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# The risk factors and error factors in cytological service of the republic of Kazakhstan

*Annotation. Cytopathology is the study of cells for the purpose of diagnostics and monitoring of diseases through the identification of primary, recurrent and metastatic tumors and their predecessors. This simple, rapid method of preoperative diagnostics contributes to early detection of tumors and supports the oncologists in determining the treatment tactics and conducting dynamic observation. The procedure of obtaining the biomaterial for examination is easy and minimally invasive. Only cytology allows defining and monitoring of early stages of cancer and precancerous conditions.*

*The quality and method of sampling allow defining the nature of growth, the size, and prevalence of the process, the information value of the biopsy. As a result, it reduces the time for examination, eliminates unreasonable procedures, excludes the anxiety of the patient's, and speeds up the start of treatment. Often, only cytological examination can give the grounds for specialized treatment. Multidisciplinary integration with molecular biology, medical genetics, and etc. creates demand for optimization of information obtained in a non-invasive way using cytological samples.*

*The modernization carried out in Kazakhstani cancer centers has led to the amalgamation of cytological and histological laboratories. At that, the incompetence and misunderstanding of the meaning of preoperative verification by the heads of some laboratories levels down the status of cytology thus creating conditions for destructive professionalism.*

*The effectiveness of cytological examination depends on good practice and motivation, proper management, competence, information value of biomaterial, standardization of procedures, and etc. Diagnostic errors can lead to undesirable consequences.*

*Kazakh Institute of Oncology and radiology (KazIOR) acts as a coordinator in improving the quality of oncological care in the Republic of Kazakhstan (RK), along with the prevention and early diagnostics issues. The adequacy of the obtained biomaterial sample is a well-known key factor which guarantees the quality of cytological examination. In clinical units, high information value of biomaterial under study is ensured by adherence to protocols and standard operating procedures regarding sampling.*

*The growing need for minimally invasive diagnostic methods requires a review of the content and methodology of specialization of cytologists. The cytologist performing a fine-needle aspiration biopsy shall possess dynamic thinking, sociability, and empathy plus to his/her professionalism. Modern standards shall govern practical issues of diagnostic cytology, the issues related to advanced training of cytopathologists in accordance with the current requirements.*

*The transition of the RK health care system to insurance medicine increases the level of mutual responsibility at all levels of diagnostics and the requirements for quality of provided services. A constructive and progressive approach to the development of cytological art in the RK is required.*

**Keywords:** screening for cervical cancer, bedside cytology, remote diagnostics, cytopathology, FNA.

**Introduction.** The demand for minimally invasive medical procedures and organ-preserving treatment methods requires obtaining diagnostic information using a minimal amount of material. Over the past 15 years, the extended capacity of using cytology has to a large extent influenced the quality of medical examination of patients. In large clinics, they prefer to have a cytological laboratory at the site of medical interventions (inside the operating unit, in endoscopic and ultrasound examination rooms, and etc.) as it allows obtaining the result within 3-5 minutes. This method is cost-efficient, absolutely harmless, low invasive; it allows a rapid assessment of relevance of the material for morphological studies and prevents the repeated invasive and expensive examinations. Cytological diagnosis shows the suitability of the sample for histological examination.

It is well-known that diagnostic cytology complies with histological studies of biopsy material by their purpose (life-time diagnostics), methodological basis (morphological analysis), study object (components of pathological areas of organs and tissues), as well as the nucleus, cytoplasm and other cell components staining methods. Cytology

is used when fine-needle aspiration biopsy (FNAB) is dangerous due to a risk of bleeding, in case of suspected melanoma, as well as when a rapid result is required during examination by vital indications and during the periodic screening of the population, and in other cases. Cytology is used in various fields of medicine for identification of both pathological processes and some physiological (hormonal) conditions (for instance, menstrual disorders, pregnancy, etc.). The wider use of cytological method increases the diagnostic efficiency. In the Republic of Kazakhstan, the prospects of cytological methods could be successfully implemented in conditions of insurance medicine. Dynamic monitoring and morphological control of risk groups is virtually impossible using other examination methods. Cytological method allows to diagnose malignant tumors of any localization, at any stage of the process and is repeatable when needed [1]. Endoscope and imaging equipment (FNAB-ENDO-Ultrasound) allow qualified specialists to verify tumors in localizations previously inaccessible without surgery (like bladder cancer, endometrial cancer, and etc.). Morphological examination of the obtained

