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ORIGINAL ARTICLE

OPTIMIZATION OF PLANNING RADIONUCLIDE DIAGNOSTIC TESTS IN OSTEOSCINTIGRAPHY

N.A.Maksimova*, V.G.Karpun, M.A.Arzamastseva, M.G.Ilchenko, O.S.Shlyk

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ABSTRACT

Purpose of the study. Determining maximum possible number of high-quality radionuclide studies by days of the generator operation.

Materials and methods. We studied the factors influencing the capacity of radionuclide diagnostic tests in osteoscintigraphy (OSG) by days of service life of a ^{99m}Tc generator GT-4K. The OSG capacity, the required resource of ^{99m}Tc and its efficiency in OSG were calculated. The optimal days for the generator delivery were determined.

The Pirfotech ^{99m}Tc radiopharmaceutical (RFP) prepared with the generator was used for OSG.

Scanning, data collection and processing of results were carried out on gamma-cameras of the systems Signature Series, Symbia T16 Siemens, and syngo M1 Applications VB10 Siemens.

Parameters of the radioactivity of ^{99m}Tc were processed by mathematical methods using the Excel program.

Results. We revealed specific factors influencing the OSG capacity: 1) three-hour accumulation of RFP after its administration to the patient; 2) generator activity by days of its operation; 3) the day of the week of the generator delivery. We calculated quantitative indicators of the maximum possible OSG capacity during the generator operation (maximum number of OSG procedures by days of operation, total capacity, preferred day of the week for the generator delivery).

Conclusion. The most significant factors in optimal OSG planning by days of the generator operation are the generator specifications, quantity and frequency of generator supply, provision of gamma-cameras.

The described technique for scheduling diagnostic procedures can be useful for the efficient use of the generator system which ensures the maximum amount of high-quality RFP from the generator eluate and contributes to the objectification of the cancer process in order to choose the treatment tactics.

Keywords:

radionuclide research, osteoscintigraphy, generator ^{99m}Tc , radiopharmaceutical, OSG planning, pirfotech, capacity.

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ОПТИМИЗАЦИЯ ПЛАНИРОВАНИЯ РАДИОНУКЛИДНЫХ ДИАГНОСТИЧЕСКИХ ИССЛЕДОВАНИЙ ПРИ ПРОВЕДЕНИИ ОСТЕОСЦИНТИГРАФИИ

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РЕЗЮМЕ

Цель исследования. Определение максимально возможного числа качественных радионуклидных исследований по дням срока эксплуатации генератора.

Материалы и методы. Для достижения поставленной цели изучались факторы, влияющие на пропускную способность радионуклидных диагностических исследований остеосцинтиграфии (ОСГ) по дням срока эксплуатации генератора ^{99m}Tc типа ГТ-4К (генератор). Рассчитывалась пропускная способность ОСГ, необходимый ресурс ^{99m}Tc и эффективность его использования при проведении ОСГ. Определялись оптимальные дни поставки генератора. Для проведения ОСГ применялся радиофармацевтический препарат «Пирфотех, ^{99m}Tc » (РФП), приготовление которого обеспечивалось с помощью генератора.

Сканирование, получение данных и обработка результатов осуществлялась на гамма-камерах систем e.cam Signature Series, Symbia T16 "Siemens, syngo M1 Applications VB10 "Siemens".

Обработка показателей параметров радиоактивности ^{99m}Tc осуществлялась математическими методами с помощью программы Excel.

Результаты. Выделены специфические факторы, влияющие на пропускную способность ОСГ: 1) трехчасовое накопление РФП после введения его пациенту; 2) активность генератора по дням эксплуатации генератора; 3) день недели поставки генератора. Рассчитаны количественные показатели максимально возможной пропускной способности ОСГ в период эксплуатации генератора (максимальное число ОСГ по дням эксплуатации, суммарная пропускная способность, предпочтительный день недели поставки генератора).

Заключение. Наиболее значимыми факторами оптимального планирования ОСГ по дням срока эксплуатации генератора являются технические характеристики генератора, количество и периодичность поставки генератора, обеспеченность гамма-камерами.

Таким образом, описанная нами методика планирования проведения диагностических процедур может быть полезной для эффективного использования генераторной системы, что обеспечивает получение максимального количества качественных РФП из элюата генератора и способствует объективизации онкологического процесса с целью выбора тактики лечения.

Ключевые слова:

радионуклидные исследования, остеосцинтиграфия, генератор ^{99m}Tc , радиофармпрепарат, планирование ОСГ, пирфотех, пропускная способность.

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RELEVANCE

The examination of cancer patients is extremely complex, including radiation, endoscopic and various laboratory methods of investigation [1]. Modern diagnostics of metastatic lesions of the skeletal bones is of great importance for the choice of treatment and prognosis for many malignancies, such as: breast, prostate, thyroid, lung, kidney, stomach, esophagus, intestine [2–5]. Among the existing methods of radiological diagnosis of bone metastases, osteoscintigraphy (OSG) occupies a priority position [6].

OSG is a method of radionuclide diagnostics based on the introduction of a radiopharmaceutical (RFP) drug to the patient's body and subsequent registration of its distribution and accumula-

tion in the skeleton using gamma-cameras. OSG is not only highly sensitive, but also allows scanning the entire skeleton, which is not possible with other more specific methods of examination (fig. 1).

Spiral computed tomography is also used to diagnose bone metastases. Although highly specific, it does not provide early diagnosis of the lesion [7].

Emission tomography (osteoscintigraphy) of the whole body remains one of the most popular methods of radionuclide diagnostics. According to our data, OSG consistently accounts for more than 80% of the total number of radioisotope studies. So, in 2017, 2057 radionuclide studies were performed in the radioisotope laboratory with the ultrasound diagnostics group based on the National Medical Research Centre for Oncology of the Ministry of Health of Russia, of which 89% (1837) is skeletal emission tomography, in 2018, 2255 were performed, of which 86% (1928) is skeletal emission tomography, in 2019, 2394 were conducted, of which 88% (2110) were OSG. The quality of the received information and the throughput is affected by the activity of the RFP: increasing the activity, in order to reduce the scanning time to increase the throughput, increases the patient's dose load [6]. Reducing the activity, in order to increase the number of OSH (RFP is distributed to a larger number of patients), reduces the image quality, affects the reliability of the conclusion. The scan time indicator affects the quality of the information received, the throughput, and also depends on the patient's condition. The radioactivity factor of the RFP inevitably affects the planning of the OSG. In the presence of low RFP activity, it is impossible to plan a large number of OSG, because in such cases, technological capabilities will not be observed and the information obtained during scanning will be of poor quality; increasing the scan time reduces throughput.

The high demand for OSG requires optimization of research planning with the maximum use of the generator resource on the days of operation, taking into account the RFP activity indicator, the scan time.

The purpose of the study. To determine the most possible number of high-quality radionuclide studies by the days of the generator's service life.

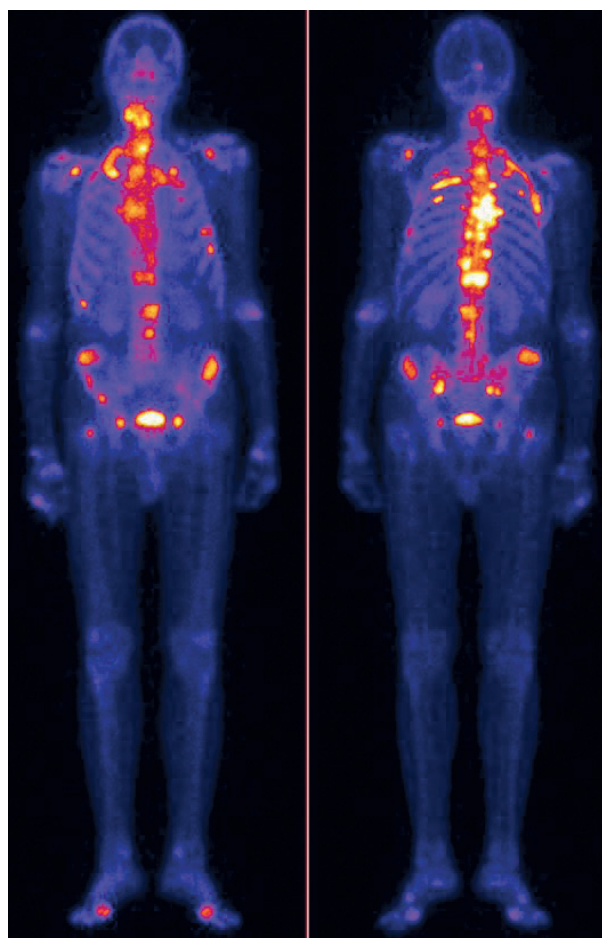


Fig. 1. Multiple foci of pathological hyperfixation of RF are detected on the osteoscintigram (osteoblastic metastatic lesion of skeletal bones in prostate cancer).

MATERIALS AND METHODS

For conducting events an OSG was applied RFP "Pirfotech, ^{99m}Tc ", cooking which one provided by using the generator ^{99m}Tc GT-4K type.

Generator set technetium-99m the GT-4K type represents is a device containing the sorbent is molybdenum-99 with a period half-life 66.02 hours in the form molybdenum ammonium $(\text{NH}_4)^+$ $(\text{MoO}_4)^+$ and destined for multiple use obtain sterile solution pertechnetate sodium with technetium-99m (eluate) [9].

Calculation General activity eluate (resource of the generator) as of the date of the event conducted by using the formula radioactive material maternal breakdown the isotope ^{99}Mo :

$$A = A_0 * 2^{-(t/T_{1/2})},$$

where A – total activity eluate for the day t, GBk;

A_0 – activity starting point on delivery date by passport to the generator and the start time (8:00 h) operating conditions of the generator, GBk;

t – elapsed time after the start operating conditions of the generator for the day and time shift starts, one o'clock;

$T_{1/2}$ – half-life molybdenum-99, equal to 66.02 hours.

Scheme radioactive materials transformations described by next one with the scheme:

^{99}Mo ($T_{1/2}=66.02$ h) $\rightarrow \beta$ -(86.3%) $\rightarrow ^{99m}\text{Tc}$ ($T_{1/2}=6.01$ h) $\rightarrow \gamma$ (140keV, 89.6%) $\rightarrow \dots$

As a result beta-minus the decay is formed by new isotope – ^{99m}Tc with a period half-life 6.01 hours Maximum value activity ^{99m}Tc achieved by after 23 hours, which provides possibility every day obtain the isotope ^{99m}Tc .

Activity radionuclide (radioactive substances) ^{99m}Tc evaluated derived form using the SI unit – Becquerel. In the calculations for amenities enjoyed a multiple of one gigabecquerel – GBk (1 GBk = 10^9 BC) [11].

Processing indicators OSG process was carried out using mathematical methods methods with using the program Excel.

OSG conducted by on gamma-cameras systems e.cam Signature Series, Symbia T16 "Siemens, syngo M1 Applications VB10 "Siemens" several timesstages.

Initial stage to patient intravenous enter the RFP, then, through 3 hours after introduction of the RFP, conducted by planar scanning full body study on average, it takes 20 minutes.

The final one this stage is used for archiving and a computer program processing received data results [10].

In calculations and in the future process analysis OSG we were systematized the following factors affecting on efficiency planning process, time of the event OSG and access card the ability of the process:

1) generator resource (volume activity received eluate 5–10 ml) the first one day of operation it is 11.59 GBk. Calculated by at the start time opening hours 8:00 from passport number values equal to 11.00 GBk as of date and delivery time 13:00;

2) total time for conducting a survey all OSG per shift compose 180 min. It turns out by subtracting out of time duration shifts (420 min) preparation time to be held OSG 30 min, time savings entered

The estimated practical and maximum possible throughput of the OSG by the days of the generator's service life when performing the OSG on a single gamma-camera with a single generator

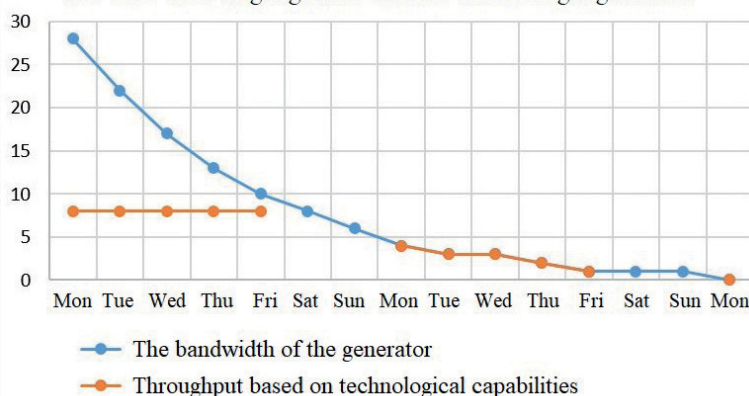


Fig. 2. Maximum throughput when conducting OSG on one gamma-camera and having one generator.

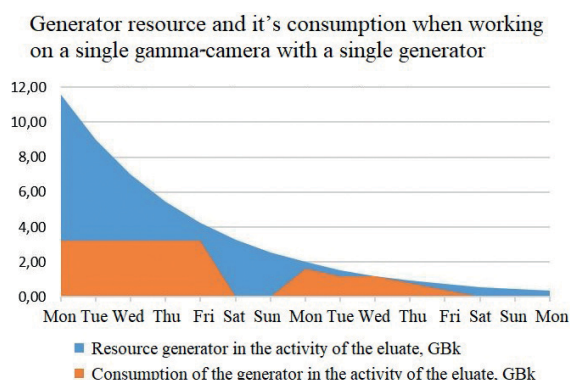


Fig. 3. The generator resource, in the activity (GBk) of the resulting eluate, by the days of its service life and its consumption, taking into account the technological capabilities when working on a single gamma-camera.

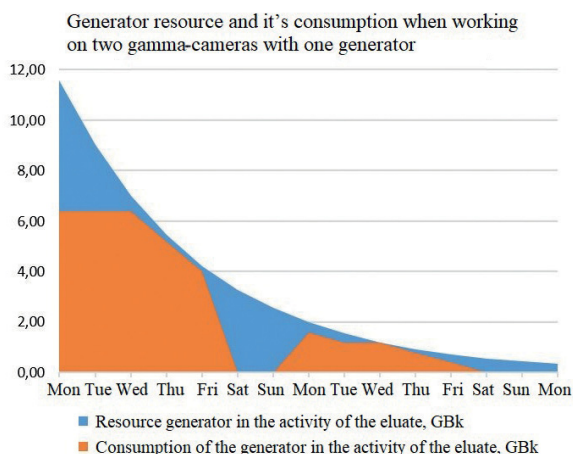


Fig. 4. The generator resource, in the activity of the resulting eluate, by the days of its service life and its consumption, taking into account the technological capabilities when working on two gamma-cameras with one generator.

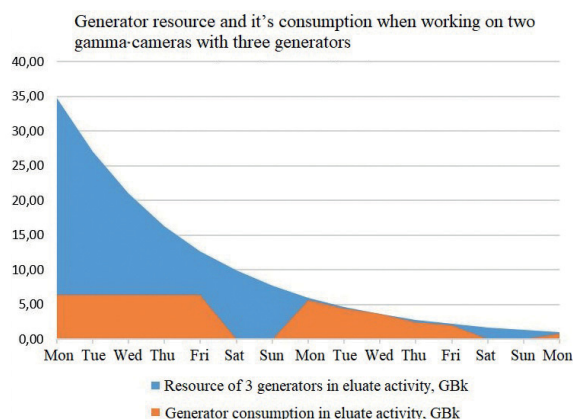


Fig. 5. Generator resource and its consumption when performing OSG on two gamma-cameras and simultaneously delivering three generators.

RFP for the patient 180 min and time complete run works on gamma-cameras in a shift of 30 minutes. 30-minute session preparation and completion works based on on technical sites and organizational issues events isotope analysis works ad blocks;

3) max. number of OSG in the change is equal to eight. It turns out by dividing the total OSG time per shift 180 min on average collection time data for one research – 22 min (adds up out of time installation/removal the patient and scan time (scan time with a height of 170 cm and speed scanning system that provides the optimal one the exhibition consists of about 17.5 min);

4) required information need the eluate for security features maximum value access point abilities for a change to 3.2 GBk. It turns out by multiplying-max. the number of OSG in change (8) to activity eluate for one research – 0.4 GBk (in accordance with The with instructions for medical purposes to use "of the drug Pirfotech, ^{99m}Tc ", – 3–6 MBq per 1 kg weight, for an adult a patient with weighing 75 kg was accepted equal to 0.4 GBk);

Calculation max. the number of OSG in the shift was made for the following to the algorithm:

defined possible max. number of OSG on the site planned day 2 dividing values generator resource for this day and the start time works on the valueactivities the eluate for conducting events one of OSG (0,4 GBk). Then, we compared this value is with the maximum the number of OSG in a shift. Ifestimated value the meaning of OSG more than or if it is equal to 8, then for planned the value accepted – 8 if less 8, then the calculated value the value was rounded up down and received the value was accepted for what is planned the number of OSG. Calculation performed by all days of the deadlineoperating conditions the generator. Figure 2 shows results calculating the actual cost of access point abilities OSG taking into account technological solutions features in the comparison with the maximum access point ability to when using total resource generator, by expiration date operating conditions of the generator when you run OSG on the one gamma-camera with one generator.

The results of the calculations were tabulated, and graphs of the OSG process indicators were plotted. Numerical values and graphical construction were analyzed. The throughput of the possible

OSG for all days of the guaranteed life of the generator was determined as the sum of all calculated values for the specified period.

The dependence of the total throughput on the day of the week of generator delivery for the operational period was calculated similarly to the algorithm described above.

We considered the following options for the OSG process under the specified conditions:

1. One gamma-camera and one generator;
2. Two gamma-cameras and one generator;
3. Two gamma-cameras and three generators set at the same time.

All patients signed an informed consent to conduct the study before the study.

THE RESULTS OF THE RESEARCH AND THEIR DISCUSSION

Fig 3–5 shows the results of calculating the generator resource and the required eluate demand to ensure maximum throughput per shift, depending on the number of generators and gamma chambers used.

We see that in the first week of operation of the generator, the generator resource significantly exceeds the necessary eluate requirement to ensure maximum throughput during the OSG, the number of which is limited by the technological capabilities of the research process.

In the second week of the generator's life, the maximum possible throughput is limited only by the

Table 1. Indicators of the efficiency of the use of the generator during the OSG				
Indicator	Unit of measurement	1 gamma-camera 1 generator	2 gamma-cameras 1 generator	2 gamma-cameras 3 generator
The resource of the generator in the activity of the resulting eluate				
Generator resource for all days of the service life	GBk	50.86	50.86	152.58
Generator resource in the first five working days of the service life	GBk	37.28	37.28	111.85
Generator resource from 8 to 15 days of operation (only for working days)	GBk	6.73	6.73	20.19
The needs of the eluate to ensure the highest possible bandwidth when performing OSG				
The need for eluate for conducting OSG for all days of the service life	GBk	21.20	33.60	50.80
Maximum eluate requirement for OSG in the first five working days	GBk	16.00	28.40	32.00
Eluate requirement for OSG from the 8th to the 15th day of operation (only on working days)	GBk	5.2	5.20	18.80
Throughput during OSG, taking into account technological capabilities				
The maximum possible number of OSG for all working days of the generator's service life	Unit	53	84	127
The maximum possible number of OSGs for the first five working days	Unit	40	71	80
The maximum possible number of OSG from 8 to 15 days of operation (only on working days)	Unit	13	13	47
The indicators of efficiency of the eluate				
The proportion of eluate to ensure maximum throughput over all days of the life of the generator over the same period	%	41.68	66.07	33.27
The proportion of the eluate to ensure maximum throughput for the first five days of the life of the generator over the same period	%	42.92	76.18	28.61
The proportion of eluate to ensure maximum throughput from 8 to 15 days of the service life of the generator resource for the same period	%	77.26	77.26	93.11

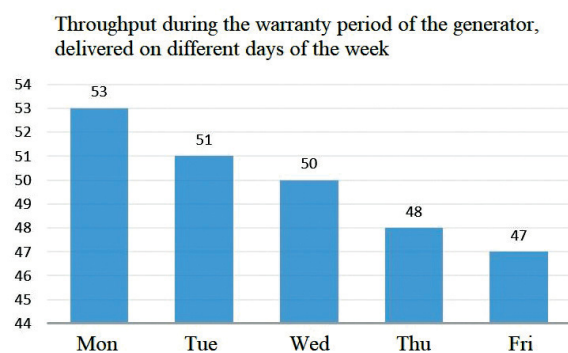


Fig. 6. The total throughput during OSG on one gamma-camera, depending on the day of the week of delivery of one generator for a five-day working week.

generator's activity on the day of the study, which decreases non-linearly with each subsequent day.

