# ONCOLOGY and RADIOLOGY of KAZAKHSTAN

№3 (49) 2018

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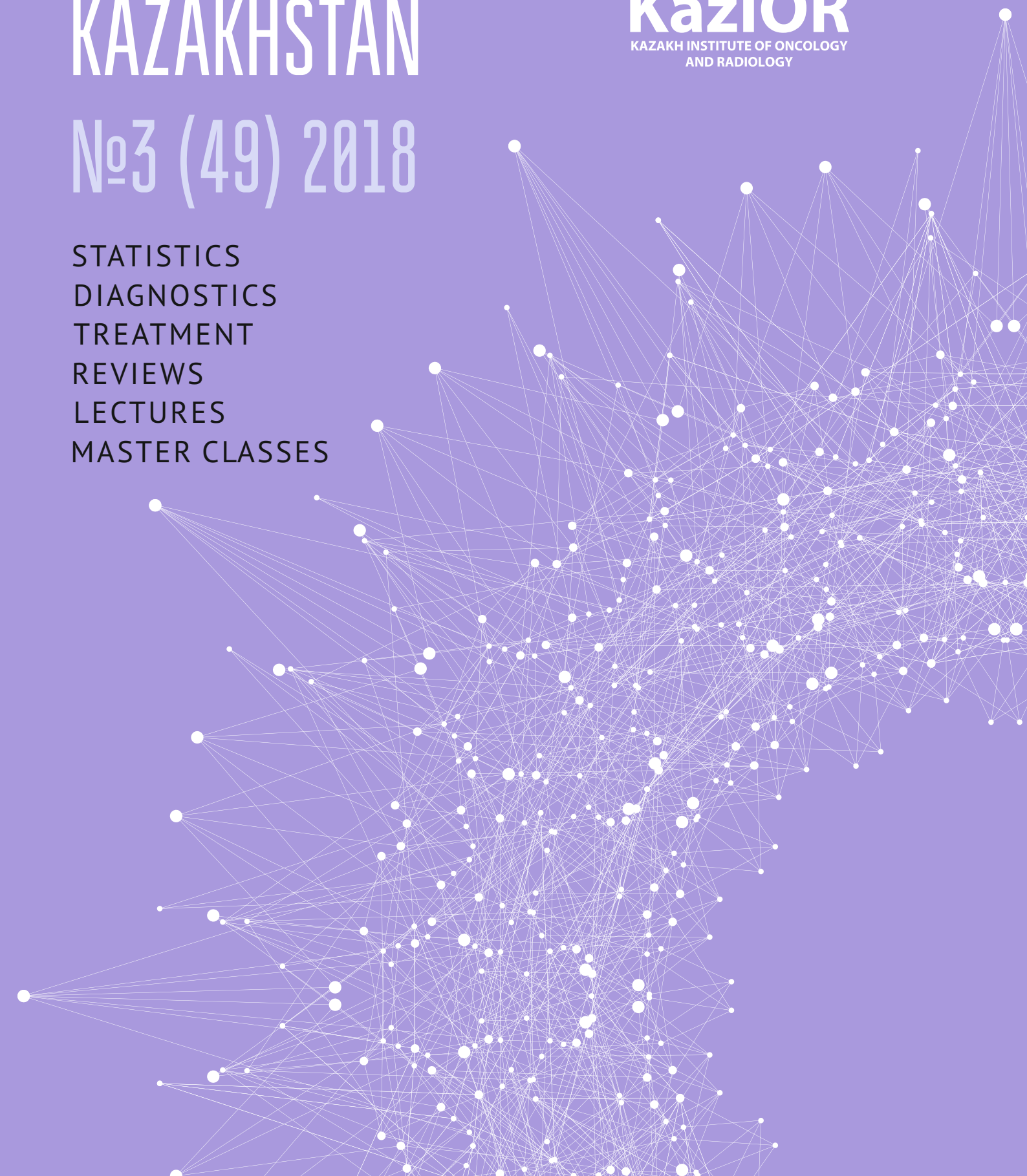

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## HISTORY

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# Use of molecular and genetic testing of BRAFV600E mutation for fine-needle aspiration cytology of thyroid gland

Relevance. *The growing interest to non-invasive methods of early preoperative verification of thyroid tumours requires further refinement of the traditional morphological methods of thyroid tumour diagnostics using molecular-genetic studies. The detection of BRAF genetic mutation in the material under study is a decisive additional method at this stage. According to foreign researchers, the BRAF gene mutation is most frequent in papillary thyroid cancer. BRAF mutation was found in 38-69% samples of histological material of patients operated for thyroid cancer. It was also found in up to 83% of cases in Fine Needle Aspiration (FNA)-washouts from the syringe and puncture needles obtained from patients with papillary thyroid cancer. No literature data from Kazakhstani researchers could be found regarding BRAF gene mutation detected in FNA biopsy materials in papillary thyroid cancer.*

Purpose of the study *is to identify the significance of BRAF mutation among Kazakhstani patients with nodular goiter to exclude papillary thyroid gland cancer.*

Results. *According to PCR in the form of dispersion of amplification products, positive BRAF gene mutations were detected in patients with diagnosed or suspected papillary cancer. The graphical characteristics were reflected on tracks H01, A03, B03, and C03. Track F03 shows the internal control for BRAF gene positive mutation. Other relevant columns were negative for BRAF gene mutations.*

Conclusions. *The detection of BRAF gene mutation in washouts from the puncture needle obtained from patients with thyroid nodules can be used in preoperative diagnostics for prognosis and treatment of papillary thyroid cancer.*

***Keywords:*** *thyroid nodules, Fine Needle Aspiration (FNA) biopsy cytology, papillary thyroid cancer, BRAF marker gene.*

***Introduction.*** Cytopathological fine-needle aspiration biopsy (FNAB) performed according to Bethesda classification is used to diagnose malignant and benign thyroid gland formations at the pre-surgery stage and contributes to systematization of the choice of further tactics of diagnostics and treatment. Firstly, the survival and mortality rates are directly dependent on a reliable and properly performed pre-surgery differential diagnostics of thyroid cancer (TC). To date, pre-surgery diagnosis is precise only in 54-61% cases [1]. Secondly, the frequency of both malignant and benign thyroid gland formations is growing every year all over the world. Thus, the TC incidence has grown by 310% from 1950 to 2004 [2]. At the same time, benign nodular thyroid gland formations (NTGF), such as colloid and hyperplastic nodes, cysts, nodal foci of lymphoplasmacytic infiltration are found in 80% of the population [3]. Thirdly, the relevance of proper differential diagnostics is proven by the fact that about 30% of NTGFs are malignant, and TC in 90% of cases develops as a nodular goiter, especially at the initial stages [4]. It should also be noted that the currently used methods of NTGF differential diagnostics at the pre-surgery stage often do not allow reliable diagnosing and providing the necessary volume of surgical treatment [5].

The currently used traditional methods of diagnosing malignant and benign thyroid gland formations shall be improved. Ultrasound, sonoelastrography, biochemical and hormonal analyzes used at the initial stage provide evidence only on the presence of nodule formations. In the past few years, fine-needle aspiration puncture biopsy (FNAB) has been the best method for distinguishing between malignant and benign nodes at the pre-surgery stage [6]. FNAB is performed under strict ultrasound control. FNAB is highly safe and low invasive, ensures high diagnostic accuracy and is not expensive. Still, FNAB does not provide enough evidence for choosing a treatment tactics for follicular neoplasia and undetermined neoplasms [7]. At the last stage, especially in undetermined situations, molecular genetic studies are used. At this stage, the presence of TC is confirmed by immunohistochemical analyzes (IHC). However, IHC is not always sufficient to determine a particular type of TC. It can be supplemented by BRAF genetic mutation determination in the test material. Some foreign researchers note the highest frequency of BRAF gene mutation in papillary TC [8]. In the study of histological material, 38–69% of patients operated for TC had BRAF mutations [9]. In the study of FNAB swabs from the syringe and puncture needles, up to 83% patients with papillary TC had BRAF gene mutation [10]. The literature search on BRAF gene mutation in papillary TC in Kazakhstan returned no result.

The use of high-tech methods of molecular genetic cancer diagnostics has significantly grown over the past decade. Molecular analyzes of biological tumor samples allow studying a whole variety of DNA markers even in the minimal content. One of such promising methods of genetic diagnostics based on the analysis of data obtained in the study of genetic markers of tumor is polymerase chain reaction (PCR). Several generations of PCR technology are known till today, the most advanced is the third generation. These methods, like Droplet Digital PCR, allow an accurate quantitative DNA assessment.

***Purpose of this study*** is to identify the significance of BRAF gene mutation in patients with nodular thyroid gland formations to exclude papillary TC in Kazakhstan.

***Materials and Methods.*** The article provides the results of research of 122 patients who independently applied to the Department of Endocrinology of the joint university clinic of S.D. Asfendiyarov Kazakh National Medical University in Almaty for nodular goiter. Cytological studies were performed at KazIOR. Average age of patients – 49.5 years; men to women ratio – 1.2:10. All the patients underwent aspiration biopsy of NTGF under ultrasound control.

In the course of our study, we collected samples with cytological opinions corresponding to the Bethesda categories (BSRTS 2010). Grouping of patients: Group 1 – papillary TC of category 6 (malignant tumor of thyroid gland). Group 2 – non-definitive neoplasm of category 5 (suspected cancer). Group 3 – follicular neoplasia, category 4. Group 4 - colloid goiter, category 2 (nodules of benign nature). The grouping of patients by cytology results is presented in Table 1.

**Table 1 –** Grouping of patients by cytology results

| FNAB results | Papillary TC, Category 6 | Suspected TC, Category 5 | Follicular neoplasia, Category 4 | Nodular colloid goiter, Category 2 |
|---|---|---|---|---|
| Number of patients | 2 | 1 | 3 | 116 |

BRAF gene mutation detection in the puncture biopsy material of all groups of patients was performed in the mo-lecular genetic laboratory of Nagasaki Medical University (Japan).

*NA extraction for BRAF gene mutation detection.*

Preparatory stage.

After biopsy, the contents of the puncture needle were carefully washed with 0.7 ml of RNA later solution and placed in a sterile 1.5 ml Eppendorf vial. The vial was left for half an hour at ambient temperature. Tightly closed vials were placed in a freezer for long-term storage at -20°C.

DNA isolation.

The genetic material was isolated according to the study protocol using the "QIA amp DNA Mini Kit only" (QIAGEN, Germany). 50 µl of aqueous solution containing the required DNA was obtained for isolation. After the isola-tion, DNA samples were stored at -20°C.

Determination of DNA concentration on NANO-Drop UV-View spectrophotometer.

After standard preparation of the spectrophotometer according to manufacturer's instructions, 2 µm from each sample were transferred to the special reading device to define DNA concentration.

PCR analysis.

Droplet Digital PCR was performed using QX200 Droplet Digital PCR System (Bio-Rad, USA) in four stages according to the instructions. At first stage, the samples together with the necessary primers were placed in the plastic cartridge of QX200 droplet generator. For the second stage of droplet generation, a special mineral oil was added to the relevant cartridge channels. The filled cartridge was installed into QX200 droplet generator. The samples and oil mixed in micro channels inside the cartridge to produce an emulsion – about 20,000 monodisperse droplets of 1 µl for each of the prepared samples. The third stage included the main polymerase chain reaction. All emulsion samples were transferred to a stand-ard PCR plate and amplified using a standard C1000 Touch thermocycler for a set time in standard conditions including initial denaturation and the cycles of denaturation, primer annealing, and final elongation. The final stage included the reading and analysis of obtained results. After PCR, the plate was loaded into a QX200 droplet reader to analyze the fluorescent signal. The drops were analyzed one after another to detect the target. The results were analyzed automatically by ddPCR Software.

