISCUSSION

The number of postoperative complications in the control group was 34 (21.1%), and in the main group — 22 (14.7%). The use of laparoscopic access compared to open access reduced the risk of surgical complications (HR=0.13, *p*=0.001) on the one hand, but on the other led to an increase in the development of complications from the cardiovascular and respiratory systems (HR=4.7, *p*=0.001), arrhythmias (HR=3.73, *p*=0.07), thrombohemorrhagic complications (HR=2.8, *p*=0.05)

The total number of complications in the main groups was 42% (68 patients), in the control group — 29% (44 patients). Hospital complications in the main group developed in 34 (21.1%) patients, in the control group — in 22 (14.7%) patients. Complications related to the cardiovascular and respiratory systems in the main group were observed in 20 (12.4%), and in the control group in 4 (2.7%; *p*=0.001). In the main group, 12 (7.5%) had thrombohemorrhagic complications, and 4 (2.7%) in the control group. Complications associated with drug removal in the control group were observed in 2 (1.2%), and in the control group — in 14 (9.3%; *p*=0.001). Thus, an increase in the number of postoperative complications in the main group of patients was observed due to an increase in the number of complications associated with the cardiovascular and respiratory systems. This is probably due to the need to apply carboxyperitoneum in patients with premorbid pathology of the cardiovascular and respiratory systems when performing laparoscopic surgery.

In the structure of postoperative complications, pneumonia was found in 7 patients in the main group (4.3%), and in the control group in 1 patient (0.7%; *p*=0.04). Acute myocardial infarction occurred in 2 patients (1.2%) in the main group — in 1 (0.7%; *p*=0.60).

PE was observed only in the main group in 3 (1.9%), (*p*=0.09), and mesenteric thrombosis in 1 (0.7%) patient from the control group (*p*=0.29). Deep vein thrombosis in the main group was in 9 patients (5.6%), and in the control group in 3 (2.0%; *p*=0.10). Acute cerebrovascular accident was observed in 1 person (0.6%) from the main group (*p*=0.33), and hypertensive crisis in 4 patients from the main group (2.5%; *p*=0.05). Arrhythmias were more common in the main group in 8 patients (5.0%; *p*=0.08), and infectious wound complications at the site of intervention in the control group — in 7 (4.7%; *p*=0.007). Intra-abdominal bleeding was observed in the control group in 2 (1.3%), and in the main group in 1 (0.6% (*p*=0.52). Peritonitis associated with anastomosis failure in the control group was 4 (2.7%), and in the main group 1 (0.6%; *p*=0.16). Relaparotomy was performed only in the control group-in 7 patients- (4.7%; *p*=0.007). Repeated laparoscopy was performed in 3 patients (1.9%) from the main group (*p*=0.09). Bile congestion was in 1 patient (0.6%) from the main group (*p*=0.29), and eventeration in 5 (3.3%) from the control group (*p*=0.7). Hospital mortality in the main and control groups was the same (5 and 6%, respectively).

Overall survival of patients in all groups was monitored for 24 months after surgery. Figure 1 shows the 2-year overall survival of patients in the control group.

In the main group, a decrease in the survival rate from 1.0 to 0.23 was observed for 2 years

after laparoscopic operations. In the group of patients using laparoscopic access, there is an increase in overall survival, compared to the group of patients using open traditional access.

CONCLUSIONS

1.Laparoscopic access in combination with the developed surgical techniques allowed to significantly reduce the frequency of infectious and inflammatory postoperative complications in the main group (p<0.05).

2. the use of laparoscopic access compared to open access reduced the risk of surgical complications (HR=0.13, p=0.001), but led to an increase in the development of complications from the cardiovascular and respiratory systems (HR=4.7, p=0.001), arrhythmias (HR=3.73, p=0.07), thrombohemorrhagic complications (HR=2.8, p=0.05).

3. in patients in the main group, compared with the control group, there is an increase in overall survival (the logarithmic rank criterion was 2.11 at p=0.035)

SUMMARY

Colorectal cancer ranks fourth in the structure of total cancer mortality. In 25% of patients have stage IV at the first treatment, with primary liver damage. The standard of treatment for such patients is combined and complex treatment.

In recent years, laparoscopic surgery for metastatic colorectal cancer has become a priority. In our study, it was proved that the use of laparoscopic access reduced the number of surgical complications compared to open operations. However, despite this, patients with comorbid pathology have a higher relative risk of developing complications from other organs and systems.

Authors contribution:

Gevorkyan Yu.A. – editing of the work.

Kolesnikov E.V., Kharagezov D.A., Dashkov V.A. – the literature review.

Soldatkina N.V. – literature review, responsible for the scientific and technical level of work.

Kaymakchi D.O., Mirzoyan A.E., Poluektov S.I., Tolmakh R.E., Stateshny O.N., Doncov V.A. – conducted analysis of data on patients treated in the National Medical Research Centre for Oncology of the Ministry of Health of Russia.

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REVIEW

ABOUT EXPANDING OPTIONS FOR USING BALB/C NUDE MICE FOR EXPERIMENTAL STUDY OF HUMAN MALIGNANT TUMORS *IN VIVO*

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ABSTRACT

The article has a problematic scripting nature. At the present stage, in addition to objective factors that make it difficult to create adequate experimental models of human oncogenesis, there is a significant backlog of domestic science in the development of this direction. This reduces the availability for Russian specialists of humanized immunodeficient animals corresponding to the level of research tasks. Based on the analysis of literature data, we discuss approaches that can expand the use of a widely available immunodeficiency animal model-BALB/c nude mice. The possibility of using human mesenchymal stem cells that are not rejected by BALB/C Nude mice for local humanization of immunodeficient animals and improving the structural and functional characteristics of xenografts is considered. The possibility of obtaining xenografts of human glioblasts supported in the body of immunocompetent BALB/c mice after serial passages of organotypic tumor spheroids in the brain of BALB/c nude mice is analyzed.

Keywords:
xenografts of human malignant tumors, BALB/c nude mice, humanization methods, mesenchymal stem cells, immunocompetent animals, sibs

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ОБЗОР

О РАСШИРЕНИИ ВАРИАНТОВ ИСПОЛЬЗОВАНИЯ МЫШЕЙ BALB/C NUDE ДЛЯ ЭКСПЕРИМЕНТАЛЬНОГО ИЗУЧЕНИЯ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ ЧЕЛОВЕКА *IN VIVO*

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РЕЗЮМЕ

Статья имеет проблемный, постановочный характер. На современном этапе, помимо объективных факторов, затрудняющих создание адекватных экспериментальных моделей человеческого онкогенеза, имеет место значительное отставание отечественной науки в разработке данного направления. Это снижает доступность для российских специалистов гуманизированных иммунодефицитных животных, соответствующих уровню исследовательских задач. В работе на основе анализа сведений литературы обсуждаются подходы, которые могут расширить варианты использования широкодоступной иммунодефицитной животной модели — мышей BALB/c nude. Рассматривается возможность использования мезенхимальных стволовых клеток человека, не отторгаемых мышами BALB/c nude, для локальной гуманизации иммунодефицитных животных и улучшения структурно-функциональных характеристик ксенографтов. Анализируется возможность получения ксенографтов человеческих глиобластом, поддерживаемых в организме иммунокомпетентных мышей BALB/c после серийных пассажей органотипических сфероидов опухоли в головном мозге мышей BALB/c nude.

Ключевые слова:
ксенографты злокачественных опухолей человека, мыши BALB/c nude, методы гуманизации, мезенхимальные стволовые клетки, иммунокомпетентные животные, сибсы

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The goal of the scientific direction for creating effective models of human tumors is to reproduce human oncogenesis and related systemic changes as completely as possible in the body of experimental animals. This model is designed to provide an objective assessment of the effectiveness of anti-cancer drugs and technologies in relation to specific patients, as well as to clarify the mechanisms of development of human malignant tumors [1, 2]. At the present stage, the most promising models of the "avatar" type are considered to be immunodeficient animals that are transplanted with human hematopoietic stem cells (HSCs) and biopsy material obtained directly from cancer patients (patient derived xenograft, PDX) [1–3]. At the same time, there are a number of problems that make it difficult to reproduce the malignant process and the main part of the human immune and hematopoietic systems in the body of such animals [1, 2, 4].

First, a significant restriction on the use of humanized animals is the development of the graft-versus-host disease reaction, which occurs at different times depending on the type of human cells that are used for humanization, and inevitably leads to the death of animals. Secondly, the modern development of humanization methods allows us to recreate only some parts of the human immune system, and they are only partially reproduced. More complete restoration of populations of various blood cells in most cases requires the inclusion of transgenesis methods and additional research, which significantly reduces the availability of such animals.

In addition to objective factors that make it difficult to create adequate experimental models of human oncogenesis, there is a historical situation of a significant backlog of Russian science in the development of this direction. In Russia, there is no industry for the production of various versions of humanized immunodeficient animal models for fundamental and clinical medicine, which is already established in the United States, Western Europe, and China [1–3]. Thus, a serious problem is the high cost of animals belonging to the modern popular immunodeficiency lines NSG (NOD/SCID gamma mouse) and BRG (BALB/c Rag2), which are produced mainly in foreign laboratories [2]. At the same time it's well known, that immunodeficient BALB/c nude mice the most available to Russian researchers are not suitable for the main humanization procedures involving the introduction of either mature human peripheral blood mononuclears (h-PBL) or human hematopoietic stem cells (h-HSCs) [1, 2].

In our opinion, in this situation, in parallel with the development in accordance with foreign standards, we should also develop other approaches that allow us to obtain scientific and practical results based on available animal models. In this regard, it seems appropriate to carry out exploratory research in two directions. The first direction involves identifying effective modes of coimplantation of BALB/c nude xenografts of malignant tumors and human mesenchymal stem cells (MSCS) in mice to approximate the growth characteristics of transplants in the body of immunodeficient animals to the parameters of the original malignant process. The second direction may be related to the use of BALB/c nude mice to produce human glioblastoma xenografts that aren't rejected by their immunocompetent heterozygous sibs.