The table 1 shows the quantitative indicators of the generator resource by the days of the service life, the capacity of the OSG, taking into account the technological capabilities and the need for eluate to ensure the maximum possible capacity during the OSG with various combinations of generator supplies.

Thus, the entire life of the generator has two periods:

- a) the period with the maximum possible throughput;
- b) the period of limited possibility of conducting the OSG.

We found that the maximum number of possible OSG (127) is performed in the presence of two gamma chambers and three generators, and according to the scheme 1 gamma-cameras – 1 generator is the minimum possible (53), but at the same time the efficiency of using the capabilities of the generator (s) is different:

1. The maximum efficiency of using the eluate (generator resource) is shown when working according to the scheme 2 gamma-cameras – 1 generator (66.07%); the minimum – according to the scheme 2 gamma-cameras – 3 generators (33.27%);

2. The maximum throughput can be provided when working according to the scheme 2 gamma-cameras – 3 generators (127); the minimum – according to the scheme 1 gamma-cameras – 1 generator (53);

The total estimated capacity of one generator for the period of operation (including weekends) was 119 OSG; the total number of OSG, taking into account technological capabilities, was 53 OSG. The resource of a single generator is sufficient to provide 2.2 times more OSG research than the actual throughput capabilities of a single gamma-camera.

The analysis shows that in the first week, the generator's resource in eluate activity significantly exceeds the needs of one gamma-camera when working with one generator: the total resource of the generator for the entire period of operation (including weekends) is 50.58 GBk, and the need for eluate is 21.20 GBk, which is 41.68% of the total resource of the generator.

All the figures show that in the second working week, the generator resource is used most efficiently.

The throughput dependence during the OSG depends on the day of the delivery week. The optimal day for the generator delivery and the start date of the OSG is Monday. Figure 6 shows the analysis of the capacity for the warranty period of the generator (15 days), when delivered on different days of the week.

CONCLUSION

The most significant factors of optimal OSG planning for the days of the generator's service life are the technical characteristics of the generator, the number and frequency of generator delivery, and the availability of gamma-cameras.

Thus, the method of planning diagnostic procedures described by us can be useful for the effective use of the generator system, which ensures the maximum amount of high-quality RFP from the generator eluate and contributes to the objectification of the oncological process in order to choose treatment tactics.

Authors contribution:

Maksimova N.A. – scientific editing, general guidance, research concept.
Karpun V.G. – collection, analysis and interpretation of data, article preparation.
Arzamastseva M.A. – collecting material during OSG, preparation of illustrations.
Ilchenko M.G. – collection of material for OSG, technical editing, article preparation.
Shlyk O.S. – collection of material for OSG, bibliography writing.

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ORIGINAL ARTICLE

EFFICIENCY MARK OF POSTOPERATIVE PAIN MANAGEMENT AND NORMALIZATION OF ADAPTATION STATUS IN PATIENTS WITH REPRODUCTIVE SYSTEM ONCOPATHOLOGY

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ABSTRACT

Purpose of the study. Studying possible management of postoperative pain and normalization of adaptation status in patients with reproductive system onychopathology using xenon-oxygen therapy.

Patients and methods. The study included 97 patients receiving surgical treatment for reproductive cancer at National Medical Research Centre for Oncology in 2016–2020. All patients were divided into the main and control groups depending on the performed corrective therapy with xenon-oxygen mixture (XOM). Inclusion criteria were: established diagnosis – endometrial cancer, cervical cancer or ovarian cancer at the surgical stage of antitumor treatment, absence of decompensated concomitant pathology. In addition to general clinical tests, the intensity of symptoms in patients was assessed using a standardized Edmonton questionnaire, adaptation status and data of a numerical rating scale of pain were recorded, the severity of endogenous intoxication was measured using calculated lymphocytic, leukocyte, nuclear and leukocyte shift index. Stages of the study included functional assessment of the patient's condition before surgical treatment and on the 1st and 5th days of the postoperative period.

Results. An analysis showed statistically significant differences between the groups: in the group of patients receiving xenon-oxygen therapy, 12.9% of patients complained of pain, while in the control group – 34.2%, on mild exertion 17.1% and 39.9%, respectively ($p < 0.05$). The therapy with XOM demonstrated its high significance in the adaptive status regulation and regression of negative clinical manifestations in patients after oncogynecological surgeries.

Conclusion. The effectiveness of the chosen therapy with XOM demonstrates the possibility of anesthesia and normalization of the adaptive status of oncogynecological patients who underwent surgical treatment for reproductive cancers.

Keywords:

reproductive cancers, postoperative pain, xenon-oxygen therapy, adaptation status, psychological status, rehabilitation treatment.

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ОЦЕНКА ЭФФЕКТИВНОСТИ КУПИРОВАНИЯ ПОСЛЕОПЕРАЦИОННОЙ БОЛИ И НОРМАЛИЗАЦИЯ АДАПТАЦИОННОГО СТАТУСА У ПАЦИЕНТОК С ОНКОПАТОЛОГИЕЙ РЕПРОДУКТИВНОЙ СИСТЕМЫ

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РЕЗЮМЕ

Цель исследования. Исследовать возможности купирования послеоперационной боли и нормализации адаптационного статуса у пациенток с онкопатологией репродуктивной системы с применением ксенон-кислородной терапии.

Пациенты и методы. В исследование включено 97 пациенток, находившихся на хирургическом лечении по поводу злокачественной опухоли репродуктивной системы в отделении онкогинекологии ФГБУ «НМИЦ онкологии» Минздрава России в период 2016–2020 гг. Данные пациентки в зависимости от проведенной корригирующей терапии ксенон-кислородной смесью были разделены на основную и контрольную группы. Критерии включения: наличие у пациенток установленного диагноза (рак тела матки, рак шейки матки, рак яичников) на хирургическом этапе противоопухолевого лечения, отсутствие декомпенсированной сопутствующей патологии. Помимо общеклинических исследований у пациенток оценивали интенсивность симптомов при помощи стандартизированного опросника ESAS (The Edmonton Symptom Assessment System), фиксировали адаптационный статус и данные числовой рейтинговой шкалы боли, выраженность эндогенной интоксикации проводили с помощью расчетных лимфоцитарного, лейкоцитарного, ядерного индекса сдвига лейкоцитов крови. Этапы исследования включали: функциональную оценку состояния пациенток до хирургического лечения, затем на 1-е и 5-е сутки послеоперационного периода.

Результаты. При проведении анализа данных установлены статистически значимые отличия, так в группе пациенток с применением терапии ксенон-кислородной смесью жалобы на боль предъявляли 12,9% пациенток, тогда как в контрольной группе – 34,2%, при незначительной нагрузке 17,1% и 39,9% соответственно ($p < 0,05$). Применение терапии ксенон-кислородной смесью продемонстрировало высокую значимость метода в регуляции адаптационного статуса и в регрессе негативных клинических проявлений у пациенток после онкогинекологических операций.

Заключение. Эффективность выбранной терапии ксенон-кислородной смесью позволяет продемонстрировать возможность обезболивания и нормализации адаптационного статуса онкогинекологических пациенток перенесших хирургическое лечение опухолевых процессов репродуктивных органов.

Ключевые слова:

опухоли репродуктивной системы, послеоперационная боль, ксенон-кислородная терапия, адаптационный статус, психологический статус, восстановительное лечение.

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According to the International Agency for Research on Cancer, published in 2018, it was noted that 18.1 million new cases and 9.6 million deaths from malignant neoplasms were registered worldwide. In 2019, more than 600 thousand new patients diagnosed with cancer were identified in Russia. Among the female population, tumors of the reproductive system account for the largest share of all malignancies, so breast cancer was diagnosed in 18.3%, uterine body cancer in 7.0%, cervical cancer in 4.7%, ovarian cancer in 4.5% of women. Consistently high rates in the structure of oncological morbidity of tumors of the reproductive system lead to an annual increase in the number of women who have undergone radical surgical treatment and need early rehabilitation measures [1, 2].

Most gynecological operations are considered to be moderately traumatic, however, according to the rating of the 2013 cohort study of painful surgical interventions, obstetric and gynecological operations took the first place in terms of pain intensity in the early postoperative period [3]. These statements partly explain the research of Gerbershagen HJ (2014), who in his work notes gender differences in the perception of postoperative pain. Moreover, women emphasize the high intensity of pain regardless of the type of surgical intervention [4]. The multicenter generalizing data of Schnabel A (2020) became the basis for the formation of prognostic risk factors for postoperative pain, which include: age less than 54 years, female gender, preoperative chronic pain and opioid use, duration of surgery more than 90 minutes, depression and anxiety in the preoperative period. The presence of three risk factors leads to an increase in pain symptoms, which can cause adverse postoperative consequences in the form of dysfunctional disorders and the development of chronic pain [5]. According to the research work of Brandsborg B. (2012), insufficiently relieved acute pain after hysterectomy forms the risk of developing chronic pain syndrome in 18–32% of women [6].

Undoubtedly, it is necessary to take into account psychological factors in the formation of pain syndrome, which play an important role during the postoperative period, as noted in the research work Sobol-Kwapinska M. (2016). So, the psychological

correlates of postoperative pain include depression, waiting for surgery and pain, anxiety, low level of optimism. As a result of this study, it was revealed that negative situational aspects before the operation, then are prerequisites for a higher level of pain activity in the postoperative period [7]. Negative psychotraumatic factors in the preoperative period in cancer patients are uncertainty and waiting for surgery, the formation of anxiety-depressive symptoms, lack of motivation to continue treatment, loss of vital energy and personal meanings [8].

In oncogynecology, surgical treatment in combination with other antitumor therapy is the dominant method regardless of the stage of the process [9]. When performing radical surgical treatment of tumors of the genital system, it is preferable to perform organ-preserving operations. However, in some clinical cases, the most appropriate is the total removal of an organ affected by a tumor with suspected metastatic foci. The high risk of implantation metastasis makes it necessary to perform an extended volume of surgery with the removal of the ovaries. The data of the study by Kolbasova EA (2014) indicate that the localization of the tumor in hormone-dependent and hormone-producing organs provokes the development of a complex of neuroendocrine and psychoemotional symptoms that are difficult to predict and correct [10]. In oncogynecology, the postoperative period is complicated by postovariectomy syndrome, where the main pathogenetic factor is hypoestrogenism. Forced surgical suppression of the ovaries is accompanied by various functional changes in the tissues and organs, provoking a sharp change in hemostasis, disorders of the functions of the neuroendocrine, cardiovascular and other systems of the body with the formation of maladaptive adaptive reactions with a complex of deviations in the psychoemotional sphere [11].

The imbalance of psychological functioning and acute changes in homeostasis with the manifestation of pain symptoms after surgical treatment in cancer patients, undoubtedly, requires a timely solution to this problem in the provision of necessary and reasonable medical care. Modern achievements and significant changes in medical technologies determine the tactics of accompanying and restor-

ative treatment. The goal of adequate analgesia in the early postoperative period is the regression of the stress response to surgical aggression, the possibility of reducing the risk of functional complications, and the maximum recovery of the patient after surgery [12]. At the same time, the basic principles of analgesia in the early postoperative period should meet the needs of the patient with the provision of adaptation of therapy depending on the functional state, effectiveness and safety. Analgesic measures should be carried out within the framework of a "multimodal approach", which provides for the use of drugs from different pharmacological groups to ensure optimal functional and emotional recovery of patients who have undergone surgical treatment. To increase the effectiveness of analgesic therapy, it is necessary to improve organizational and methodological approaches and use modern achievements of anesthesiology, resuscitation and surgery [13, 14].

Thus, the strategy of leveling pain after gynecological cancer operations should be based, first, on knowledge of the characteristics operations in oncological pathology characterized by aggressive surgical approach with the formation of extensive wound surfaces and demonstration of the surgical stress response with production of inflammatory mediators [3], and secondly, be aware of the emotional imbalance that occurs in 42–68% of women with loss of fertility and reproductive functions [10, 15]. It is obvious that the need to eliminate pain and normalize the psychoemotional state equally are important components of the early restoration of the functional balance of the body of patients after radical surgical treatment in oncogynecology.

The data of modern literature reflect the multidirectional methods and techniques that are united by a common goal of regression of pathological disorders with compensatory possibilities of restoring the functionally balanced state of the body of women after hormone-reducing operations. Thus, the use of plasmapheresis and xenon therapy in cancer patients with the manifestation of postovariectomy syndrome led to an improvement in the clinical condition, normalizing hormonal parameters, reducing reactive anxiety, and improving the quality of life [16]. The use of xenon therapy in oncology

is based on its analgesic, detoxifying properties, as well as on the ability to influence the mechanisms of adaptation by means of implementing the action on the stress-limiting and stress-implementing systems of the body, including in persons in a state of psychoemotional stress. It is known that when dosed, xenon is able to block the processes of lipid peroxidation and reduce the activity of epinephrine and glucocorticoids, and also contributes to the suppression of the activity of NMDA receptors in the structures of the nociceptive system. This feature of xenon is used to relieve pain in cancer patients with nociceptive pain, as well as during painful surgical manipulations [17–20].

Taking into account the unique properties of this inert gas, we made the choice of using a course of therapy with a xenon-oxygen mixture (XOM) as the main component of therapy for the correction of a complex complex of postoperative changes, regression of pain symptoms and altered psychoemotional signs with normalization of the adaptive status in oncogynecological patients.

Purpose of the study: to investigate the possibilities of postoperative pain relief and normalization of adaptive status in patients with oncopathology of the reproductive system using xenon-oxygen therapy.

PATIENTS AND METHODS

The study included 97 patients who were undergoing surgical treatment for a malignant tumor of the reproductive system in the Department of Oncogynecology of the National Medical Research Centre for Oncology of the Ministry of Health of Russia of the Ministry of Health of the Russian Federation in the period 2016–2020. Part of this study was carried out within the framework of the grant of the President of the Russian Federation "New technologies of molecular detoxification and cellular immunotherapy in the complex of treatment and rehabilitation of cancer patients with malignant tumors of the genitals". All patients received informed consent for the study and processing of personal data, in accordance with the ethical standards of the Helsinki Declaration (1964, as amended in 2013). The cancer diagnosis was confirmed in accordance

with the accepted clinical recommendations based on the examination data, objective methods of examination and morphological analysis [9]. The criteria for inclusion in the study were the presence of an established diagnosis in the patients: cancer of the uterine body, cervical cancer, ovarian cancer at the surgical stage of antitumor treatment, and the absence of decompensated concomitant pathology. The exclusion criteria were the presence of decompensated pathology and mental illness. The patients, depending on the corrective therapy with XOM, were divided into the main and control groups. In the postoperative period, on the 2nd, 3rd and 4th days, in the main group, in addition to the standard pain relief therapy recommended by WHO, in order to regress pain and normalize the adaptive status, the patients were treated with XOM. The patients of this group were provided with information about the possibilities of xenon therapy in oncology, about the absence of carcinogenicity and toxicity of the gas, the essence of manipulations, indications and contraindications were described in detail. In addition to standard general clinical studies, patients were assessed the intensity of symptoms using the standardized ESAS questionnaire (The Edmonton Symptom Assessment System), recorded the adaptation status according to L.H.Garkavi and analyzed the data of the numerical pain rating scale (NRS), the severity of endogenous intoxication was carried out using calculated lymphocyte (LI), leukocyte (LII), nuclear (NI) and the white blood cell shift index (ISL). The stages of the study included: functional assessment of the patients' condition before surgical treatment, on the 1st and 5th days of the postoperative period.

The main group was represented by 49 patients with a diagnosis of cervical cancer 21 (42.8%), uterine body cancer 16 (32.6%), ovarian cancer 12 (24.6%). Median age 53.1 years, mean age 47.2 ± 1.8 years, range 30–75 years, underwent surgical treatment, according to clinical recommendations [9]. All patients received a course of xenon-oxygen therapy. The control group consisted of 48 patients diagnosed with cervical cancer 22 (45.7%), uterine body cancer 19 (39.8%), ovarian cancer 7 (14.5%). Age median 51.4 years, mean age 49.1 ± 1.4 years, range 29–72 years, with similar surgical treatment without XOM

therapy. The prevalence of the tumor process (TNM classification, 2011) in the main group is represented by the following indicators: stage II-24 (48.9%), stage III – 21 (42.8%), stage IV – 4 (8.3%), in the control group stage II – 22 (45.7%), stage III – 22 (45.7%), stage IV – 4 (8.6%). In the main group, concomitant pathology is presented: oncological disease in anamnesis in 2 (4.2%) patients, cardiovascular pathology in 26 (53.1%) patients, cerebral circulation disorders and other neurological nosology in 4 (8.3%) patients, gastrointestinal diseases in 5 (10.2%) patients, burdened allergic history in 4 (8.3%) patients. In the control group, the manifestation of concomitant diseases was represented by: pathology of the cardiovascular system in 24 (49.9%) patients, neurological pathology in 3 (6.2%) patients, gastrointestinal diseases in 3 (6.2%) patients, oncopathology in the anamnesis in 3 (6.2%) patients, allergic reactions in the anamnesis in 6 (12.5%) patients. The clinical and anamnestic data of the patients in the main and control groups showed no statistically significant differences in the localization and stage of the tumor process, as well as concomitant pathology. The obtained data were processed using standard computer techniques (Statistica 10, Microsoft Excel). In comparison of the groups, the Student's parametric T – test and the nonparametric Mann-Whitney U – test were used, and the critical significance level of p was assumed to be 0.05.

Therapy with XOM was carried out in the morning hours by specialists who have passed certification training in this medical technology. The legal basis for this therapy was a permit for the use of medical technology FS No. 2010/227 "Method for the correction of acute and chronic stress disorders based on the inhalation of therapeutic doses of xenon brand "Xemed" [17]. Indications for the use of this medical technology is the relief of pain and stress disorders of any etiology. Technical support of the procedure was carried out using the CPC-1 – therapeutic circuit for xenon inhalation with gas flow regulation (TU 9444–002–39791733–2009) (License No. 64/0125-L/02, LLC "KseMed", Russia, Moscow region, Khimki, Michurinsky 1st dead end, 20; Registration certificate No. FSR 20006037 of 05.11.2009). For monitoring the concentration of the gas flow of xenon and oxygen in the respi-

ratory mixture and measuring the volumetric the combined medical gas analyzer "GKM-03-Insovt" (CJSC "Insovt", Moscow) was used in the binary gas mixture. St. Petersburg, Russia) and a medical xenon dosimeter (DKM-01) (manufactured by AKE-LA-N LLC, Russia). Inhalation of the mixture was carried out through a mask tightly attached to the patient's face. In the first 2 minutes, the inhalation mixture contained air with an increased concentration of medical oxygen of 35–40%. Then, at a gas flow rate of 5–6 l/min, xenon was gradually added to the inhaled mixture to 14–15% and the mixture concentration was maintained for 20 minutes, subsequent procedures proceeded with an increase in the xenon concentration to 20%, and then 25% with a reduction in the time exposure to 15 minutes and in the final procedure to 10 minutes. The criteria for sufficient exposure and achieving the effect of xenon were the appearance of signs of superficial sleep with a decrease in the respiratory rate and heart rate. To prevent possible complications from the respiratory and cardiovascular systems, constant monitoring of blood oxygen saturation was carried out, and hemodynamic parameters were monitored.