***Results and Discussion.*** In numerous studies on this problem, the presence of BRAF mutation was determinant for choosing the tactics of treatment of thyroid gland tumors [11, 12]. Standard morphological studies in biopsy specimens in some cases cannot give an unambiguous answer about the nature and prognosis of the tumor to allow the clinician to make a definite decision. In such cases, the presence of BRAF gene mutation definitely indicates the aggressive nature of the neoplasm. Such neoplasm requires more careful observation over time and, if necessary, prescription of a complex treatment or other more radical measures.

The results of the analysis are shown in Figure 1. Categories V-VI samples were positive for BRAF gene mutation. Category II samples had no BRAF gene mutation.

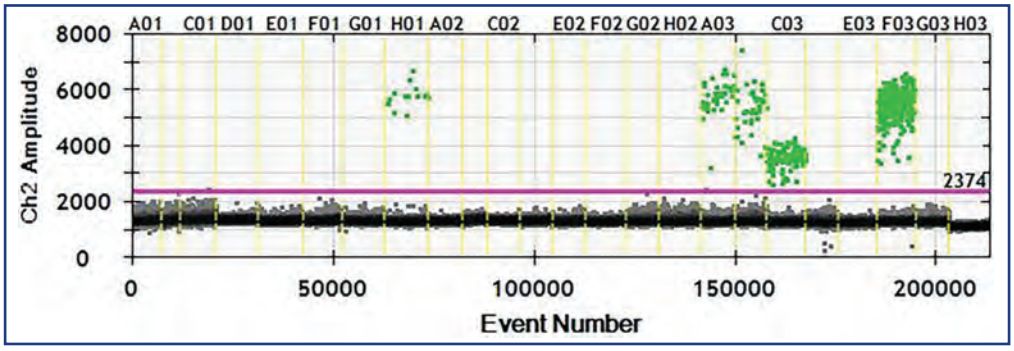


**Figure 1** – Amplification products dissemination diagram. H01, A03, B03, C03 tracks – positive for BRAF gene mutation; F03 track – the internal control for positive BRAF gene mutation; other columns – negative for BRAF gene mutations.

***Conclusions***

1. The presence of BRAF gene mutation is a diagnostic marker for highly differentiated thyroid cancer and a high probability of malignancy of the process that will require more radical treatment approaches. The absence of this mutation is characteristic only for benign diseases that require only conservative therapy and observation over time.

2. The detection of BRAF gene mutation using the most advanced Digital Droplet PCR method can be used as an additional method for pre-surgery diagnostics of highly differentiated thyroid cancer.

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# Multispiral computed tomography in tongue cancer diagnostics

Relevance. *Oral cancer morbidity and mortality is growing worldwide in recent years delivering 2.2% in the structure of oncopathologies. Cancer tongue occurs in 50-60% cases of malignant oral cavity tumor. Computed tomography (CT) with contrast enhancement is the "gold standard" in examination of patients with tongue cancer.*

Purpose of the study *was to evaluate the capacity of multispiral CT in diagnosing and assessing the prevalence of tongue cancer.*

Results. *The obtained data allowed assessing primary localization of the pathological process – the dorsum and root of tongue (52%), the spread of the process beyond organ (8%) - to the walls of oropharynx. In most cases (78%), soft tissues of the neck had metastatic lesions of lymph nodes. In patients with conglomerates of hyperplastic lymph nodes (16%), CT has visualized the involvement of large neck vessels (the common carotid artery and its branches, the jugular veins) into the process.*

Conclusion. *In tongue cancer, multispiral CT with contrast enhancement allows clarifying the prevalence of the process, assessing the condition of neck vessels, determining the condition of the neck lymph nodes which is important in choosing the appropriate method of treatment.*

***Keywords:*** *tongue cancer, computer tomography.*

***Relevancy.*** Malignant tumors of oral cavity rank second in frequency among malignant tumors of head and throat after malignant tumors of the larynx. Oral cavity cancer makes about 2.2% in the structure of all malignant tumors. Tongue cancer accounts for 50–60% of malignant tumors of oral cavity. By location, the tumors are frequent in the middle third of the tongue lateral surface and in the root of the tongue, less frequent – on the lower surface of the tongue, and very rare – on the dorsal surface and the tip of the tongue.

From the point of histology, 90% of malignant tumors of the tongue belong to extensive cell cancer. Small salivary glands in the rear parts of a tongue can be affected by gland cancer (adenocarcinoma), sometimes – malignant lymphomas. Small salivary glands in the root of the tongue often produce epithelial tumors (mucoepidermoid carcinoma).

Risk factors for malignant tumors of the oral cavity are smoking, alcohol abuse, eating very hot food, incorrectly adjusted dentures traumatizing the tunica mucosa of the oral cavity, and unsanitary condition of the oral cavity.

Pre-malignant conditions of the tongue include leukoplakia, papillomatosis, and decubital tongue.

Neoplastic process in the tongue spreads rapidly and affects the surrounding tissues; it belongs to the extremely aggressive malignant tumors. Tongue cancer metastasis spread via the lymphatic system.

Computed tomography is a recognized way to visualize tumors of oral cavity including tongue tumors. Multispiral computed tomography requires increased contrast. It allows localizing the tumor, evaluating the state of the oral cavity and the cervical vessels, and plays an important role in evaluating the distribution and nature of the cervical lymphadenopathy.

***Purpose of the study*** is to evaluate the capacity of multispiral computed tomography in the determination of spread and diagnostics of tongue cancer.

***Materials and methods.*** 87 patients with suspected tongue cancer underwent multispiral computed tomography of oral cavity and soft tissues of the neck and pathological examination at the Department of Radiology of the Kazakh Institute of Oncology and Radiology. Age of the patients – 42 to 76 years, average age – 58. Multispiral computed tomography was performed using Light Speed VCT (GE) apparatus with enhanced contrast due to bolus administration of Visipaque (Takeda).

***Results and analysis.*** In the study, the limited lesion of the back of the tongue was observed in 9 cases (10%), in the root of the tongue - in 26 (30%) cases, of them 1 patient had a lesion on the dorsal surface of the tongue. In 45 (52%) cases, the tumor process was localized on the back and root of the tongue, in 7 (8%) cases, the process was spread on the pharyngeal walls.

On computer-tomographic scans, tongue tumors were more often visualized as areas with uneven high density and different levels of clarity; nodular formations with clear edges and spreading non-structured tissue masses on the pharyngeal walls were less often. After enhancing contrast, the contrast agent was not intensively, non-uniformly absorbed by the masses, areas and modified pharyngeal walls.

During examination, 68 (78%) patients had metastatic lymph nodes in the soft tissues of the neck. Of them, 21 (30%) patients had multiple metastases in lymph nodes less than 1.0 cm in diameter; 47 (70%) patients had hyperplastic lymph nodes of more than 1.2 cm in diameter with an increase to large conglomerates. After enhancing contrast, the hyperplastic lymph nodes encapsulated the contrast agent.

In 11 patients (16%) with the conglomeration of hyperplastic lymph nodes, the common carotid artery with the offshoots and the jugular vein were also affected by the process.

***Conclusion.*** In tongue cancer, multispiral computed tomography with contrast enhancing allows evaluating the process distribution, the condition of cervical blood vessels and the cervical nodes. It is an important tool in choosing the adequate treatment methods.

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# Lung cancer with metastatic lung lesions: treatment outcome

Relevance. *Lung cancer (LC) is one of the most unfavorable forms of tumors in terms of timely diagnostics and treatment outcome. Therefore, early detection of LC remains the main organizational medical measure to improve resectability and treatment outcome.*

Purpose of this study – *to increase the treatment efficiency in potentially resectable LC with metastatic lung lesions.*

Results. *103 cases of histologically proven LC with multiple pulmonary nodules detected by computer tomography and regarded as multiple metastases were studied. Video-assisted thoracoscopy has revealed metastases in contralateral lung in 64 (62.1%) patients, of them, 4 (3.9%) had a second extra-pulmonary tumor. 39 (37.9%) patients had non-neoplastic disseminates: fibrosis – 22, anthracosis – 13, tuberculosis and sarcoidosis – 4. 9.3%, 10.3%, and 20.6% of the patients had LC stage I, II and III, respectively. 32 patients underwent surgery: lobectomy – 20, segmentectomy – 2, pneumonectomy – 10. 3 (9.3%) patients had postoperative complications. Nosocomial mortality – 1 (3.1%). 5-year post-surgery survival – 44.1%, with neoplastic metastatic lung lesions – 0% (p<0.0001).*

Conclusions. *Potentially resectable LC with metastatic lung lesions requires a biopsy of pulmonary nodules as a significant number of patients have non-neoplastic lesions. The developed modality using video-assisted thoracoscopy improves the survival rates due to the increase in the number of operable patients.*

***Keywords:*** *metastatic lung lesions, lung cancer, lung biopsy, thoracoscopy.*

***Introduction.*** Lung cancer (LC) is one of the most adverse forms of tumors in terms of timely diagnosis and treatment outcomes. Surgical treatment remains the only radical method that provides satisfactory long-term results of treatment. Only 10–20% of initially registered patients can undergo radical surgery [1]. Therefore, early detection of LC remains the main organizational measure of practical healthcare to increase resectability and improve treatment outcomes [2].

One of the ways to increase resectability is the improvement of differential diagnostics of associated diseases (syndromes) that can mimic an advanced tumor process. One of such syndromes is the disseminated pulmonary disease (DPD) that can manifest not only a metastatic lesion but also a competing non-neoplastic disease — tuberculosis, sarcoidosis, etc. According to M.M. Ilkovich, this syndrome accounts for up to 20% of respiratory diseases and can occur in more than 100 different non-neoplastic diseases [3]. Still, the medical literature lacks data on the incidence, structure, and survival of patients with LC and non-neoplastic DPD.

The purpose of this study is to improve diagnostics and increase the survival rate of patients with X-ray detected LC in combination with DPD.

**Materials and methods.** The study included retrospective analysis of case histories of 103 patients examined and treated at N.N. Alexandrov National Cancer Center from January, 2001 to December, 2015. The average age was 59.7±8 (35-78) years. 80 of 103 patients were men (78.7%), 23 were women (21.3%). All patients had a morphologically verified LC and CT-detected DPD treated as multiple metastases. 17 patients were diagnosed with primary multiple cancer at admission.

All patients underwent video-assisted thoracoscopy (VATS) with a lung biopsy according to standard methods in order to clarify the prevalence of the tumor process [4]. It was mandatory to receive a preliminary urgent intraoperative morphological conclusion on the sufficient amount and quality of the biopsy material. At detection of Non-neoplastic DPD, a part of the biopsy material was sent for bacteriological examination. Enlarged mediastinal lymph nodes were subject to biopsy.

The patients with proven metastatic nature of dissemination received chemotherapy or symptomatic treatment. The patients with Non-neoplastic DPD underwent radical surgery for LC followed by transfer to pulmonology (TB) hospital.

The overall patient survival was estimated according to the data of the Cancer Register of the Republic of Belarus and was calculated by Kaplan-Meier method using the log-rank test (SPSS Statistics v. 20).

***Results.***

Table 1 shows the main parameters and efficiency indicators of VATS with lung biopsy.

**Table 1 –** Indicators of video-assisted thoracoscopy (VATS) efficiency in disseminated pulmonary disease (DPD)

| Indicator | Value |
|---|---|
| Duration of surgery (min) | 60±31* (10-180) |
| Duration of drainage (day) | 2,0±1.6 (0-10) |
| Need for opioids (patients, %) | 4 (3,9%) |
| Complications | 4 (3,9%) |
| Hospital mortality | 1 (0,9%) |
| Duration of hospital stay (days) | 7.5±2.6 (1-14) |
| Diagnostic efficiency | 100% |

According to Table 1, most of the patients could be discharged two days after VATS (after removal of drainage). The duration of hospital stay encounters future treatment (surgery, chemotherapy).

4 (3.9%) patients had postoperative complications. Unstable aerostasis was observed in 3 patients and resolved

independently after 5–10 days. One patient developed ischemic stroke, and he subsequently died of swelling and dislocation of the brain.