About the possibility of implantation of xenografts of human malignant tumors and human mesenchymal stem cells (MSCs) in mice BALB/c nude

When experimentally using xenografts of human malignant tumors, the key question is whether their structural, kinetic, invasive and metastatic characteristics correspond to the parameters of the initial malignant process [1–4]. It is known that cells of the immune system actively participate in the development of tumors, exerting an inhibitory or, on the contrary, stimulating effect on malignant cells, depending on specific systemic and local changes in the tumor-bearing organism [5–7]. In addition to the modifying action of the immune system cells, the achieve-

ment of such compliance is largely determined by the adequate xenograft microenvironment, which may strongly influence on the development of the tumor and its sensitivity to therapeutic effects [4, 5, 8]. This is why orthotopic PDX transplantation, which involves the transfer of biopsy material to areas similar to the loci of the original tumor development, has undoubted advantages over heterotopic subcutaneous transplantation [1, 2, 4]. Thus, in the case of orthotopic transplantation, PDX growth is supported by cells that are heterologous to human tissues, but functionally similar to them, and their constellations of the animal body located in the peritumoral zone. At the same time, orthotopic PDX transplantation cannot fully provide similarity to the malignant process in the human body [4, 5, 8].

Meanwhile, the results of a number of studies indicate the prospects of using human mesenchymal stem cells (MSCs) to overcome significant differences between the growth of primary tumors and their transplants in the body of immunodeficient animals, mainly NOD/SCID mice. As you know, MSC are multipotent stromal cells that are localized in different organs and tissues (cord blood, bone marrow, adipose tissue, dental pulp, placenta, etc.), which have the ability to differentiate into varied types of cells (osteocytes, chondrocytes, adipocytes, etc.) and migrate to the area of the tumor or the focus of inflammation [11, 12]. At the same time, it is assumed that MSCs can be differentiated directly in the tumor zone. It is known about the immunoregulatory effects of human MSCs in NSG mice [13]. Of great importance is the question of the interaction of human MSC and malignant cells, about which there is conflicting information. Thus, the inhibitory effect of human MSCs on the growth of orthotopically transplanted xenografts of the U87MG line cells was shown [14]. At the same time, accumulated data indicate the key role of MSCs in tumor progression due to their ability to facilitate epithelial-mesenchymal transition and increase tumor metastatic potential by their interaction with tumor cells [11, 15]. The ability of MSC to enhance regenerative processes also indirectly indicates the tumor-stimulating potential of these cells [16, 17]. The diverse effects of human MSCs on xenograft growth, obviously are depended on the difference in the types of interaction between human MSC and tumor cells — direct intercellular interaction or indirect modulation through the release of cytokines and other biologically active factors [18].

Recently, however, the view of MSCs as tumor-stimulating factor has begun to dominate. Thus, the results of a meta-analysis and a systematic review of a number of studies published in 2018 indicate that the introduction of MSCs contributes to an increase in the number of metastases and the frequency of metastasis by 1.25–2.0 times compared to the control parameters [19]. Very impressive results were obtained in an earlier period by American researchers from the University of Salt Lake City [20]. It was shown that orthotopic transplantation of breast tumors of major molecular subtypes directly from patients to NOD/SCID mice, accompanied by implantation of human MSCs supports a significant number of characteristics of the original tumors. The authors used fresh tissue fragments from primary tumors or samples of metastatic breast cancer cells collected immediately after surgery or ascitic fluid drainage from 42 different patients. At the same time, xenografts of the tumor were propagated by serial transplantation without any stages of in vitro cultivation, which eliminated the problem of selective adaptation to the conditions of cultivation. As a result, new models of breast tumor growth and metastasis in the form of transplantable tumors obtained directly from patients were proposed. The grafted material largely reflected the diversity of breast cancer forms and preserved critical features of parent tumors, including histological features, metastasis sites, clinical markers, gene expression profiles, number of DNA copies, and estrogen dependence for ER+tumors. At the same time, the combined administration of human MSCs with the tumor material maintained the stability of the properties of the original tumors and accelerated

the proliferation of malignant cells, stimulating angiogenesis. Moreover, the survival rate of the obtained xenografts had a prognostic value by clearly correlation with the patient's lifespan [20].

In our opinion, the above information suggests the prospects of using human MSCs to improve the growth of xenografts of human malignant tumors in BALB/c nude mice. Unlike h-PBLs and h-HSCs human MSCs are not rejected by these immunodeficient animals [12, 16], so the introduction of such cells can be considered as a kind of local humanization of BALB/c nude mice. At the same time, attention should be paid to a number of conditions and strategies, the significance of which for optimizing the growth of xenografts using human MSC should be subjected to a conscientious study. In our opinion, first of all, it is the use of PDX, rather than immortalized cell cultures, as well as the search for effective modes of administration of human MSCs, that may be especially important in the case of subcutaneous xenograft transplantation.

About the possibility of using BALB/c nude mice to produce human glioblastoma xenografts that are not rejected by their immunocompetent heterozygous sibs

The second direction of research, which may also be promising, is related to the use of immunocompetent animals. This circumstance seems to us very important due to the fundamental impossibility of comprehensive reproduction of human oncogenesis and, especially, human immune and hematopoietic systems in the body of immunodeficient laboratory animals [1, 4. 8]. In this regard, it is of great importance to create immunocompetent animal models that can support the growth of xenografts of human malignant tumors. In this case, we are talking about the feasibility of reproducing and further developing studies on BALB/c nude mice and their immunocompetent sibs that were previously carried out by researchers at the University of Bergen (Norway) on nude rats and immunocompetent heterozygous animals of the same brood [8].

The aim of this work was to create a model of human infiltrative glioblastoma growing in immunocompetent animals. The choice of an animal model with a complete immune system was due to the low translational significance of the results obtained on immunodeficient animals. The objects of the research were nude and immunocompetent Rowett rats of both sexes at the age of 8–12 weeks. The biopsy material obtained from patients during neurosurgical interventions was initially cultured as organotypic spheroids in accordance with a previously developed procedure [21]. The study of spheroids involved light and electron microscopy revealed morphological features similar to those of the original tumor tissue. They differed from the features of spheroids obtained from permanent cell cultures. The spheroids contained vessels, connective tissue, and macrophages, showing a marked similarity to the structure of the original tumor. Flow cytometry with an assessment of the cell cycle in the samples revealed the same ploidy and the same number of proliferating cells in the spheroids as in the original tumor. For transplantation, spheroids were selected that did not show a decrease in size after 80 days of cultivation. Spheroids with a diameter of 400 microns were implanted in the right hemisphere of the cerebral cortex to a depth of 2.5 mm. the Growth of spheroids in the brain of animals was evaluated using MRI.

It was shown that human glioblastoma xenografts in the form of organotypic spheroids serially passed in the brains of Rowett nude rats later can develop in the brain of their immunocompetent sibs, in contrast to spheroids obtained directly from the biopsy material of patients. In the case of engraftment in immunocompetent rats, growth of xenotransplants was observed in the absence of leukocyte infiltration of the tumor bed, just as it occurred in nude animals. Graft rejection was associated with massive infiltration of the tumor bed by white blood cells, mainly ED1 + microglia/macrophage cells, CD4 + T-helper cells, and CD8 + effector T-cells, and also correlated with elevated levels of pro-inflammatory cytokines IL-1β, IL-18, and TNF-α in serum. It was noted that the adaptation of the human tumor

to the brain of an immunocompetent animal occurred after several cycles of passivation in the brain of nude rats and was characterized by a pronounced weakening of the infiltration of the tumor by microglia cells. In addition, there was a decrease in tumor production of those chemokines that contributed to the migration of white blood cells and their penetration into the Central nervous system. Thus, during serial passaging in the brain of nude rats, human glioblastoma cells acquired the ability to avoid and/or suppress host immune responses and subsequently take root in immunocompetent rats without signs of an inflammatory response.

Currently, it's not possible to characterize the mechanisms that provide the tolerance of immunocompetent heterozygous Rowett rats to human glioblastoma cells. The authors assumed that the development of tolerance is associated with a sufficiently high content of regulatory immune cells [22]. There is also an important question about the therapeutic context of this phenomenon — whether a human tumor that develops in animals with a complete immune system can retain its structural and functional features and sensitivity to the action of antitumor agents. If the response is positive, this model can provide significant progress in the development of effective personalized antitumor treatment. Thus, it seems appropriate to carry out the similar researches on BALB/c nude mice and their heterozygous sibs. If the result obtained in Rowett rats is reproduced on mice, further research should be carried out to determine whether the characteristics of xenografts supported by immunocompetent animals correspond to the indicators of the malignant process in the human brain. In our opinion, in the latter case, experimental and clinical studies should include a comparative analysis of neuronal-glial relations [23], as well as changes in the immune system of the brain [24] with the growth of xenografts and original tumors, both as in cases of coincidence as at mismatch of their structural and functional characteristics and sensitivity to the action of tested antitumor agents.

CONCLUSIONS

We assume that the successful realisation of the suggested research directions, one of which is related to the local humanization of immunodeficient BALB/c mice with human mesenchymal stem cells, and the other — with the use of immunocompetent BALB/C nude mouse sibs to ensure the growth of xenografts of human glial tumors in the absence of immune deficiency, can make a significant contribution to the development of informative experimental models of the malignant process in humans.

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REVIEW

UNITED IMMUNOLOGICAL FORUM: CURRENT TRENDS IN THE DEVELOPMENT OF FUNDAMENTAL AND APPLIED ONCOIMMUNOLOGY (NOVOSIBIRSK, 2019)

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ABSTRACT

The work provides information on the results of the Joint Immunological Forum, which was held from June 24 to 29, 2019 in Novosibirsk. The modern directions of the development of fundamental and applied immunology are analyzed. Particular attention is paid to the discussion of the most issues identified in the section "Immunopathogenetic bases of tumor growth", which also presented the results of studies conducted at the National Medical Research Centre for Oncology of the Ministry of Health of Russia for the study of isolation and study of the biological properties of tumor stem cells. Noteworthy are the new advances in modern immunology, which clarify the hierarchical structure of lymphocyte populations, with the separation of various minor subpopulations based on the phenotypic, molecular genetic and functional properties of cells, whose role in ensuring the integrity of the body has not been fully studied. In addition to theoretical reports, during this Forum the results of using new methodological approaches to study the structural and functional organization of individual links of innate and adaptive immunity both under model conditions and during the development of various human diseases were presented, the most promising ways to improve analytical and technological platforms were identified. In the crayfish of the Forum, several advanced training programs were implemented for employees of various levels of practical health care and fundamental science.