RESEARCH RESULTS AND DISCUSSION

The negative consequences of radical surgical treatment of oncogynecological pathology are manifested by irreversible stress-induced systemic disorders in the body of women, which requires the development of a comprehensive approach to recovery measures at all stages of antitumor treatment. Undesirable clinical manifestations in the early postoperative period and side effects of antitumor treatment significantly worsen the quality of life of women, which undoubtedly has a dominant character in the choice of the patient's decision to continue therapy [21]. The fact of a high risk of neurovegetative and psychoemotional disorders in women with oncopathology of the reproductive organs after hormone-reducing operations is proven.

In our work, we pursued two goals of applying a course of therapy with XOM, to stop postoperative pain and to minimize the manifestations of psychoemotional manifestations of postovariectomy

syndrome in patients who underwent radical oncogynecological intervention.

The analysis of the analgesic effect of XOM was carried out taking into account the assessment of the adequacy of anesthesia in 97 patients in the early postoperative period after radical oncogynecological surgery. All patients, on the eve of the evening and immediately before the operation, were prescribed a drug from the benzodiazepine group in order to normalize their psychological state. In the main group, the following surgical procedures were performed: extended extirpation of the uterus with appendages (type Piver III) in 21 (42.8%) patients, extirpation of the uterus with appendages and resection of the large omentum in 12 (24.6%) patients, extirpation of the uterus with appendages in 16 (32.6%) patients. In the control group, the following operations were performed: extended extirpation of the uterus with appendages (type Piver III) in 22 (45.7%) patients, extirpation of the uterus with appendages and resection of the large omentum in 7 (14.5%) patients, extirpation of the uterus with appendages in 19 (39.8%) patients. General combined anesthesia in the main group was 53.1%, in the control group – 54.3%, spinal-epidural anesthesia in the main group – 46.9% and in the control group – 45.7%. The average duration of operations in the groups was 78.2 ± 0.45 minutes in the main group and 86.1 ± 0.21 minutes in the control group. The average intraoperative blood loss had no statistical differences and was: in the main group 210.1 ± 0.21 ml, in the control group 242.4 ± 0.11 ml. Postoperative analgesia in the groups was carried out in accordance with WHO recommendations. The duration of operations, the volume of intraoperative blood loss and the type of anesthesia did not have significant differences in the groups. For all indicators, the groups are comparable, the differences in the indicators are not statistically significant ($p < 0.2$).

Pain intensity was assessed at rest and with moderate physical activity (changes in the position of the body in bed) according to the subjective data of the questionnaire of the numerical rating scale of pain on the 1st and 5th days after surgery. The indicators were evaluated in points, with 0 points-no pain, with 10 points-the most pronounced pain syndrome. It was found that on the 1st day after the operation, the

patients assessed the level of pain, which was 3.9 points (range 3–4), which was regarded as average pain. Pain in the area of the postoperative wound on the first day at rest was recorded by 46.5% of patients, and 65.2% of patients with a slight load, the data are shown in the table 1.

When analyzing the data, it was found that on the 5th day of the postoperative period, statistically significant differences were revealed, so in the group of patients with the use of XOM, complaints of pain at rest were presented 2.7 times less than in the control group. During exercise, a similar trend was observed: in the main group, the pain decreased by 3.8 times compared to the first day, while in the control group it was only 1.6 times (data processing using standard methods (Statistica, 10. Microsoft Excel) using the parametric T – student test and non-parametric U – Mann-Whitney test, the critical level of significance $p=0.05$).

The analysis of the leaves of the purpose of anesthesia is established that in the group with applica-

tion of XOM anesthesia drugs NSAIDs decreased by 2.2 times compared with the control group, and the introduction of narcotic analgesic was not done at all. These indicators demonstrate the effectiveness of the analgesic effect when using XOM therapy in the early postoperative period.

It is proved that the activity of sex hormones is associated with the psychological state and behavioral reactions in women, which is manifested by emotional disorders in the form of depression and anxiety [22]. To determine the dynamics of the functional state, the intensity of symptoms and the psychological status of patients after radical operations in oncogynecology on the 1st and 5th days of the postoperative period, we used the indicators of the standardized ESAS questionnaire recommended for assessing the functional state of cancer patients [23]. The questionnaire data includes the 8 most common clinical symptoms in cancer patients at the stages of antitumor treatment (nausea, weakness, shortness of

Table 1. Indicators of the rating scale of pain in oncogynecological patients with the use of XOM therapy

Indicator	1 st day after surgery, $n=97$		Main group (5 th day), $n=49$		Control group (5 th day), $n=48$		p
	%	Score	%	Score	%	Score	
Pain in rest	46.5	3.9±1.2	12.9	2.1±0.2	34.2	2.6±0.1*	0.02
Pain in strain	65.2	4.8±1.1	17.1	2.1±0.3	39.9	3.1±0.2*	0.01

Note: * – statistically significant difference between the indicators in the control group and the main group ($p<0.05$).

Table 2. Indicators of the standardized ESAS questionnaire in oncogynecological patients at the stage of surgical treatment with the use of XOM

Indicator	After surgery, $n=97$		Main group, $n=49$		Control group, $n=48$		p
	%	Score	%	Score	%	Score	
Feeling bad	57.3	3.8±1.1	26.5	1.4±0.1	41.0	4.7±0.1*	0.03
Dyspnea	18.5	0.8±0.1	11.2	0.4±0.1	13.1	0.7±0.2	0.4
Nausea	79.21	3.9±0.9	5.2	1.7±0.1	22.9	4.9±0.2*	0.03
Weakness	82.1	4.4±1.2	38.1	2.7±0.2	33.9	3.6±1.1	0.2
Depression	55.0	4.1±1.1	14.2	1.9±0.1	35.1	4.9±1.2*	0.02
Sleep disturbance	59.2	5.2±1.2	15.5	2.0±0.2	62.0	3.1±1.1	0.4
Appetite disturbance	43.6	2.9±0.8	22.6	1.8±0.1	24.4	2.1±0.1	0.6
Anxiety	66.5	5.9±1.6	22.1	3.0±1.2	50.8	5.9±0.2*	0.01

Note: * – statistically significant difference between the indicators in the control group and the main group ($p<0.05$).

breath, general health, as well as depression, anxiety, sleep disorders and appetite). The data are shown in table 2.

As a result of the study, it was found that in the group with the use of XOM, there was a statistically significant decrease in clinical manifestations of depression by 2.9 times, nausea by 4.1 times, poor health by 1.9 times, and anxiety by 2.3 times ($p<0.05$). Weakness, loss of appetite and sleep-there were no statistical confirmations. The data of the ESAS questionnaire analysis show a positive trend in the regression of psychoemotional and autonomic disorders when using XOM therapy.

Numerous literature sources indicate the functional features of cancer patients, which are expressed in a decrease in the reserves of the metabolic and detoxification systems with clinical manifestations in the form of polypocal functional disorders of homeostasis [24]. Detoxification and anti-inflammatory properties of xenon therapy should be considered as the trigger components of restorative treatment. In order to objectify the study, for rapid assessment of the body's reactivity to surgical intervention in oncogynecological patients and the possibility of anti-inflammatory effects of XOM therapy, we analyzed the indicators of the blood leukocyte formula, taking into account the generally accepted intoxication indices, the data are presented in the table 3.

Changes in the leukocyte formula of the blood on the 1st day after surgery indicated local reactive processes, an increase in the monocyte and lymphocyte links, and a decrease in immature forms of elements in the blood determine the activation of immune processes that provide detoxification. Comparable numerical values of the nuclear index

(NI) indicated the state of intoxication at various stages of the study, which corresponded to the moderate severity of the clinical manifestation of the inflammatory reaction [25]. On the 5th day, the NCI index in patients with XOM therapy decreased by 42% compared to the 1st day after surgery, and in the control group by 14%, i.e., 3 times less. Such dynamics, in cases of the use of XOM therapy, indicated the restoration of neutrophil and monocyte regeneration. The lymphocytic index (LI) after surgery in patients with oncogynecological disease had the lowest level of values, close to the lower limits of the norm, indicating immunosuppression (table 3). However, on the 5th day of the postoperative period, LI indicators increased 4.1-fold in the group with XOM therapy, and in the control group increased 2-fold ($p<0.001$), which indicates the recovery potential of XOM therapy. The index of the shift of white blood cells (ILC), as an indicator of the body's reactivity to irritation, clearly showed a significant dynamics of values with an increase relative to the initial values on the 1st day of the postoperative period, with the achievement of the normal level in the treatment of XOM compared to the control group (table 3).

Thus, the dynamics of calculated indicators of intoxication indices indicated that after surgery in oncogynecology, patients have a pronounced reaction from the blood system. As a result of XOM therapy, the estimated indicators of intoxication indices were close to the baseline level, in contrast to the group without XOM therapy. The obtained data suggest that the detoxification effect of xenon therapy is manifested in the form of a decrease in the accumulation of endotoxins and products of incomplete metabolism in the body of cancer patients.

Table 3. Dynamics of calculated indicators of intoxication indices in oncogynecological patients using XOM therapy, c.u.

Indicator	Condition before surgery, n=97	1 st day after surgery, n=97	Main group (5 th day), n=49	Control group (5 th group), n=48
LII	2.09±0.33	4.71±1.09	2.02±0.31 ^{1,2}	4.56±1.09
NI	0.27±0.03	0.67±0.14	0.23±0.01 ^{1,2}	0.46±0.03
LI	0.41±0.11	0.14±0.03	0.58±0.09 ^{1,2}	0.29±0.05
ILC	1.91±0.32	3.65±0.43	1.49±0.12 ^{1,2}	3.26±0.73

Note: LII – leukocyte intoxication index; NI – nuclear index; LI – lymphocytic index; ILC – index of the shift of blood leukocytes; ¹ – differences between the indicator after surgery and the treatment of XOM in the main and control groups are significant, $p<0.05$; ² – differences in the indicators in the main and control groups are significant, $p<0.05$.

The psychopharmacotherapeutic effect of xenon in small doses is applicable for the correction of adaptive disorders and the elimination of stress syndrome of various origins [17, 26]. To objectify the effectiveness of XOM therapy in oncology, we used the determination of the adaptive status of patients before surgery (baseline), on the 1st and 5th days of the postoperative period. Determining the type of general non-specific adaptive response of the body is an indicator of the level of health with an assessment of the immune and neuroendocrine systems. When conducting a parametric analysis of the cell composition of the leukogram, we determined the type of adaptive response and the level of reactivity. The calculation of the quantitative share and the formation of the cluster of adaptive status in the groups was analyzed using the calculated coefficient of the ratio of the total cluster of antistress and stress reactions ($K = AS/S$) [27].

The analysis of the dynamics of the structure of adaptive reactions in oncogynecological patients showed significant changes. Thus, in the majority of patients, acute stress after radical surgery was identified in 71.9% of cases (more than 2.2 times relative to the background state before surgery) and with an anti-stress/stress ratio of 0.39, which is 5.1 times less than the level before surgery. Integral indicators of the adaptive status of antistress/stress indicated a natural shift in the ratio towards pathological reactions after surgery. The frequency of balanced reactions of quiet activation decreased by 4 times, and increased activation was not recorded in any case (table 4).

The recovery period without XOM therapy had almost no positive dynamics, the stress response

prevailed in 66.3% of patients, and the anti-stress/stress ratio did not actually change in comparison with the 1-day postoperative period. The frequency of the training response was 2.8 times less than the stress response. The use of XOM therapy contributed to the formation of a different adaptive status. The dynamics of the antistress/stress ratio increased significantly, exceeding the postoperative values by 6.5 times and reaching the initial level. The dominant type was the training reaction, which is characterized by the predominance of anabolic processes with the development of protective inhibition in the central nervous system, functional activity of the endocrine system with an increase in non-specific, including antitumor resistance [27].

CONCLUSION

Thus, the study showed that the majority of patients with oncogynecological pathology after radical surgical treatment and standard treatment on the 1st day experience moderate pain at rest in 46.5%, with a slight load in 65.2%. After the use of sessions of xenon-oxygen therapy on the 2nd, 3rd, and 4th day of the postoperative period, the relief of pain was noted in 2.7 times more patients than in the group without this therapy. Complaints of pain in the main group were presented by 12.9% of patients, while in the control group – 34.2%, with a slight load of 17.1% and 39.9%, respectively ($p < 0.05$). When conducting an objective rapid assessment of the indicators of intoxication indices in the group with XOM therapy, the approach of these indicators to the initial level before surgical treatment was noted, which indirectly determines

Table 4. Structure of adaptive reactions in oncogynecological patients when using therapy in the postoperative period

Adaptive reaction types	Condition before surgery, n=97	1 st day after surgery, n=97	Main group (5 th day), n=49	Control group (5 th day), n=48
Stress, %	33.1	71.9	28.2	66.3
Training response, %	8.4	21.3	56.2	28.2
Rest activation, %	20.6	6.8	8.8	-
Increased activation, %	37.9	-	6.8	5.5
$K = AS/S$, c.u.	2.02	0.39	2.54	0.5

Note: AS – antistress, S – stress.

the decrease in the body's systemic response to surgical trauma.

The use of XOM therapy demonstrated the high significance of the method in the regulation of the adaptive status and in the regression of negative clinical manifestations in patients after oncogynecological operations. According to the ESAS questionnaire revealed a positive trend in the recovery of psychosomatic well-being in group therapy XOM, there was a statistically significant decrease in symptoms of depression 2.9 times of illness 1.9 times, anxiety 2.3 times, nausea 4.1-fold ($p < 0.05$). The data of the questionnaires were objectified by indicators of the dynamics of adaptive reactions during treatment with xenon therapy. Thus, in the postoperative period, the adaptive status in

oncogynecological patients was functionally low reactivity with the identification of acute stress in 71.9% of cases, which is more than 2.2 times higher than the background state. On the 5th day of the postoperative period, no positive dynamics were observed in the group without XOM therapy, the acute stress response was recorded in 66.3% of patients, with no changes in the antistress/stress ratio. Xenon therapy helped to restore the adaptive status of oncogynecological patients in the form of a predominance of a balanced training response and normalization of the antistress/stress ratio, which reached the initial indicators and exceeded the postoperative value by 6.5 times, which undoubtedly indicates the recovery capabilities of XOM therapy.

Authors contribution:

Rozenko D.A. – determination of research objectives, study design, analysis of results.

Shikhlyarova A.I. – conduction of the study, assessment of the adaptation status of patients.

Popova N.N. – direct conduction of the study end conducting xenon-oxygen therapy, assessment of parameters of the psychosomatic state of patients, manuscript writing.

Verenikina E.V. – determination of research design, participation in the analysis of results.

Menshenina A.P. – setting clinical research objectives, monitoring patients' condition.

Ardzha A.Yu. – formation of patient groups and clinical support of the study.

Shulga A.V. – participation in the study, processing and analysis of results.

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ORIGINAL ARTICLE

USING THE DIGITAL ARCHIVE OF PATHOLOGY REPORTS OF STOMACH CANCER AS INTERNAL QUALITY CONTROL OF CODING ACCORDING TO THE ICD-O SYSTEM

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ABSTRACT

Purpose of the study. Demonstrate the possibilities of statistical analysis of the digital archive at pathological department (PD). To conduct internal quality control of the coding of malignant tumors according to the ICD-O-3 system of pathology reports using the example of gastric cancer (GC).

Materials and methods. We retrospectively analyzed the digital archive of 368,157 pathology reports of the National Medical Research Centre for Oncology of the Ministry of Health of Russia from 2000 to 2019. For the study, 4,857 pathology reports of patients operated for gastric malignancies (ICD-X codes: C16.0 – C16.9) were selected for the period from 2000 to 2019.

Results. The analysis of 368,157 protocols of the digital archive of PD revealed 4,614 malignant epithelial tumors of the stomach: tubular adenocarcinoma – 2,958, signet ring cell carcinoma – 791, undifferentiated cancer – 565, mucinous adenocarcinoma – 210, neuroendocrine neoplasia – 90. A significant increase in the ICD-O codes for "adenocarcinoma NOS" was found in 2018 and 2019. The pathology reports for these 2 years were reviewed by an independent pathologist and changes were made to the ICD-O codes according to the WHO classification digestive system tumors 2019. The adenocarcinoma NOS (8140/3) was replaced by the codes: tubular adenocarcinoma (ICD-O: 8211/3) – 41%, papillary adenocarcinoma (8260/3) – 9% and adenocarcinoma with mixed subtypes (8255/3) – 29%.

Conclusion. The study, based on analysis of coding ICD-O stomach MN demonstrated the importance of digital archive at the PD, as a tool for rapid static analysis pathology reports and quality control of coding. The coding system can be the basis for large multicenter studies in oncology. Therefore, it is important to control the quality of coding of the pathology reports and to timely update the codes when new pathological classifications are released.

Keywords:

quality control, stomach cancer, signet-cell adenocarcinoma, poorly cohesive adenocarcinoma, tubular adenocarcinoma, diffuse type, intestinal type.

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ИСПОЛЬЗОВАНИЕ ЭЛЕКТРОННОГО АРХИВА РЕЗУЛЬТАТОВ ПРИЖИЗНЕННЫХ ПАТОЛОГОАНАТОМИЧЕСКИХ ИССЛЕДОВАНИЙ, КАК ИНСТРУМЕНТ ВНУТРЕННЕГО КОНТРОЛЯ КАЧЕСТВА КОДИРОВАНИЯ ПО СИСТЕМЕ МКБ-О-3 (ICD-O), НА ПРИМЕРЕ АНАЛИЗА ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ ЖЕЛУДКА

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РЕЗЮМЕ

Цель исследования. Продемонстрировать возможности статистического анализа электронного архива ПАО. Провести внутренний контроль качества кодирования злокачественных опухолей по системе МКБ-О-3 (ICD-O) прижизненных патологоанатомических исследований (ППАИ) на примере ЗНО желудка.

Материалы и методы. Нами был ретроспективно произведен экспресс-анализ 368 157 протоколов прижизненных патологоанатомических исследований электронного архива ПАО ФГБУ «НМИЦ онкологии» Минздрава России с 2000 по 2019 год включительно. Для исследования были отобраны 4 857 протоколов прижизненных патологоанатомических исследований пациентов, прооперированных в ФГБУ «НМИЦ онкологии» Минздрава России по поводу злокачественных новообразований желудка (коды МКБ-Х: С16.0 – С16.9), в период с 2000 по 2019 год включительно.

Результаты. При анализе 368 157 протоколов электронного архива ПАО было выявлено 4614 злокачественных эпителиальных опухолей желудка, которые распределились следующим образом: аденокарцинома БДУ – 2958, перстневидноклеточный рак – 791, недифференцированный рак – 565, муцинозная аденокарцинома – 210, нейроэндокринные опухоли – 90. Обнаружено значительное увеличение кодов МКБ-О «Аденокарцинома БДУ» РЖ в 2018, 2019 годах. Протоколы ППАИ за эти 2 года были пересмотрены независимым врачом-патологоанатомом и внесены изменения в коды МКБ-О согласно классификации ВОЗ опухолей ЖКТ 2019 года. На смену коду АК БДУ (8140/3) пришли коды тубулярной АК (МКБ-О: 8211/3) – 41%, папиллярной АК (8260/3) – 9% и аденокарциномы со смешанными подтипами (8255/3) – 29%.

Заключение. В результате проведенного исследования, на примере анализа кодирования МКБ-О ЗНО желудка было продемонстрировано важное значение электронного архива в ПАО, как инструмента быстрого статистического анализа ППАИ и контроля качества кодирования. Система кодирования ППАИ может быть основой для проведения крупных многоцентровых исследований в области онкологии. Важно своевременно обновлять коды МКБ-О при выходе новых морфологических классификаций.

Ключевые слова:

контроль качества, рак желудка, перстневидно-клеточная карцинома, карцинома из плохо сцепленных клеток, тубулярная аденокарцинома, диффузный тип, кишечный тип.

