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## Contents

### ORGANIZATION OF PUBLIC HEALTHCARE

D. Kaidarova, A. Zhylkaidarova, A. Jumanov, O. Shatkovskaya, B. Mukhametbek. Colorectal screening in Kazakhstan: analysis of accessibility, problems, and prospects for further improvement............................................................... 3

ZH.B. Yeleubayeva. The risk factors and error factors in cytological service of the republic of Kazakhstan......................... 8

A. Shinbolatova, A. Abdrahkhananova. Role of the Center for postgraduate education in training staff for the cancer service of the Republic of Kazakhstan ......................................................... 12

### DIAGNOSTICS


### CLINICAL CASE


### TREATMENT


### LITERATURE REVIEW


Colorectal screening in Kazakhstan: analysis of accessibility, problems, and prospects for further improvement

Abstract. This article offers an analysis of the screening program for colorectal cancer (CRC) conducted in the Republic of Kazakhstan. According to the authors' assessment, the staffing level is 100%, the availability of the relevant equipment is 65%. The accessibility of the first stage of screening for the population is high as confirmed by the coverage of both urban and rural population. However, the rural population of Aktobe, Almaty, Karaganda, Kostanay, and Mangystau Regions undergo colonoscopy less often than the urban population. The proportion of CRC detected by screening among the total number of cancer cases in a population of target age has increased from 29.8% in 2011 to 52.2% in 2014. It is a good indicator given only 23.6% of CRC cases detected at an early stage in 2018 and the decrease in the number of cases diagnosed at stage IV of the process from 15.1% in 2011 to 1.6% in 2018. However, the observed decline in mortality is only from 9.6‰ in 2013 to 8.4‰ in 2017. The article focuses on the problems faced at different stages of screening and the prospects for the further improvement of the screening program.

Keywords: colorectal cancer, screening, hemoccult test, colonoscopy.

Relevance. According to Globocan data (2018), the incidence of colorectal cancer (CRC) in Kazakhstan is lower than in all other OECD countries (15.4‰) except Mexico (11.2‰). The highest CRC incidence in the OECD countries is noted in Hungary (51.2‰); the incidence is also high in South Korea, Slovakia, Norway, Slovenia, Denmark, and Portugal where it reaches 40-44.5‰ [1].

In Kazakhstan, the CRC incidence is steadily increasing (from 15.2‰ in 2006 to 16.5‰ in 2012 and 17.5‰ in 2017). Since 2013, CRC ranking in the incidence of cancer has changed from 4th to 3rd in both sexes [2].

Taking into account the situation in the Republic and worldwide, in 2011 Kazakhstan has introduced a screening program for early detection of pre-tumor and tumor colon pathologies.

Purpose of the study is to analyze the CRC screening coverage in Kazakhstan, challenges in the implementation of the screening program, and to determine prospects of its further improvement.

Materials and methods. The research targeted the statistical data of patients covered by screening for early detection of pre-tumor and malignant colon neoplasms in 2011-2018. The data was obtained from the reporting forms provided by Medinform LLP based on the data from the Outpatient Automated Information System. Population information was obtained from the Covered Population Register (CPR) of the Republican Electronic Health Center.

In 2011-2017, the CRC screening covered men and women at the age of 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, and 70 years; since 2018, it covers men and women aged 50 to 70 years.

Occult blood in feces (FOB) test is the basis of screening. Since 2013, the screening includes an immunochemical (immunofluorescent) hemoculture analysis. Also, since 2013 the in-depth diagnostics stage includes total colonoscopy.

Since 2011, the cancer cases detected during screening are synchronized with the data from the Cancer Patients' Electronic Register (CPER).

Stages of the screening:
1) Preparatory stage includes making a list of the target group, invitation, program assistance.
2) Administration of hemoccult test.
3) Colonoscopy.

In case of a positive hemoccult test, the patient is sent for the examination of the entire colon section (total colonoscopy). The district nurse invites/visits the patient, clarifies the importance and necessity of further endoscopic examination, refers the patient to the endoscopy department, recommends medicines to clean the intestines, and instructs on the preparation of intestines for examination. Colonoscopy is conducted in the endoscopy departments of the city, district outpatient clinics, consulting and diagnostic centers/diagnostic departments.