Keywords:
fundamental and applied immunology, oncoimmunology, state and prospects of development of science, innate and adaptive immunity, antitumor immunity, lymphocytes, cytokines

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ОБЗОР

ОБЪЕДИНЕННЫЙ ИММУНОЛОГИЧЕСКИЙ ФОРУМ: СОВРЕМЕННЫЕ НАПРАВЛЕНИЯ РАЗВИТИЯ ФУНДАМЕНТАЛЬНОЙ И ПРИКЛАДНОЙ ОНКОИММУНОЛОГИИ (НОВОСИБИРСК, 2019)

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РЕЗЮМЕ

В работе представлена информация об итогах проведения Объединенного иммунологического форума, который проходил с 24 по 29 июня 2019 г. в Новосибирске. Анализируются современные направления развития фундаментальной и прикладной иммунологии. Особое внимание уделено обсуждению вопросов, обозначенных на секции «Иммунопатогенетические основы опухолевого роста», на которой также были представлены результаты проводимых в ФГБУ «НМИЦ онкологии» Минздрава России исследований в области выделения и изучения биологических свойств опухолевых стволовых клеток. Обращают на себя внимание новые достижения современной иммунологии, уточняющие иерархическую структуру популяций лимфоцитов, с выделением на основе фенотипических, молекулярно-генетических и функциональных свойств клеток различных минорных субпопуляций, роль которых в обеспечении целостности организма изучена не полностью. Помимо теоретических докладов, в ходе данного Форума были представлены результаты использования новых методических подходов для изучения особенностей структурной и функциональной организации отдельных звеньев врожденного и адаптивного иммунитета как в модельных условиях, так и при развитии различных заболеваний человека, обозначены наиболее перспективные пути совершенствования аналитических и технологических платформ. В раках Форума были реализованы несколько программ повышения квалификации для сотрудников различных звеньев практического здравоохранения и фундаментальной науки.

Ключевые слова:
фундаментальная и прикладная иммунология, онкоиммунология, состояние и перспективы развития науки, врожденный и адаптивный иммунитет, противоопухолевый иммунитет, лимфоциты, цитокины

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INTRODUCTION

The achievements of practical Oncology are largely related to new data obtained using a number of modern methodological approaches that allow us to identify the features of the structural and functional organization of innate and adaptive immunity elements. It is generally accepted that the immune system is involved in the control of antigenic homeostasis of the human body and, as a result, the fundamental importance of this system both in the fight against cancer, and, with a number of defects or its failure, in the occurrence and progression of the tumor.

For the further development of oncoimmunology, it's important to exchange experience with representatives of various scientific and practical teams, discuss new experimental data obtained by them, and involve promising theoretical approaches to explaining the facts observed in practice, what happens at forums and congresses of various levels.

The purpose of this report was to briefly highlight the results of the Joint immunological forum with international participation. The source of information was direct personal participation in the Forum, as well as the study of new theoretical and practical results of oncoimmunology presented in publications.

One of the most important events for immunologists this year was the holding of the "United immunological forum-2019" with international participation in Novosibirsk from 24 to 29 June 2019.

This forum brought together a number of events: VI Congress of the Russian scientific immunological society (RNOI); VIII Conference of the Russian cytokine society (RCO); VIII reproductive immunology conference; VIII Neuroimmunology conference; XV conference of immunologists of the Urals; Conference on targeted and cellular immunotherapy; Oncohematology and oncoimmunology conference; primary immunodeficiency international conference; School of flow cytometry; school of rheumatology; professional development Cycles.

The forum was attended by more than 500 people (12 academicians of the Russian Academy of Sciences, 12 corresponding members of the Russian Academy of Sciences, 111 doctors of science, 102 candidates of science, more than 190 people-practical health workers, postgraduates and students). The forum participants are representatives of 30 Russian cities, speakers and participants from near and far abroad: the USA, the Netherlands, Japan, the Czech Republic, Hungary, Bangladesh, Uzbekistan, and Kazakhstan.

During the forum 376 oral reports were presented at 43 symposiums, 22 reports were presented at 7 plenary sessions, and two round tables were held (problems of teaching immunology in medical Universities, the state and prospects of immunological journals). More detailed information is available on the official websites of the event (http://niikim.ru/ru; http://rnoi.ru; https://bs-sib.ru).

Analysis of the work of the «United immunological forum-2019»

During the Forum, various specialized sections and plenary sessions discussed the molecular and genetic basis of innate immunity, infectious and inflammatory diseases of the mucous membranes and lymphoid organs: new aspects of diagnosis and therapy of immuno-mediated diseases, the possibilities of modern flow cytometry in solving the problems of fundamental and applied immunology. The relevant sections covered such aspects as: the use of cytokines in the diagnosis, pathogenesis and treatment of human diseases, the state of the problem of autoimmunity, ophthalmoimmunology, tuberculosis immunology, immunological aspects of atherosclerosis, tumors of the immune system, and vaccination. The issues of fundamental and clinical psychoneuroimmunology, the state and prospects of hematopoietic stem cell transplantation, gene therapy and cell technologies in immunology, allergology and clinical immunology, etc. were considered.

Undoubtedly, special attention was drawn to the work of the section "Immunopathogenetic foundations of tumor growth" (27.06.2019). Within the framework of this section, reports were presented on both fundamental and applied oncoimmunology.

Would like to focus on the report of I.A.Baldueva (FSBI «N.N.Petrov National Medical Research Center Of Oncology» of The Ministry Of Healthcare of The Russian Federation, Saint Petersburg), which provided information about immuno — mediated adverse events (IAE) that occur in the body of a cancer patient during immunotherapy (IT) with drugs that inhibit the control points (ICT) of the immune response (anti CTLA-4 and anti PD-1/PDL-1). The development of Ionia is associated with excessive activity of effector mechanisms of the immune system against the background of it, which can lead to autoimmune damage to almost any organ and organ system [1].

After considering the main mechanisms of ion exchange, attention was drawn to the cytokine release syndrome as a modulator of cell-mediated reactions. Based on the analysis of a clinical case of a patient with melanoma of the skin, with the progression of the disease after surgical treatment, the mechanism of development of Ionia against the background of it (anti-CTLA therapy) was considered. The features of changes in some cellular parameters of the immune status (IC) are determined. An increase in individual subpopulations of cytotoxic lymphocytes ($CD3^+CD8^+$, $CD8^+$H-LA-DR^+, $CD3^+CD38^+$, $CD3^+CD16^+CD56^+$) was shown after. In the patient's body, elimination of $FoxP3^+$ Tged, an increase in the number of eosinophils and their activation was noted, which is accompanied by the release of a number of chemokines (CXCL9, CXCL10, CCL5), which cause chemotaxis of cytotoxic $CD8^+$ T lymphocytes, their migration to the tumor. The speaker noted that "IAE arise from the overall immune response to the tumor and, in most cases, effective treatment of ICTs can temporarily be subjected to immunosuppression with glucocorticosteroids (GCS)". GCS do not inhibit the cytotoxic activity of activated T-lymphocytes, and a number of studies have proven the synergy of their use with certain types of immune therapy.

Summing up, I.A.Baldueva noted: the mechanisms of development of antitumor immune response and IAE are identical; GCS are pathogenetic therapy for IAE, support a specific antitumor $CD8^+$ — T cell immune response to therapy with immune synapse modulators.

Novik A. V. (FSBI «N.N.Petrov National Medical Research Center Of Oncology» of The Ministry Of Healthcare of The Russian Federation, Saint Petersburg) in the report "Problems of immunotherapy in clinical practice: the need for immunological research" continued the discussion of issues related to it, noting the urgent need for immunological research. Assessment of quantitative and qualitative (functional) parameters of individual links of innate and adaptive immunity in cancer patients against the background of it, will identify new prognostic factors, the probability of development, the achievement/end of the effect, as well as identify and manage risks.

Savchenko A.A. (Krasnoyarsk scientific center of the Siberian branch of the Russian Academy of Sciences, Krasnoyarsk) in the report "Regulatory mechanisms of the formation of the phenotype and functional activity of dendritic cells", having considered modern ideas about the heterogeneity and mechanisms of maturation of dendritic cells (DC), as well as factors that determine these processes, focused on the features of the phenotype of blood monocytes ($CD14^+CD16^+$) in patients with kidney cancer [2]. The speaker noted that the work revealed a decrease in the number and functional activity of blood monocytes against the background of an increase in the content of Treg lymphocytes, and the phenotypic differences between DC are in the level of expression of CD80 and HLA-DR. An increased content of activated Treg lymphocytes in kidney cancer is accompanied by an increase in the number of Mature DCS with increased expression of CD80-a marker that contributes to the formation of immune suppression in the patient's body. Summing up, Savchenko A.A. he noted that the tumor's tolerogenic effect is realized in the formation of regulatory interactions with the immune system, the phenotype and functional activity of DC depends on the state of the monocytes from which they are formed, and in cancer, an important factor will be the tumor-associated progression factors.

Would like to draw attention to a number of facts presented in the report of N.V.Cherdintseva (research Institute of Oncology, Tomsk National Research Medical Center of the Russian Acade-

my of Sciences, Tomsk) "Macrophages and tumor progression: on the way to macrophage-specific therapy". In particular, there is no doubt that each person is a unique ecosystem, in which the outcome of the disease during the formation of a tumor is determined by the exposure of damaging factors, constitutive genetic parameters of the person, features of systemic and local (microenvironment) regulation, as well as tissue architecture, which guide the development of the somatic cell. In the occurrence of a tumor and the severity of antitumor immunity, a special role is assigned to tumor-associated macrophages (TAM), for which high plasticity is shown, participation in such key processes as the regulation of the proliferative activity of tumor cells, the influence on their invasive properties, angiogenesis, the severity of the epithelial-mesenchymal transition, the ability to metastasize and resistance to radio and chemotherapy. We discussed the ideas that have been accumulated to date about the methods being developed for reprogramming stromal-inflammatory elements to counteract the tumor, while specialized populations of tumor-promoting macrophages can act as a target for cancer therapy.