FNAB sample allows identifying the tumor by its type/attribution, origin and malignancy. The remaining material can be used for a number of molecular and other supporting examinations [2]. The traditional or liquid cytology and cytological blocks can be used depending on the purpose. Molecular genetic testing can significantly improve the diagnostic and prognostic efficiency based on the analysis of cytogenetic and molecular genetic features of the tumor. Thanks to the discovery of the causes of certain tumors, modern clinics actively use molecular genetic methods together with FNAB, and the possibilities for choosing targeted therapy before surgery are growing.

Sequencing methods, fluorescent hybridization in situ (FISH), polymerase chain reaction (PCR) and other methods allow studying the causes for pathology on the basis of genetic mapping of the human genome. The progress in computer technologies has contributed to the development of the new generation of flow cytometers. The cell cycle is analyzed by cell cytometry using computerized image analysis. Major modern achievements – the new technologies used in large scientific centers, “microchips” and “liquid biopsy” – increase the productivity of cell sample analysis using a large number of biological molecular markers. An increased informative value of diagnostic cytology results could change the algorithm of tumor examination and preoperative treatment.

In order to diagnose correctly, clinicians and cytopathologists should work together, in professional collaboration. The clinicians should follow a certain algorithm of actions, should know the approach and requirements for biomaterial referred to cytology, should correctly and in full fill out the referral form indicating the age, gender, the medical record number, the status localis of the pathological focus (or several foci). All this information is very important for a cytologist. In case of sampling from several segments of the same formation or different formations, the referring physicians shall mark the slides and provide relevant information in the referral form. The cytologists should also mark the samples in the cytological examination results and conclusion. The compliance with the rules for collecting, fixing and processing of biomaterial for cytology ensures to make an adequate diagnosis. In addition, it allows to briefly specify the purpose, data of the medical examination with indication of the numbers of all previous studies in referral of finished material for re-evaluation. In order to exclude the diagnostic errors, the cytologist needs to have the information from the patient history. The lack of adequate data can lead to incorrect evaluation of various cell changes (medicative pathomorphosis, etc.) and followed false diagnosis [3].

The interpretation and formulation of cytological changes is a complex and diligent process. It should be considered that there are absolutely no pathognomonic signs inherent only for a malignant tumor, thus, only an experienced cytologist will be able to correctly recognize this distinction within the course of comparing the entire set of signs of the cell changes and critically reviewing their presence and degree of manifestation. Each of the signs when considered separately has no independent and clinical significance. The result depends on the relevance and information value of the obtained sample, compliance with the standards of prepa-

ration in the laboratory, analytical expertise, knowledge and intuition of the cytologist. It also depends on the ability to combine different signs into entire one, conceptually imagine the normal structure of the organ or tissue from which the material has been extracted, knowledge of variability of this tissue in different physiological states and pathologies, for benign and malignant tumors (with account of clinical data, medical history and the drug background, etc.) [4].

The integration of autopsy diagnostics of postoperative material and cytological diagnostics is the unavoidable result of adoption of cytological diagnostics by pathologists. The expansion of the sphere of influence of both sub-specialties (cytological, histological) gradually destroys the barrier that separates them [5].

In clinics where the life-time diagnostics is relevant, the pathologists who work with surgical material understand that utilization of cytological information (smears, squashes (compression), express-cytology (bedside cytology), FNAB-cytology) obtains the valuable information [6] and ensures to reduce the time for preparation of algorithm for composing of additional studies, without waiting of response from histologist on the hematoxylin-eosin staining. The cytological analysis is informative by its findings of intraoperative biopsy, biopsy of liver, lung and brain tumors, etc. The essential material, such as the minimum tissue fragments derived from a pituitary gland, pancreas, etc., often lost at the tip of the paraffin section. If smears obtained prior the thermostatic cooler, it could facilitate in establishing of the definite diagnosis.