Results. Availability of resources and personnel. Hemoccult test is procured centrally and by all primary health care organizations at all levels, including rural health posts.

The following equipment is available at this stage: 115 colonoscopes, of them, 75 are video colonoscopes (65%); only 79 (68.7%) are equipped with a set of surgical instruments for neoplasm biopsy, submucosal resections, pol-
ypectomy of small polyps. Not all endoscopic cabinets have automatic devices for processing endoscopes, more often 1 device accounts for a gastroscope and a colonoscope.

There are 123 endoscopists for 81.5 spaces. According to the current issue of the Order of the Minister of Health-care of the Republic of Kazakhstan of April 7, 2010 No. 238 “On approval of typical staffing and staffing standards of healthcare organizations”, 1 examination shall take 100 minutes what means 1,000 examinations per year. Based on the number of screening colonoscopies in the country (10-12,000), the staffing level of endoscopists is 100%.

Accessibility for the public is high including rural population. No specialists or special tools except test materials are required to perform the tests. The screening accessibility for rural population is also confirmed by the CRC screening results for 2016-2017 (see Tables 1 and 2).

### Table 1 – Coverage of urban and rural population by CRC screening, 2017-2018

<table>
<thead>
<tr>
<th>Regions</th>
<th>Examined in 2017</th>
<th>Examined in 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urban population</td>
<td>Rural population</td>
</tr>
<tr>
<td></td>
<td>Abs. No.</td>
<td>% of plan</td>
</tr>
<tr>
<td>Akmola Region</td>
<td>11 716</td>
<td>52.5*</td>
</tr>
<tr>
<td>Aktobe Region</td>
<td>25 257</td>
<td>87.4</td>
</tr>
<tr>
<td>Almaty Region</td>
<td>23 674</td>
<td>87.1</td>
</tr>
<tr>
<td>Atyrau Region</td>
<td>12 550</td>
<td>102.9</td>
</tr>
<tr>
<td>West Kazakhstan Region</td>
<td>17 937</td>
<td>109.6</td>
</tr>
<tr>
<td>Zhambyl Region</td>
<td>22 256</td>
<td>97.8</td>
</tr>
<tr>
<td>Karaganda Region</td>
<td>62 084</td>
<td>99.6</td>
</tr>
<tr>
<td>Qostanay Region</td>
<td>29 650</td>
<td>97.2</td>
</tr>
<tr>
<td>Qyzylorda Region</td>
<td>12 327</td>
<td>92.8</td>
</tr>
<tr>
<td>Mangystau Region</td>
<td>12 167</td>
<td>91.8</td>
</tr>
<tr>
<td>South Kazakhstan Region</td>
<td>48 479</td>
<td>92.5</td>
</tr>
<tr>
<td>Pavlodar Region</td>
<td>31 885</td>
<td>92.9</td>
</tr>
<tr>
<td>North Kazakhstan Region</td>
<td>12 704</td>
<td>107.8</td>
</tr>
<tr>
<td>East Kazakhstan Region</td>
<td>43 223</td>
<td>95.1</td>
</tr>
<tr>
<td>The city of Astana</td>
<td>34 888</td>
<td>100.1</td>
</tr>
<tr>
<td>The city of Almaty</td>
<td>78 180</td>
<td>100.5</td>
</tr>
<tr>
<td>The Republic of Kazakhstan</td>
<td>478977</td>
<td>94.7</td>
</tr>
</tbody>
</table>

* Underperformed due to the late delivery of hemoccult tests

### Table 2 – Coverage of urban and rural population by colonoscopy as part of CRC screening, 2017-2018, % of positive hemoccult tests