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RELEVANCE

The International Statistical Classification of Diseases and Related Health Problems (ICD) is a document used as a leading statistical and classification framework in health care, ensuring the unity of methodological approaches and international comparability of materials. In Russia, health authorities and institutions made the transition of statistical accounting to ICD-10 in 1999 [1]. ICD-O is an extension of the ICD for tumor diseases, widely used by cancer registries.

Accurate coding systems allow for statistical accounting of the incidence, prevalence and mortality of malignant neoplasms of various localizations, for example, gastric cancer (GC). In world statistics, GC is in 5th place in terms of occurrence and in 3rd place in mortality among all cancers. According to statistics from the International Agency for Research on Cancer, in 2018 about 1,033,701 new cases of GC and 782,685 deaths were registered in the world [2]. The highest morbidity is observed in the Russian Federation, with a relative increase in the incidence of diffuse type of GC [3].

The presence of clear criteria for the diagnosis of GC allows pathologists to correctly use the ICD-O coding systems.

Since 1965, the histological classification of GC has been based on the Lauren criteria: adenocarcinoma of the intestinal type (occurs in 54% of cases), diffuse type (occurs in 32% of cases), and indeterminate type (occurs in 15% of cases) [4, 5]. According to the literature data, diffuse GC is associated with sex (more often detected in female) and with age (found on average 7.3 years earlier) [6, 7], while intestinal GC is more often associated with intestinal metaplasia and infection *Helicobacter pylori* [8, 9]. GC demonstrates pronounced histological and cytological heterogeneity, and often several histological types are found in one tumor [10, 11].

The WHO classification for gastrointestinal tumors, published in 2019, identifies 5 main histological types of GC: tubular, papillary, mucinous, poorly cohesive cell carcinoma (including the signet-ring cell carcinoma) and mixed carcinoma [12]. We noticed that in most publications the WHO classification is considered alternative, and the main focus is

on the Lauren classification [13-17]. Despite differences in terminology, the main subtypes are similar in clinical and morphological characteristics. For example, the diffuse type according to the Lauren classification and the poorly cohesive carcinoma according to the WHO classification more often contains a signet-ring cells and are associated with poor survival [18-20].

The greatest difficulty is the coding of the mixed subtype of adenocarcinoma, in view of the fact that in the WHO classification there are no clear criteria for the % ratio of various histological components in the tumor. For example, in a similar mixed subtype of gastric neuroendocrine tumors (MiNeN) there is a precise indication of "at least 30% of each of the components". Among the publications, data on the frequency of histological types of GC vary [21-23]. According to the literature, the incidence of mixed gastric adenocarcinoma is indicated from 6 to 22% [24].

We believe that the differences in the frequency of occurrence of histological types of gastric adenocarcinoma may be associated with different approaches to morphological diagnostics in different institutions. And therefore, the analysis of the use of the codes of histological types of gastric adenocarcinoma according to pathology reports from the digital archive of the pathology department (PD) of the National Medical Research Centre for Oncology of the Ministry of Health of Russia for the last 20 years became relevant for us.

Purpose of the study: demonstrate the possibilities of statistical analysis of the digital archive of pathology reports. To conduct internal quality control of malignant tumors coding according to the ICD-O-3 system of pathology reports using the example of GC.

MATERIALS AND METHODS

The digital archive of the pathology reports has been maintained at National Medical Research Centre for Oncology of the Ministry of Health of Russia in the Microsoft Access program since 1993 and contains the following patient data: registration number of the pathology reports, date of study, number of slides, personal name, gender, age, date of birth, place of residence (region, district, city), medical history num-

ber, department that sent the material, name of the investigated organ, localization of the pathological process in the organ, histological type of tumor, code according to the ICD-O-3 system, code according to the ICD-X system, Grade of differentiation, the nature of the material (biopsy, surgery), the type of tumor (epithelial, non-epithelial, tumor-like lesions), the nature of growth (primary cancer, metastatic cancer, benign neoplasm), full name of the pathologist, the category of complexity pathology reports. To date, since 1993, the digital archive has stored data from more than half a million pathology reports of biopsy and surgical material. Initially, the digital archive was created in Microsoft Access 9.0 with constant internal coding according to the 2000 WHO classifications, which over the years imposed certain difficulties in updating the coding when publishing new versions of the WHO classification.

For this research, data from Microsoft Access 9.0 were exported into the ".xlsx" table format for further express analysis of an digital database in Microsoft Excel 16.0 using the pivot table method. Taking into account the diversity of histological subtypes encoded by the corresponding ICD-O codes, GC was selected among all localizations for further analysis. It should be noted that by design this study is exploratory, not confirmative.

As a result, we selected pathology reports for patients with surgery for GC (ICD-X codes: C16 – Malignant neoplasms of the stomach: C16.0-C16.9) in the period from 2000 to 2019, with considering the current software version for this period. Each pathologist participating in the diagnosis of GC was assigned a number for statistical processing.

Statistical analysis was performed using the Statistica 10.0 software package. Quantitative data are presented as values in the form of Median [Lower quartile; Upper quartile]; comparison was carried out using Spearman's test. A p-value<0.05 was considered statistically significant.

RESULTS OF THE STUDY

From 2000 to 2019, the digital archive contains information from 368,157 pathology reports including 4,857 patients with surgery for GC (gastrectomy, distal gastric resection, proximal gastric resection).

Among these pathology reports of GC, malignant epithelial tumors – 4,614, non-Hodgkin's lymphomas – 112, malignant mesenchymal tumors (GIST) – 121 (fig. 1). According to the ICD-O codes, the data were distributed as follows: adenocarcinoma NOS (ICD-O: 8140/3) – 2,958 patients, signet-ring cell carcinoma (ICD-O: 8490/3) – 791, undifferentiated

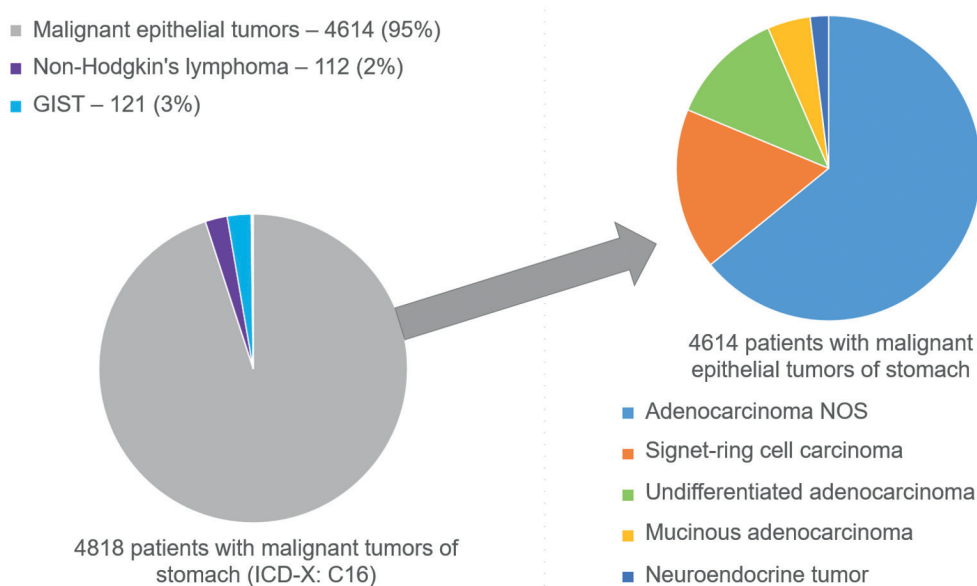


Fig. 1. The frequency of detection of various histological types of GC among patients with surgery for GC at the National Medical Research Centre for Oncology of the Ministry of Health of Russia from 2000 to 2019.

cancer (ICD-O: 8020/3) – 565, mucinous adenocarcinoma (ICD-O: 8480/3) – 210, neuroendocrine tumors (ICD-O: 8240/3, 8246/3) – 90.

According to anatomical sites, malignant epithelial tumors were coded as follows: body (ICD-10: C16.2) – 2,318 patients (50%), pylorus (ICD-10: C16.4) – 1,228 patients (27%), cardia (ICD-10: C16.0) – 1,024 patients (22%), lesser curvature (ICD-10: C16.5) – 38 patients (1%), fundus (ICD-10: C16.1) – 6 patients (0%).

In the WHO classification for gastrointestinal tumors 2000, the codes of adenocarcinoma NOS

(8140/3), intestinal adenocarcinoma (8144/3), tubular adenocarcinoma (8211/3) could be used for a specific diagnosis of GC. The pathologist could choose any of them, but in this case it was impossible to maintain internal statistics on the frequency of types if several codes were used each time to designate one type. With each new edition of the WHO classification of gastrointestinal tumors, the coding system also undergoes changes. In PD of National Medical Research Centre for Oncology of the Ministry of Health of Russia, a pathologist in his

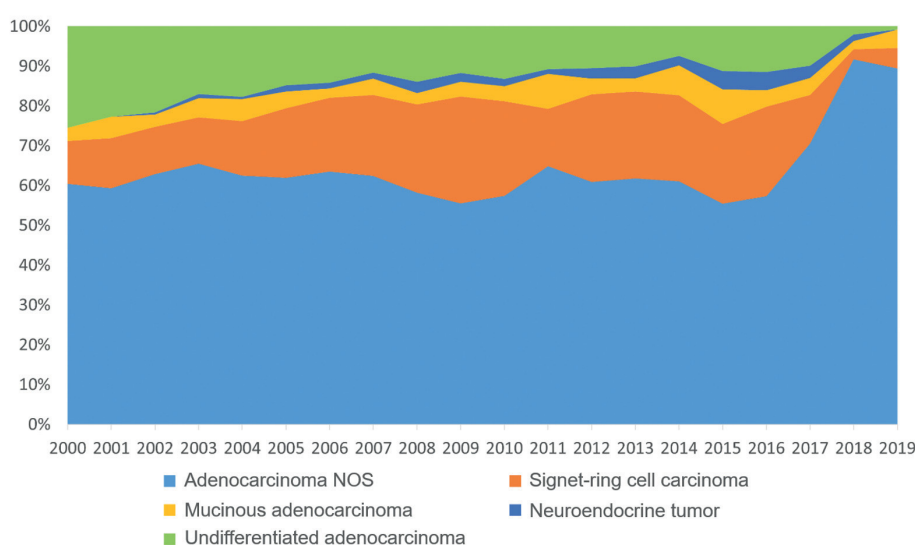


Fig. 2. Dynamics of the detection rate of various histological types of GS among patients with surgery for GC at the National Medical Research Centre for Oncology of the Ministry of Health of Russia in percentage terms from 2000 to 2019.

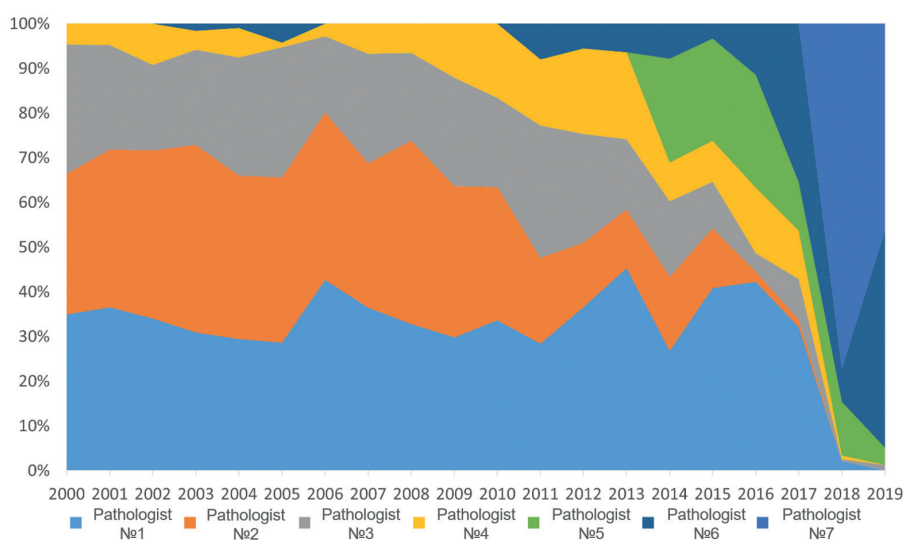


Fig. 3. Dynamics of distribution in percentage ratio of the number of pathology reports of epithelial GC between pathologists from 2000 to 2019.

pathology reports used a single code "adenocarcinoma NOS" (8140/3) to designate tubular, papillary and mixed AK, along with a detailed description of the slides indicating the percentage of each of the components. It should be noted that due to the heterogeneity of GC, this code allows you to get only general ideas about the diagnosis, since is established by the most predominant component in the tumor.

Since 2018, the Ministry of Health of the Russian Federation has recommended coding according

to the ICD-O-3 system, we decided to revise the approaches to coding, taking into account the current classifications. We analyzed the frequency of histological types as a percentage by year (fig. 2). There was a statistically significant decrease in the number of diagnoses of "undifferentiated cancer" from 42 in 2000 to 2 in 2019 (median 30.5 [25.5; 34.75], $R^2=0.638$, $p<0.01$) and an increase in the number of diagnoses "Neuroendocrine tumor" from 1 in 2000 to 11 in 2016 (median 5 [3; 7.5], $R^2=0.525$, $p<0.01$). At the same time, the number of diagnoses

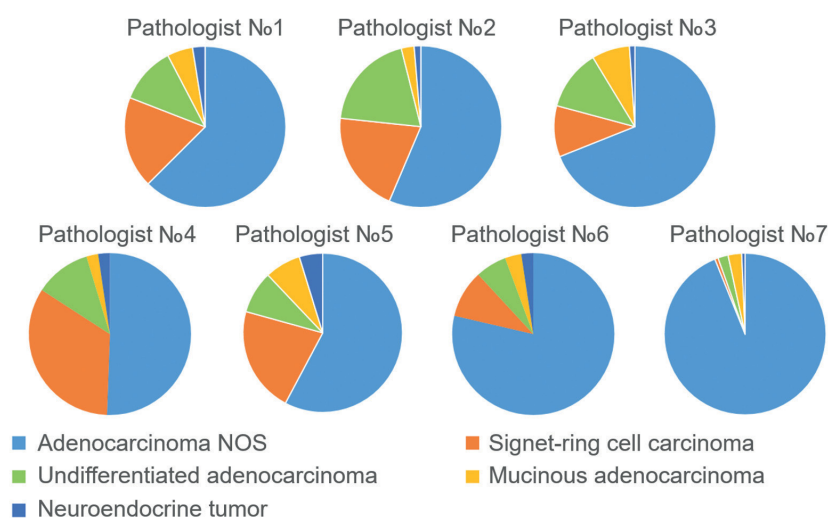


Fig. 4. Distribution of codes for histological types of GC for each of the pathologists separately.

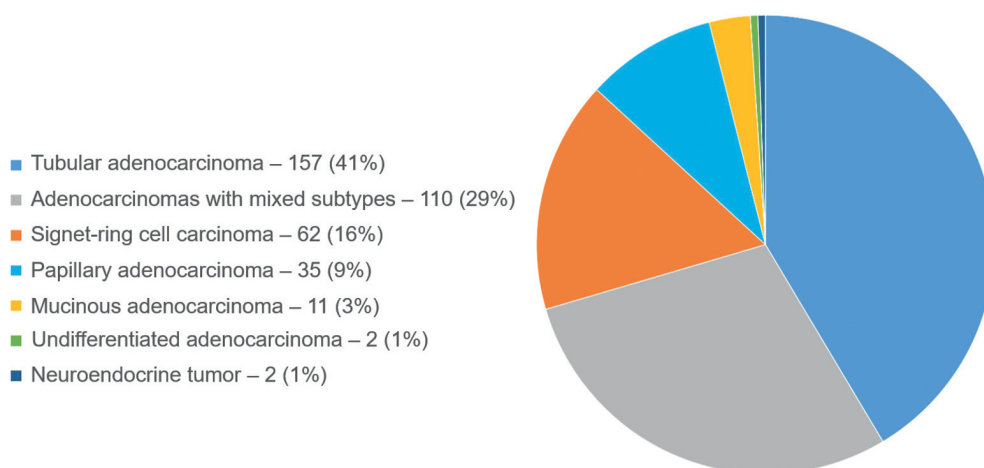


Fig. 5. The frequency of histological types of epithelial malignant neoplasms after revision of the pathology reports by an independent pathologist from 2018 to 2019 (379 patients).

of NOS adenocarcinoma increased significantly from 90 in 2000 to 221 in 2019, especially over the last 2 years (median 146.5 [123; 165.25], $R^2=0.598$, $p<0.01$).

We found an abnormal increase in the number of diagnoses of "adenocarcinoma NOS" and we analyzed the percentage distribution pathology reports of epithelial GC between pathologists from 2000 to 2019. The specifics of the work of a large oncological institution made us to introduce of narrow specializations among pathologists. Over the past 2 years, the morphological diagnosis of GC was assigned mainly to two pathologists (pathologists No. 6 and pathologists No. 7) (fig. 3).

We analyzed the distribution of codes for histological types of GC for each of the pathologists. As a result, pathologists No.1, pathologists No.2, pathologists No.3, pathologists No.4 and pathologists No.5 had approximately similar distribution of histological type codes. While pathologists No.6 and pathologists No.7 were much more likely to use the code for adenocarcinoma NOS (8140/3) in the conclusion (fig. 4).

The pathology reports from 2018 to 2019 were reviewed by an independent pathologist and recoded according to the 2019 WHO classification of gastrointestinal tumors (fig. 5). As a result, after the revision of the pathology reports, the code of adenocarcinoma NOS (8140/3) was replaced by the codes of tubular adenocarcinoma (ICD-O: 8211/3) – 41%, papillary adenocarcinoma (8260/3) – 9% and adenocarcinomas with mixed subtypes (8255/3) – 29%.

In the 5th edition of the WHO classification of gastrointestinal tumors, adenocarcinoma with mixed subtypes is established based on the identification of two or more histological subtypes in the tumor, however, the proportion of these subtypes is not discussed. In turn, in the recommendations of the College of American Pathologists (CAP), adenocarcinoma with mixed subtypes means "approximately equal ratio of intestinal to diffuse components". The question remains, which recommendations should be followed by a pathologist in Russia.

DISCUSSION

As a result of the study, using the example of the analysis of GC coding, it was demonstrated the importance of the digital archive in PD as a tool for rapid static analysis of pathology reports and quality control of coding of pathologists. Moreover, it is not so much the fact of the presence of such databases in the department that is important, but control over the maintenance of digital archives data, namely, training specialists in the principles of accurate coding of the detected pathology and timely updating of the coding system in accordance with modern editions of WHO classifications. In the order of the Ministry of Health of the Russian Federation of March 24, 2016 N 179n "On the Rules for conducting pathological and anatomical examinations" in Appendix No. 2 "Recommended staff standards of the PD and bureau", the position of a physician-statistician is provided for every 15 positions of doctors and specialists with a higher non-medical education only for the pathology bureau, and is not provided for the PD. We consider it expedient to introduce the position of a doctor-statistician in PD of large oncological institutions for accurate coding, maintenance and analysis of the digital archive.

CONCLUSION

Analysis of the digital archive of PD National Medical Research Centre for Oncology of the Ministry of Health of Russia on the example of GC revealed the unjustified frequent use of the code "adenocarcinoma NOS" (8140/3) by pathologists. Thanks to the research carried out, the PD digital archive system is being updated. In particular, new clinical and morphological parameters (TNM classification) are being introduced and combined with other information systems of the institution. The pathology reports coding system can be the basis for large multicenter trials of oncology, therefore, it is important to control the quality of coding of pathology reports and timely update of codes when new morphological classifications are released.