The intraoperative cytology is a modern, effective and demandable method, which optimizes the tactics of a surgeon in each specific case.

In large-scale clinics the cytologists have the opportunity to compare different samples, with access to ample archive and some equipment advantages, as well as they have the possibility to work within a multi-disciplinary system approach. Therefore, it is necessary to establish the remote microscopy between the regional cytologists and reference center for collegial discussion and consultation. The modern technology and computer morphometric programs permit to move from subjective, only qualitative methods, to objective and quantitative methods of cytological analysis. The internet potentials and universal digitalization in medicine ensures to inform interested parties (clinicians, regulatory authorities, etc.) and address the issues of the quality control management. The online cytology and digital archivation have a high potential for accurate diagnostics and obtain of second opinion via remote microscopy.

The information about the role, importance, features and principles of cytological diagnostics is not included to the curricula of students and residents of medical institutions, which would be useful for learning of the diagnostic terminology.

Rare and spontaneously organized courses for cytologists do not provide conditions for the development of practical skills, there is no demonstration of methods and protocols at different stages of cytological examination. Such specializations and trainings in the field of cytology cover only the financial interest of organizers. Further development of cytological studies in the Republic of Kazakh-

stan is facilitated by cooperation with various public organizations, including the International Academy of cytologists, Society of Papanicolaou cytopathology, which regularly conduct the cytological congresses. The International cell research organization, European cytopathology organization and other societies establish the working groups to study the individual cytology aspects, organize relevant courses to study the methodologies, provide the information exchange and, in turn, require an active participation of cytologists from Kazakhstan.

Over 40 scientific journals devoted to cytological studies are published globally, a multi-volume manuals and books are issued periodically, as well as publication of a specialized editions, such as: "International cytology review", "Acta Cytology" magazine, "Diagnostic cytopathology" journal and other. The KazIOR management actively supports and initiates the training of cytologists of the Republic of Kazakhstan in order to improve the knowledge level on the tumors diagnostics. In 2017, for the first time in CIS, the International Tutorial on cytological diagnostics of various pathologies was held in Almaty city, where the leading scientists from USA, Japan, Germany, Turkey, France, Portugal delivered the lectures on pathology of various organs (salivary, thyroid and mammary glands, lungs, gastrointestinal tract, uterus, kidney, bladder, etc.).

Majority of physicians-cytologists and laboratory technicians of the Republic of Kazakhstan are the members of professional association of clinical cytologists of Kazakhstan, which has been established in 1993 and included to IAC composition. The team of Kazakhstani cytologists, in the lead of professor Azat I. Shibanova, the honorary president of the Association, made an invaluable contribution to the development of cytological service of the Republic of Kazakhstan. The following physicians-cytologists and laboratory assistants who worked from the beginning of Kazakhstani cytology: Aisarova A.M., Kozbagarova R.G., Turmukhanova T.Zh., Smolyar T.M., Kubasheva N.S., Olshevskaya N.V., Borovitskaya E.I., Utebayeva G.N., Togyzbaeva R.S., Tyumeneva F.Kh., Zharikhina T.A., - in 2013 were elected a honorary members of the Association of cytologists of Kazakhstan. Our veterans-cytologists - are true professionals who continue their work for the benefit of patients, since in cytological diagnostics the performance is directly proportional to presence of advanced, invaluable experience.

The issues of early detection of cervical cancer all over the world are under the close attention of the World Health Organization (WHO). At the initiative of WHO, the year 2019 has been declared to be the year of fight against the cervical cancer [7].