<table>
<thead>
<tr>
<th>Regions</th>
<th>Examined in 2017</th>
<th>Examined in 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urban population</td>
<td>Rural population</td>
</tr>
<tr>
<td></td>
<td>Abs. No.</td>
<td>% of conducted colonoscopies</td>
</tr>
<tr>
<td>Akmola Region</td>
<td>247</td>
<td>70.0</td>
</tr>
<tr>
<td>Aktobe Region</td>
<td>311</td>
<td>92.3</td>
</tr>
<tr>
<td>Almaty Region</td>
<td>292</td>
<td>75.0</td>
</tr>
<tr>
<td>Atyrau Region</td>
<td>117</td>
<td>67.5</td>
</tr>
<tr>
<td>West Kazakhstan Region</td>
<td>207</td>
<td>94.7</td>
</tr>
<tr>
<td>Zhambyl Region</td>
<td>210</td>
<td>88.1</td>
</tr>
<tr>
<td>Karaganda Region</td>
<td>959</td>
<td>92.8</td>
</tr>
<tr>
<td>Qostanay Region</td>
<td>538</td>
<td>75.7</td>
</tr>
<tr>
<td>Qyzylorda Region</td>
<td>166</td>
<td>57.8</td>
</tr>
<tr>
<td>Mangystau Region</td>
<td>133</td>
<td>90.2</td>
</tr>
<tr>
<td>South Kazakhstan Region</td>
<td>482</td>
<td>74.7</td>
</tr>
<tr>
<td>Pavlodar Region</td>
<td>511</td>
<td>71.6</td>
</tr>
<tr>
<td>North Kazakhstan Region</td>
<td>395</td>
<td>67.3</td>
</tr>
<tr>
<td>East Kazakhstan Region</td>
<td>533</td>
<td>66.0</td>
</tr>
<tr>
<td>The city of Astana</td>
<td>833</td>
<td>54.4</td>
</tr>
<tr>
<td>The city of Almaty</td>
<td>949</td>
<td>92.2</td>
</tr>
<tr>
<td>The Republic of Kazakhstan</td>
<td>6 883</td>
<td>77.3</td>
</tr>
</tbody>
</table>

It should be noted that not all rural population has access to endoscopic examination. Thus, the access to colonoscopy is limited for the rural population of Aktobe, Almaty, Karaganda, Qostanay, and Mangystau Regions (Table 2). Low coverage of rural population with colonoscopy may be due to a low awareness of the population about the necessity to pass endoscopic examination in case of positive hemoccult test results, or the nursing staff...
may not be sufficiently conclusive regarding the need to pass further examinations. The opposite situation is noted in Atyrau, Zhambyl and North Kazakhstan Regions, where the number of colonoscopies performed is higher among the rural population than among the urban population.

The results of screening.

The screening has covered 790,000 people in 2015 vs. 1,174,000 people in 2012. In total, 7,291,950 men and women have been examined from 2011 till 2018.

The annual screening coverage was about 800,000 to 1,000,000 people. It corresponded to 50-65% coverage in 2 years of the target group aged 50 to 70 years (Table 1). Since 2015, the examination plan was reduced due to the reduction in financing. In 2018, 860,612 people were examined because the target group was increased to include the entire population aged 50 to 70 years.

### Table 3 – Coverage and efficiency of CRC screening

<table>
<thead>
<tr>
<th>Years</th>
<th>No. of examined men and women</th>
<th>% of the total no. of men and women 50-70 y.o. acc. to CPR</th>
<th>No. of cancer cases detected by screening</th>
<th>Total no. of detected cancer cases acc. to CPR</th>
<th>Share of cancer cases detected by screening in the total no. of cases detected at target age</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>982,919**</td>
<td>32.8*</td>
<td>199</td>
<td>0.02</td>
<td>2,563</td>
</tr>
<tr>
<td>2012</td>
<td>1,174,155</td>
<td>39.2*</td>
<td>228</td>
<td>0.02</td>
<td>2,766</td>
</tr>
<tr>
<td>2013</td>
<td>896,278</td>
<td>29.9*</td>
<td>366</td>
<td>0.04</td>
<td>2,948</td>
</tr>
<tr>
<td>2014</td>
<td>970,056</td>
<td>32.4*</td>
<td>514</td>
<td>0.05</td>
<td>3,086</td>
</tr>
<tr>
<td>2015</td>
<td>791,904</td>
<td>24.6</td>
<td>467</td>
<td>0.06</td>
<td>3,148</td>
</tr>
<tr>
<td>2016</td>
<td>796,781</td>
<td>24.8</td>
<td>475</td>
<td>0.06</td>
<td>3,158</td>
</tr>
<tr>
<td>2017</td>
<td>819,245</td>
<td>24.0</td>
<td>349</td>
<td>0.04</td>
<td>3,131</td>
</tr>
<tr>
<td>2018</td>
<td>860,612</td>
<td>25.2</td>
<td>309</td>
<td>0.04</td>
<td>3,210</td>
</tr>
<tr>
<td>Bcero</td>
<td>7,291,950</td>
<td>2,907</td>
<td>0.04</td>
<td>24,010</td>
<td>8,380</td>
</tr>
</tbody>
</table>