This section presents the results conducted in the National Medical Research Centre for Oncology of the Ministry of Health of Russia studies aimed at the isolation and study of biological properties of tumor stem cells (report, "Tumor stem cells and their microenvironment: role in tumor development", Sahakyants A.B.), implemented in the framework of public procurement "Study of possibility of using the tumor stem cells to create models of xenogeneic tumors in the experiment". 19 tumor cells with the stem phenotype were isolated from postoperative material of patients by immunomagnetic separation using reagents from MiltenyiBiotec (Germany). The selection was made in accordance with the manufacturer's instructions. For each case, depending on the type of tumor, the necessary set of primary antibodies conjugated with magnetic particles was selected. Also, depending on the number of cells, the concentration of reagents and the type of magnetic column were selected. The cells of the target population were adsorbed (positive separation) on magnetic spheres and separated into a single fraction upon completion of separation. To isolate tumor stem cells (OSC), antibodies to the following antigens were used (table 1).

Among these, glial brain tumors accounted for 9 cases, breast cancer-7 cases and 3 more cases-brain metastases (ovarian cancer, lung cancer).

The cell population isolated as a result of separation (positive fraction) was from 0.2 to 1 million cells. Cells were transferred to a T25 vial in a culture medium without serum with insulin, transferrin and L-glutamine (GMP DC, CellGenix, Germany) in an amount of at least 0.5 million per 5 ml vial. A negative fraction that does not contain the target cell population was used as a control. The composition and volume of the medium, the type of vial, and the number of cells in the negative fraction were similar

Table 1. List of markers and reagent kits used to isolate tumor cells with the stem cell phenotype

№	Antigen OSC	The set of reagents	type of neoplasm
1	CD133	CD133 MicroBeadKit, human (130-097-049)	Glial tumors; metastasis of lung cancer to the brain ovarian cancer metastasis to the brain; breast cancer (BC)
2	CD90	CD90 MicroBeads, human (130-096-253)	Glial tumors
3	CD44	CD44 MicroBeads, human (130-095-194)	BC, metastasis of lung cancer to the brain
4	CD24	CD24 MicroBeadKit, human (130-095-951)	BC
5	CD117	CD117 MicroBeadKit, human (130-091-332)	Ovarian cancer metastasis to the brain

to the positive fraction. After 1–3 days, the growth of free — floating spherical colonies-oncospheres was observed in the vials, while the number of colonies in vials with an enriched target cell fraction was several times greater than in the corresponding control samples, which is evidence of the presence of stem properties in the isolated subpopulations of tumor cells. It is known that in conditions of low adhesion, differentiated tumor cells and non-malignized cells undergo anoikis-apoptosis as a result of incorrect cell adhesion or its absence [3], while OSCs survive and selectively multiply, forming free-floating in the environment of the oncosphere [4, 5]. In the future, the first experiments were carried out on the experimental creation of a xenogenic model of a human brain tumor on immunodeficient mice. A total of 6 transplants of oncospheres with the phenotype ($CD90^+CD133^+$) obtained from OSC isolated from gliomas were performed [6].

The attempts made to create xenograft models of gliomas by transplanting isolated OSC did not give the expected result — no visible macroscopic growth of the tumor was obtained in the experiment after three months. Taking into account a number of methodological features and practical experience, work in this direction continues.

Summing up the information presented in the reports on this section, it should be noted that much attention was paid to modern ideas about the immunology of tumors, the role of both individual lymphocytic and myeloid representatives in the occurrence, progression and response to treatment of various tumors. Special attention was paid to the consideration of dendritic cells, monocytes, and macrophages in oncological diseases

During the presentations, the mechanisms of tumor occurrence in multicellular organisms were discussed, as well as the recognition of the mutation theory of multistage carcinogenesis, according to which the malignant properties of a cell are the result of the accumulation of genetic disorders (mutations and chromosomal aberrations). Driver disorders are changes in the activity of genes that determine the lifecycle of cells-proto-oncogenes and anti-oncogenes [7].

It is noted that the appearance and development of a tumor is not always accompanied by the presence of a pronounced immunodeficiency or signs of immune disorders. Thus, the incidence of most types of solid tumors does not increase with immunosuppression, and the incidence of breast cancer actually decreases. In addition, the incidence of spontaneous tumors in mice bastianich not higher than that of immunocompetent animals. The ambiguous experience of using immune system stimulation in the vast majority of patients with malignant tumors-all this points to the complex, contradictory nature of the interaction between the tumor and the immune system, the ambiguous role of the latter in the progression of the disease, which is reflected in such a concept as the idea of immunoreduction of tumors [8].

The malignant tumor development is the result of exogenous and endogenous nature combination factors that increase the probability of survival, increase the number and spread of tumor cells, which is a consequence of genetic instability, reprogramming of cell metabolism, manifested in changes in the nature of biochemical processes and affecting almost all their aspects. Of particular importance in the occurrence and progression of a tumor is its ability to "escape" from immune surveillance, as well as the impact of tumor-promoting chronic inflammation [7, 9].

Considering the mechanisms of "eluding" the tumor from the immune response, the special role of immune selection of tumor cells (loss of neo-antigens and/or changes in the expression of HLA-I and costimulatory molecules), as well as the formation of an indifferent microenvironment and the induction of immunosuppression, which in turn can be associated with:

with the expression of molecules that induce apoptosis of effector cells (soluble forms of FasL and MICA);

— release of soluble ligands that block T-cell receptors;

— secretion of cytokines that inhibit the activity of lymphocytes and dendritic cells (IL-10, TGF-β, VEGF);

— isolation of cytokines and factors that attract T-reg and macrophages with immunosup-

pressive activity (GM–CSF, G-CSF, IL-6, IL-10, VEGF, PGE2, IL-1).

There is no doubt about the special role of immune control points in inducing immune suppression, the role has been discussed in several reports.

The study of the widest possible range of factors of the tumor microenvironment is the key to a better understanding of the biology of tumors, searching for the most effective ways to diagnose and treat these diseases. It is important to determine the molecular and genetic characteristics of tumors, and to study the system for controlling gene expression: epigenetic, post-transcriptional, and post-translational. In addition, the study of transcription factors and functional specialization of lymphocytes and leukocytes continues [10], the role of heterogeneous micro-RNAS as regulators of inflammatory and immune responses during tumor growth [11].

The information about the classification of tumors depending on the phenotype of transformed cells (PD-L1 expression) and prevailing immunological components (TIL– tumor-infiltrating lymphocytes) in their microenvironment was interesting [12]:

— type 1-acquired resistance to cellular immune responses, which is associated with the expressed expression of PD-L1 tumor cells against the background of the presence of TILs with the phenomenon of inhibition of their activity;

— type 2-immunological ignoring, developing in the absence of PD-L1 simultaneously with a number of features of the antigenic properties of the tumor, without its infiltration of TILs. In this case the ICCS do not identify the transformed cells and do not respond to them;

— type 3-internal PD-L1 induction, a number of factors contribute to the expression of PD-L1 by cancer cells, but there is no penetration of cytolytic lymphocytes into the tumor;

— type 4-immunological tolerance that occurs without the presence of PD-L1 on tumor cells under conditions of its pronounced infiltration of TILs that do not show cytolytic activity. Probably, in this case, additional immunosuppressive pathways are involved.

Despite the fact that the proposed classification scheme of tumors is simplified, it can probably be used to discuss the strategy of immunotherapy, depending on the microenvironment of the tumor.

We should also mention the role of the microbiota in determining the type of immune response, the probability of developing tumors, as well as the nature of the body's response to antitumor treatment, including inhibitors of immune response control points, which was reflected in the report of T.A.Karmakova [13, 14].

When discussing the strategic prospects for the development of tumor Immunobiology, it was pointed out that it is necessary to characterize the individual characteristics of the immune response in each patient, as well as to monitor changes in immune indicators during treatment, which is a General trend in Oncology at the moment. The range of defined indicators, as well as the multiplicity of the research is not unified, but is actively discussed at various specialized events. However, General approaches are being developed to develop these standards and determine the most informative indicators that reflect the state of the immune system of the cancer patient.

Considering the methodological aspects of studying the immune response in the development of tumors, it was pointed out the need to reconstruct the network of intercellular signals, which involves the use of new information technologies and accumulated empirical data, the study of the relationship between local and systemic indicators of the immune system, as well as the need to harmonize data obtained with the use of modern technologies.

Without touching on the methodological aspects, which was not the purpose of this work, we should note those modern technologies that, in our opinion, and in the opinion of colleagues, are promising for studying the immune response [15]:

— Multiplex immunohistochemistry;
— Mass cytometry;
— Multiplex analysis methods;
— Omix technologies;
— Cluster analysis.

At the section "New models, research methods and diagnostic systems in immunology"

(28.06.2019), our attention was drawn to the report of Tarasevich A.A. on the topic "from cells to tissues: mass cytometry-the latest method of cell phenotyping in immunology and Oncology".

This report provided information about a new technology — CyTOF®, used for cell phenotyping and combining traditional approaches in cytometry with mass spectrometry [16].

It is known that standard approaches to phenotyping, such as immunohistochemistry combined with microscopy, flow cytometry, high-content Screening, are based on the analysis of the fluorescence of labeled antibodies interacting with corresponding markers in target cell populations. However, there are a number of known features that must be taken into account when using these technologies: the probability of overlapping dye spectra, different signal intensity from different fluorophores, and background fluorescence, which imposes a number of restrictions for multiparametric analysis. These limitations significantly complicate the design of the experiment and the interpretation of the resulting data.

CyTOF® technology eliminates the limitations of fluorescence, since signal separation is based on detecting the mass of labels, not the wavelength of the fluorescent molecule. In this case, special tags are used, consisting of non — radioactive isotopes of rare earth metals (lanthanides) attached to various probes-the same monoclonal antibodies, intercalators, etc. the Main advantages of using rare earth metals are that they are not detected endogenously in biological samples. After performing all the necessary preanalytical procedures, the samples are examined on a mass cytometer (mass spectrometer), in which the material is sprayed in special media into individual drops. Subsequently, the droplets containing the cells are separated, followed by the measurement of metal isotopes on each individual cell in the suspension. Modern devices can analyze more than 40 parameters [16].

However, according to a number of authors, this technology is not without disadvantages: the presence of impurities used in the analysis of metals in accompanying samples; the probability of formation of metal oxides, which shifts the signals in terms of molecular weight and, as a result, leads to overlap between the probes; incompatibility with living cells; relatively low throughput (5–7 min per sample) [17].