The diagnosis was morphologically verified in all patients. VATS with lung biopsy showed a 100% diagnostic efficacy in DPD.

CT has revealed metastatic lung lesions in all patients. However, the histological examination of biopsy material disproved malignant lung injury in 37.9% of patients. Adenocarcinoma and squamous cell carcinoma prevailed in the structure of Neoplastic DPD (Table 2).

**Table 2 –** Histological forms of Neoplastic DPD

| Histological form of DPD | n (%) |
|---|---|
| Adenocarcinoma | 39 (37.9) |
| Squamous cell carcinoma | 14 (13.6) |
| Small cell cancer | 4 (3.9) |
| Glandular squamous cancer | 2 (1.9) |
| Large cell carcinoma | 2 (1.9) |
| Leiomyosarcoma | 1 (0.97) |
| Malignant neurolemma | 1 (0.97) |
| Renal cell carcinoma | 1 (0,97) |
| Total | 64 (62.1) |

In 3 patients, the histological form of disseminates was not characteristic of LC (leiomyosarcoma, renal cell carci-noma, neurolemma), and in 1 patient it was different from the primary tumor. Further examination resulted in finding a second tumor in those 4 (3.9%) patients, and they were prescribed an adequate chemotherapy.

Focal pneumofibrosis and anthracosis of the lungs prevailed in the structure of Non-neoplastic DPD. Tu-berculosis and pulmonary sarcoidosis were less common (Table 3).

Thus, the preoperative CT diagnoses and postoperative morphological diagnoses coincided in 64 (62.1%) patients, with 37.9% of diagnostic errors. After VATS, the treatment plan was changed for 43 (41.8%) patients.

19 (18.4%) patients with Non-neoplastic DPD had intrathoracic (intrapulmonary and/or mediastinal) metastatic lymph nodes.

**Table 3 –** Histological forms of Non-neoplastic DPD

| Histological form | n (%) |
|---|---|
| Pulmonary fibrosis | 22 (21.4) |
| Pneumoconiosis | 13 (12.7) |
| Sarcoidosis | 2 (1.9) |
| Tuberculosis | 2 (1.9) |
| Total | 39 (37.9) |

*Treatment of patients with Non-neoplastic DPD.* 39 patients with LC with DPD NTG had the following tumor staging according to VATS: Ia – 4, Ib – 5, IIa – 4, IIb – 6, IIIa – 14, IIIb – 6. 32 patients underwent radical surgery (Table 4), 20 patients underwent lobectomy with systematic mediastinal lymphadenectomy, and 10 underwent pneumonectomy. In two patients, the intervention volume was limited to segmentectomy due to low spare capacity of lungs (FEV1<30%).

**Table 4 –** Immediate results of surgical treatment

| Indicator | Value |
|---|---|
| Duration of drainage (day) | 2.0±1.6 (0-10) |
| Duration of the operation (min) | 138.8±72 (110-300) |
| Complications | 3 (9.3%) |
| Hospital mortality | 1 (3.1%) |

Seven patients were denied surgery due to the local prevalence of the process or functional intolerance. They received chemotherapy.

3 (9.3%) patients had postoperative complications (2 – coagulated haemothorax, 1 – myocardial infarction). One of these patients died of pulmonary embolism.

The median survival of all 39 patients with LC and Non-neoplastic DPD after special antitumor treatment was 22±9 months (95% CI 4.2-39.7). In the presence of Neoplastic DPD, the median survival was 11±1.2 months (95% CI 8.5–13.4). The overall 1-, 3-, and 5-year survival was 75.4±7.1%, 44.5±8.7%, and 36.4±8.8%, vs. 42±6.3%, 8.8±4.5% and 0%, respectively, in the presence of Neoplastic DPD (p<0.0001) (Figure 1).

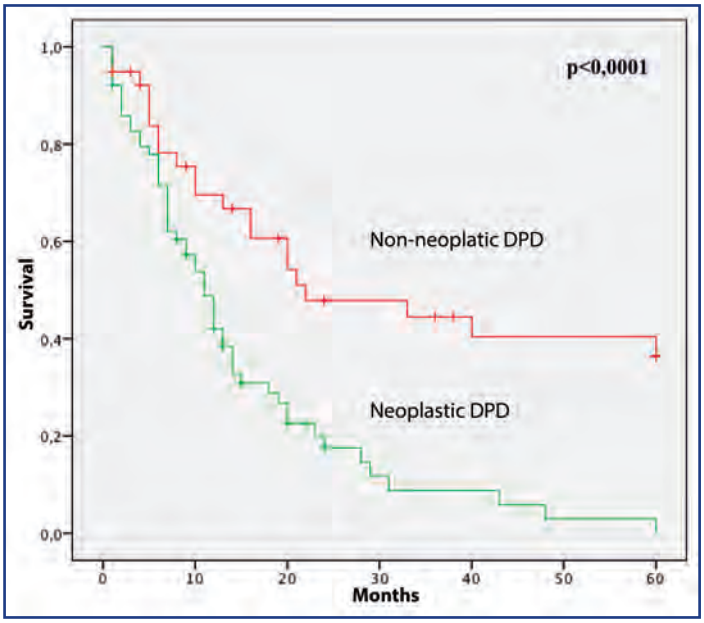


**Figure 1 –** Survival with lung cancer and neoplastic and non-neoplastic DPD

1-, 3- and 5-year survival of 32 patients after surgical treatment was 80.1±7.3%, 53.9±9.5% and 44.1±10%, p<0.0001 (Figure 2). The median was 40±28 months (95% CI 0-95).

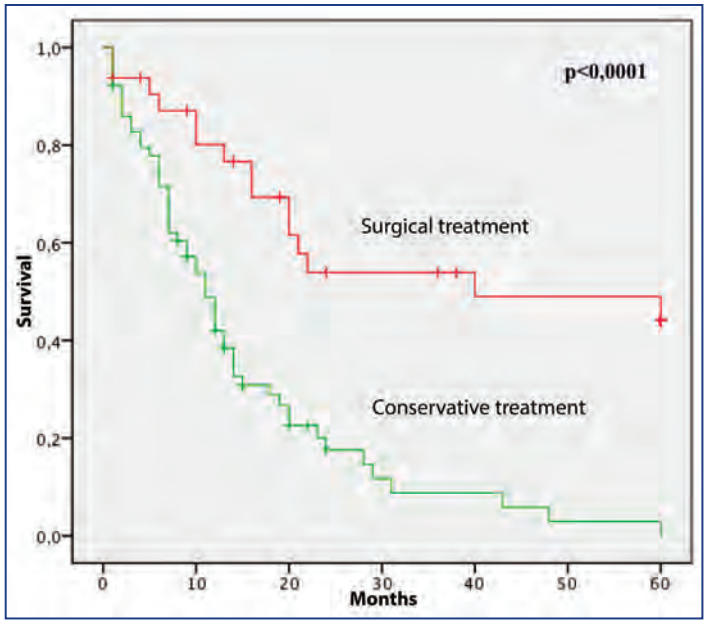


**Figure 2 –** Survival with lung cancer with DPD after surgical and conservative treatment

***Discussion.*** The generally accepted approach based on US studies [8, 9] does not recommend morphological verification of seeds in patients with histologically confirmed LC in case of CT-detection in the parenchyma of multiple foci more than 5 mm in diameter [5-7]. Therefore, this category of patients is automatically prescribed chemotherapy or symptomatic treatment. There are papers on etiological differences in single (solitary) pulmonary nodes among the population of Asia and North America which are attributed to the epidemiological situation on TB and fungal infections in a particular country [10]. We believe a similar situation is typical for DPD.

Our results confirm the need for morphological verification of seeds in LC. After VATS, the staging was reduced from the 4th to the lower in 38% of patients, and they could receive radical treatment. Diagnostic error frequency was comparable to the frequency in patients with DPD without oncopathologies [3].

A large number of primary-multiple tumors and the detection of seeds of the second (not previously detected) tumor during VATS convince us to go beyond morphological verification of the primary tumor found during bronchoscopy. We found even more inappropriate to perform transthoracic lung biopsy (TTLB) for only peripheral cancer because it does not give an answer to the nature of dissemination but delays the diagnostic search when followed by VATS.

The use of TTLB has limitations in interstitial lung diseases due to low efficiency with a high incidence of complications: intrapleural bleeding – in up to 14–30% of cases, pneumothorax – in up to 35–40% [11–15]. Yaffe D. et al. (2015) and Rotolo N. et al. (2015) report a diagnostic accuracy of more than 90% when conducting TTLB of single nodules under CT control. However, the authors note that the average formation size exceeded 2 cm [16, 17].

Clinical guidelines of the British Thoracic Society for interstitial lung diseases recommend taking pulmonary samples of more than 4 cm in the largest dimension in the inflated state and 3 to 5 cm deep from the pleural surface to obtain a sufficient amount of biopsy material [18]. That being said, the recommendations to use TTLB and EBUS in the initial stages cause perplexity since they provide little material for morphological research. In the end, it delays the examination, increases costs and the risk of complications.

In our study, 18% of patients had Non-neoplastic DPD in combination with metastases in peribronchial or paratracheal lymph nodes (which were a substrate for biopsy in EBUS). In case of EBUS, they would be denied radical treatment as DPD would be automatically interpreted as metastatic.

Thus, planning of adequate treatment requires verification of the diagnosis for each descriptor – T, N, and M what is consistent with the principles of evidence-based medicine.

Immediately after surgery, the frequency of postoperative complications and mortality were comparable to patients without DPD. Still, some researchers have noted a higher incidence of postoperative complications (up to 9.3%) and mortality (up to 4.1%) in patients with LC in the setting of fibrosing alveolitis or other forms of pulmonary fibrosis and a decrease in survival by half vs. the control groups [19-21]. This may be due to the differences in the structure and stage of interstitial lung diseases and in the accounting of complications.

Although non-neoplastic DPD can worsen the results of surgical treatment of lung cancer, it remains the only chance for these patients to cure.

***Conclusions.*** VATS with lung biopsy is the optimal method for obtaining material for histological examination in LC with DPD (diagnostic efficiency – 100%).

1. Seed biopsy is required in the presence of morphological verification of the primary tumor and intrathoracic lymph nodes, since non-neoplastic DPD is detected in 37.9% of patients, who can therefor receive radical surgical treatment.

2. The developed diagnostic and treatment algorithm helps improving the survival of patients with LC and DPD by increasing the number of resectable cases.

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# Detection of somatic EGFR mutations in patients with non-small cell lung cancer

Relevance: *EGFR mutations can serve as a clinical marker that allows predicting and evaluating the efficiency of non-small cell lung cancer (NSCLC) therapy with tyrosine kinase inhibitors. The increased enzyme activity of EGFR due to mutations is a determining factor in cancer development, including NSCLC. Study of the mutations allows establishing a link between genome alterations and NSCLC development.*

Purpose of the study: *Determination of frequency and spectrum of EGFR mutations for justification of choice of target therapy with tyrosine kinase inhibitors. Study of mutation frequency related to gender and other demographical parameters of the target population.*

Results: *138 NSCLC patients were included in the study of frequency and spectrum of gene mutations. Their post-operational or biopsy material was delivered from Almaty or regional oncological dispensaries to the Center for Morphological Research of Kazakh Institute of Oncology and Radiology (KazIOR) or they were treated in KazIOR during 2017. About 78% of the studied patients had no common EGFR exon 21 or exon 19 mutations. The most common was the EGFR exon 21 mutation – 10.14%, exon 19 deletion was detected in 7.25%, with 1 (0.72%) case of exon 20 insertion.*

Conclusion: *The lack of the mentioned mutations indicates the presence of possible unstudied mutations. The introduction of new target medications into clinical practice necessitates the study of molecular-genetic profile of the tumor to implement personalized approach to treatment.*

***Keywords:*** *lung cancer, EGFR, mutation frequency, non-small cell lung cancer (NSCLC), tyrosine kinase inhibitors (TKI).*

***Introduction.*** EGFR is the gene that encodes the epidermal growth factor receptor. It is responsible for cells signals and the attachment of specific ligands [1]. EGFR is expressed in many tissues, including the skin, placenta, and thyroid. It is placed on the short arm of chromosome 7 (Figure 1). This gene is responsible for transmembrane glycoprotein from the family of protein kinases, that is, it is located on both external and internal sides of the plasma membrane [2]. Such location allows the EGFR to form dimers from the outside of the membrane and to transmit signal in the cell cascade by tyrosine kinase, located on the cytosolic side of the plasma membrane [3].