Authors contribution:

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CLINICAL CASE REPORTS

EXPERIENCE OF PEMETREXED IN MAINTENANCE THERAPY FOR METASTATIC LUNG ADENOCARCINOMA

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ABSTRACT

Lung cancer is among the most common malignant diseases in Russia. In 80–90%, its morphological type is non-small cell lung cancer. Stage IV primary advanced lung cancer is diagnosed in 41% of patients. Median overall survival in stage IV patients receiving chemotherapy is 7–12 months. Treatment for stage IV lung adenocarcinoma is based on predictive and prognostic factors. Chemotherapy, chemoimmunotherapy or immunotherapy is recommended in the absence of driver mutations in the EGFR (exons 19 and 21) and BRAF genes, ALK and ROS1 translocations. Platinum-based regimens are preferred as the first-line chemotherapy. Stabilization, partial or complete response after 4–6 chemotherapy cycles allow for maintenance therapy with pemetrexed to increase progression-free survival and overall survival.

Purpose of the study. Using a real clinical case, to confirm the efficacy of pemetrexed in the treatment for stage IV lung adenocarcinoma in the second-line therapy in combination with platinum-based agents and in a maintenance therapy. A clinical case of a patient with central cancer of the lower lobe of the right lung St IV (cT3N2M1) is presented; the first treatment stage involved 3 cycles of the first-line polychemotherapy (paclitaxel 175 mg/m² intravenously on day 1, carboplatin AUC 5 intravenously on day 1, every 3 weeks), and 6 cycles of the second-line polychemotherapy (pemetrexed 500 mg/m² intravenously on day 1, cisplatin 75 mg/m² intravenously on day 1 of the 21-day cycle). Stabilization of the disease was achieved, and 20 cycles of maintenance therapy with pemetrexed followed; the achieved effect persisted and was confirmed by spiral X-ray computed tomography every 3 months. The objective effect of anticancer therapy was assessed according to the RECIST 1.1 criteria. It took 20 months from the beginning of the second-line anticancer medical therapy to progression, and 16 months from the start of maintenance pemetrexed to progression. The safety profile was satisfactory, and the ECOG performance status 0 maintained. Only one adverse effect, degree I general weakness, was noted, which did not have a negative impact on the patient's quality of life.

Keywords:

non-small cell lung cancer, adenocarcinoma, pemetrexed, maintenance therapy, adverse effects, disease stabilization.

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ОПЫТ ИСПОЛЬЗОВАНИЯ ПЕМЕТРЕКСЕДА В ПОДДЕРЖИВАЮЩЕЙ ТЕРАПИИ МЕТАСТАТИЧЕСКОЙ АДЕНОКАРЦИНОМЫ ЛЕГКОГО

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РЕЗЮМЕ

Лидирующие позиции в структуре онкологической заболеваемости населения России занимает рак легкого. В 80–90% случаев встречается немелкоклеточный морфологический вариант. Первично генерализованный рак легкого IV стадии выявляется у 41% больных. Медиана общей выживаемости при проведении химиотерапии пациентам с IV стадией составляет 7–12 месяцев. Лечение аденокарциномы легкого IV стадии назначают с учетом предиктивных и прогностических факторов. При отсутствии драйверных мутаций в генах EGFR (рецептор эпидермального фактора роста) (19 и 21 экзоны), BRAF, транслокаций ALK (киназа анапластической лимфомы), ROS1 рекомендуется назначение химиотерапии, химиоиммунотерапии или иммунотерапии. В качестве химиотерапии первой линии предпочтительнее использовать комбинации на основе платины. При стабилизации, частичном или полном ответе после 4–6 курсов химиотерапии возможно проведение поддерживающей терапии пеметрекседом с целью увеличения выживаемости без прогрессирования, общей выживаемости.

Цель исследования. На случае из реальной клинической практики подтвердить эффективность применения пеметрекседа в лечении аденокарциномы легкого St IV во второй линии терапии в комбинации с препаратами платины в поддерживающем режиме.

Представлено клиническое наблюдение пациентки с центральным раком нижней доли правого легкого St IV (cT3N2M1), на первом этапе лечения которой было проведено 3 курса полихимиотерапии 1 линии (паклитаксел 175 мг/м² внутривенно капельно в 1-й день, карбоплатин AUC (площадь под фармакокинетической кривой) 5 внутривенно капельно в 1-й день, каждые 3 недели), 6 курсов полихимиотерапии 2 линии (пеметрексед 500 мг/м² внутривенно капельно в 1-й день, цисплатин 75 мг/м² внутривенно капельно в 1-й день 21 дневного цикла). В связи с достигнутой стабилизацией заболевания далее проведено 20 циклов поддерживающей терапии пеметрекседом, на протяжении которых достигнутый эффект сохранялся и подтверждался рентгенологически при выполнении спиральной рентгеновской компьютерной томографии каждые 3 месяца. Оценка объективного эффекта противоопухолевой лекарственной терапии проводилась согласно критериям Response evaluation criteria in solid tumours (RECIST) 1.1. От начала 2 линии противоопухолевой лекарственной терапии до прогрессирования прошло 20 месяцев, а от начала введения пеметрекседа в поддерживающем режиме до прогрессирования – 16 месяцев. Профиль безопасности был удовлетворительным, сохранялся статус ECOG 0. Отмечено только одно нежелательное явление – общая слабость I степени, что не оказывало отрицательного влияния на качество жизни пациентки.

Ключевые слова:

немелкоклеточный рак легкого, аденокарцинома, пеметрексед, поддерживающая терапия, нежелательные явления, стабилизация заболевания.

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Lung cancer occupies a leading position in the structure of cancer incidence in the Russian population. In 2018, malignant diseases of the lung, trachea and bronchi were first diagnosed in 51,573 people. At the same time, the proportion of patients with stage IV from the number of patients with a first-time diagnosis of a malignant neoplasm was 41% [1]. Non-small cell morphological variant of lung cancer occurs in 80–90% of all cases [2]. According to the clinical recommendations of the Ministry of Health of the Russian Federation for stage IV lung adenocarcinoma, treatment is prescribed taking into account predictive and prognostic factors. Thus, when activating mutations of the EGFR gene (exons 19 and 21) or translocations of ALK, ROS1, and BRAF mutations are detected, targeted therapy is recommended. In the absence of driver mutations in these genes, chemotherapy, chemoimmunotherapy or immunotherapy is recommended, the purpose of which depends on a number of clinical and laboratory parameters, in some cases taking into account the level of PD-L1 expression by tumor cells [3, 4]. As a first-line chemotherapy, it is preferable to use platinum-based combinations [5, 6]. The median overall survival during chemotherapy in patients with locally advanced (III b) and metastatic (IV) stages is 7–12 months [6–8]. One of the chemotherapeutic options is to use a combination of pemetrexed 500 mg/m² intravenously drip on day 1 with cisplatin 75 mg/m² or carboplatin AUC 5 intravenously drip on day 1 every 3 weeks. With stabilization, partial or complete response after 4–6 courses of treatment, maintenance therapy with pemetrexed is recommended. Maintenance therapy is prescribed to increase progression-free survival, overall survival, while the number of side effects should be minimal and not have a significant negative impact on the quality of life of patients. Maintenance therapy is performed until progression or unacceptable toxicity. Conducting maintenance therapy immediately after line 1 therapy may lead to an increase in the number of patients who may benefit clinically from additional lines of therapy [9]. It is important that pemetrexed therapy has a low incidence of side effects and controlled toxicity [10].

The efficiency of maintenance therapy with pemetrexed in patients with late-stage non-small cell lung

cancer (NSCLC) was confirmed in a double-blind randomized controlled trial of phase III PARAMOUNT. This study involved patients with late-stage non-squamous cell NSCLC aged 18 years and older, with at least one measurable tumor site, and with an Eastern Cooperative Oncology Group (ECOG) score of 0–1, who had not previously received systemic chemotherapy for lung cancer. The study included two phases: the induction phase without randomization and the maintenance phase with randomization. Before randomization, patients (939 people) underwent 4 cycles of therapy with pemetrexed (500 mg/m²) and cisplatin (75 mg/m²), which were administered intravenously by drip on the 1st day of the 21-day cycle. Further, patients without signs of disease progression (539 people) were randomized into two groups (in a ratio of 2:1). In group 1, consisting of 359 people, patients received maintenance therapy with pemetrexed (500 mg/m² on day 1 of each 21-day cycle) and optimal symptomatic therapy (OST), in group 2 (180 people)-placebo (on day 1 of each 21-day cycle) and OST. Maintenance therapy was carried out until the disease progressed or unacceptable toxicity, and it was discontinued at the decision of the patient or doctor. From 1 to 19 cycles of maintenance therapy with pemetrexed were performed (an average of 4.9). More than 6 cycles of pemetrexed were received by 23% of patients (84 people out of 359 patients in the pemetrexed group). The main criterion for effectiveness in this study was progression-free survival. The objective effect frequency, quality of life, use of medical resources, adverse events, and overall survival (S) were additionally studied. Median progression-free survival, calculated from the date of randomization, was 4.1 months (95% CI 3.2–4.6) in the pemetrexed group and 2.8 months (95% CI 2.6–3.1) in the placebo group. Grade III–IV hematological adverse events, possibly related to treatment, were more common in the pemetrexed group (33 [9%] of 359 patients) compared to the placebo group (1 [< 1%] of 180 patients; $p < 0.0001$), the same trend was observed for non-hematological adverse events of grade III–V (32 [9%] of 359 patients in the pemetrexed group; 8 [4%] of 180 patients in the placebo group; $p = 0.080$). In each group, one fatal outcome was recorded, possibly related to treatment. The most common grade III–IV adverse events in the pemetrexed group were anemia

(16 [4%] of 359 patients), neutropenia (13 [4%]), and fatigue (15 [4%]). In the placebo group, the above adverse events were less common: anemia (1 [$< 1\%$] of 180 patients), neutropenia (0), and fatigue (1 [$< 1\%$]). The most common serious adverse events were anemia (8 [2%] of 359 patients in the pemetrexed group vs 0 in the placebo group) and febrile neutropenia (5 [1%] vs 0). At the same time, 19 (5%) patients from the pemetrexed group and 6 (3%) patients from the placebo group aborted participation in the study due to adverse events associated with treatment [11].

The efficiency of pemetrexed in maintenance therapy in late-stage NSCLC after induction chemotherapy with pemetrexed-free duplets was evaluated in a multicenter, randomized, double-blind phase III trial [12]. This study included patients with squamous and non-squamous cell histological tumor types, who were randomized in a 2:1 ratio after completing 4 cycles of induction chemotherapy with duplets based on platinum derivatives and not containing pemetrexed in the absence of progression. A total of 663 patients were randomized, 441 of them received maintenance therapy with pemetrexed (500 mg/m²) in combination with optimal symptomatic therapy, and 222 patients received placebo in combination with optimal symptomatic therapy on day 1 of the 21-day cycle. The main criterion for effectiveness was progression-free survival (PFS), which was determined from the date of randomization. Secondary end points were overall survival (OS), the frequency of the objective effect, safety. The use of pemetrexed as maintenance therapy resulted in a statistically significant increase in the median progression-free survival (4.3 months; 95% CI 4.1–4.7) compared to placebo (2.6 months; 95% CI 1.7–2.8). A more significant advantage in IBD was demonstrated in patients with the non-squamous cell histological subtype-IBD: HR 0.47; 95% CI 0.37–0.6; $p < 0.001$; 4.4 months for the pemetrexed group and 1.8 months for the placebo group. In the pemetrexed group, the incidence of treatment – related adverse events of grade III–IV was significantly higher (16%; $n=70$) than in the placebo group (4%; $n=9$, $p < 0.0001$). No deaths from treatment-related toxicity were observed in any of the groups.

In the publications we found, maintenance therapy with pemetrexed was carried out from 1 to 19 cycles

(an average of 4.9), after which treatment was discontinued due to progression or unacceptable toxicity. We found it interesting to publish a clinical case in which a patient with stage IV NSCLC underwent 20 cycles of antitumor drug therapy with pemetrexed after platinum and pemetrexed chemotherapy in a supportive mode.

In patient S., born in 1955, during a routine examination on a chest X-ray, pathological changes were found in the right lung. In this regard, in April 2018, she turned to the clinical and diagnostic department of the Federal State Budgetary Institution of the National Research Center of Oncology of the Ministry of Health of Russia. According to the spiral X-ray computed tomography of the chest organs (05.04.2018), metastatic foci were found in the lung tissue on both sides, larger on the right from 0.5 cm to 1 cm. Pulmonary fibrosis. Peripheral tumor of the lower lobe of the right lung 4.2 x 4.6 cm (target focus) with centralization and damage to the segmental bronchus, sprouting into the pleura paravertebral at the level of the 9th thoracic vertebra. In the upper mediastinum, lymph nodes up to 1.7 cm, retrocaval up to 1.7 cm, bifurcation up to 2.3 cm, aortic window up to 2.3 cm, bronchopulmonary on the right up to 2.3 cm, on the left up to 1.1 cm. (fig. 1).

On 10.04.2018, a fibrobronchoscopy was performed, which revealed a peribronchial, mainly submucosal tumor of the right lung with the involvement of the lower lobe, intermediate, and upper lobe bronchi. A biopsy was performed and a histological conclusion was obtained: "a fragment of the bronchial mucosa with diffuse infiltration from large cells suspected of tumor cells, an immunohistochemical study (IHC) is necessary to clarify the diagnosis." According to the IHC data, the morphological picture and immunophenotype most closely correspond to low-grade lung adenocarcinoma, a solid variant with invasion of the bronchial wall. A molecular genetic analysis was performed. When studying the obtained sample of deoxyribonucleic acid (DNA), no mutations were found in the EGFR gene, and no rearrangement was detected in the ALK and ROS-1 genes.

According to spiral X-ray computed tomography of the brain, abdominal cavity and pelvis (11.04.2018), no foci of pathological density in the brain substance were detected, in the lower parts of the lungs on the

right, multiple metastatic foci up to 1 cm, the density of the liver parenchyma is uniform.

The patient complained of discomfort in the chest on the right (in the lower parts), bad habits and occupational hazards did not have. A clinical diagnosis was made: central cancer of the lower lobe of the right lung, metastases to the lymph nodes of the root and mediastinum, metastases to the lungs on both sides of St IV (cT3N2M1), clinical group 2. Concomitant diseases (I 11) hypertension stage 2, risk 2, NC 0, (I 83.9) varicose veins of the lower extremities. Since May 2018, 3 courses of 1-line polychemotherapy have been carried out according to the scheme: paclitaxel 175 mg/m² intravenously drip on day 1, carboplatin AUC 5 intravenously drip on day 1, every 3 weeks. When performing a control spiral X-ray computed tomography (SRCT) of the chest, abdominal cavity and pelvis (27.07.2018) in the lung tissue on the right, a centralized peripheral tumor of the lower lobe of 5.6 x 4.9 cm on both sides, multiple metastatic foci up to 1.2 cm, hypoventilation, pulmonitis of the lower lobe on the right. The lumen of the lower lobe bronchus on the right is narrowed. Retrocaval lymph nodes 2 cm, aortic window 1.5 cm, right root up to 2.2 cm, upper mediastinum on the right 1.4 cm. The density of the liver parenchyma is uniform. Uterus 5 x 4.5 cm, appendages on the left with a liquid structure 4 x 2.4 cm. (fig. 2).

According to the RECIST criteria marked by the growth of targeted lesion in 21%, in this connection, the decision of the medical Council of National Medical Research Centre for Oncology of the Ministry of Health of Russia recommended a change of line chemotherapy and conduct of chemotherapy line 2 on the scheme, pemetrexed 500 mg/m² intravenously 1 day, cisplatin 75 mg/m² intravenously 1 day 21-day cycle. The above scheme of antitumor drug therapy was started in August 2018. After 3 cycles of polychemotherapy, SRCT of the brain, neck, chest, abdominal cavity and pelvis was performed (10.10.2018) in the lungs, multiple metastatic foci on both sides up to 0.4 cm. The central tumor of the right lung is 6.6 x 4.5 cm with a lesion of the lower lobe, middle lobe and intermediate bronchi. Retrocaval lymph nodes 1.5 cm, aortic window 1.8 cm, bifurcation 2.1 cm, right root up to 1.4 cm. The density of the liver parenchyma is uniform. The concretion of the gallbladder is 1.6 cm, the wall is not thickened. The retroperitoneal lymph nodes are not enlarged. There are no foci of abnormal density in the substance of the brain (fig. 3).

The growth of the target focus was revealed by 17%, according to the RECIST criteria, the tumor process was stabilized, antitumor drug therapy was continued according to the previous scheme (pemetrexed 500 mg/m² intravenously drip on day 1, cisplatin

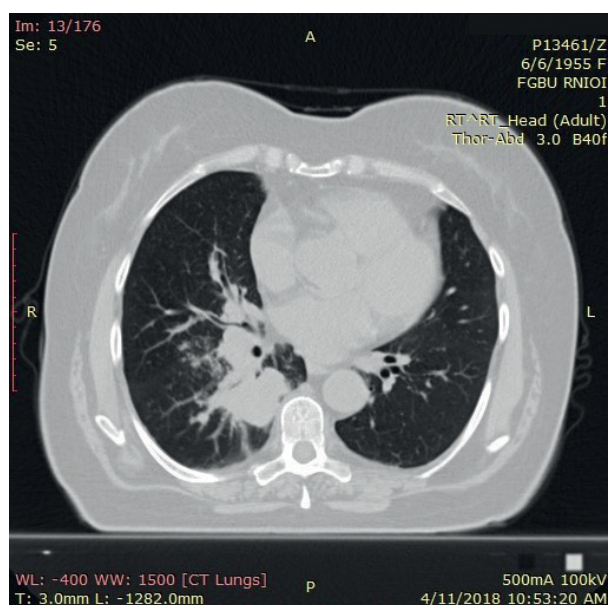


Fig. 1. SRCT of the chest organs before the start of antitumor drug therapy.

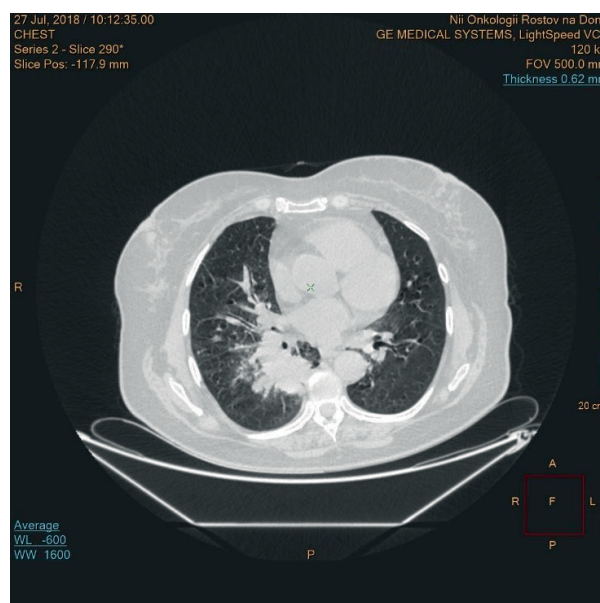


Fig. 2. SRCT of the chest organs before starting line 2 chemotherapy with pemetrexed and cisplatin.

75 mg/m² intravenously drip on day 1 of the 21-day cycle) up to 6 courses. Further, SRCT of the brain and chest organs was performed (17.12.2018) – no foci of abnormal density in the brain substance were detected. In the lung tissue on both sides, there are multiple metastatic foci up to 1 cm. Hypoventilation of the lower lobe on the right. On the right, a central tumor with a lesion of the lower lobe bronchus of 4.5 x 4.4 cm with a non-uniform structure. The lymph nodes of the aortic window are 1.3 cm. The tumor process remains stable according to the RECIST criteria. In connection with the above, according to the clinical recommendations of the Association of Oncologists of Russia, the Ministry of Health of Russia has continued to administer pemetrexed 500 mg/m² intravenously on the 1st day of the 21-day cycle as a maintenance therapy since December 2018. Every 3 months, SRCT of the brain, chest, abdominal and pelvic organs was monitored, which still maintained the stabilization of the tumor process. 20 cycles of maintenance therapy were performed. During the entire period of antitumor drug therapy, only general weakness of the first degree was observed among the adverse events, which did not affect the quality of life, social activity and the conduct of antitumor drug therapy.