Despite this, mass cytometry is finding more and more applications in various fields of fundamental and applied science and its use allows you to get new data. Thus, Li N. and colleagues, examining biopsies of frozen intestinal tissue of human embryos, showed the presence of memory T-cells in the embryos, which allows us to state the fact that the embryo's immune system is more mature than it was previously thought [18].

The use of these methodological approaches will allow the most effective modeling of tumor growth processes, forecast the response to immunotherapy, and select an adequate personalized treatment.

A promising direction is the development of relevant experimental models [19]:

— a new generation of humanized mouse models (transgenic expression of cytokines, HLA antigens, hormones, human MHC molecules);

— study of the genetics of induced tumors (search for models with high mutation load);

— comparative immunology and immunogenetics of human and laboratory animals;

— *ex vivo* surrogate models (primary organoid cultures: co-culture with lymphocytes and monocytes, selection of personalized treatment regimens, genetic manipulations (CRISP-CAS9; SIRNA), research of stem tumor cells).

Separately, it should be noted that the forum held a full-time part of the professional development program "Flow cytometry in clinical practice". The following issues were raised during the program (some of them were discussed):

— Multicolored analysis-basic principles and approaches (Kudryavtsev I.V., Saint Petersburg);

— Application of standardized technology of leukocyte immunophenotyping in the clinic. Role of assessment of small subpopulations of lymphocytes (Zurochka A.V., Chelyabinsk);

— Assessment of the cellular component of the "immune status" for monitoring the state of the immune system (S.V.Khaydukov, Moscow);

— Features of assessment of cellular immunity in newborns and young children (Semykina E.L., Moscow);

— Study of markers of lymphocyte activation in the clinic of various pathological conditions (Kalinina N.M., Saint Petersburg);

— Immunograms. Diagnostic possibilities of assessing the cellular level of immunity (Nikitin Yu V., Saint Petersburg);

— The role of flow cytometry in Oncohematology (Lugovskaya S.A., Moscow);

— Flow cytometry in clinical oncoimmunology (Zabotina T.N., Moscow);

— Multicolored flow cytometry. Advantages and methodological approaches (Savitsky V.P., Moscow).

Course participants and forum participants had the opportunity to get new information about modern developments in the creation of the most effective fluorochromes used for the identification of phenotypic markers of immunocompetent cells, which, in turn, allows improving multiparametric flow cytofluorimetry. Undoubtedly, new issues and problems related to the need to improve the software used in the analysis of the obtained data were also discussed, as well as the discussion of the rules for creating working panels of monoclonal antibodies and the most appropriate strategies for gating.

During the practical classes, there was an opportunity to get acquainted with the work and capabilities of the new cytometer, to review and analyze the results of the analysis of the immune status (flow cytometry) for primary and secondary immunodeficiency, allergic diseases, and various oncohematological diseases. A General strategy for processing and analyzing the results of determining the parameters of cellular immunity using flow cytometry was presented.

CONCLUSION

Based on the results of the visit and work of a number of sections and plenary sessions of the forum, the Following General trends can be identified in the study of the mechanisms of the functional organization of the immune system in various human diseases:

1) identification and assessment of the contribution of heterogeneous subpopulations of (minor) white blood cells and lymphocytes to the immune system and immunopathogenesis of diseases;

2) special emphasis on the study of effector leukocytes (monocytes, macrophages, dendritic cells, neutrophils) and lymphocytes (T -, B -, NK), the mechanisms of their functional activity and interaction with each other in the development of the pathological process;

3) study of heterogeneity and functional activity of regulatory subpopulations of leukocytes and lymphocytes with the allocation of 3–4 separate functional types of cells with regulatory function in each population;

4) assessment of the expression level of PD-1/PD-L1, -L2 on various somatic cells and study of their contribution to the implementation of the immune system function in a particular individual (norm and pathology);

5) relevance of screening studies using modern methodological approaches (e. g. multiplex analysis), which allows us to identify new patterns of the immune system both in normal and in various pathological conditions;

6) certain prospects for the development of immunology are associated with the further improvement and implementation of mathematical modeling of immunological reactions, the work of individual organs of the immune system in normal and pathological conditions.

Thus, the result of the work of the "United immunological forum-2019" with international participation was the accumulation and systematization of information about the immunology of tumors, current views on the immunological mechanisms of infectious and inflammatory, allergic diseases, trends in approaches to the diagnosis and treatment of these pathologies, as well as the designation of a number of promising areas in the organization and conduct of research in the field of fundamental and applied immunology.

Author contribution:
Sagakyants A.B – the concept and study design, writing text, processing of the material.

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CLINICAL CASE REPORTS

HORMONE-POSITIVE HER2-NEGATIVE METASTATIC BREAST CANCER: DECISION MAKING IN REAL CLINICAL PRACTICE

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ABSTRACT

Breast cancer (BC) is the most common female cancer and the first leading cause of cancer death in women. Luminal phenotypes represent about 70% of this disease. Treatment for metastatic hormone-dependent HER2-negative breast cancer in most cases involves various lines of endocrine therapy since their sequential use improves overall and relapse-free survival while maintaining a high quality of life. Disease progression during such therapy may be associated with the development of primary or secondary resistance to the treatment. The reason for the secondary resistance is both a mutation of receptors for steroid hormones and activation of new signaling pathways. The study of these mechanisms has led to the creation of highly effective drug combinations for the treatment of hormone-positive HER2-negative metastatic breast tumors. To date, clinical trials of three agents from the group of cyclin-dependent kinases has been developed and successfully completed: palbociclib, ribociclib and abemaciclib. These agents in combination with non-steroidal aromatase inhibitors or estrogen receptor antagonists in randomized clinical trials increased direct treatment efficacy, overall survival and progression-free survival rates. Clinical case of a menopausal patient with metastatic hormone-positive HER2-negative breast cancer with visceral metastases who received successive chemotherapy and a combination of the highly selective oral kinase inhibitor CDK4\6 ribocyclib with the aromatase inhibitor letrozole allowed to achieve a response to therapy for 27 months with CR for 8 months. The safety profile was satisfactory; side effects included grade 2 neutropenia, grade 1 arthralgia, grade 1 hyperglycemia and grade 1 increase in urea which did not had an adverse effect on the patient's quality of life.

Keywords:
metastatic breast cancer, hormone therapy, cyclin-dependent kinases, ribocyclib, palbocyclib, abemacyclib

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

ГОРМОНОПОЛОЖИТЕЛЬНЫЙ HER2-НЕГАТИВНЫЙ МЕТАСТАТИЧЕСКИЙ РАК МОЛОЧНОЙ ЖЕЛЕЗЫ: ПРИНЯТИЕ РЕШЕНИЙ В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

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РЕЗЮМЕ

Рак молочной железы (РМЖ) занимает 1-е место в структуре онкологической заболеваемости и смертности женского населения. Около 70% этой патологии составляют люминальные фенотипы. Лечение метастатического гормонозависимого HER2-негативного РМЖ в большинстве случаев предполагает применение различных линий эндокринотерапии, их последовательное применение обеспечивает увеличение показателей общей и безрецидивной выживаемости при сохранении высокого качества жизни. Прогрессирование заболевания на фоне такой терапии связано с развитием резистентности к проводимому лечению, которая может быть первичной и вторичной. Причинами возникновения вторичной резистентности являются как мутация рецепторов к стероидным гормонам, так и активация новых сигнальных путей. Изучение этих механизмов привело к созданию высокоэффективных комбинаций препаратов для лечения гормоноположительных HER2-негативных метастатических опухолей молочной железы. На сегодняшний день в мире разработаны и успешно завершены клинические исследования трех препаратов из группы циклинзависимых киназ: палбоциклиб, рибоциклиб и абемациклиб. Применение этих препаратов в сочетании с нестероидными ингибиторами ароматазы или антагонистами эстрогеновых рецепторов в рандомизированных клинических исследованиях увеличило показатели непосредственной эффективности лечения, общей выживаемости и частоту выживаемости без прогрессирования. Клиническое наблюдение пациентки с метастатическим гормонопозитивным HER2-негативным РМЖ в менопаузе, с висцеральным поражением, получившей последовательно химиотерапию и комбинацию перорального высокоселективного ингибитора киназ CDK4/6 рибоциклиба с ингибитором ароматазы летрозолом, позволило достигнуть длительности ответа на терапию 27 мес, с достижением полного ответа на лечение, сохранявшегося в течение 8 мес. Профиль безопасности был удовлетворительным, из побочных явлений наблюдались: нейтропения 2 степени, артралгия 1 степени, гипергликемия 1 степени и повышение мочевины 1 степени, что не повлияло отрицательным образом на качество жизни пациентки.

Ключевые слова:
метастатический рак молочной железы, гормонотерапия, циклинзависимые киназы, рибоциклиб, палбоциклиб, абемациклиб

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Breast cancer (BC) is consistently ranked 1st in the structure of cancer incidence and mortality among the female population. BC is a heterogeneous group of tumors. Among all phenotypes, luminal (defined by the expression of estrogen and/or progesterone receptors) HER2-negative tumors predominate, their specific weight can reach 70% [1].

The treatment principles of hormone-dependent HER2-negative metastatic BC have remained unchangeable for several years until nowadays [2]. In 1977, tamoxifen was registered as a drug for the treatment of metastatic BC, and this led to a significant success in the treatment of this disease. After the appearance of aromatase inhibitors in the Arsenal of oncologists and their use in the first line therapy, it was possible to achieve a progression-free survival of 10–13 months (in the case of tamoxifen, it was from 6 to 9 months). The introduction of the next generation drug, fulvestrant, and its use in first-line treatment of metastatic BC increased the median time to progression to 16.6 months compared to 13.8 months for an aromatase inhibitor (anastrozole), as it's demonstrated in the FALCON study [3].

Sequential use of various variants of endocrinotherapy provided a significant increase in overall and relapse-free survival rates while maintaining a sufficiently high quality of life. However, with this tactic, the disease invariably progressed over time. The main reason was the development of resistance to treatment. Tumor resistance to endocrinotherapy can be either primary (initial lack of sensitivity of tumor cells to drug- induced receptor block) or developing during treatment [4, 5].