This gene triggers a series of cascades responsible for changing the expression of other key genes in the cell. Unlike other genes, this gene has only 7 specific ligands, and it determines its targeted action in the cell.

Genetic mutations in EGFR were found mainly in the domain responsible for enzymatic activity of tyrosine kinase [4]. The most common mutations are small deletions in the reading frame, deletion of exon 19, and deletion of exon 21 (L845R) (Figure 2).

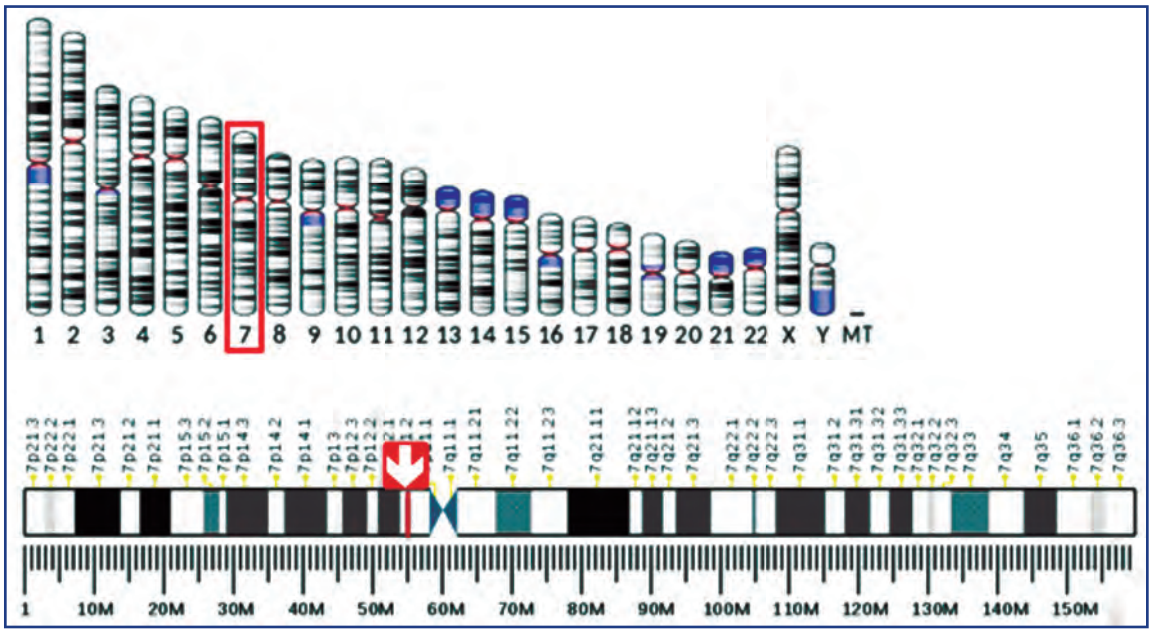


**Figure 1 -** Location of EGFR gene on chromosome 7.

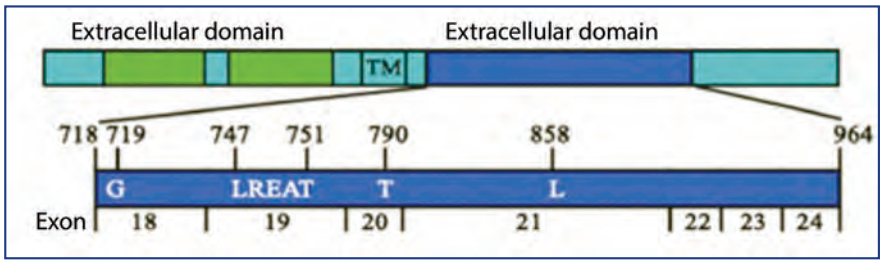


**Figure 2** – Scheme of the EGFR receptor and the position of the major mutations [5].

These mutations explain the relevance of studying EGFR in cancer development as they affect the ATP adherence site leading to a 50-fold increase in the enzyme activity. This increased activity inhibits the signals for apoptosis and increases the signals for survival. At that, the cells subject to safe removal, apoptosis, survive and proliferate. With the accumulation of mutations, the cells gradually acquire the properties of cancer cells, as well as the ability to migrate and cause the proliferation of neighboring, healthy cells. These genetic mutations are irreversible and persist throughout the life of the individual.

The most common drugs for the treatment of cancer caused by EGFR gene mutations are tyrosine kinase inhibitors (TKI). Gefitinib was the first drug synthesized and approved in that line, followed by Erlotinib and Afatinib [6]. Those drugs selectively displaced ATP, the tyrosine kinase substrate occupying the active site of the enzyme with its struc-ture. It prevented phosphorylation of the cytosolic part of the protein and blocked the transmission of signal through the cascade. Those drugs reduced the proliferation and survival of cancer cells, increased apoptosis and improved ef-ficiency of chemotherapy and radiotherapy. In other words, the efficacy of therapy is improved only by combination of drug therapy and other therapies. Drugs of the second or third generation are used In case of resistance due to secondary mutations. The comparative efficacy analysis of different TKIs substantiates the need for an individual ap-proach in the choice of treatment due to differences in the course of the disease in different patients.

Today, the EGFR mutations are an essential clinical marker which allows predicting and assessing the efficacy of NSCLC therapy with TKI [7]. Purpose of the study was to analyze and characterize the EGFR mutations in Kazakhstani population. This study allows determining the role of mutations in NSCLC as they serve as a justification for the choice of targeted therapy. For this reason, TKIs in the treatment of NSCLC are prescribed only after the EGFR mutation is de-tected. Since TKI has become a part of the protocol of treating NSCLC in Kazakhstan, it is important to assess the fre-quency and range of EGFR genes mutations in Kazakhstani patients.

***Materials and methods.*** The study included 138 patients with NSCLC whose postoperative or biopsy material was deliv-ered from Almaty Regional Cancer Center to the Center for Morphological Studies of Kazakh institute of Oncology and Radiology (KazIOR) or they were treated at KazIOR during 2017. Most of them (60.87%) were men. The average age of men and women was almost the same – 60.5 and 59.9 years, respectively. 68.84% of the included patients were from Almaty, 13.04% - from Karaganda, the rest – from other 10 regional centers of Kazakhstan (Table 1).

**Table 1 –** Characteristics of the group of patients with NSCLC who underwent genetic testing

| Parameter | Number of patients | |
|---|---|---|
| | abs | % |
| **Sex** | | |
| Men | 84 | 60,87% |
| Women | 54 | 39,13% |
| **Average age, years** | | |
| Men | 60.5 | |
| Women | 59.9 | |
| **Admitted from** | | |
| Aktau | 3 | 2.17% |
| Aktobe | 1 | 0.72% |
| Almaty | 95 | 68.84% |
| Astana | 6 | 4.35% |
| Karaganda | 18 | 13.04% |
| Kostanay | 3 | 2.17% |
| Semey | 1 | 0.72% |
| Taldykorgan | 2 | 1.45% |
| Taraz | 1 | 0.72% |
| Uralsk | 1 | 0.72% |
| Ust-Kamenogorsk | 4 | 2.90% |
| Shymkent | 3 | 2.17% |

The material for the analysis included tumor cells from paraffin blocks containing postoperative and biopsy mate-rial. DNA from tumor cells fixed in formalin and enclosed in paraffin blocks (FFPE) was extracted by liquid-phase method using BioLink set for DNA extraction in accordance with the manufacturer's instructions. To detect muta-tions, DNA was amplified by real-time PCR using the sets of reagents for determining the EGFR mutations from Bi-oLink (exon 21: L858r, exon 19: deletions) and Roche (exon 18: G719X (G719A, G719C, and G719S), exon 19: dele-tions and complex mutations, exon 20: S768I, T790M, and insertions, exon 21: L858R and L861Q).

***Results and discussion.*** In the examined cohort of patients, most of the samples, 108 (78.26%), had no EGFR mutation. The L858R mutation of exon 21 was the most frequent – 14 (10.14%) patients, with less frequent dele-

tions of exon 19 – 10 (7.25%) patients, and 1 (0.72%) case of insertion of exon 20. 3.62% samples were not suitable for analysis, mainly due to DNA degradation or insufficient number of tumor cells in the sample (table 2).

**Table 2 -** Spectrum of EGFR mutations in patients with NSCLC

| Mutation status | Number | % |
|---|---|---|
| No mutations detected | 108 | 78.26% |
| Exon 21 L858R mutation | 14 | 10.14% |
| Exon 19 deletion mutation | 10 | 7.25% |
| Exon 20 Ins Mutation | 1 | 0.72% |
| Unable to perform analysis | 5 | 3.62% |

The L858R mutation of exon 21 was more frequent in the considered cohort than the deletion of exon 19 – 56% and 40% of the total number of patients with EGFR mutations, respectively. This is somewhat different from the litera-ture data on cohorts from different countries [8-10] where an exon 19 deletion is most frequent.

Distribution of EGFR mutations by sex in the examined cohort was as follows. Men composed 60.87% of the cohort (n=84) vs. 39.13% of women (n=54). Gene mutations in women (n=12, 22.22%) were more frequent than in men (n=13, 15.48%). The most frequent mutation in both sexes was exon 21s L858R mutation – 9.52% in men and 11.11% in wom-en. The deletion of exon 19 was less frequent – 5.95% in men and 9.26% in women. Also, 1 (1.85%) patient had a rare EGFR 20 Ins mutation (table 3).

**Table 3 –** Distribution of EGFR mutations in the study cohort by sex

| Men (n=84; 60.87%) | | | Women (n=54; 39.13%) | | | |
|---|---|---|---|---|---|---|
| Mutation detected (n=13; 15.48%) | | No mutation detected (n=71, 84.52%) | Mutation detected (n=12; 22.22%) | | | No mutation detected (n=42, 77.78%) |
| L858R | del19ex | | L858R | del19ex | Exon20 Ins | |
| 8 (9.52%) | 5 (5.95%) | | 6 (11.11%) | 5 (9.26%) | 1 (1.85%) | |

***Conclusions.*** In its clinical practice, KazIOR utilizes Real-Time PCR to diagnose clinically significant EGFR mutations as they are strong predictors of the response to EGFR-TKI treatment in NSCLC.

78.26% of patients with NSCLC had no EGFR mutations. This indicates a possible presence of other mutations not studied in this spectrum. Further research is needed to determine the exact causes of such results.

EGFR mutations in exons 19, 20 and 21 were found in 15.48% of male and 22.22% of female patients with NSCLC. An exon 19 deletion was detected in 40%, and point replacements of Leu858Arg – in 56% of NSCLC cases.

Diagnostics of gene mutations allows choosing an optimum scheme of treatment based on the tumor drug sensitivity analysis. Thus, the study of the tumor molecular-genetic profile is becoming increasingly important as it allows imple-menting a personalized approach to treatment. It becomes possible with the accumulation of experimental and clinical experience in molecular oncology, better understanding of tumor growth genetic mechanisms, and the introduction of new targeted drugs into clinical practice.