At the next control examination of the SRCT of the brain, neck, chest, abdominal cavity and pelvis

(28.04.2020), no foci of pathological density in the brain substance were detected. The right eyeball is enlarged in relation to the left to 2.9 x 2.7 cm, the left eyeball 2.3 x 2.3 cm. In the lung tissue on both sides, there are multiple metastatic foci up to 1.5 cm, an increase compared to the previous study in December 2019. On the right, a centralized peripheral tumor of the lower lobe is 4.7 x 3.3 cm, an increase compared to the previous study in December 2019. On both sides of the pleura there are multiple metastatic foci up to 0.5 cm. The density of the liver parenchyma is uniform, local areas of decrease or increase in density are not observed. In the bones of the skeleton without focal changes. The uterus is 5 x 4 cm, the appendages on the left with a liquid structure up to 3.2 x 3 cm, on the right are not visualized (fig. 4).

Taking into account the appearance of previously undetected metastatic foci in the pleura, the progression of the disease was revealed. Atezolizumab 1200 mg intravenously once every 21 days was chosen as the next line of antitumor drug therapy. Since May 2020, immunotherapy has been started (continues to the present). From the beginning of the third line of antitumor drug therapy to the submission of the article to the journal, 6 months have passed (the effect of stabilization remains).

This clinical observation is interesting for the long period of maintenance therapy with pemetrexed,

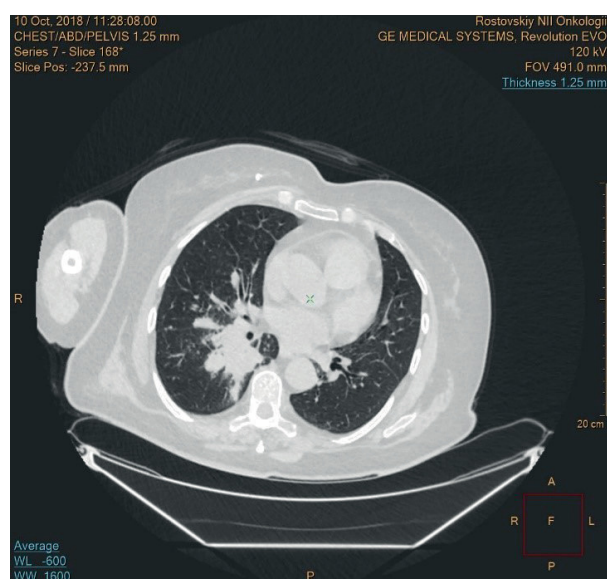


Fig. 3. SRCT of the chest organs after 3 courses of 2-line chemotherapy (pemetrexed, cisplatin).

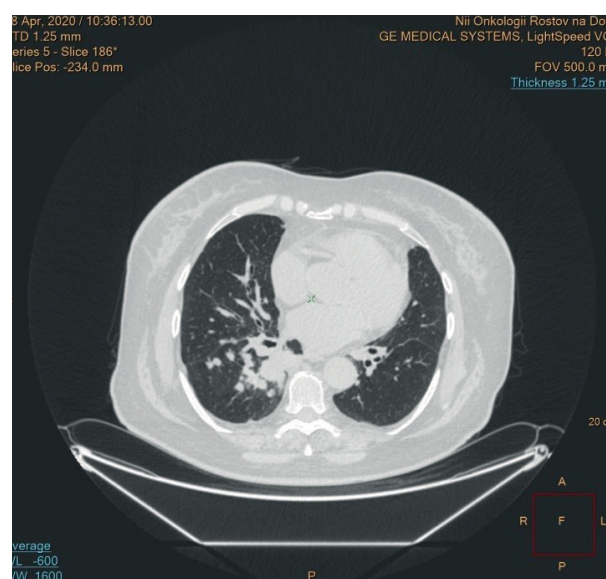


Fig. 4. SRCT of the chest organs (tumor progression after 20 cycles of maintenance therapy with pemetrexed).

the continued long-term stabilization of the disease against this background, and the absence of toxicity.

As mentioned earlier, in the double-blind randomized controlled trial of phase III PARAMOUNT, only 23% of patients received more than 6 cycles of pemetrexed in the maintenance mode, while the maximum number of cycles was 19. Our patient underwent 20 cycles of pemetrexed maintenance therapy, which exceeds the number of cycles described in the literature. According to our clinical observation, 20 months passed from the beginning of the 2 – line antitumor drug therapy to the progression, and 16 months passed from the beginning of the administration of pemetrexed in the maintenance mode to the progression. In the PARAMOUNT phase III study, the median IBD from the date of randomization was 4.1 months, and from the start of induction therapy was 6.9 months.

The long-term preservation of the stabilization effect, despite the primary metastatic tumor process, the ECOG 0 status, allowed the use of the immunotherapy option during the progression. At the time of our patient's diagnosis (April 2018), immunotherapy drugs in the treatment of NSCLC were not yet widely used. So, atezolizumab was registered in Russia

only on 18.01.2018 (and in the clinical and statistical group (CSG) appeared only in 2019). At the time of the beginning of treatment of our patient, the only registered immuno-oncological drug for the treatment of metastatic NSCLC in Russia was pembrolizumab (registration date 18.11.2016). Today, indications for the use of immunotherapy in monotherapy and in combination with chemotherapy are expanding. A regimen of antitumor drug therapy with pembrolizumab in combination with pemetrexed and cisplatin/carboplatin was introduced, followed by the transition to the maintenance regimen of pemetrexed+pembrolizumab, which opens up new prospects for the treatment of patients with non-small cell non-small cell lung cancer without activating mutations.

CONCLUSIONS

The presented clinical case demonstrates the possibility of long-term disease control in a patient with metastatic lung adenocarcinoma without activating mutations in the EGFR, BRAF, ALK, ROS1 genes when using a combination of platinum and pemetrexed drugs with further maintenance therapy with pemetrexed.

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Storozhakova A.E. – research concept and design, scientific editing, data analysis and interpretation.

Kalabanova E.A. – collection, analysis and interpretation of data, writing of the text, material processing, preparation of a bibliography, preparation of the article.

Meshcheryakov P.N. – preparation of illustrations.

Oskin S.V. – preparation of illustrations.

Kabanov S.N. – design of the bibliography.

Samaneva N.Yu. – technical editing.

Svetitskaya Ya.V. – design of the bibliography.

Tishina A.V. – technical editing.

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CLINICAL CASE REPORTS

PENETRATION INTO FREE ABDOMINAL CAVITY DURING TRANSANAL ENDOSCOPIC RECTAL RESECTION FOR ADENOMA

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ABSTRACT

Benign and malignant tumors are the most common diseases of the rectum and tend to grow. Various techniques have been developed for the treatment of rectal tumors: endoscopic electroexcision through a colonoscope, transanal removal of tumors, and transabdominal removal. The use of all these methods made it possible to determine their advantages and indications, as well as limitations and disadvantages. Technical advances in modern oncology resulted in developing a method for transanal tumor removal with a number of advantages: radical surgery, adequacy, and functionality. This technique can be used in benign and malignant rectal tumors. One of its main advantages involves a small number of postoperative complications, while intra-operative complications such as penetration into the free abdominal cavity during transanal endoscopic resection of the rectum are quite rare. It is also important that the method of transanal endoscopic resection of the rectum also has good oncological and functional results (according to various studies). We present a clinical case of penetration into the free abdominal cavity during transanal endoscopic rectal resection for adenoma. This case is also interesting in that the patient also had another complication – postoperative bleeding from the rectum, which required surgical intervention, also with the use of a minimally invasive approach. This clinical observation demonstrates successful suturing of penetrating openings into the abdominal cavity arising during transanal endoscopic removal of rectal tumors with the upper pole located above the pelvic peritoneum and effective minimally invasive tactics in the development of postoperative bleeding.

Keywords:

transanal endoscopic tumor removal, transabdominal removal, organ-preserving treatment, benign rectal tumors, malignant rectal tumors, rectal tumors.

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ПРОНИКНОВЕНИЕ В СВОБОДНУЮ БРЮШНУЮ ПОЛОСТЬ ПРИ ТРАНСАНАЛЬНОЙ ЭНДОСКОПИЧЕСКОЙ РЕЗЕКЦИИ ПРЯМОЙ КИШКИ ПО ПОВОДУ АДЕНОМЫ

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РЕЗЮМЕ

Доброкачественные и злокачественные опухоли являются самыми распространенными заболеваниями прямой кишки и имеют тенденцию к росту. Для лечения опухолей прямой кишки разработаны различные методики: эндоскопическая электроэксцизия через колоноскоп, трансанальное удаление опухолей, трансабдоминальное удаление. Применение всех этих методов позволило определить их преимущества и как показания, так и ограничения и недостатки. Технические достижения современной онкологии привели к разработке метода трансанального удаления опухолей, имеющего ряд преимуществ: радикальность оперативного вмешательства, адекватность, функциональность. Область применения данной методики – это доброкачественные, а также малигнизированные опухоли прямой кишки. Одним из основных преимуществ данной технологии является минимальная частота послеоперационных осложнений, а такие интраоперационные осложнения, как проникновение в свободную брюшную полость при трансанальной эндоскопической резекции прямой кишки встречаются достаточно редко. Немаловажным является также то, что метод трансанальной эндоскопической резекции прямой кишки отличается также хорошими онкологическими и функциональными результатами (по данным различных исследований). Представляем клинический случай проникновения в свободную брюшную полость во время трансанальной эндоскопической резекции прямой кишки по поводу аденомы. Этот случай также интересен тем, что у больного было также еще одно осложнение – послеоперационное кровотечение из прямой кишки, которое потребовало оперативного вмешательства, также с применением миниинвазивного доступа.

Данное клиническое наблюдение демонстрирует возможность благополучного ушивания проникающих отверстий в брюшную полость, возникающих при трансанальном эндоскопическом удалении опухолей прямой кишки, верхний полюс которых оказывается расположенным выше тазовой брюшины и эффективной малоинвазивной тактики при развитии послеоперационного кровотечения.

Ключевые слова:

трансанальное эндоскопическое удаление опухоли, трансабдоминальное удаление, органосохраняющий метод лечения, доброкачественные опухоли прямой кишки, малигнизированные опухоли прямой кишки, опухоли прямой кишки.

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RELEVANCE

The focus of modern oncology on organ-preserving methods of treatment and technical developments have contributed to the emergence of a method for transanal removal of rectal tumors using a system for enabling microsurgical manipulations [1–3]. In the world practice, there is already experience in using the method of transanal endoscopic resection of the rectum with the removal of tumors, which revealed its obvious advantages: first, it is the radical nature of the surgical intervention itself (since the method allows you to remove tumors in a single block surrounded by healthy tissues); secondly, it is the adequacy of surgical intervention (that is, minimizing the risks of intra- and postoperative complications); thirdly, it is the functionality of surgical intervention (that is, the preservation or rapid restoration of rectal function after surgery) [4–8]. The main field of application of the method of transanal endoscopic surgery is currently benign, malignized tumors of the rectum, as well as the initial forms of malignant tumors that are located below the pelvic peritoneum. The minimal number of postoperative complications is also a clear advantage of the method of transanal endosurgery of rectal tumors. Data from different authors indicate that bleeding after transanal endoscopic resection of the rectum occurs in 3.7–9.1% of surgical interventions, fistulas and abscesses in the pelvic cavity-up to 1.7–4.1% [9]. Even less common are intraoperative complications such as penetration into the free abdominal cavity during transanal endoscopic resection of the rectum.

In connection with the information given above, our clinical observation is interesting.

Clinical case description

Patient S., born in 1946, was admitted to the Department of Abdominal Oncology No. 2 of the National Medical Research Centre for Oncology of the Ministry of Health of Russia on 10.02.2019 with complaints of an admixture of blood, mucus in the feces, tenesmus. Considers himself ill for 3 months. Examination: FCS from 25.01.2019. from 5 cm to 15–17 cm from the anus along the anterior wall, a creeping flat tumor up to 4 cm wide. Histo-

logical analysis No. 85905–909: papillary adenoma. Ultrasound of the abdominal cavity on 17.01.2019 revealed no pathological changes. Objectively: Height – 166 cm, weight – 65 kg, BMI – 23.6. The patient's condition is relatively satisfactory. The skin and visible mucous membranes of the usual color. The peripheral lymph nodes are not enlarged and are not palpable. Heart rate is 78 per minute, blood pressure is 130/80 mmHg. Heart tones are rhythmic. In the lungs, during auscultation, vesicular breathing is heard over the entire surface of the lungs, wheezing is not heard. The tongue is moist, without plaque. The abdomen is soft and painless on palpation. Pounding in the lumbar region is painless on both sides. Peripheral edema is not detected. Finger examination of the rectum: from 5 cm from the anus along the anterior wall of the rectum, a soft formation, the upper edge of the finger is not accessible. The diagnosis was made: villous tumor of the rectum. Clinical and laboratory examination revealed no significant deviations, and preoperative preparation was standard. On 11.02.2019, the patient was taken to the operating room. It was decided to perform a transanal endoscopic resection of the rectum with a full-layer removal of the intestinal wall with a tumor. Stages of surgical intervention: under general anesthesia, in the position of the patient on his stomach with his legs spread apart, after processing the operating field, an operating rectoscope is installed in the rectum (KarlStorz, Germany), which is adapted to the laparoscopic stand, while a special device is used to fix the rectoscope to the operating table. An insufflator for injecting carbon dioxide into the rectum during the intervention and a set of tools for endoscopic manipulations (electrocoagulator, "Harmonic" coagulation scissors, scissors, clamps) were also used. A creeping flat tumor from 5 cm to 15 cm from the anodermal junction along the posterior wall of the rectum with a width of up to 4 cm was visualized (fig. 1). The first stage was the point marking of the rectal wall resection line with a coagulator, retreating from the edge of the tumor by 1 cm. The next step was a full-wall excision of the rectal wall area with a tumor with "Harmonic" coagulation scissors within healthy tissues along the line of marking the intestinal wall with a part

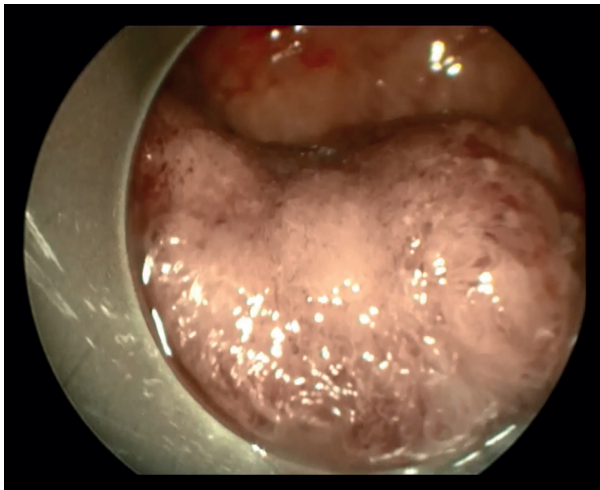


Fig. 1. Type of rectal tumor.

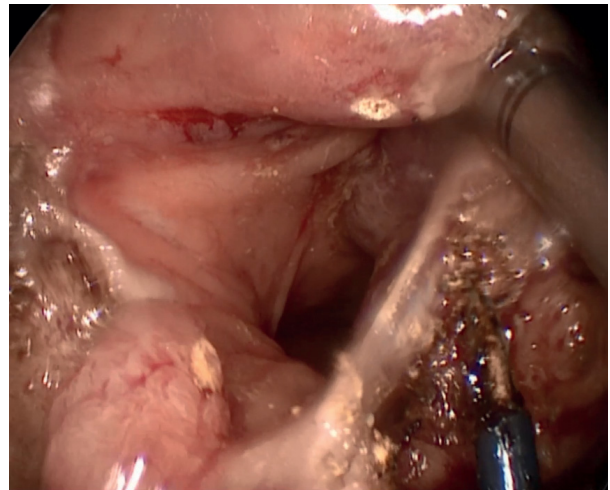


Fig. 2. Removal of the upper part of the rectal tumor.

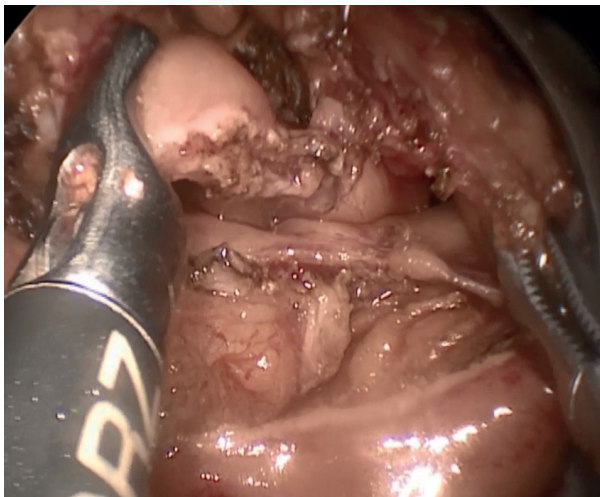


Fig. 3. Penetrating hole in the free abdominal cavity.

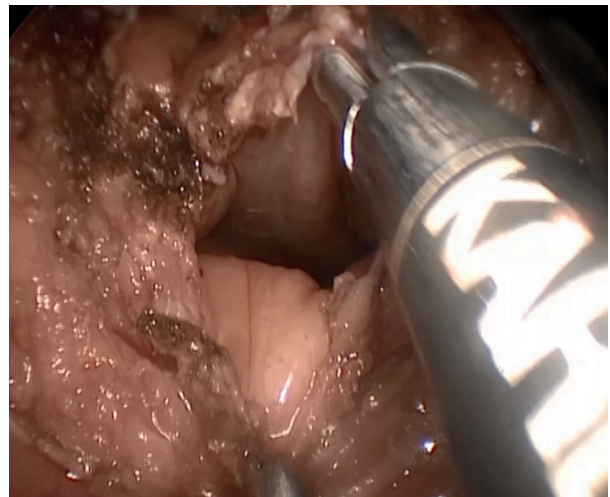


Fig. 4. Through the opening in the rectum, the pelvic peritoneum and rectal serosa are visible.

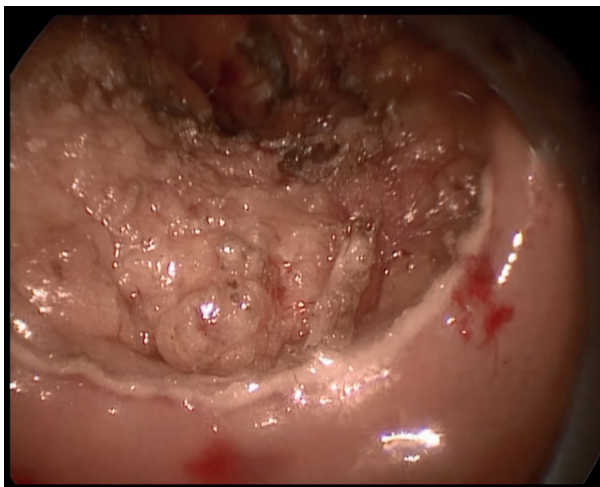


Fig. 5. Rectal wall after wall resection.