Kazakhstan is the only country among the CIS states where assistance to cancer patients and population screening for cervical cancer are carried out at the government expense. Annually, over 1.5 million women of age range from 30 to 70 years old are subject to screening for cervical cancer in Kazakhstan, every 4 years. Despite the fact that screening for cervical cancer in the Republic of Kazakhstan has been conducted since 2008, the incidence and mortality due to the cervical cancer remains relevant up to date, therefore, improving the quality of cytological screening for cervical cancer is also the matter of concern for cytologists

in Kazakhstan. The experience of screening organizers in the United States of America could serve as important lesson for us. At the end of 1980<sup>th</sup>, the mass public discontent and indignation due to a wrong diagnosis in gynecological practice emerged in the USA. In the course of relevant investigation, the low quality of cover-glass preparations has been revealed, the obtained cells have remained in the instruments led to uninformative smears. Also the repeated examinations have been assigned, thereby the patients missed their work hours, lost income and time. The fact of indignation of the population has been grown up to so-called "Pap-scan-dal", resulting in the reputation damage for clinics and specialists. Subsequently, relevant measures have been taken to address that fact, the quality standards have been developed and the new technologies have been introduced (fluid-based cytology, immunocytochemistry, etc.) [8].

The cytologists of all cancer centers of the Republic of Kazakhstan, working within the screening program for cervical cancer (CC), are facing various problems in performance of microscopy, organization and delivery of samples, finally affecting the quality of screening. Meanwhile the cytologists are trying to solve these challenges on their own, by discussion of emerging issues with each other via mobile telecommunication, however, these attempts not always meet their expectations. All hopes of enthusiasts-cytologists postponed until the better time.

Due to the lack of appropriate regulatory document for the cytological service activity, the rates of cytologists in staffing list in many places do not correspond to the work load. Overall, young doctors avoid this specialty due to a low wages, high workload, low prestige and fee-paying education. In certain regions (WKO, Taraz, Atyrau, etc.) the shortage of cytological personnel is observed, the majority of experienced cytologists are people of retirement age, there is no continuity. A high work load and tight work schedule can lead to serious errors due to a lack of time for analysis and assessment of own performance, as well as for correction of errors. With such a load, the quality is left behind, and sensitivity in detection of early signs of a tumor development is lost. If the initial cell changes are missed during microscopy at the stage of previous screening, then after 4 years the process might have already a malignant pattern. According to WHO recommendation, the results of screening tests for cervical cancer should be evaluated only by the Bethesda system criteria. The proper analysis is possible to conduct only by performance of the Papanicolaou staining. The formulation of cytological conclusion requires an evaluation of cell changes according to the Bethesda system. When the cytologist works under pressure of continued time shortage, there is a high risk of the attention loss, therefore it is required to reduce the screening burden to 20,000 examinations per year. The diagnostic cytology load should be established in the amount of 3,000 examinations per year, taking into account that all materials obtained by FNAB and rapid cytology belong to a high category of complexity. In order to address the challenging cases, the cytologists need to review the special literature, articles and discuss relevant issues with their colleagues. Taking into consideration that in many centers one cytologist is assigned to perform the duties on screening and diagnostic cytology, it is not sur-

prising that during cytological examinations the cancer is mainly detected in advanced stages.

The decent compensation of performance is one of the important motivation factors for healthcare workers. Yet, the basic price for the cytology screening remains scanty and there is no differentiated wage scale for cytologists. The constant search for an additional income source and drudgery - result in elevated risk of emotional burnout of cytologists.

**Conclusion.** The Republic of Kazakhstan is the only country of the Commonwealth of Independent States where the care to cancer patients is provided at the state expense and mass screening for cervical cancer is carried out within the frames of the state program. Upon condition of exclusion of the negative factors and on the assumption of compliance with the quality standards requirements, the positive effect in diagnostics and early detection of cancer in the Republic of Kazakhstan will become apparent. The raising of effectiveness of cytological studies will improve the diagnostics of tumor diseases at preoperative stage. Besides, the clinicians will have more opportunities to select the treatment tactics before surgery, the prediction and monitoring will be improved. The cytologists of Kazakhstan have an optimistic attitude and look forward to commencing work on elimina-

tion of risk factors and positive solution in addressing the issues within on-going activities.

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