* Calculation based on the CPR data for 2014

An important screening indicator is the patients’ participation in colonoscopy in case of positive hemoccult test results. This indicator was increasing annually, from 59.3% in 2013 to 74% in 2016-2017 and 76% in 2018. According to European recommendations, an acceptable level of colonoscopy is 90%.

The level of precancer detected during colonoscopy has increased from 11.5% in 2013 (when the endoscopic evaluation system was optimized to identify polyps) to 14.4% in 2015 and 20.3% in 2017. The level of adenoma detection was 17.8% in 2018 (international recommendations are 25% and more). This indicator is included in the quality indicators of screening programs in the implementation of the Comprehensive Plan and shall be increased up to 23% by 2022.

CRC detection was increasing annually till 2017, from 199 cases in 2011 and 228 cases in 2012 to 514 cases in 2014. In 2017-2018, it amounted to 0.04% of the screened population.

The share of CRC cases detected by screening in the total number of cancer cases in the target age population has increased from 29.8% in 2011 to 52.2% in 2014, i.e. every third case of cancer at target age was detected by screening.

The highest share of CRC detection by screening in 2011-2018 was noted in West Kazakhstan, Qostanay, Pavlodar, and North Kazakhstan Regions (an average annual detection rate of 0.06% and higher); the detection in the South Kazakhstan Region and the city of Almaty was low.

The share of Stage I CRC detected was 18.1% (Table 4). That indicator was growing in the first 4 years of screening; since 2014, it varies from 19 to 23%. In 2018, the early detection of CRC was 23.6%. There is a pronounced positive downward trend of the number of cases diagnosed at Stage IV of the process, from 15.1% in 2011 to 1.6% in 2018.

### Table 4 – The structure of CRC cases detected by screening

<table>
<thead>
<tr>
<th>Years</th>
<th>Detected CRC cases, Abs.</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>199</td>
<td>14</td>
<td>128</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>2012</td>
<td>228</td>
<td>14</td>
<td>117</td>
<td>65</td>
<td>32</td>
</tr>
<tr>
<td>2013</td>
<td>366</td>
<td>45</td>
<td>227</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>2014</td>
<td>514</td>
<td>118</td>
<td>299</td>
<td>71</td>
<td>26</td>
</tr>
<tr>
<td>2015</td>
<td>467</td>
<td>95</td>
<td>292</td>
<td>63</td>
<td>17</td>
</tr>
<tr>
<td>2016</td>
<td>475</td>
<td>101</td>
<td>298</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>2017</td>
<td>349</td>
<td>67</td>
<td>215</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>2018</td>
<td>309</td>
<td>73</td>
<td>200</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>2,907</td>
<td>527</td>
<td>1,776</td>
<td>447</td>
<td>157</td>
</tr>
</tbody>
</table>

In the structure of CRC cases detected in all age groups, the share of Stage I-II cases was 40.9% in 2008. It increased up to 49.2% after the introduction of screening in 2011, and up to 61.5% in 2017. It indicates a marked increase in the share of localized forms of the disease (Figure 1).
A high level of early Stage I CRC detection in 2011-2018 was noted in West Kazakhstan, Karaganda, Mangystau, South Kazakhstan, and North Kazakhstan Regions. A low level of Stage I CRC detection was noted in Aktobe, Atyrau, Zhambyl, and Qyzylorda Regions.