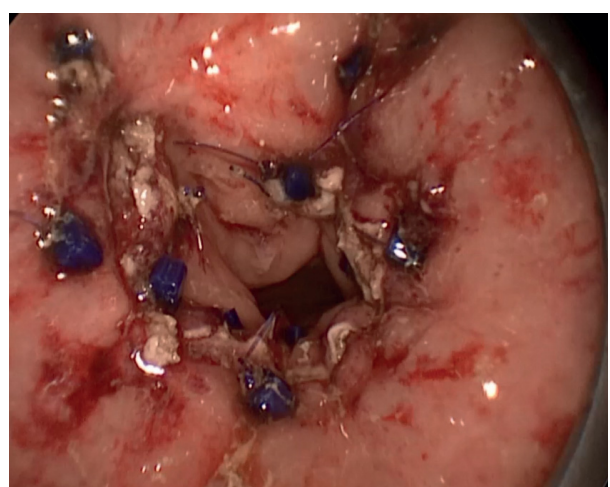


Fig. 6. The defect of the rectal wall is sutured transversely.

of the adjacent mesorectal tissue. For the convenience of excision of the intestinal wall, a clamp was used to capture the intestinal wall with a tumor, and then we lifted it. Excision of the bowel wall is produced in the proximal direction (fig. 2) when removing the upper part of the tumor was that it is located above the pelvic peritoneum, a hole with a diameter of 4 cm, penetrating into the free abdominal cavity (fig. 3, 4). Given the development of this complication, it is possible to have the following solution: low resection of the rectum or closure of the defect of the rectal wall. In the literature, the issues of applying a preventive colostomy in the case of suturing a defect in the intestinal wall are discussed. We decided to suture the defect of the rectal wall. We sutured the rectal wall (fig. 5) in the transverse direction with a continuous suture (Poli-sorb, Monocryl 2/0), while the edges of the thread were fixed with special clips (Lapra) (fig. 6). Based on the data on the absence of tension and sufficient tightness of the suture line, we did not apply a preventive intestinal stoma. The total duration of the surgical intervention was 135 minutes. Intraoperative blood loss was minimal – 20 ml. Postoperative morphological study No. 9384–87/19: tubular-papillary adenoma of the rectum, no tumor resection lines. The postoperative period in this patient was also complicated by intestinal bleeding in the amount of about 300 ml on the 2nd day after the operation. An emergency operation was decided, and an operating rectoscope with a laparoscopic stand was also used. During the operation, blood and clots were removed from the rectum, and the rectal suture line was visualized. There were no signs of ongoing bleeding. In the future, the postoperative period proceeded smoothly. The patient underwent antibiotic therapy for 3 days, a slagless diet – for 6 days. The stool was on the 4th day. The patient was discharged on day 8 after repeated surgery. No relapse of the tumor has occurred during the follow-up to the present time.

DISCUSSION

Such intraoperative complications as penetration into the free abdominal cavity during transanal endoscopic resection of the rectum are rare, so in

our clinical practice it occurred in one of 46 transanal endoscopic interventions on the rectum. Postoperative intestinal bleeding with such interventions is also rare. According to the literature, the overall rate of complications in transanal endoscopic rectal resection for benign and malignant tumors ranges from 6% to 31%. In this case, intraoperative complications (penetration into the free abdominal cavity and bleeding) may require laparotomy. The frequency of penetration into the free abdominal cavity is observed up to 9%, the frequency of bleeding – 1%–13% [10, 11]. Al-Najami et al. [12] report that in their study, 5 out of 12 patients (42%) with penetration into the free abdominal cavity required conversion to open surgery (Hartmann operation, low anterior rectal resection, transperitoneal suturing of the bowel defect), the remaining patients (58%) managed to suture the bowel defect transanally. The literature even describes one observation of the development of sepsis in pneumoperitoneum after transanal endoscopic resection of the rectum [13]. However, when penetrating into the free abdominal cavity, laparotomy is not always required, local suturing is possible. Thus, in a study by Ganai S. et al. [14] in 9 out of 144 patients with transanal endoscopic resection, penetration into the free abdominal cavity occurred, and in all cases it was possible to locally suture the defect and avoid anterior resection of the rectum. However, penetration into the free abdominal cavity significantly increases the duration of the patient's stay in the hospital [12, 15]. We have not seen any descriptions in the literature of a combination of penetration into the abdominal cavity and bleeding. Our patient collected two complications: both penetration into the free abdominal cavity, and intestinal bleeding. At the same time, despite various tactical approaches to solving this problem, up to performing rectal resection, it is possible to maintain a minimally invasive approach to surgical intervention, even with the development of complications.

CONCLUSIONS

The described clinical observation demonstrates the possibility of successful suturing of penetrating

holes in the abdominal cavity that occur during transanal endoscopic removal of rectal tumors, the upper pole of which is located above the pelvic peritoneum, as well as the possibility of not applying a preventive intestinal stoma with reliable suturing of a defect in

the rectal wall. Our clinical observation also demonstrates the possibility of repeated transanal surgical interventions in the event of urgent postoperative complications, such as intestinal bleeding.

Authors contribution:

Gevorkyan Yu.A. – concept and design of the study.

Soldatkina N.V. – scientific editing, writing of the text.

Kolesnikov V.E. – the design of bibliographies, preparation of illustrations.

Kharagezov D.A. – the design of bibliographies, preparation of illustrations.

Dashkov A.V. – data collection, analysis and interpretation.

Poluektov S.I. – the preparation of this article.

Samoylenko N.S. – the preparation of this article, technical editing.

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REVIEW

PREVENTIVE MEASURES AGAINST DEVELOPMENT OF BREAST CANCER

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ABSTRACT

According to Russian statistics, breast cancer ranks first among malignant neoplasms among women (20.9%). The largest proportion of breast cancer cases is detected in women aged 35 to 55 years. Therefore, an urgent issue is not only the provision of specialized medical care to patients, but also the prevention of the development of the disease. Almost 70% of malignant neoplasms, including breast cancer, are provoked by exogenous factors. This article provides an overview of the literature on primary breast cancer prevention. It is established that a woman's lifestyle, diet, physical activity, and bad habits can have a potentiating effect on the development of breast cancer.

Conclusions. Currently, breast cancer prevention plays a key role in the fight against this disease. middle-aged women (who account for the main peak of morbidity) should understand that by changing behavior, it is possible to reduce the risk of developing breast cancer. In addition, increasing women's awareness of breast cancer and its prevention can help reduce the incidence and financial costs of treatment.

Keywords:

breast cancer, prevention, morbidity, body mass index, alcohol consumption, nutrition.

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ПРОФИЛАКТИКА РАЗВИТИЯ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

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РЕЗЮМЕ

По данным российской статистики рак молочной железы занимает первое место среди злокачественных новообразований среди женщин (20,9%). Наибольшая доля случаев рака молочной железы выявляется у женщин в возрасте от 35 до 55 лет. Поэтому актуальным вопросом становится не только оказание специализированной медицинской помощи пациентам, но и профилактика развития этого заболевания. Почти 70% злокачественных новообразований, в том числе и рак молочной железы, провоцируются экзогенными факторами. В этой статье представлен обзор литературы о первичной профилактике рака молочной железы. Установлено, что образ жизни женщины, питание, ее физическая активность, вредные привычки могут оказывать потенцирующее влияние на развитие рака молочной железы.

Заключение. В настоящее время профилактика рака молочной железы играет ключевую роль в борьбе с этим заболеванием. Женщины среднего возраста (на который приходится основной пик заболеваемости) должны понимать, что путем изменения поведения возможно снизить риск развития этого заболевания. Кроме того, повышение осведомленности женщин о раке молочной железы и его профилактике может способствовать снижению заболеваемости и финансовых затрат на лечение.

Ключевые слова:

рак молочной железы, профилактика, заболеваемость, индекс массы тела, употребление алкоголя, питание.

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INTRODUCTION

Breast cancer (BC) is the most common cancer among women [1–4]. All over the world, BC cases account 22.9% [5]. BC ranks first in Russia and is the leading oncological pathology among women [6]. The proportion of BC is 20.9% in the structure of malignant neoplasms in women [7].

In the United States, more than 20% of BC cases are diagnosed in women under the age of 50, and only more than 4% are diagnosed in women under the age of 40 [8]. The specific weight of BC depending on the age of patients in Russia is shown in the figure 1 [7]. According to Russian statistics, the largest proportion of BC cases is detected in women aged 35 to 55 years [7]. Therefore, prevention of BC should begin in advance for women of 25–30 years. An important target of prevention is triple negative BC, which occurs in 10% to 20% of all breast malignancies [9]. It is known that triple negative BC is difficult to treat [10].

Almost 70% of malignant neoplasms are provoked by exogenous factors. In case of BC, these indicators reach 90–95% [11]. Currently, there are many studies indicating the influence of lifestyle (high-fatty diet, alcohol consumption, lack of physical activity) and environmental factors on the devel-

opment of BC, the elimination of which can contribute to reducing morbidity and mortality [11].

Regular physical activity and maintaining a normal body weight are key areas in the prevention of BC [12]. According to Chinese researchers, daily exercise reduces the risk of developing BC in women in the premenopausal and postmenopausal periods, and the elimination of inactivity can prevent about 10% of cases of BC [13]. Active sports activities help to reduce the risk of developing BC. Even moderate physical activity, such as brisk walking, is beneficial. According to the study carried by the American Cancer Society, women who walked at least 7 hours a week had a 14% lower incidence of postmenopausal BC than women who walked less than 3 hours a week [14]. In women with high physical activity, the risk of BC decreased by 25% compared to the least active respondents [14]. In another study, it was recorded that if a postmenopausal woman takes daily walks for one hour, the risk of BC is reduced by 15% compared to women who lead a sedentary lifestyle [15]. It is interesting to note that the risk of developing BC in a middle-aged woman is significantly reduced if she is engaged in sports throughout her life [16].

A low-activity lifestyle often correlates with

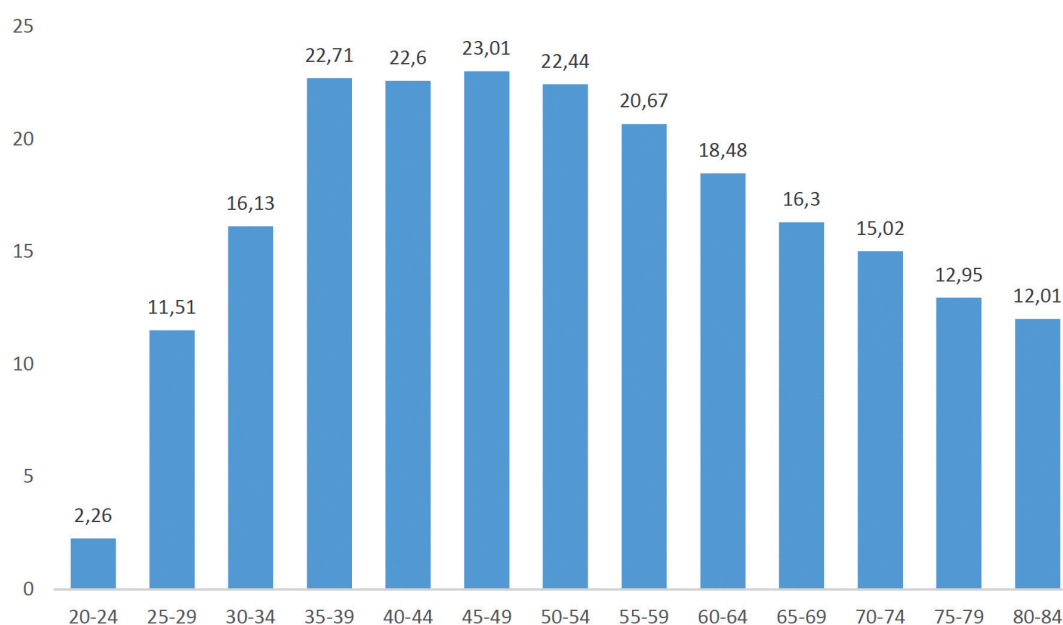


Fig. 1. Specific weight (%) of BC depending on the age of patients [7].

being overweight. Thus, according to US statistics, more than two-thirds of the adult population are overweight body mass index (BMI) – 25.0–29.9 kg/m², or obese (BMI, ≥30.0 kg/m²) [17]. In the study "Health of Nurses", it was recorded that increased body weight in 18-year-old girls significantly increases the risk of developing BC in the future, and is directly related to the number of pounds added [15]. Scientists pay special attention to weight correction in menopausal women. Since the metabolism of androgens into estrogens in adipose tissue increases the level of circulating estrogens, and their excess increases the risk of developing BC [18]. In a 2008 meta-analysis, it was noted that an increase in BMI for every 5 kg/m² increases the risk of developing postmenopausal BC by 12% [19]. Among postmenopausal women who monitored their weight, or reduced it by 10 kg or more, the risk of developing BC is reduced by half compared to women who had a stable high weight. Thus, the correction of body weight in a woman in adulthood is one of the important areas of primary prevention of BC.

Alcohol consumption is a risk factor for BC in women [8]. It is known that ethanol affects the concentration of estrogen by several mechanisms [20]:

- increases the activity of aromatase,
- inhibits the enzymes involved in the degradation of estrogen,
- increases the oxidative stress of the liver, which leads to inhibition of the metabolism of steroids,
- reduces the secretion of melatonin, which suppresses the production of estrogen

As a result, estrogens can have a carcinogenic effect on breast tissue.

It is noted that the consumption of alcohol 10 g per day (in terms of alcohol) leads to an increase in the risk of developing BC by 7–10% [21]. Women who consume alcoholic beverages on average three to six times a week have a 15% higher chance of developing BC, compared to those who lead a sober lifestyle [18]. Female alcoholics who consume alcoholic beverages twice a day or more have a 51% higher risk of developing BC [8].

The risk of developing BC is affected not only by the amount of alcohol consumed, but also by the

age of the woman. Alcohol consumption in adolescence has been shown to significantly increase the risk of proliferative benign breast changes in middle-aged women [20]. Alcohol consumption at a young age provokes the development of invasive BC in women in the premenopausal period [8].

The risk of developing BC is higher in women who consume industrial soft drinks more than once a month [22]. Industrial soft drinks are high in calories and lead to an increase in BMI, obesity and insulin resistance, which are mediators of the risk of BC.

Many authors note that improper and unbalanced nutrition potentiate the risk of developing BC [23]. Red and processed meats, foods rich in carbohydrates, and saturated fats are considered potential risk factors for BC, as they increase the level of circulating endogenous estrogen, an insulin-like growth factor – 1 [24]. In a comprehensive meta-analysis involving 17 prospective studies, the association of red and processed meat consumption with the risk of BC was evaluated [25]. It has been shown that the consumption of red meat is associated with an increase in the risk of BC by 6%, and the use of processed meat leads to an increase in the risk of BC by 9% [25]. Sodium nitrate in processed meats such as sausage, hamburgers, and pizza is known to convert to nitrosamine, which is a known carcinogen. Researchers from Poland reported that the probability of BC increases by 3 times with daily consumption of fast food [26]. Also, the processes of carcinogenesis are affected by high temperature processing of meat. Thus, cooking red meat at high temperature increases the formation of carcinogenic substances, including heterocyclic amines, N-nitroso compounds, and polyaromatic hydrocarbons [5]. Regular consumption of fried food increases the risk of developing BC by 4.5 times (95% confidence interval, 2.1–9.4) [27].

Consumption of milk and dairy products containing saturated fat, calcium, vitamin D, butyrate, lactoferrin, and conjugated linoleic acid reduces the risk of developing BC [5]. A meta-analysis of 18 prospective cohort studies ($n=24,187$) showed that increased consumption of dairy products leads to a reduced risk of BC (OR 0.85; 95% confidence interval: 0.76–0.95; $P=0.01$) [28]. These data were con-

firmed by Zang J. et al. the largest meta-analysis included 22 prospective cohort studies (1,566,940 participants) and five case-control studies (33,372 participants) [29]. The authors found a significant relationship between the dose, duration of use and type of dairy products and the development of BC: high (>600 g/day) and moderate (400–600 g/day) consumption of dairy products more effectively reduces the risk of BC compared to low consumption of dairy products (<400 g/day) [29].

The consumption of plant foods, fruits and vegetables contributes to the reduction of oxidative stress [30] and the prevention of carcinogenesis. An Italian study by the European Prospective Investigation of Cancer and Nutrition (EPIC) showed a direct link between high consumption of leafy and fruit vegetables, as well as raw tomatoes, and a low risk of developing BC [31]. The use of carotenoid-containing foods in the diet also reduces the proliferative processes in the mammary gland [15]. High consumption of plant protein and fiber is inversely proportional to the risk of developing breast neoplasms [32]. Regular consumption of vegetables and fruits (up to 2–3 times a day) reduces the likelihood of developing BC (OR, 2.8; 95% CI, 1.7–4.5) [27].

The consumption of seafood with a high content of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids (Omega-3 PUFA) reduces the frequency of BC by more than 5% [5]. Omega-3 PUFAs inhibit the antioxidant activity of cancer cells and can bind to nuclear receptors in tumor cells, modulating the expression of target genes involved in lipid metabolism and cell apoptosis [33].

A significant relationship was found between the consumption of sugary foods and the risk of developing BC [27]. Thus, the relative risk of developing

BC in women who regularly consumed sweets for more than a month was 2.6 (95% CI; 1.7–3.9) [27].

Some exogenous factors may influence the development of a certain type of BC. For example, breastfeeding prevents the development of triple negative BC [34]. In a prospective study, breastfeeding for 4 months or longer was shown to reduce the risk of basal-like BC by 40% (relative risk 0.6; 95% confidence interval 0.4–0.9) [35]. The EPIC study, conducted on a large ($n=337,327$) heterogeneous cohort of women, showed a positive correlation between high consumption of fatty foods with a high content of saturated fat and the development of an estrogen-positive subtype of BC [31].

Thus, according to experts, more than half of all cases of BC can be prevented by promoting and implementing a healthy lifestyle [8]. It is clear that risk factors for BC, such as obesity and lack of physical activity, will never be completely eliminated. But, early prevention of these diseases can prevent thousands of new annual cases of BC [8, 36].

CONCLUSIONS

Prevention of BC currently plays a key role in the fight against this disease. The main strategy of primary prevention of BC is to position a healthy lifestyle of a woman: regular physical activity, proper nutrition, weight correction and moderate alcohol consumption. Middle-aged women (who account for the main peak of the incidence) should understand that by changing behavior, it is possible to reduce the risk of developing BC. In addition, increasing women's awareness of BC and its prevention can help reduce the incidence and financial costs of treatment.

Authors contribution:

Vykhristyuk Yu.V. – study concept, text writing.

Roitberg G.E. – study design, scientific editing.

Dorosh J.V. – text writing, literature selection.

Karaseva N.V. – working with illustrations, technical work with text.

Akobova R.A. – design of the references list, translation of the abstract into English.

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ON THE ISSUE OF INTRODUCING AN ELECTRONIC DATABASE OF CHILDREN WITH ONCOLOGICAL DISEASES INTO SPECIALIZED MEDICAL ORGANIZATIONS: RESULTS OF A MEDICAL AND SOCIAL RESEARCH

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ABSTRACT

Accounting for children with cancer is characterized by low reliability of statistics. In addition, the available data do not have significant scientific value. Since they represent only an approximate number of patients identified annually and some general information (incidence, prevalence, etc.). Moreover, subsequent analysis of the accumulated information is of particular importance. An electronic database of children with cancer has been developed that meets these requirements and has been introduced into the clinical practice of pilot medical organizations.

Purpose of the study. Our aim was to study the opinions of pediatric oncologists on the issues of registration of children with oncological diseases.

Materials and methods. In order to assess the results of the implementation of the electronic database, a "Questionnaire for a survey of a pediatric oncologist to assess the effectiveness of the implementation of an electronic database" was developed, which contained 15 questions. For objectivity, the questionnaires were filled in anonymously by the respondents.

Results. The medico-social study involved 187 pediatric oncologists. The majority of respondents ($71.3 \pm 3.3\%$) noted that currently there is no register of children with cancer in the Russian Federation, $15.4 \pm 2.6\%$ noted the regional register, $9.1 \pm 2.1\%$ – independent in individual medical organizations, $1.7 \pm 0.9\%$ is a single register for the Russian Federation and $2.5 \pm 1.1\%$ are not aware of this. Among respondents, $81.9 \pm 2.8\%$ noted that the electronic database is an effective tool for recording children with cancer, while as an advantage, $15.1 \pm 2.6\%$ noted an increase in the reliability of statistical data, $9.2 \pm 2.1\%$ – reduction of time for searching patient information, $4.4 \pm 1.5\%$ – optimization of working time, $71.3 \pm 3.3\%$ – a combination of the above options.

Conclusion. A medical and social study showed the feasibility of introducing an electronic database of children with cancer into the clinical practice of pediatric oncologists.

Keywords:

pediatric oncology, malignant tumors, health care organization, sociological studies, digital data base, informing.