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# The use of electrochemotherapy in treating superficial melanoma metastases

Relevance. *Electrochemotherapy (ECT) is a novel modality for treatment of skin, cutaneous, or subcutaneous malignant tumours.*

Purpose of the study – *to study the effectiveness of ECT for treatment of superficial metastases of melanoma.*

Methods and materials. *4 patients with stage IV skin melanoma received ECT in the Center of bones, Soft Tissue Tumours and Melanoma of the Kazakh Institute of Oncology and Radiology (KazIOR). ECT was made using CliniporatorTM (IGEA, SpA, Italy) and hexagonal needle electrodes inserted subcutaneously directly into deep tumour tissues and surrounding areas. Electric pulses were administered during 8 minutes after intravenous injection of 15 mg / m2 of bleomycin. ECT was performed according to the European Standard Operating Procedures of Electrochemotherapy (ESCOPE).*

Results. *All patients had a complete response (CR) of tumour nodes 15-30 days after ECT. 2 patients had no recurrence and growth of new lesions 10 months after ECT. One patient had tumour recurrence 3 months after ECT, and one – 5 months after ECT.*

Conclusion. *ECT can be a method of choice in treating patients with superficial melanoma metastases. ECT increases the effectiveness of systemic and local therapy.*

***Keywords:*** *metastatic melanoma, electrochemotherapy, bleomycin, superficial skin melanoma.*

***Introduction.*** Since 1973, worldwide incidence of melanoma has increased by 200% [1]. The same trend is observed in Kazakhstan. In 5 years, 2011 to 2015, the morbidity has increased by 25%. 330 patients in average were newly diagnosed with melanoma in Kazakhstan yearly. The total number of registered patients with that diagnosis has amounted to 2238 in 2015. Despite the fact that the patients with stage IV have accounted for only 8%, the 5-year survival has remained rather low – 58.5% [2].

Melanoma is one of the most malignant tumours. Melanoma is characterized by rapid metastasis into vital organs and systems. The risk of its recurrence and progression depends on the primary stage of the disease. 5-year survival in local-regional stages differs from 97% at IA to 40% at IIIC stage. In the metastatic process, 5-year survival depends on the localization of metastases: 62% in case of metastatic lesions and lymphatic lymph node involvement; the involvement of lungs reduces 5-year survival to 53%; and the involvement of other visceral organs results in a decrease to 33 % [3].

Despite a relatively favourable prognosis for superficial metastases, the treatment of this category of patients remains one of the most complex and urgent. The presence of skin recurrences and metastases worsens the quality of life of patients due to the presence of a visible tumour, severe pain syndrome, the need for regular surgical dressings, and the development of inflammatory and infectious complications.

The existing methods of treatment of patients with skin metastases – from systemic therapy, surgery, radiotherapy to local-regional chemotherapy – are not efficient enough [4, 5]. The possibility for targeted therapy is limited to a group of patients with a proven mutation of BRAF gene. In this regard, the search for new, most efficient methods of treatment of this category of patients remains relevant.

To date, the effectiveness of this method was demonstrated in multiple studies [6-8]. According to the obtained results, an objective response was observed in 80 patients (94%) one month after the first ECT. Partial response (PR) was achieved in 39 patients (48%), with a complete response (CR) in 19 patients (24%) after the reinitiation of treatment. 19 out of 41 patients (48%) with CR after the first ECT underwent a second cycle because of the new lesions after a median of 6 months. During a follow-up of an average of 26 months, 6 patients had local recurrence, with a 2-year local progression-free survival rate of 87%. Advantages of the method: the time of treatment is less than 30 minutes; repeated sessions are possible; minimal side effects; and the possibility of combination with other methods of treatment [6]. ECT remains an effective method of palliative treatment of superficial metastases [9].

The clinical studies have revealed the following side effects of ECT technique:

- Local pain syndrome at the site of application of the electrode
- Nausea
- Vomiting
- Slightly expressed itching, erythema, peeling of the skin in the area of exposure passing without treatment.
- Permanent hyperpigmentation of skin in the area of cytostatic administration. The highest risk of hyperpigmentation – with bleomycin.
- Moderate aseptic inflammation of skin surrounding the tumour during treatment [10, 11].

In Kazakhstan, electrochemistry was first applied in the Center for Bone, Soft Tissue Tumours and Melanoma of the Kazakh Institute of Oncology and Radiology (KazIOR) in December 2016. The first experience of using this technique is presented in this study.

***Purpose of the study*** – to study the effectiveness of electrochemical method of treatment of superficial metastases of melanoma.

***Methods and materials.*** 4 patients with stage IV melanoma selected for ECT treatment met the following criteria: satisfactory general status, ECOG <2, inoperable multiple superficial melanoma metastases. Those patients have refused standard chemotherapy and were not subject to targeted therapy.

ECT contraindications taken into account during patient selection: confirmed allergy to bleomycin; pulmonary, cardiac, renal and hepatic insufficiency; probable life expectancy not more than 3 months; brain metastases; progressive metastases in internal organs; an installed pacemaker, insulin pump or electronic implants; impaired blood clotting; epilepsy; pregnancy or breastfeeding; acute infections including acute skin inflammation.

ECT procedure: all the patients received i/v bolus of Bleomycin at the rate of 15 mg / m2 during 8 minutes. Then electrical impulses were applied to each tumour site and adjacent tissues at a distance of 15-20 mm. The electric currents were supplied with a needle electrode 2-3 cm long based on the size of the source. The electrodes were attached to a high-voltage impulse generator Cliniporator™ (IGEA, SpA, Italy). The voltage up to 1000V was supplied as a compressed circuit of eight pulses at the frequency of 5000Hz. The voltage and current supplied to each tumour node were software regulated. Maximum duration of the procedure – 30 minutes. Each patient received one treatment session. The method of anaesthesia was determined depending on the anatomical location of the tumour. In the event of pain syndrome after the procedure the patients received analgesic therapy with standard NSAIDs. No other side effects except pain syndrome stopped by NSAIDs were observed during our first application of ECT.

The efficiency of ECT was determined by comparing the size of metastatic lesion before and after treatment, the number of lesions, the presence of M1b-c metastases, the relapses and the appearance of new metastatic lesion during 8 months after treatment.

***Results.*** One of the peculiarities of the method was that the treatment effect was evident already 20 days after the procedure and remained in force for a different period without additional treatment. All patients had a complete response of cutaneous metastases to treatment after 20 days. In 2 patients with pulmonary metastases, there was no growth of the metastases. 2 patients who had skin tumour nodes 5-30 mm and 5-40 mm before treatment had a relapse after 3 and 5 months, respectively. 2 other patients had no skin metastases throughout the follow-up period of 10 months.

Summarized results of treatment:

• CR of tumour nodes was observed in all patients 15-30 days after ECT.

• 2 patients had no recurrence and growth of new lesion within 10 months from the date of ECT.

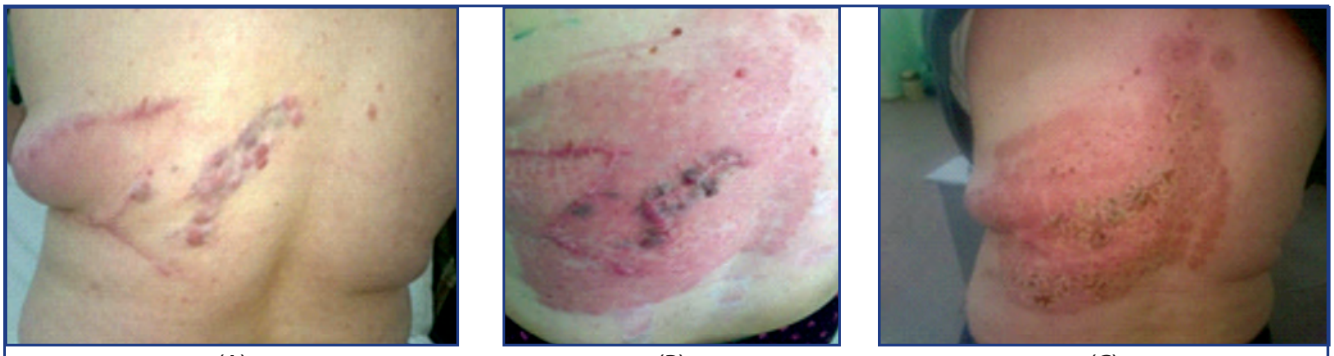
• 1 patient had a tumour recurrence 3 months after ECT.

• 1 patient had a relapse of metastatic formations and the appearance of new lesions in nearby anatomical areas 5 months after ECT (Table 1).

**Table 1** – Evaluation of ECT efficiency in patients with skin metastases of melanoma

| Clinical cases | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Sizes of metastatic lesions before treatment | 5-20mm | 10-50mm | 5-40mm | 5-30mm |
| Number of lesions before treatment | 20 | 5 | 6 | 25 |
| Size and number of metastatic lesions after treatment | No lesions | | | |
| Presence of M1b-c metas-tases before treatment | Multiple le-sions in the lungs | No | No | Multiple le-sions in the lungs |
| Presence of M1b-c metas-tases after treatment | Multiple le-sions in the lungs (stable CT picture) | No | The appearance of metastatic lesions of the lungs 6 months after treatment | Multiple le-sions in the lungs (stable CT picture) |
| Time before relapse and the appearance of new local metastatic lesions after treatment (months) | No | No | 6 months | 3 months |

Clinical case №1. Patient B., 38years old. Back skin melanoma St IV (T3bN1M1b). Condition: after surgery, 8 courses of chemotherapy (3 lines of chemotherapy). Stabilization of lung metastases. Progression: metastatic lesion of the back skin.



(A) (B) (C)

**Figure 1** – Patient B. 38years old. Back skin melanoma St IV (T3bN1M1b): (A) Before treatment; (B) 20 days after treatment; (C) 5 months after treatment

20-30 days after treatment, CR of metastatic lesions was determined by visual examination and palpation. There was no progression of metastatic lesions of the back skin within 10 months. The stabilization of metastases in the lungs was confirmed by computed tomography (CT) (Table 1).

Clinical case №2. Patient D., 58years old. Melanoma of the left leg skin St IV (T4bN1M1a). Condition: after surgery (wide excision of the left leg skin tumour + Duchene's operation on the left leg).

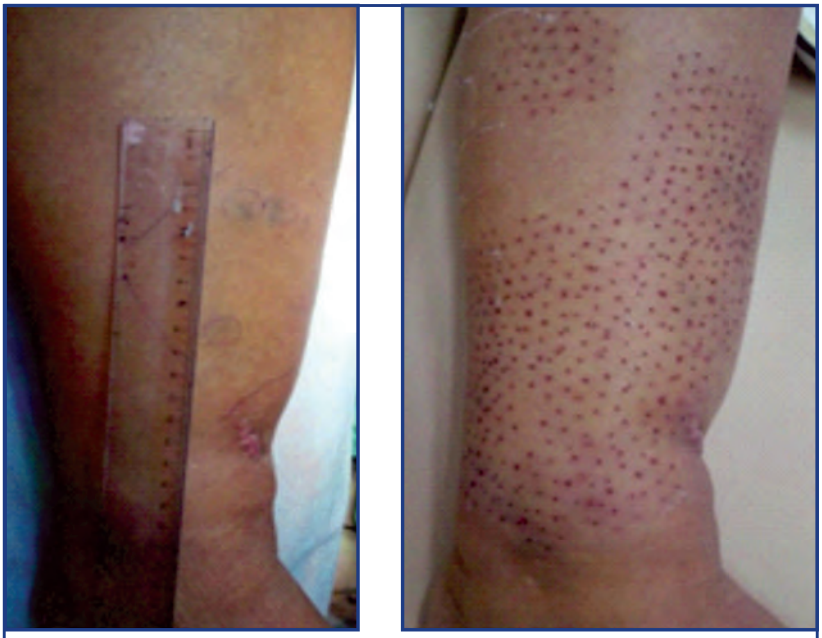



**Figure 2** – Figure 2 - Patient D., 58years old. Melanoma of the left leg skin St IV (T4bN1M1a): (A) Before treatment, (B) 15 days after treatment

15-20 days after treatment, the resorption of metastatic foci was determined by visual examination and palpation. There was no local recurrence of melanoma metastasis within 10 months. The absence of distant haematogenous and lymphogenous metastases was confirmed by CT and MRI (Table 1).