Over the years of screening in Kazakhstan, there is a positive trend of increasing CRC incidence (as a compensating result of the early detection program implementation) and decreasing CRC mortality. Figure 2 shows the dynamics of CRC incidence and mortality in Kazakhstan in 2008-2017. The CRC incidence has increased from 14.6‰ in 2008 to 17.9‰ in 2014, and decreased to 16.9‰ by 2017. The mortality curve has a pronounced downward trend, from 9.6‰ in 2013 to 8.4‰ in 2017.

**Discussion and Conclusions.** The analysis of the screening program implementation stages and results has revealed a number of challenges.

The quality of sampling:

a) A low level of positive hemoccult tests may be due to improper instructions on using the hemoccult test given by the nurse.

b) A lack of objective assessment of hemoccult testing process.

c) A delay in the hemoccult tests’ delivery: in case of centralized procurement – in April or later.

The stage of colonoscopy:

a) Refusal of the patients to pass the examination (25-30%).

b) Only 35% of patients receive sedation during colonoscopy (according to allocated funding).

c) The volume of total colonoscopy is not controlled.

d) Micro-invasive manipulations are not always performed since the endoscopy rooms are underequipped with surgical instruments (68.7%).

e) Low level of precancer detection (13% during colonoscopy in 2017, at the internationally recommended levels of 23% or higher).

f) The current rates cover only a half of organizational expenses on purchasing medicines to clear the intestines (due to the devaluation of Tenge).

CRC screening can be modified by using automated quantitative hemoccult test. Its introduction will allow to:

- increase the detectability of inflammatory diseases, precancerous conditions and early stages of CRC followed by confirmation by colonoscopy;

- reduce the number of false positive results in order to reduce the number of unreasonably prescribed colonoscopies (using only the hemoglobin test, without transferrin) by 30%;

- form risk groups for CRC development and perform efficient monitoring;

- timely carry out adequate therapeutic actions;

- ensure the study objectiveness by eliminating the human factor;

- connect to information systems.

Despite the significant advantages of using automated quantitative hemoccult test, its high cost remains its main disadvantage.
The following recommendations have been developed taking into account the urgency of the problem, the experience gained by Kazakhstani specialists and the available resources:

1) to raise awareness, improve communication skills of the medical personnel needed to motivate the population to pass screening and colonoscopy;

2) to revise the methodological approaches to the screening strategy by introducing a validated automated hemoccult test with the quantitative determination of hemoglobin in feces;

3) to increase liability of the specialists of the relevant PHC organizations for the final results of screening, to strengthen the interaction between the stages of screening: PHC-screening -> a general practitioner -> an endoscopy room, i.e., to harmonize direct communications and feedback in the system of treating the patients with identified pre-tumor pathology;

4) to increase the level of training of endoscopists in conducting total diagnostic colonoscopy as well as minimally invasive endoscopic surgical interventions;

5) to develop and introduce the information system of screening that will allow monitoring the examinations and improving their quality component.

In the future, an analysis of medical and economic efficiency is needed for an economic assessment of conducted screening and identifying the most efficient and cost-effective approach to the further implementation of the screening program.

References:


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 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.
FNAB sample allows identifying the tumor by its type/attribute, 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 preparation 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 or 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-volumemanuals and books are issued periodically, as well as publication of a specialized edition, 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., Turgalikhanova T.Zh., Smolyar T.M., Kubasheva N.S., Olshhevskaya N.V., Borovitskaya E.I., Utebayeva G.N., Togyzbaeva R.S., Tyumeneva F.Kh., Zharikhina T.A., - in 2013 were elected a member of the Association of cytologists of Kazakhstan. Our veterans-cytologists - are true professionals and honorary members of the Association of cytologists of Kazakhstan. Tyumeneva F.Kh., Zharikhina T.A., - in 2013 were elected a member of the Association of cytologists of Kazakhstan. Those who continue their work for the benefit of patients, since in cytological diagnostics the performance is directly proportional to the 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 1980th, 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 elimination of risk factors and positive solution in addressing the issues within on-going activities.