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К ВОПРОСУ О ВНЕДРЕНИИ ЭЛЕКТРОННОЙ БАЗЫ ДАННЫХ ДЕТЕЙ С ОНКОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ В ПРОФИЛЬНЫЕ МЕДИЦИНСКИЕ ОРГАНИЗАЦИИ: РЕЗУЛЬТАТЫ МЕДИКО-СОЦИАЛЬНОГО ИССЛЕДОВАНИЯ

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РЕЗЮМЕ

Учет детей с онкологическими заболеваниями характеризуется низкой достоверностью статистических данных. Кроме того, имеющиеся данные не имеют значимой научной ценности, поскольку представляют собой лишь приблизительное число пациентов, выявляемых ежегодно и некоторые общие сведения (заболеваемость, распространенность и т.д.). При этом особую значимость представляет последующий анализ накопленной информации. Разработана электронная база данных детей с онкологическими заболеваниями, отвечающая данным требованиям, внедрена в клиническую практику пилотных медицинских организаций. **Цель исследования.** Изучить мнения врачей детских онкологов по проблемам учета детей с онкологическими заболеваниями.

Материалы и методы. В исследовании приняли участие 187 врачей детских онкологов. Респондентам разослана разработанная авторами «Анкета опроса врача детского онколога для оценки результативности внедрения электронной базы данных», которая содержит 15 вопросов. Анкеты заполнялись респондентами анонимно.

Результаты. В исследовании приняли участие 187 врачей детских онкологов. Большая часть респондентов (71,3 ± 3,3%) отметила, что в настоящее время в Российской Федерации отсутствует регистр детей с онкологическими заболеваниями, 15,4 ± 2,6% известен региональный регистр, 9,1 ± 2,1% – независимый регистр в отдельных медицинских организациях, 1,7 ± 0,9% – единый регистр для Российской Федерации, 2,5 ± 1,1% не знают о существовании регистров. Среди респондентов 81,9 ± 2,8% отметили, что электронная база данных является эффективным инструментом учета детей с онкологическими заболеваниями, при этом в качестве преимуществ 15,1 ± 2,6% указали повышение достоверности статистических данных, 9,2 ± 2,1% – сокращение времени на поиск информации о пациенте, 4,4 ± 1,5% – оптимизацию рабочего времени, 71,3 ± 3,3% – сочетание перечисленных вариантов.

Заключение. Проведенное исследование показало целесообразность внедрения электронной базы данных детей с онкологическими заболеваниями в клиническую практику.

Ключевые слова:

детская онкология, злокачественные новообразования, организация медицинской помощи, медико-социальное исследование, электронная база данных, информатизация.

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JUSTIFICATION

The development of healthcare is impossible without the introduction of information technologies [1–3]. At the same time, it is important not only to create resource databases aimed at collecting and storing data, but also the subsequent automated analysis of the accumulated information in order to assess the quality of medical care provided, optimize patient routing, as well as continuity in the treatment process [4]. Modern information technologies also include a system for supporting medical decision-making, that is, digitized clinical recommendations [5].

Accounting for children with cancer is characterized by a number of significant drawbacks – low reliability, the inability to use the accumulated information to control and improve the treatment process, as well as in scientific activities [4].

Given the above, developed an electronic database of children with cancer, which since 1 September 2017 introduced into clinical practice of pediatric oncology Arkhangelsk Regional Kid's Clinical Hospital P.G.Vyzhletsov and the laboratory of complex methods of treatment of oncological diseases in children of the Russian Scientific Center of Radiology [4].

Purpose of the study: study the opinions of pediatric oncologists on the problems of accounting for children with cancer.

MATERIALS AND METHODS

A medical and social study was conducted, which included pediatric oncologists who have worked in the departments of pediatric oncology of the subjects of the Russian Federation in 2018–2019 and filled out the "Questionnaire of the survey of pediatric oncologists to assess the effectiveness of the introduction of an electronic database" developed by the authors. The questionnaire contained 15 questions, and respondents were asked to choose one or more answer options or enter their own version. For objectivity, the questionnaires were filled out anonymously by the respondents [1].

The questionnaire included the following questions:

1. Currently, in the Russian Federation, the system of accounting for children with cancer (register) is:
 1. Unified (for the Russian Federation)
 2. Regional (for individual entities)
 3. Independent in individual medical organizations
 4. There is no case
 5. I don't know
2. Do you know about the use of an electronic database of children with cancer in pilot medical organizations:
 1. Yes, I heard about it from colleagues
 2. Yes, I received information from scientific articles
 3. Yes, I received the information from the report at the scientific conference
 4. Yes, I received information from users
 5. Yes, I use it myself
 6. No
3. Do you use an electronic database of children with cancer:
 1. Yes
 2. No
 3. I find it difficult to answer
4. Do you know the main functions of the electronic database:
 1. Yes, there are
 2. No, I don't
 3. I find it difficult to answer
5. If so, please indicate what functions the electronic database has:
 1. Patient records
 2. Treatment planning
 3. Medical decision support system
 4. Plan the routing of patients
 5. Formation of electronic sheets of temporary disability
 6. None of the above
 7. Other answer
6. If not, are you ready to use the electronic database of children with cancer in clinical practice:
 1. Yes, I am ready
 2. No, I am not ready
 3. I find it difficult to answer
7. If not, why not:
 1. An effective accounting tool already exists
 2. Requires significant time costs

3. There is no necessary material base
4. I find it difficult to answer
5. The use is meaningless
6. Other
8. In your opinion, the use of an electronic database is necessary in the activities of:
 1. Every doctor who provides specialized medical care to children with cancer
 2. Management staff of medical organizations
 3. Executive authorities in the field of health protection of citizens of the subjects of the Russian Federation
 4. Ministry of Health of the Russian Federation
 5. No need to use it
 6. I don't know
 7. Other
9. Is the electronic database of children with cancer an effective tool for recording children with cancer:
 1. Yes
 2. No
 3. I don't know
10. If not, why not:
 1. An effective accounting tool already exists
 2. Requires significant time costs
 3. There is no necessary material base
 4. I don't know
 5. Other
11. If so, what are the advantages of an electronic database of children with cancer:
 1. Improving the reliability of statistical data
 2. Reduce the time to search for information about the patient
 3. Optimizing the use of working time
 4. Other
12. What can prevent you from using an electronic database of children with cancer in your daily clinical practice:
 1. Lack of time
 2. Lack of necessary qualifications to use the software
 3. Lack of a personal computer in the workplace
 4. Not included in the job description
 5. Other
13. Compared to the existing system of accounting for children with cancer, the electronic database is more efficient:
 1. Yes
 2. No
 3. Not familiar with the existing accounting system
 4. I find it difficult to answer
 5. Other
14. What are the most important functions of the electronic database of children with cancer for you:
 1. Reducing the time for maintaining medical records
 2. Ability to monitor the implementation of treatment protocols
 3. The possibility of using a medical decision support system
 4. Automation of routing of patients
 5. Improving the efficiency of using the department's bed capacity
 6. Formation of annual reports on the state of medical care for children with cancer
 7. Other
15. What additional functions do you think are necessary for the effective use of the electronic database?

The study was conducted in the period from 01.03.2019 on 30.04.2019 in pediatric Oncology departments of medical organizations of the federal districts of the Russian Federation: Central (Central Federal District), Northwestern (Northwestern Federal District), Southern (Southern Federal District), North Caucasus (North Caucasus Federal District), Volga (Volga Federal District), Ural (Ural Federal District), Siberian (Siberian Federal District) and Far Eastern (Far Eastern Federal District) [1].

The objects of the study were the questionnaires completed by the respondents.

Ethical expertise

The study was approved at a meeting of the Local Ethics Committee FGAOU VO at the Sechenov First Moscow State Medical University (Sechenov University) No. 05–19 of 11.04.2019.

Statistical analysis

Principles for calculating the sample size
The volume of sample populations for the

study was calculated according to the formula of A. M. Merkov (1962) with a known number of observations in the general population [6]:

$$n = \frac{(p \times q \times t^2 \times N)}{(N \times \Delta^2 + p \times q \times t^2)},$$

where n is the minimum sample size, t is the confidence coefficient ($t=2$ when $p=0.05$); p – frequency of the trait in the aggregate indicator of the probability of the phenomenon under study (in this situation is unknown, therefore, is taken as the maximum possible value 50%); $q=100$; p – a measure of alternative, alternative p -index; Δ – limit error indicator (5%) [7]; N – the number of the General population [1].

Calculations to determine the representativeness of a sample of the minimum number of pediatric oncologists:

$n=300$ – the number of pediatric oncologists in the Russian Federation in 2018 (data from the Federal State Statistics Service, provided by the Department of Medical Statistics of the Department of Monitoring, Analysis and strategic development of healthcare of the Ministry of Health of the Russian Federation) [1].

$$n = \frac{50 \times 50 \times 2^2 \times 300}{300 \times 5^2 + 50 \times 50 \times 2^2} = 171,42$$

That's why, the minimum number of pediatric oncologists to ensure the representativeness of the

study is 172 people. Taking into account the stratification of the number of doctors of pediatric oncologists in 2018 in the Federal districts of the Russian Federation CFD – 37.6%, NWFD – 12%, SFD – 11,7%, NCFD – 3%, PFD – 10,7%, UFD – 9.7% of the NFD and 10.3%, FEFD – 5% [1].

Statistical processing of the material was carried out on a personal computer using the programs Office Excel 2013 (Microsoft, USA) and SPSS 22.0 (IBM, USA) [1].

RESULTS OF THE STUDY

187 pediatric oncologists took part in the sociological study. The stratification by the number of pediatric oncologists in 2018 in the federal districts of the Russian Federation is shown on the figure 1.

Women predominated – $51.3 \pm 3.7\%$. The age distribution of respondents is shown in the figure 2. The average age was 43.1 ± 3.4 years [1].

Employees of medical organizations of federal subordination made up $31.9 \pm 3.4\%$. Senior positions (heads of departments) were held by $10.1 \pm 2.2\%$ of respondents, positions of researchers – $33.7 \pm 3.5\%$, ward doctors – $56.2 \pm 3.6\%$ [1].

The total medical experience up to 5 years was $7.1 \pm 1.9\%$ of respondents, from 6 to 10 years – $29.4 \pm 3.3\%$, from 11 to 15 years – $43.5 \pm 3.6\%$, from

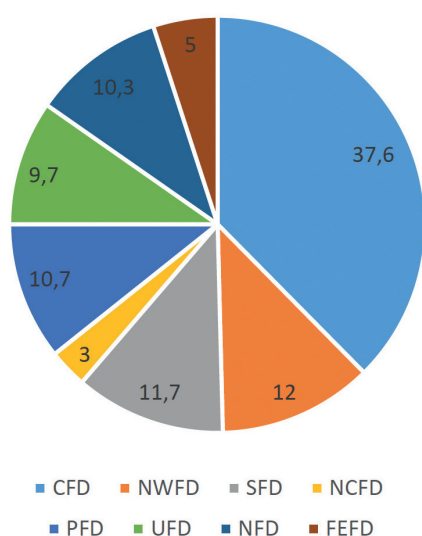


Fig. 1. Distribution of respondents by territory of residence in the federal districts of the Russian Federation, %.

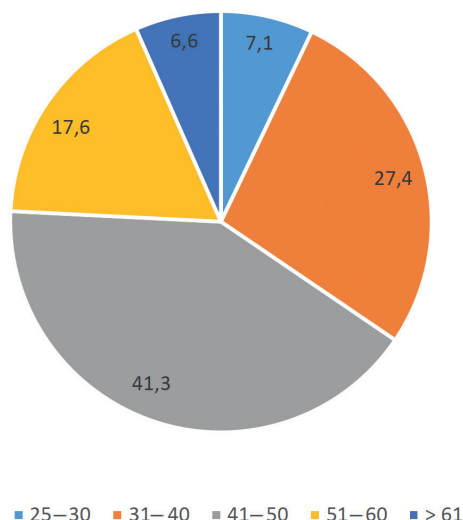


Fig 2. Distribution of respondents by age, years, %.

16 to 20 years – $11.4 \pm 2.3\%$, from 21 to 30 years – $7.3 \pm 1.9\%$, over 30 years – $1.3 \pm 0.8\%$ [1].

Among the respondents, $71.3 \pm 3.3\%$ noted that there is no register of children with cancer in the Russian Federation, a regional register is known to $15.4 \pm 2.6\%$, $9.1 \pm 2.1\%$ are aware of an independent register in individual medical organizations, $1.7 \pm 0.9\%$ are aware of a single register for the Russian Federation, and $2.5 \pm 1.1\%$ are unaware of the existence of registers [1].

$17.3 \pm 2.8\%$ of respondents heard about the use of an electronic database of children with cancer in pilot medical organizations from colleagues, received information from scientific articles – $15.7 \pm 2.7\%$, from a report at a scientific conference – $11.3 \pm 2.3\%$, from users – $9.3 \pm 2.1\%$, use themselves – $1.7 \pm 0.9\%$, do not know – $11.9 \pm 2.4\%$. The combination of options was indicated by $32.8 \pm 3.4\%$ [1].

The main functions of the electronic database are known to $27 \pm 3.2\%$ of respondents, and $11.7 \pm 2.4\%$ found it difficult to answer [1].

$71.9 \pm 3.3\%$ of respondents indicated patient registration, treatment planning, a system for supporting medical decision-making, and a patient routing plan as the functions known to them. Only $11.3 \pm 2.3\%$ noted the formation of electronic sheets of temporary disability. At the same time, this function is not available in the electronic database. None of the above was noted by $16.8 \pm 2.7\%$ of respondents [1].

Among those respondents who do not use an electronic database, ready to use in clinical practice was $97.4 \pm 1.2\%$. Among the main reasons for those who are not ready, provided that this is a time-consuming ($15.3 \pm 2.6\%$), lack the necessary material base ($9.7 \pm 2.2\%$) and effective accounting tool already exists ($8.1 \pm 2.0\%$). The combination of these options was noted by $66.9 \pm 3.4\%$ of respondents [1].

The majority of respondents ($81.9 \pm 2.8\%$) indicated that the use of an electronic database is necessary in the activities of every doctor who provides specialized medical care to children with cancer, the administration of medical organizations, executive authorities in the field of health protection of citizens of the subjects of the Russian Federation, the Ministry of Health of the Russian Federation. At the same time, $4.7 \pm 1.5\%$ of respondents believe that there is no need to use it [1].

The fact that the electronic database is an effective tool for accounting for children with cancer was indicated by $81.9 \pm 2.8\%$ of respondents, while $15.1 \pm 2.6\%$ noted an increase in the reliability of statistical data, $9.2 \pm 2.1\%$ – a reduction in the time spent searching for information about the patient and $4.4 \pm 1.5\%$ – optimization of working time. The combination of options was indicated by $71.3 \pm 3.3\%$ of respondents [1].

Respondents from among those who do not consider the electronic database to be an effective accounting system ($13.6 \pm 2.5\%$) indicated as a reason that an effective accounting tool already exists

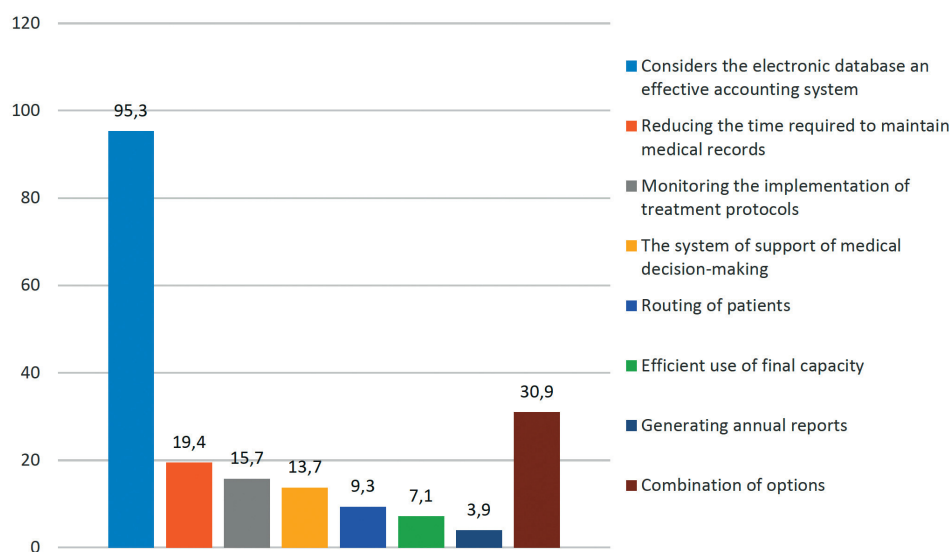


Fig. 3. Opinion of pediatric oncologists on the functions of the electronic database of children with cancer, %.

($11.7 \pm 2.4\%$), that it requires significant time costs ($9.3 \pm 2.1\%$) and that the necessary material base is not available ($7.1 \pm 1.9\%$) [1].

Among the reasons that may make it difficult to use an electronic database, the majority of respondents ($17.9 \pm 2.8\%$) indicated a lack of time, $7.1 \pm 1.9\%$ – lack of necessary training for using software, $7.1 \pm 1.9\%$ – lack of a personal computer in the workplace, $32.2 \pm 3.4\%$ indicated that this is not included in the job descriptions. The combination of these options was noted by $35.7 \pm 3.5\%$ of respondents [1].

The majority of respondents ($95.3 \pm 1.5\%$) noted that, in comparison with the existing system of accounting for children with cancer, the electronic database is more efficient, $2.5 \pm 1.1\%$ of respondents are not familiar with the existing system of accounting, $2.2 \pm 1.0\%$ found it difficult to answer [1].

Reducing the time for maintaining medical records as the most important function of the electronic database was noted by $19.4 \pm 2.9\%$ of respondents, the ability to monitor the implementation of treatment protocols – $15.7 \pm 2.7\%$, the ability to use the system to support medical decision-making – $13.7 \pm 2.5\%$, automation of patient routing – 9.3% , improving the efficiency of using the bed capacity of the department – $7.1 \pm 1.9\%$, the formation of annual reports on the state of medical care for children with cancer – $3.9 \pm 1.4\%$. The combination of these options was noted by $30.9 \pm 3.4\%$ of respondents (fig. 3) [1].

DISCUSSION

In modern conditions, informatization is of decisive importance [4]. The developed electronic database of children with cancer has a number of significant advantages: the collection, processing and accumulation of reliable statistical data, optimal patient routing, a system for supporting medical decision-making, and maximum convenience for parents (legal representatives) of patients [4].

One of the main conditions for improving the survival rate of children with cancer is compliance with treatment protocols [8, 9]. An innovative develop-

ment is a system for supporting medical decision-making (digitized clinical recommendations), which allows you to choose treatment tactics depending on a specific clinical situation. In the literature, we have not been able to find descriptions of another similar system. It is quite possible that similar solutions will be presented on the market in the medium term, but at present the authors do not have any information about them [1].

It is important that medical professionals understand the importance of informatization: more than 80% of pediatric oncologists noted that the electronic database is an effective system for recording patients. According to the authors, only reliable statistical data are the basis for planning the development of the industry, including for national programs, which have recently received a lot of attention from representatives of the executive and legislative branches of government, as well as the media. But in an era when anyone can pay for a purchase in a store using a smartphone, no one has the exact number of children with cancer, not only in the Russian Federation, but also in individual subjects. At the same time, the number of such patients detected annually is less than 4 thousand people [1].

It should be noted that improving the reliability of statistical data is possible only with the introduction of an electronic database in the clinical practice of all departments of pediatric oncology in the subjects of the Russian Federation and medical organizations of federal subordination.

CONCLUSIONS

Medical and social research has shown the feasibility of introducing an electronic database of children with cancer in clinical practice.

The proposed digital contour provides conditions for creating a unified electronic cartographic framework and provides access to large amounts of data, their analysis and the use of the results obtained in making management decisions on the organization of medical care for children with cancer in the subjects of the Russian Federation and at the federal level.

Authors contribution:

Rykov M.Yu. – research concept and design, data collection and analysis, material processing, text writing.

Manerova O.A. – text writing, scientific editing.

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