Secondary resistance may be associated with mutation of the steroid hormone receptors themselves, or by activation of other signaling pathways. The study of these mechanisms eventually led to the development of the latest highly effective drug combinations for the treatment of hormone-positive HER2-negative metastatic breast tumors.

The discovery of the role of cyclin-dependent kinase (CDK) in the regulation of the cell cycle was awarded the 2001 Nobel prize in medicine [6], and eventually led to the creation of the first CDK inhibitor palbociclib, which in combination with letrozole or fulvestrant fundamentally improved the results of hormone therapy for metastatic and locally advanced luminal breast cancer, which was convincingly demonstrated in several multicenter randomized phase II and III studies. Thus, the addition of palbociclib to letrozole in the 1st line of endocrine therapy led to a significant increase in overall survival and immediate effectiveness of treatment, the median progression-free survival was 27.6 months vs. 14.5 months (HR 0.563; 95% CI 0.461–0.687; p<0.000001), and the overall response rate in the entire population was 42.1% vs. 34.7% (p=0.031) [7].

Nowadays, two other drugs have been developed and successfully completed clinical trials in the world: ribociclib and abemaciclib, which were also studied in the first line of therapy for hormone-positive metastatic breast cancer in randomized placebo-controlled phase III trials. The MONALEESA-2 study evaluated the effectiveness of ribocyclib in combination with letrozole, and the median progression-free survival for ribocyclib and placebo was 25.3 and 16 months, respectively (HR 0.568; 95% CI 0.457–0.704; p=9.63 × 10–8). In the subgroup with measurable disease, the combination of ribocyclib with letrozole provided a 52.7% overall response rate compared to 37.1% for placebo with letrozole (p<0.001) [8].

Abemaciclib was studied in the study phase III MONARCH-3, combined with nonsteroidal aromatase inhibitors demonstrated the increased effectiveness of hormone therapy: the median survival without progression in the group with abemaciclib at the time of data collection was not achieved in the placebo group amounted to 14.73 month (OR 0,543; 95% CI 0,409– 0,723; p=0,000021), in the subgroup with measurable lesions abemaciclib combination with anastrozole or letrozole provided the overall frequency response of 59% compared with 44% for placebo (p=0.04) [9].

The FDA has approved the use of all three drugs in both premenopause and menopause,

and ribociclib and palbociclib are registered and available in the Russian Federation. Despite the fact that their clinical effectiveness is almost identical, there are some differences in the toxicity profile, principles of dose reduction, and monitoring during treatment [10].

Clinical Case

Patient P., born in 1959 (58 years old), went to the national medical research center of Oncology (RNIOI) in April 2017 in a good performance status (ECOG 1), complaining of moderate general weakness, decreased performance, and discomfort in the right hypochondrium.

From anamnesis: a tumor in the right breast was discovered in September 2014, and she went to the RNIOI in December 2014, where a comprehensive examination revealed the diagnosis: right breast cancer cT2NxM0 stage II. During a puncture biopsy of the tumor, verification was not obtained. The first stage of complex treatment on 17.12.14 was performed radical mastectomy on the right, histological conclusion was obtained: G2 invasive ductal carcinoma, metastatic lesion of three axillary lymph nodes. The result immunohistochemical expression of estrogen receptors expressed in 80%, expression of progesterone receptors is moderate — 70%, an index of proliferative activity ki67–15%, expression Her2neu — 0. Postoperative diagnosis: right breast cancer pT2N1M0 stage IIB, luminal a subtype. From 23.01.2015 to 14.07.2015, she received 6 courses of adjuvant therapy according to the FAC scheme in standard dosages, a course of remote gamma therapy for postoperative scar and lymph nodes pathways up to 40 Gy of total focal dose. An adjuvant endocrinotherapy with tamoxifen was prescribed, which the patient received further.

In April 2017 the above complaints appeared and she was examined by place of residence. Magnetic resonance imaging of abdominal organs revealed multiple metastases to the liver. The patient was sent to the institute.

During the treatment, a spiral x- ray computed tomography (RCT) of the brain, chest, abdominal cavity and pelvis was performed on 19.04.2017. Multiple metastatic liver lesions were detected up to 5.5 cm, the concretion of the gallbladder up to 2 cm, in the other organs studied without pathological neoplasms. In the biochemical analysis of blood, an increase in the level of transaminases > 3 UNL, a moderate increase in the level of alkaline phosphatase was noted. The clinical data combined with laboratory changes were considered as a visceral crisis.

Thus, based on the examination, a clinical diagnosis was established: right breast Cancer cT-2NxM0 pT2N1M0 stage IIB, complex treatment 2014–2015, generalization in 2017, metastasis to liver. Concomitant diseases: arterial hypertension stage II, cholelithiasis.

Due to the generalization of the disease, the patient underwent 6 courses of chemotherapy (carboplatin and docetaxel in standard dosages) from 22.04.2017 to 15.08.2017. The effect was evaluated every 3 courses. After the 6th course a partial remission was achieved (according to the RECIST criteria). A decrease in the number and size of metastatic leasions in the liver — in the right lobe of the node up to 1.4 cm, in the left lobe — up to 2.7 cm) was found. In the biochemical blood analysis, the level of transaminases and alkaline phosphatase was normalized comparing to the beginning of the treatment. The therapy was accompanied by toxicity in the form of grade II nausea, grade I–III leukopenia, grade III neutropenia, grade I–II peripheral sensory neuropathy, and grade 2 alopecia. The Patient also found an improvement in general well-being, but general weakness persisted.

Since 19.09.2017, in order to continue the effect achieved after chemotherapy, antitumor drug therapy was started according to the scheme: ribociclib 600 mg per day inside for 1–21 days, a break up to 28 days, letrozole 2.5 mg per day p. o. continuously, 24 cycles were performed, and treatment continued until 08.07.2019.

The therapy tolerability was satisfactory, the following side effects were noted comparing to the beginning of treatment: neutropenia 2 gd,

during treatment was recorded three times, for the first time in 9 months from the beginning of ribociclib therapy, lasting 5, 4 and 1 month, which did not require the cancellation or reduction of the dose of ribociclib. Arthralgia 1 gd. with damage to the joints of the hands and feet, after 12 months of hormone therapy. Alopecia 1 gd. appeared after 9 months of treatment with ribociclib and persisted throughout the whole treatment period. From laboratory abnormalities, hyperglycemia 1 gd., developed in 18 months after the start of therapy, which lasted for 3 months, and an increase in urea of 1 gd was sound in 19 months after the start of treatment. Adverse effects didn't affect the patient's quality of life. ECG was performed monthly and significant changes, including the QTc interval, were not revealed.

Every 12 weeks, the effectiveness of the therapy was evaluated according to the RECIST criteria.

During 14 months, the disease remained stable according to CT control, and the control measurable leasions decreased by 30% from the initial ones, the next CT control performed on 16.11.2018, discovered complete remission — metastatic leasions measurable and immeasurable in the liver were not visualized, there were no new metastatic leasions in organs and systems. The complete response continued for 8 months. In July 2019, control CT revealed the progression of the disease. Response to the treatment with the use of letrozole and ribociclib and maintained for 22 months. The duration of response to treatment with chemotherapy followed by the appointment of a CDK 4/6 inhibitor with letrozole was about 27 months.

CONCLUSION

The use of cyclin-dependent kinase inhibitors (CDK 4/6) is a new option in the treatment of hormone — positive HER2-negative metastatic BC. The article presents a clinical case of a patient with hormone-positive HER2-negative BC in menopause, who after complex treatment and endocrinotherapy with tamoxifen in 2 years revealed the progression of the disease with multiple metastatic liver damage and visceral crisis development. The administration of chemotherapy followed by the use of a combination of the oral highly selective CDK4\6 kinase inhibitor ribocyclib with the aromatase inhibitor letrozole allowed to achieve a duration of response to therapy of 27 months, with the achievement of a complete response to treatment within 8 months.

The tolerability of therapy was satisfactory and well-managed, during the treatment, the symptoms of the disease were stopped and the quality of life was improved.

Based on the information above, it can be concluded that the use of cyclin-dependent kinase inhibitors in real clinical practice is the optimal therapy option for patients with metastatic hormone -positive HER2-negative BC.

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CLINICAL CASE REPORTS

THE SURGICAL TREATMENT EFFECTIVENESS OF PATIENTS WITH MIDDLE EAR CANCER

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ABSTRACT

Among human malignant tumors, middle ear cancer is rare: up to 0.06%, and among ear tumors — up to 5%. Due to the late detection of the tumor, patients turn to a specialist with advanced, nearly or completely unresectable disease, and it limits the treatment to conservative one with poor results. Combination treatment is the most effective option, where surgery plays a leading role. During surgery, temporal bone tissues affected by a tumor are removed.

Over the decade from 2003 to 2018, we operated on 10 patients with advanced cancer of the middle ear who had previously received radiation therapy (cumulative dose 40 Gy). Lymphadenectomy was first performed in 3 patients with neck metastases. During surgery, the temporal bone was removed in all patients. The results of treatment demonstrated that relapse-free survival in 3 patients was 2 years, in 4 patients — 3, in 2 patients — 4 years; 1 patient — no data available. Two patients who survived 3 years received repeated surgery due to recurrence. Upon discharge, patients underwent chemotherapy at the place of residence. A clinical case of a 42-years old patient with advanced disease is presented. Cranial spiral x-ray computed tomography showed advanced middle ear cancer affecting cranial bones. The patients underwent radical surgery on the temporal bones with isolation of the facial nerve and exposure of the jugular bulb. Histological examination of tumor tissues of the external auditory canal and parotid salivary gland confirmed squamous cell carcinoma.

Temporal bone tissues affected by the tumor were removed during surgery. The elements of the organ of corti and cochlea were exposed and preserved: the horizontal semicircular canal, the oval and round windows. A wide external auditory canal was formed, and the wound was packed; skin grafting was performed. The patient has been in remission for 8 months.

Keywords:
middle ear cancer, resection of temporal bone, dura mater, inner ear, auditoty ossicles, tumor

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

ЭФФЕКТИВНОСТЬ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ БОЛЬНЫХ РАКОМ СРЕДНЕГО УХА

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РЕЗЮМЕ

Среди злокачественных опухолей человека рак среднего уха встречается редко: до 0,06%, а среди опухолей уха — до 5%. В связи с поздней выявляемостью опухоли больные обращаются к специалисту с распространенным на грани резектабельности или с нерезектабельным процессом, что вынуждает онколога ограничиться консервативным лечением, которое обычно не способствует выздоровлению и ухудшает результаты. Наиболее эффективным является комбинированное лечение, в котором операции отводится ведущая роль. В процессе операции удаляются пораженные опухолью костные ткани височной области.