Clinical case №3. Patient I., 78years old. Metastasis of melanoma to the right leg skin without primary-identified lesion StIV(TxN0M1a).

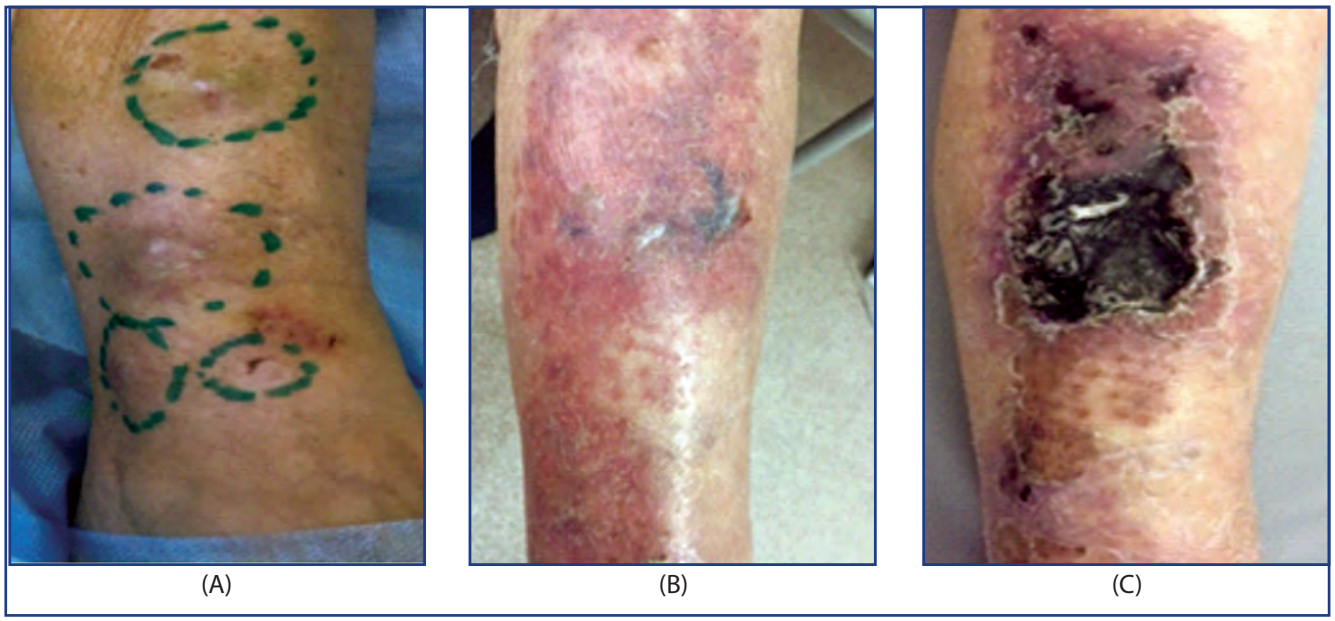
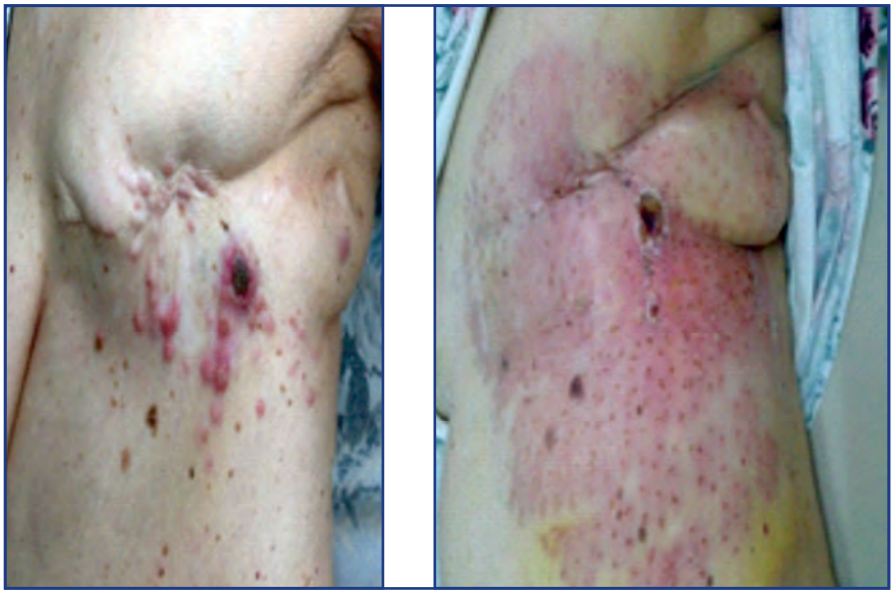



**Figure 3** – Patient I., 78years old. Metastasis of melanoma to the right leg skin without pri-mary-identified lesion StIV(TxN0M1a): (A) Before treatment, (B) 30 days after treatment, (C) Complete necrosis of tumour nodes after 3 months.

25 and 30 days after treatment, the resorption of metastatic lesions was confirmed by visual examination, palpation and ultrasonography. Six months after ECT the disease progressed as the new metastatic lesions appeared in soft tissues, on the left leg skin and in the lungs, as evidenced by local examination and CT (Table 1).

Clinical case №4. Patient A., 68 years old. Skin melanoma of the left inguinal area with a metastatic lesion of inguinal lymph nodes, lung, and soft tissues of the anterior thoracic wall. St IV (T4vN1M1b).



(A) (B)

**Figure 4** – Patient A., 68 years old. Skin melanoma of the left inguinal area with a metastatic lesion of inguinal lymph nodes, lung, and soft tissues of the anterior thoracic wall. St IV (T4vN1M1b): (A) Before treatment, (B) 20 days after treatment.

20 days after treatment, the resorption of metastatic lesions was confirmed by visual examination, palpation and ultrasonography. 3 months after ECT, the disease progressed as the new metastatic lesions appeared in soft tissues, on the skin of the anterior chest wall, and the metastatic lesions in the lungs have progressed as evidenced by local examination and CT (Table 1).

***Conclusion.*** Our first experience with ECT has shown the possibility of using this method in treating melanoma skin metastases. ECT can be a method of choice for treating superficial melanoma metastases of different localities with a high risk of local recurrence and further dissemination of the tumour.

ECT provides good results with minimal side effects and allows improving the quality of life of patients.

Further study involving more patients and a longer monitoring of the treated patients are required to completely evaluate the efficiency of this method of treatment.

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# At the origins of soviet oncology: scientific priorities

Relevance: *The modern state of Russian oncological science is the result of the evolutionary development of oncology in the USSR at various stages. This development is of certain interest for specialists.*

Purpose of the study: *To show the main scientific priorities at the dawn of the development of Soviet oncology.*

Results: *In the first half of the 20th century, biochemical and viral concepts of malignant tumors' etiology were the most popular. The studies on the role and meaning of viruses in the emergence and development of tumors headed by professor L.A. Zilber have used immunological reactions to establish the presence of specific antigens in neoplasms and blood of cancer patients. In blood, they were connected to erythrocytes. A.D. Timofeevsky also supported the viral theory of cancer. At the II Congress of Oncologists of the Ukrainian SSR, he reported finding the virus-like globular formations which he had managed to cultivate. He considered the obtained data as an indirect proof of the viral etiology of human malignant tumors. The conducted studies of the thin structure of malignant tumor proteins have illustrated the abnormalities in protein synthesis at the oncological process. N.N. Petrov has promoted biochemical concept as a more probable and better explaining the observed facts. The discussion between the supporters of the two theories remained lively for many years. The experiments and clinical practice of the Leningrad Institute of Oncology at the USSR Academy of Medical Sciences have evidently proven the blastomogenic properties of chemical and physical agents which still could be considered specific. Harmful agents could become active and blastomogenic through their direct impact from the external environment or as a result of disruption of the normal relations of the organism and the environment.*

Conclusion: *In the first half of the 20th century, Soviet oncology was deeply studying the main issues of theoretical and applied medicine in general. At that time, surgical disciplines, including oncology, have started the study of pathogenesis and clinical picture of the disease being guided by the doctrine of the academician I.P. Pavlov on the role and meaning of the central nervous system in the life of a living organism.*

***Keywords:*** *Soviet oncology, formation and development of oncology in the USSR, the founders and scientific directions of Soviet oncology.*

***Introduction.*** Currently, solving the problems of oncology remains a medical task of primary importance for healthcare as a whole, and for surgery in particular. A significant portion of all surgical interventions is associated with malignant tumors. And though the tumor etiology is still not established, we are now much closer to the study and understanding of many aspects of this matter. Cancer surgeons have added many famous pages to the history of Soviet medicine in the process of development of the medical scientific thought and practice.

In October 1926, the government of the young Soviet state has supported the suggestion of Nikolay Nikolaevich Petrov, the founder of the Soviet oncology, and decided on the establishment of the Scientific and Practical Institute of Oncology in Leningrad. That historical decision was the first step towards the creation of a large medical center – the future Oncology Research Institute, awarded the Order of the Red Banner of Labor, at the USSR Ministry of Health. Nowadays, this Institute is named after its founder – Professor N.N. Petrov and is officially named as the Federal State Budget Institution "N.N. Petrov National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation.

N.N. Petrov expected the Institute to become a research center for an interrelated study of etiology, nosogenesis, diagnostics and clinical picture of malignant neoplasms to ensure a solid scientific basis for the organization of cancer control. The Institute started from three clinical units with 110 beds (two surgical units and one gynecological

Nikolay Nikolaevich Petrov (1876-1964)

unit), a small outpatient clinic, the departments of X-ray diagnostic and X-ray therapy, and the USSR's first laboratory of experimental tumors. In the 1930s, a dispensary department with a diagnostic station was established at the central municipal outpatient clinic to serve the city and the region. Specialized oncology offices were opened in three large municipal polyclinics and large-scale educational activities started.

In 1931, a special office was opened at the Institute for the accounting and analysis of treatment outcome. Its stuff collected the reliable information and systematically catalogued 5 year-results of treatment of cancer patients. In 1934, the world's first growth prevention inpatient department was established at the Institute to study precancer diseases, their prevention and treatment methods.

During the next years, the laboratories of experimental morphology and cytology, biochemistry, morbid anatomy, clinical diagnostics as well the world's first department of social oncology were organized at the Institute.

In 1944, during the Great Patriotic War, in spite of all the difficulties of the war time, the Soviet Government has found the opportunity to allocate to the Institute a new territory and a building in one of the picturesque areas of Leningrad, on the Kamenny Island. Soon after the war, another special building was built to host several more laboratories in order to expand modern experimental and theoretical research in the field of nosogenesis, biochemistry, and morphogenesis of malignant growth.

In 1945, the first Soviet laboratory for experimental cancer therapy was organized at the Institute to lay the foundation of the Soviet school of chemotherapy of malignant tumors. In 1947, employees of that laboratory together with the specialists of the Lensovet Technological Institute have synthesized and tested Embihin which appeared to be efficient in treating systemic cancer diseases [1].

The scientific and practical activity of the staff of Cancer Departments at national medical universities has played an important part in the development of Soviet oncology. Let us see the sample of Leningrad cancer school.

The establishment of the Oncology Department at the Leningrad Institute of Advanced Medical Studies is directly connected with the name of Nikolay Nikolaevich Petrov, the founder of Soviet oncology, and his closest followers and colleagues. For many years (from 1913 till 1958), N.N. Petrov headed the Surgery Department at the Leningrad Institute of Advanced Medical Studies. Under his direction, the problems of oncology were dominating in the activity of the Department. N.P. Napalkov rightly pointed out that "The main merit of N.N. Petrov is that he has not only created and substantiated the concept of poly-etiology of malignant tumors but also put maximum efforts to organize a country-wide oncology service on its basis. N.N. Petrov has not only managed to implement his ideas but has also raised the problem of cancer control to the state level." Already in 1923, N.N. Petrov wrote in one of his articles: "Cancer disease is a public disaster of huge size" and further "... the main basic principle lies in the fact that the practical implementation of cancer control is recognized as a state task in the Soviet Union" [2].