За десятилетний период, с 2003 по 2018 гг., нами прооперировано 10 больных с распространенным раком среднего уха, предварительно получивших лучевую терапию (суммарная очаговая доза 40 Гр). Трем больным, имеющим шейные метастазы, вначале была осуществлена лимфаденэктомия. В процессе операции у всех больных резецировалась височная кость. Результаты лечения показали, что 3 больных без рецидива прожили 2, а 4 – 3 года. 2 больных прожили 4 года. Судьба одного больного неизвестна. Двум больным, пережившим 3 года, из-за рецидива была проведена реоперация. При выписке по месту жительства пациенты подвергались химиотерапии. Представлен клинический случай 42-летней больной с распространенным процессом. Проведенная спиральная рентгеновская компьютерная томография (СРКТ) черепа выявила распространенный рак среднего уха с поражением костей черепа. Больная была подвергнута радикальной операции на височной кости с выделением лицевого нерва и обнажением луковицы яремной вены. Результаты гистологического исследования опухоли наружного слухового прохода и околоушной слюнной железы подтвердили наличие плоскоклеточного рака.

В процессе операции удалены пораженные опухолью костные ткани височной области. При этом были обнажены и сохранены элементы кортиева органа и улитки: горизонтальный полукружный канал, «овальное и круглое окна». Сформирован широкий наружный слуховой проход. Рана тампонирована. Кожная пластика. Ремиссия 8 мес.

Ключевые слова:
рак среднего уха, резекция височной кости, твердая мозговая оболочка, внутреннее ухо, слуховые косточки, опухоль

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Middle ear cancer is a rare oncopathology: accounts 1–2% of all human malignancies and up to 10% of ear cancer. The disease proceeds by covert penetration into the temporal bone [1, 2].

The tumor occurs in patients who associate it with chronic purulent inflammation of the middle ear. They are treated by an otolaryngologist, and the disease is considered as a prolonged chronic otitis media. The tumor process spreads from the middle ear to the external auditory canal, which is mistakenly regarded as a polyp [3]. The performed biopsy establishes the malignant process, and the patient is sent to the oncologist. Histologically, squamous cell carcinoma with a tendency to keratinization is mainly detected. Other types of cancer (adenocarcinoma, adenocystic carcinoma, etc.) develop extremely rarely. At the same time, metastases to regional lymph nodes are usually observed in the late stage of the disease [4].

Patients are treated by an oncologist, usually with an already common, on the verge of resectability, or with an unresectable process, which forces the oncologist to limit himself to conservative treatment, which usually does not contribute to recovery [5]. Best results are achieved with the complex treatment, which is dominated by the operation [5, 6].

The purpose of the study: to improve the effectiveness of treatment of patients with a common malignant tumor of the middle ear.

PATIENTS AND METHODS

For the period from 2003 to 2018, we've operated on 10 patients aged 35–65 years: 6 male and 4 female. In 5 patients, the process was complicated by facial nerve paralysis. The external auditory canal was obstructed by a tumor in all patients. The diagnosis in all cases was verified-squamous cell cancer with keratinization. 9 patients had enlarged cervical lymph nodes of II AB levels, and one had metastases to both cervical and parotid lymph nodes. In all cases, a puncture biopsy revealed the presence of metastases.

All patients had previously received preoperative irradiation on the primary lesion — the region of the middle ear and temporal bone, and cervical metastases. Irradiation was carried out in static mode with 2 fields, the single dose was 2.0 Gr, the cumulative dose was 40–45 Gr.

Surgical interventions were performed the type of classical operations on the middle ear according to the method of Zaufl-Levin, but with a more expanded volume due to radical removal of the tumor-affected bony parts of the temporal bone and cervical metastases. The Dura mater of the temporal lobe of the brain was exposed in 8 patients, while removing the affected and destroyed bone tissue, and in 6 patients the mastoid process was removed, the sigmoid sinus was opened, followed by tamponade of its lumen with a hemostatic sponge. In 5 patients with facial nerve paralysis, the horizontal part of the nerve was exposed and removed, and if necessary, the modified bone tissue of the temporal bone was removed. After removal of the affected bone tissue, a common cavity was formed in the temporal bone including the middle ear cavity (*cavum tympani*), its communication (*aditus ad antrum*) with the mastoid cave (*antrum mastoideum*). Removal of the tumor from the middle ear cavity was performed using an operating microscope. At the same time, elements of the cortical organ and the cochlea were exposed and preserved. As a rule, the auditory bones were destroyed: "hammer" and "anvil". "Stapes" in all patients was intact — it was preserved.

The external auditory canal was expanded for good visualization of the postoperative wound after radical removal of the tumor. It was performed by a T-shaped incision of the cartilaginous part of the external auditory canal with the expansion and fixation of the formed triangular cartilage flaps. The operating wound was loosely tamponed with an ointment swab with antiseptic. The wound was sutured tightly with the end of the tampon removed out through the newly formed external auditory canal.

After 10–15 days, patients were discharged for outpatient observation and postoperative

chemotherapy with cisplatin and 5 fluorouracil.

The results of treatment showed that 3 patients without relapse lived 2 years, and 4–3 years. 2 patients lived for 4 years. The fate of one patient is unknown. Two patients who survived 3 years, due to a relapse that occurred in the bone tissue bordering the Dura mater, were re-operated, after which they died 6 months later. Lethality occurred from brain metastasis (4) and 2 — from lung metastases. At this time, 3 patients are alive (more than 4 years).

Clinical observation

A patient of 62 years old turned to an oncologist at the Federal state institution National Medical Research Centre for Oncology of the Ministry of Health of Russiaof the Russian Ministry of health for a tumor of the right middle ear. Was under the supervision of an ENT doctor for 1 year without achieving a therapeutic effect. When viewed in the clinic RCRI the tumor was growing into the ear canal. The cervical and parotid lymph nodes were enlarged. A biopsy of the tumor in the auditory canal and cervical lymph nodes was performed. In the projection of the zygomatic process with the transition to the parotid salivary gland, a dense painless subcutaneous tumor-like formation of 4.0×3.0 cm with disintegration was determined. Enlarged upper cervical, manually dense, weakly mobile, painless lymph nodes of II a-B levels (Fig. 1). A SCT study was conducted.

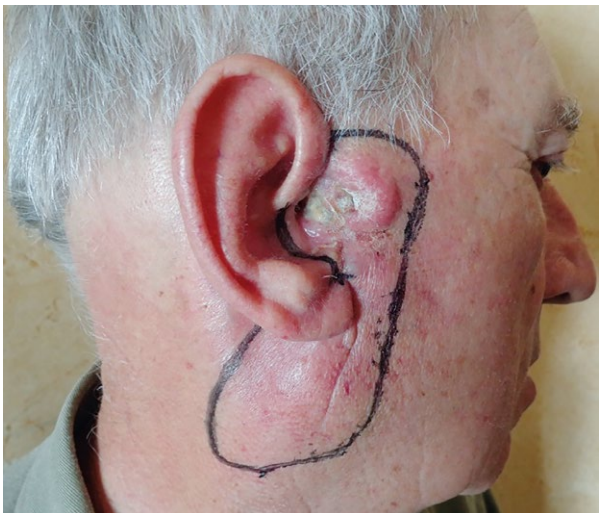
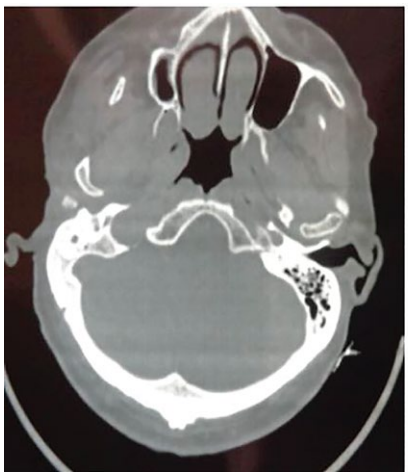


Fig. 1. Patient S. The appearance when entering RCRI. D-z: skin Cancer of the external auditory canal with spread to the middle ear and parotid salivary gland. Level IIA-B cervical metastases

It was revealed that air conduction on the right ear is missing during the acumetry. At the same time, bone conduction was preserved, and it's lateralization (Weber's symptom) was in the sick side, which indicated a violation of sound conduction while maintaining sound perception. Conclusion: the inner ear is not affected.

The results of histological tumors examination of the external auditory canal and parotid salivary gland confirmed the presence of squamous cell cancer.

CT scans of the skull revealed a common right-sided cancer of the middle ear with damage to the skull bones (Fig. 2).



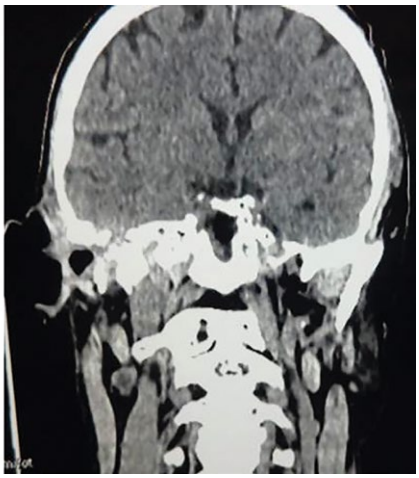


Fig. 2. Patient S. a Computer tomogram of the skull in 2 projections: an infiltrative tumor affecting the subcutaneous tissue anteriorly from the auditory canal on the right with a spread to the parotid salivary gland, affecting the skin of the external auditory canal with a transition to the middle ear. Destruction of the anterior walls of the external auditory passage and the roof of the tympanic cavity with partial destruction of the pyramid of the temporal bone

An operation was suggested, to which the patient consented. Preoperative radiation therapy was performed in a cumulative dose of 45 Gr.

The operation was performed under General anesthesia with intubation through the mouth. Initially, on the side of the lesion, lymphodissection was performed in the volume of IIA-B, III levels with the removal of the affected skin and soft tissues of the parotid region. The facial nerve was isolated and preserved. Surgery on the temporal bone was performed according to the method Zaufl- Levin using an operating microscope.