Officially, since its foundation in 1931, the Oncology Department was a subdivision of the Leningrad Institute of Advanced Medical Studies. At the same time, Research Institute of Oncology was and remains the clinic and scientific base of the newly founded department. N.N. Petrov, S.A Kholdin, and A.I. Rakov were the first leaders of the department, its founders. They worked at the Institute for many decades making a great contribution in the development of Russian oncology [3].

S.A. Kholdin rightly said that "When the Institute has started its activity, the only oncologist there was its founder and organizer Nikolay Nikolaevich Petrov. He was facing a challenge to train the first cohort of oncologists, "the trainers for trainers", and it took the first 5-6 years of the Institute's activity" [3].

N.N. Petrov wrote: "…as for the doctors sent to the advanced courses and specializations, the cycles of medical knowledge should include a course in oncology aimed to [3]:

1. Train the oncologists able to work at large cancer centers.

2. Train the lecturers skilled in oncology for medical departments.

3. Improve skills of specialists working in preventive healthcare centers in the regions."

In conclusion, N.N. Petrov summarized: "The experience of delivering lectures and demonstrations to the surgeons during the first six semesters of short courses in oncology conducted by me at the Leningrad Institute of Oncology has proven the significant interest in these courses and the possibility of practical success of expanding them up to a cycle."

Since 1935, N.N. Petrov has delegated the main duties of teaching at the Department of Oncology to S.A. Kholdin. The Oncology Department was officially legalized only in 1944. The oncological course consisted of 510 hours, of them, 136 hours of oncological lectures and 374 hours of practical studies. At that, 86 lecture hours were dedicated to complementary sciences such as epidemiology, biochemistry, biology, and general pathology [3].

In 1953, S.A. Kholdin left his position at the Oncology Department of the Leningrad Institute of Advanced Medical Studies and focused on his activity at the position of the Head of the 1st Surgery Department at the Institute of Oncology which he occupied from 1927 till the end of his life in 1975 [3]. Semen Abramovich Kholdin was one of the main Soviet oncologists and was widely known

abroad. He was a member of USSR Academy of Medical Sciences and the author of numerous writings dedicating to the development of breast cancer and colorectal cancer treatment methods. Semen Abramovich has made a great scientific contribution and trained many honorable followers who continue his practice till today.

In the first part of the 20th century, biochemical and virus conceptions of cancer growth had prevailed. The studies under the guidance of Prof. L.A. Zilber had proven that in the presence of human cancer the immune reactions revealed specific antigens in the neoplasms and the blood of cancer patients. In blood, those antigens were linked with erythrocytes [4]. A.D. Timofeevsky who also supported a virus theory of cancer reported at the II Congress of Oncologists of the Ukrainian SSR that he had managed to find and incubate virus-like globular formations [5]. Taking into account the serological tests, anaphylaxis and deallergization, the author supposed a specific nature of the incubated virus-like globular formations. The obtained data allowed A.D. Timofeevsky to consider those formations as an indirect proof of the viral etiology of human cancer [5].

However, Professor A.I. Serebrov was not sure about the role of viruses in etiology of tumors. Virus-like bodies found by L.A. Zilber in patients with polyposis gastrica and urinary bladder could hardly be real viruses and not parts of the patients' body [6]. There was not enough evidence to consider tumor antigens as viruses, and not modified proteins of the body. All those issues required further research.

Prof. N.N. Petrov also doubted the role of viruses in the etiology of tumors. In his opinion, tumor growth was a kind of the body reaction to the damage of its tissues leading to a dystrophy occurring locally and in the central nervous system, with a future formation of a cell reproduction site with the finest changes in tissue proteins.

A.D. Timofeevsky (1887-1985)

In March 1957, at a conference in Moscow organized by the Institute of Experimental Pathology and Cancer Therapy of the Academy of Medical Sciences of the USSR together with the Society of Oncologists of Moscow and the Moscow Region, A.D. Timofeevsky reported on the views on viral etiology of human cancer. Sharing his impressions about that conference with the Leningrad Association of Oncologists, N.N. Petrov pointed out that the findings of A.D. Timofeevsky had greatly extended the knowledge about the virus-like bodies in the human tumors which were the composite elements malignant tissues and cells [1, 7]. The issues raised at the conference were at the stage of accumulation of material and no final conclusions could be made. The followers of the viral origin of tumors made no practical proposals that could be applied the prevention of that horrible disease.

L.A. Zilber (1894-1966)

A.I. Serebrov (1895-1980)

In those years, I.B. Zbarsky, K.A. Perevoshchikova, S.R. Mardashev and others were involved in the study of fine struc-ture of proteins of a malignant tumor; certain data was obtained on the violation of protein synthesis during the oncological process. According to R.E. Kavetsky, neoplastic growth was strongly influenced by profound disorders in protein metabo-lism and general metabolism. The nervous system trophism, the functionality of endocrine glands and connective tissue were declared as the main factors for "cancerous disposition" [1].

N.N. Petrov believed that biochemical conception was more probable and better explained the available observations. Supporters of both theories led a lively discussion for many years.

The experimental and clinical studies conducted at the Leningrad Institute of Oncology at the USSR Academy of Medical Sciences have definitely demonstrated the blastomogenic properties of chemical and physical agents. Still, those properties could not be considered absolutely specific. Harmful agents could become active and blastomogenic at their direct impact from the external environment or as a result of a breach in the normal balance of the body and the environment (Prof. L.M. Shabad) [8, 9].

L.M. Shabad (1902-1982)

Physical and chemical agents were believed to be specific, and that circumstance could be a way to eliminate in advance their harmful impact on the human body.

In the meantime, the methods of rapid determination of carcinogenic substances by their physical properties were developed. For example, fluorescent-spectral methods could be used to detect 3, 4-benzpyrene in a number of mixtures that turned out to be carcinogenic. It was hard to overestimate the significance of those studies for the prevention of occupational and community-acquired cancer.

The importance of clinical and experimental studies should be mentioned that gave a certain idea about the existence of precancer that allowed monitoring the premalignant changes in the body. The detection of premalignant changes made it possible to timely diagnose the emerging cancer process and take preventive and treatment measures to prevent the progression of cancer. "Each cancer has its own precancer" but not every "precancer" becomes a cancer: the premalignant stage is the most variable stage of the tumor disease," said L.M. Shabad [9].

N.N. Petrov believed that such an approach could bring us closer to solving the problem of cancer. Premalignancy was to be diagnosed only in the presence of clear definite symptoms of malignization.

A.I. Serebrov emphasized the need for a countrywide study of regional features of the spread of tumors [10, 11].

The possibility of studying the geographical features of the spread of cancer was noted in the pre-revolutionary Russian literature. I.e., as early as in 1914, V.S. Levit discussed in in his book "On the issue of gastric cancer and its palliative surgical treatment" (Kazan, 1914) [1].

The report made in 1956 A.F. Yastrebov on the use of epidemiological analysis in the study of characteristics of regional spread of cancer deserved a certain attention. The reports of N.G. Znachkovsky, L.N. Korenevsky, and D.M. Yudovich on the regional features of malignant tumors in the Ukrainian SSR and the report of A.V. Chaklin on the role of clinical and statistical method in the study of the regional features of the spread of cancer caused considerable interest. Those reports have partly shed the light on the role and impact of climatic and soil conditions on the occurrence and spread of that terrible disease.

The availability of a wide network of cancer dispensaries in the USSR has allowed a deeper study of the regional features of the spread of malignant tumors and the formation of a clearer view of the geographical dissemination of cancer.

In those years, cancer control in the Soviet Union was managed by the leading cancer research institutions - the Institute of Oncology at the Academy of Medical Sciences of the USSR, P.A. Hertsen State Institute of Oncology, and the Institute of Experimental Pathology and Therapy at the Academy of Medical Sciences of the USSR. The institutes, large laboratories and clinical cancer institutions were established in Kiev, Sverdlovsk, Baku, Tbilisi and a range of other national cities. A wide network of cancer institutions performed sanitary, educational, preventive, therapeutic, and diagnostic activities. In such institutions, doctors of various specialties were fighting together against cancer. The implementation of massive public preventive medical examination allowed preventing certain cancer diseases, timely detect and treat premalignant processes.

A lot of attention was paid to the social aspect of cancer control. A high rate of utilization of medical services by the population ensured in some cases an early diagnostics of a developing tumor.

The correctly organized periodic health examination was the surest way to detect tumors early and created the most suitable conditions for preventive measures. According to N.N. Petrov, the current knowledge of the causes of cancer not only allowed but necessitated the preventive fight against this disease.

The Guide on General Oncology of 1958 edited by N.N. Petrov deserved special attention. Its value was evidenced even by its introduction written by N.N. Petrov. It said that the Guide considered "of course, not the individual forms of malignant tumors described in the guides on special cases of oncology but the general properties of all such forms, while determining their place in a number of diverse pathological disorders of normal life, the distribution of nature, causes and mechanisms of their development, recognition, prediction, as well as the basic principles of their treatment and prevention at the present level of our knowledge" [2]. The authors of the Guide intended to present the major views of modern medicine on both more or less firmly established facts and the difficult unresolved, controversial issues of the modern oncology. And they sensationally managed to do it in a succinct format.

Major issues of oncology developed in the USSR were reflected in 11 reports presented by the Soviet delegates at the VII International Anticancer Congress in London in 1958. Soviet doctors worked a lot on the pathogenesis, diagnostics, and treatment of cancer tumors of various organs, widely applied the up-to-date methods of complex treatment (surgical treatment, radiation therapy and combined surgical-radiation therapy) and the methods of hormonal influence on neuroendocrine mechanisms of tumor growth [1].

In the first half of the 20th century, the Soviet oncology was deeply studying the major issues of theoretical and practical medicine in general. Surgical disciplines, including oncology, were approaching the study of pathogenesis and the whole picture of the disease guided by the teachings of Acad. I.P. Pavlov on the role and importance of the central nervous system in the life of a living organism.

In summary, it should be noted that since the 1930s the Soviet surgeons and oncologists, together with other Soviet scientists have achieved significant results thanks to the contribution of outstanding personalities and purposive professionals. Modern cancer schools inherit the old schools of Russian and Soviet surgery and oncology. Modern oncologists honor and develop the best traditions of the past, the scientific thoughts of their predecessors, trying, in turn, to pass them on to the younger generation of doctors.