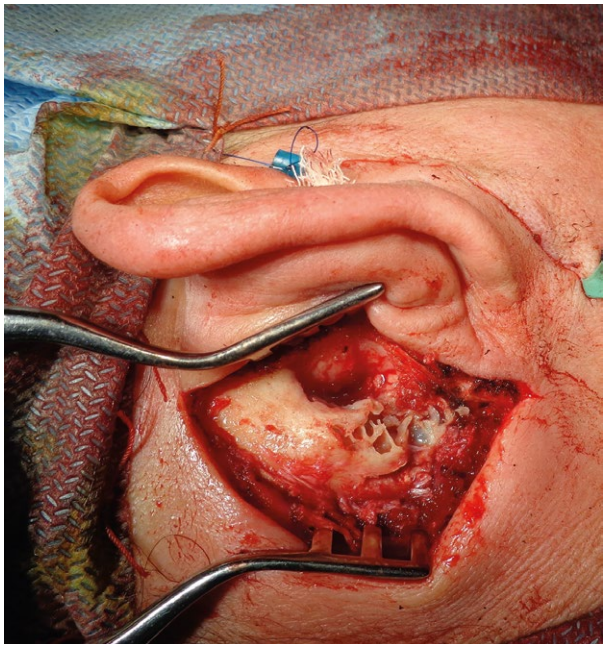


Fig. 3. Exposed mastoid process with areas of bone destruction

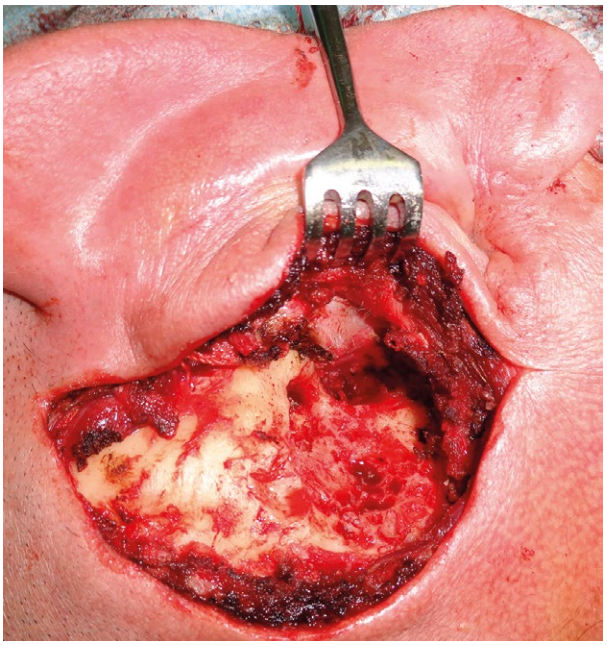


Fig. 4. after removal of the surface bone tissue, tumor masses were detected in the mastoid process

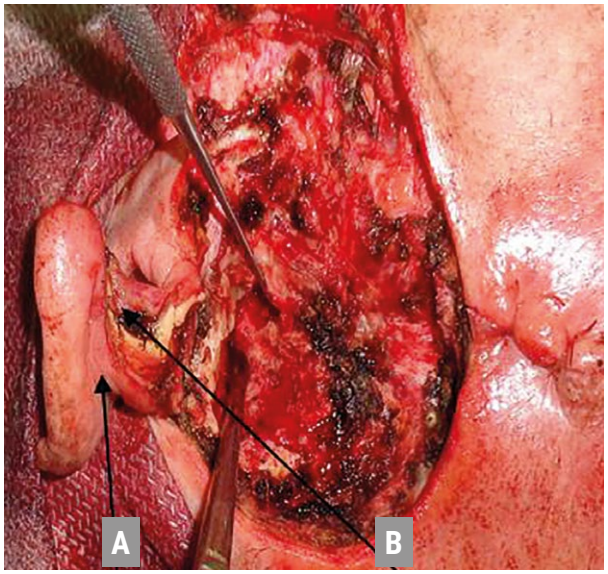


Fig. 5. the lumen of *antrum mastoideum* (A) and *aditus ad antrum* (B) is isolated. the Surrounding bone tissue is affected by a tumor

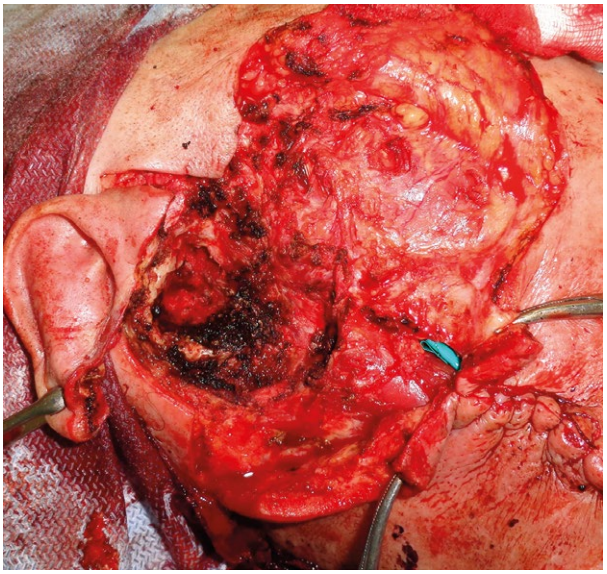


Fig. 6. The temporal bone after removal of the tumor – a common bone cavity is formed, including the *antrum, aditus ad antrum* and *cavum tympani*. The skin of the parotid region affected by the tumor was removed

During the operation, the tumor-affected bone tissues of the temporal region were removed (Fig. 3, 4, 5). One common cavity was created, including the *antrum mastoideum, aditus ad antrum*, and *cavum tympani* (Fig. 6). The tumor-affected part of the temporal bone was removed to its healthy part without exposing the Dura mater. The auditory bones: the Malleus and stepladder, as well as the horizontal semicircular canal were not destroyed by the tumor, while the remains of the anvil were in the General tumor mass — they were removed. The hammer was removed because it was not needed, while the stepladder was saved and left in the oval window (Fig. 7).

A wide external auditory canal is formed. The wound is swabbed. Skin plastic (Fig. 8). Bandage.

The postoperative period passed without complications. After 2 weeks, the tampon was removed. The relapse-free period is more than 3 years. Improved hearing to the perception of spoken speech in the ear.

CONCLUSION

Unfortunately, relatively few publications are devoted to middle ear cancer. This can be explained by the fact that this disease is mostly asymptomatic, simulating banal otitis media. Patients are treated by an otorhinolaryngologist. In the absence of a positive effect, the progression of the process and the appearance of a tumor clinic, patients are referred to an oncologist. By this period, the process becomes widespread, and the results of its treatment are not always satisfactory. Patients die from the progression guidance or metastasis in the brain. The best results are achieved with complex treatment, where the operation dominates. However, due to topographical and anatomical features, it is not always possible to conduct it radically. Reasons: difficulty of surgical access, with an extremely limited volume of the middle ear cavity. It should be noted that the effectiveness of the operation depends much on the experience of the surgeon, accumulated during the development of the operation technique, first with cadaverous material, with visual knowledge of the limit of surgical activity, and subsequent accumulated clinical experience. Taking into account the peculiarities of the pathology under consideration, it is always necessary to objectively assess the volume of the planned operation and the possibility of complications.

You need a precise knowledge of topographic and anatomical features of the middle ear

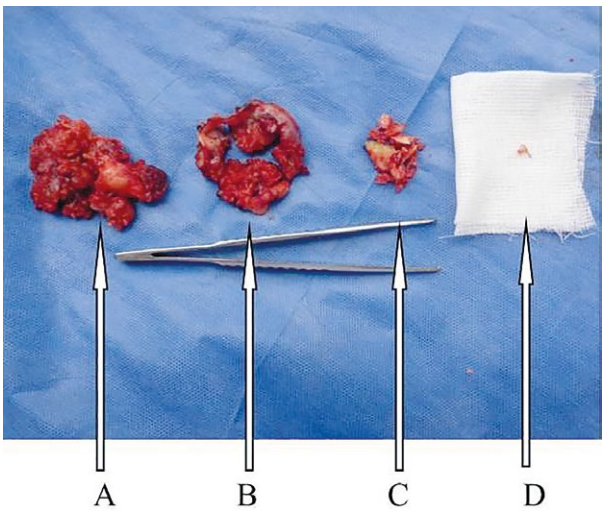


Fig. 7. Removed tissue: A – cervical and parotid metastases; B – tumor-affected tissue of the temporal bone; C – affected bone covering the Dura mater; D – unchanged auditory bone-Malleus

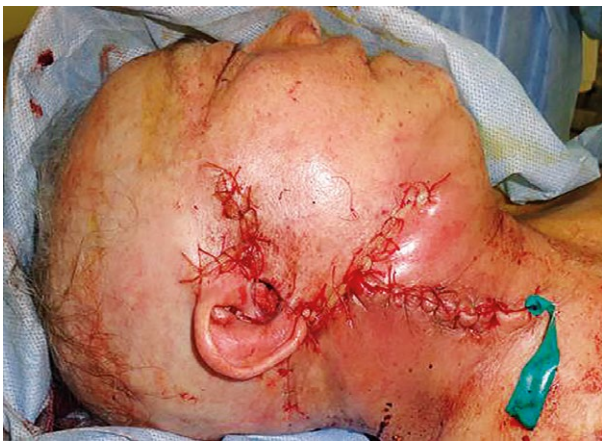


Fig. 8. The appearance of the patient after surgery

and it's borders with the vital organs: upper middle ear bordering the cavity of the skull, at the front, the internal carotid, from below — the horizontal branch of the facial nerve and a fragment of the internal carotid artery, behind — the sigmoid sinus, the lower edge of which enters the bulb of the internal jugular vein. The inner (medial) wall of the middle ear cavity is represented by the outer wall of the inner ear-a snail with a cortical organ and semicircular channels. The outer part of the cavity is the most calm and is represented by the eardrum. Damage to vital parts of the middle ear cavity is fraught with serious complications.

Authors contribution:
Svetitskiy P.V. – research concept and design
Engibaryan M.A. – surgical assistance
Meshceryakov P.N. – performing and interpreting x-ray studies

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