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# In memory of the Academician N.N. Trapeznikov (1928 - 2001) (To the 90th anniversary)

Relevance: *The academician N.N. Trapeznikov has led the development of original Soviet titanium knee, shoulder and hip joint endoprostheses. They could completely restore the limb function and were much cheaper than the foreign analogues.*

*His pedagogical activity, articles, textbooks and manuals also deserve high praise.*

Purpose of the study: *to show the main milestones of N.N. Trapeznikov's activity.*

Results: *In 1974, N.N. Trapeznikov was elected a corresponding member of the Academy of Medical Sciences of the USSR, and in 1978 – its full member (RAMS since 1992). In 1977, N.N. Trapeznikov with a group of co-authors was awarded the State Prize of the USSR for the experimental substantiation, clinical development and introduction of the method of large bone allografts. In the future, the successful development of that area of oncology was twice marked by N.N. Petrov's awards of the USSR Academy of Medical Sciences (1980, 1987). A series of works in the field of immunodiagnostics, immunotherapy and immunochemotherapy of tumors published in the late 1970s and early 1980s has put him forward as a prominent clinical immunologist. The most important areas of that field were: specific and non-specific immunotherapy of malignant tumors, immunochemotherapy and prevention of metastasis in skin melanomas, immunotherapy with the patient's activated lymphocytes. At that time, the use of interleukins has been a completely new approach in cancer therapy.*

*In recent years, N.N. Trapeznikov has been engaged in endoprosthetics of bones and joints in patients with bone tumors. Endoprostheses of knee and hip joints, the diaphysis of the femur, the proximal end of the shoulder from a new isoplastic material are widely used till today to solve a number of problems of stable fixation of implants. The author substantiates a complex approach to therapy using organ-preserving surgical interventions, highly active antitumour drugs, irradiation, and influence on the immune status of the body.*

Conclusion: *N.N. Trapeznikov has definitely been one of the creators of modern oncology and, above all, of its scientific foundations.*

***Keywords:*** *N.N. Trapeznikov, biography, bone tumors, bone allografts, immunodiagnostics, tumor immunotherapy, sarcomas, skin melanoma, bone endoprosthetics in oncology.*

***Introduction.*** The creative heritage of Nikolay Nikolaevich Trapeznikov deserves a careful examination.

Love for the national science was a distinguishing feature of this scientist, organizer, clinician, and teacher. For more than 35 years, N.N. Trapeznikov was heading and continuously managing the Department of General Oncology of N. N. Blokhin National Medical Research Cancer Centre adhering to foremost views on the content and value of that discipline.

N.N. Trapeznikov was born on May 21, 1928, in Gorky in the family of Nikolay Ivanovich Trapeznikov and Elizaveta Nikolaevna Trapeznikova. In his youth, Nikolay Nikolaevich was actively engaged in sports: skiing, volleyball, basketball (he was the captain of the university team, the champion of the city of Gorky). He always had a big passion for history. His selection of a medical path was occasional to a certain degree. Since 1940, his father, a graduate of the Tomsk Polytechnic Institute, was a Chief Utility Engineer at the construction of Kuibyshev Aviation Plant. Nikolay Nikolaevich also had to encounter with aviation: in 1943, in the midst of the Great Patriotic War, he graduated from the 7th grade and was sent to Kuibyshev Air Force Aviation School where he studied till the end of the war. Nikolay finished comprehensive school in the native city of Gorky and had to face a difficult choice of the university: polytechnic or medical. He had to cast lots…

Nikolay Nikolaevich Trapeznikov (1928–2001)

In 1952, N.N. Trapeznikov graduated with honors from the medical faculty of S.M. Kirov Gorky State Medical Institute and entered a residential program. He became

a physician and a scientist under the guidance of Acad. N.N. Blokhin in the walls of the Institute of Experimental and Clinical Oncology of the Academy of Medical Sciences of the USSR (now – N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of Russia). He worked there as a junior scientist, senior scientist, and then the Scientific Secretary of the institute. In 1956, he passed his Ph.D. defense on the topic of "Comparative Evaluation of Materials for Surgical Sutures and Ligatures." In that period, N.N. Trapeznikov got interested in the tumors of bone and soft tissue, and all his further scientific activities were devoted to the development of that area of oncology. He has headed the search for the new approaches to treatment of those malignancies except surgery. He has developed the principles of using regional intra-arterial chemotherapy in sarcomas of extremities which allowed a significant improvement in the survival rate of patients [1, 2].

The materials obtained during the complex clinical and experimental work were summarized and presented in 1964 in his doctoral thesis "Treatment of Primary Bone Tumors" [3]. N.N. Trapeznikov supervised and participated in determining the indications for the use of preserving surgery in bone neoplasms. The capacity for chemotherapy in the treatment of osteosarcoma metastases was clearly evidenced [4]. Since 1965, N.N. Trapeznikov was the irremovable head of the General Oncology Department at N.N. Blokhin National Medical Research Center of Oncology. In 1967, he was awarded the academic title of Professor in Oncology.

Most of the schemes of radical treatment of malignant tumors of the musculoskeletal apparatus necessarily include extensive surgeries which often cripple and lead to disability. In his numerous papers, N.N. Trapeznikov has developed the principles of remedial treatment of such patients [5]. The team of the General Oncology Clinic has developed and implemented methods for rapid prosthetics after amputations and endoprosthetics. Before those studies, large joints were not subject to prosthetics in oncological pathology. That approach has significantly accelerated rehabilitation of patients and in many cases even allowed restoring their full working capacity [6].

N.N. Trapeznikov has supervised the development of original Soviet titanium endoprostheses of the knee, humeral and hip joints. Those prostheses could completely restore the extremity function and were considerably cheaper than their foreign analogs. The originality of a number of created constructions was confirmed by three inventor's certificates. The priority, relevance and high efficiency of studies and developments headed by N.N. Trapeznikov were highly appreciated by the country's scientific and medical community. In 1974, N.N. Trapeznikov was elected as a corresponding member of the Academy of Medical Sciences of the USSR, and in 1978 – as its full member (since 1992 – the Russian Academy of Medical Sciences).

In 1977, N.N. Trapeznikov with the group of co-authors was awarded the USSR State Prize for his work on the experimental substantiation, clinical development and implementation in practice of the method of large human bone allografts. In the future, the successful development of that direction of oncology was twice awarded with the prizes of N.N. Petrov Academy of Medical Sciences of the USSR (1980, 1987).

N.N. Trapeznikov tended to conduct large-scale and multidiscipline studies in oncology. A range of papers in immunodiagnostics, immunotherapy and immunohistochemistry of tumors published in the late 1970s - early 1980s has promoted Nikolay Nikolaevich to the ranks of outstanding clinical immunologists. The most important matters in that area included the specific and nonspecific immunotherapy of malignant tumors, immunochemotherapy and prevention of metastasis in skin melanomas, and immunotherapy with activated lymphocytes of the patient. The use of interleukins was an entirely new approach to cancer therapy at that time. He headed co-operative study of efficiency of various melanoma and sarcoma treatments methods [7]. His achievements in clinical and experimental area of oncology led to his election as a full member (Academician) of the Department of Physiology of the Russian Academy of Sciences. In his last years, N.N. Trapeznikov headed the activities on endoprosthetics of bones and joints in patients with bone tumors. The endoprostheses of the knee and hip joints, femoral bone diaphysis, proximal end of the shoulder from new isoplastic material became widely used.

Today these endoprostheses allow solving the issues of stable fixation of implants [8, 9]. Preserving surgeries in patients with primary and recurrent tumors of pelvic bones are being developed. During a long period of activity of the General Oncology Department, various schemes of soft tissue sarcoma treatment have been analyzed, with the substantiation of using a complex approach combining organ-preserving surgical interventions, highly active anticancer drugs, radiation therapy, and the impact on the immune status of the body. The use of modern schemes of chemotherapy together with preserving surgery in osteogenic sarcomas has increased the 5-year survival of patients from 10-12 to 50%. The latest innovations include the method of extra-focal compression and distraction osteosynthesis using spike-rod apparatus by Ilizarov to treat pathological fractures of tubular bones. The technique of surgical treatment of the spinal cord decompression in metastatic lesions of the spine was developed together with the Department of Traumatology and Orthopedics of the I.M. Sechenov Moscow Medical Academy. The new methods of osteoplasty, myoplasty and angioplasty in the surgical treatment of bone and soft tissue sarcomas are successfully introduced.

For the results achieved in that direction, in 1999 the authoring team headed by N.N. Trapeznikov was awarded the State Prize of the Russian Federation in the area of science and technology for their paper "Development and Introduction into Clinical Practice of Osteosarcoma Combined Treatment Methods" [1, 8].

As the head of the largest cancer center in Russia and Europe (since 1993), N.N. Trapeznikov could not stand aside from the solution of methodological issues related to the organization of cancer control. Years of work at the International Anti-Cancer Union, close contacts with foreign colleagues from Europe and the USA, an excellent knowledge of the situation with cancer morbidity and the operation of the cancer service in Russia led him to the idea of the need to create the Russian Anticancer Society. It was established in 1994 as an independent and non-professional organization with the goal to engage the public in solving the cancer-related issues. The main priorities in cancer control were defined that allow a quick and efficient reduction of mortality and morbidi-

ty such as a primary prevention of malignant tumors, including fight against smoking and anti-nicotine propaganda, as well as secondary prevention (early detection of cancer through screening programs), the enhancement of fundamental science in order to define the causes and mechanisms of tumor growth, further improvement of methods of diagnostics and treatment of cancer patients, information support and training of staff for cancer service in Russia. Those priorities were presented in the order in which they, according to N.N. Trapeznikov, contribute to the improvement in mortality and morbidity rates of patients.

N.N. Trapeznikov has also done a lot as a lecturer. Since 1975, he was the head of the Department of Oncology of I.M. Sechenov Moscow Medical Academy at N.N. Blokhin National Medical Research Center of Oncology. Traditionally, each academic year started from an introductory lecture of the head of the chair on the achievements and prospects of oncology development. For the thousands of the Academy graduates, their first acquaintance with oncology has started at that Chair, and for some of them, it determined their future life as they became oncologists.

N.N. Trapeznikov has constantly paid a lot of attention to fostering and training of specialists and scientific personnel. Every year, young doctors from many regions of Russia and CIS countries received residency training and postgraduate education at the General Oncology Department. N.N. Trapeznikov was the scientific supervisor for more than 40 doctor and 50 candidate theses. His students have become directors and deans of medical institutes, professors (more than 10), heads of chair and clinical departments.

The Moscow Department of the European School of Oncology (ESO) opened in 1992 at N.N. Blokhin National Medical Research Center of Oncology offers quarterly courses on various aspects of clinical oncology for specialists in oncology. N.N. Trapeznikov has been the regional director and scientific coordinator of ESO operations in Russia and CIS countries [2, 6].

N.N. Trapeznikov is the author of 10 monographs, a textbook on oncology for medical institutes, has near 400 scientific publications. He possessed outstanding organizational abilities and has done a lot in organization of science. He was the manager of the oncology direction of the State Scientific and Technical Program "National Priorities in Medicine and Healthcare", chaired the Interdepartmental Scientific Council on Malignant Tumors, was a presidium member of the All-Russian Scientific Society of Oncologists, the chief oncologist of the Medical Center at the Administrative Department of the President of the Russian Federation, a member of a number of medical, surgical and cancer societies and foundations in Europe and the United States. In 1990, he supervised the establishment of a scientific-practical journal "Vestnik of N.N. Blokhin National Medical Research Center of Oncology" and remained its editor-in-chief till his last days. He was also editorial board member of several Russian and foreign journals.

N.N. Trapeznikov was the Vice-President of the Union for International Cancer Control (UICC), one of the founders of the WHO International Melanoma Committee, the head of the CMEA Coordination Centre on Oncology. He has initiated the formation of the Board of Directors, followed by the Association for Director of Institutes of Oncology and Radiology and Nuclear Medicine, CIS & Eurasia in January 1994. In December 1996, N.N. Trapeznikov was elected the President of the 1st Congress of Oncologists of CIS countries by more than 1,000 participants of that scientific forum. He was also the scientific supervisor of the 2nd Congress of the Association in 2000 in Kiev.

The merits of N.N. Trapeznikov in cancer control and his achievements in clinical activity were awarded with prestigious state awards — the Order of the October Revolution (1989), the Order of the Red Banner of Labour (1981), the Order of October Revolution (1989), the Order of Friendship of Peoples and of Honor (1994), "For Merit to the Fatherland" III degree (1998), many medals of the USSR and Russia, as well as foreign awards [1].

Nikolay Nikolaevich has died on September 27, 2001. He loved teaching and conducted practical classes with students and doctors besides lecturing. He read a lot, was always aware of the latest novelties in surgery and oncology, could perfectly deliver his thoughts, and widely and successfully used those skills in his lectures.

Modern doctors lovingly honor the memory of the most important representatives of the Soviet and Russian medicine, including the talented scientist and great patriot Nikolay Nikolaevich Trapeznikov.

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