**References:**
7. WHO press release № 264 www.cancer.org World Cancer Day 04.02;
Role of the Center for postgraduate education in training staff for the cancer service of the Republic of Kazakhstan

Relevance: Kazakh Institute of Oncology and Radiology (KazIOR) provides long- and short-term programs of postgraduate education which is one of the key directions of cancer care in the Republic of Kazakhstan in the light of reaching the main strategic targets of this sphere and implementation of the Comprehensive plan of combating cancer diseases.

Purpose: The article represents the main directions of postgraduate education that includes residency programs, as well as retraining and advanced training programs, international master classes and training of cancer service specialists abroad.

Results: KazIOR successfully implements the principle of the triunity of practice, education, and science. In 2016, the Institute and its programs were accredited in three specialties (Oncology, Radiology and Radiation therapy). The accreditation had a positive impact on the improvement of educational activities and the conditions provided for the staff and the students. In 2015-2018, the Institute has successfully performed the Republican Budget Programs. 91 students have completed the residency program; 103 resident students are studying now. 13 master classes with the involvement of foreign experts have attracted 325 listeners. 689 cancer service specialists from all regions of the country have received advanced training and retraining in the frames of the Republican Budgetary Program 005. Also, we attracted sponsors to conduct master classes in the most popular areas that have been attended by 3,653 listeners. 476 specialists have completed training at KazIOR on a paid basis. 2167 physicians, nurses, psychologists and social workers of primary health care organizations were trained in cancer awareness and early detection of cancer.

Conclusion: highly qualified personnel, the triunity of practice, education, and science, partner relations with leading scientific and clinical centers, the availability of appropriate infrastructure and modern technologies for providing highly specialized care are fundamental factors for the success of postgraduate education provided by KazIOR.

Keywords: postgraduate education; triunity of practice, education, and science; cancer care.

The Center for Postgraduate Education on the basis of the Kazakh Institute of Oncology and Radiology (KazIOR) offers educational activities and implements the following functions:

– Recruitment of residents, preparation of residency plan, individual plans, academic calendar, the formation of study groups, distribution by clinical sites, the appointment of curators and clinical mentors, supervision of current and boundary control, intermediate and final attestation;
– Planning and organization of the offsite practice of residents in regional cancer centers and primary health care institutions;
– Planning, organization, and implementation of advanced training and retraining of specialists of the Republican cancer service at the expense of the Republican budget and extra-budgetary funds;
– Planning, organization, and formation of teams of practitioners offering advanced training in the regions on cancer alertness and early detection of cancers;
– Planning, selection, and participation of employees in domestic and international conferences;
– Planning and organization of master classes with the participation of international experts, training of cancer service specialists at the leading clinical and educational centers of the world.

KazIOR leads the cancer service in the Republic of Kazakhstan. The Institute was established by the Order of the Ministry of Healthcare No. 1-15-33 dated July 5, 1960 (based on the resolution of the Council of Ministers of the Kazakh Soviet Socialist Republic No. 962 dated September 24, 1959). During its long history, the Institute has become the leading oncology and radiology scientific, treatment, and organizational and methodological center of the Republic.

The Institute is licensed for providing postgraduate education in 3 specialties: oncology, radiation diagnostics, and radiation therapy.

KazIOR is successfully implementing the principle of the triunity of practice, education, and science by efforts of 16 Doctors of Sciences, 35 Candidates of Sciences, as well as teachers with Ph.D. and Master Degrees.

In accordance with the Law of the Republic of Kazakhstan “On Education”, the institute was accredited in three specialties of postgraduate education on the basis of the state educational order: Oncology, Radiology, and Radiotherapy.

On the basis of the Agreement No. 47-jur dated February 12, 2016 (No. 175-16-I updated on 01.04.2016) between the Republican State Enterprise on the Right of Economic Jurisdiction “Kazakhstan Institute of Oncology and Radiology” and the non-profit institution “Kazakhstan Independent Agency for Quality Assurance in Education (IQAA)”, a workshop on the accreditation procedure training of heads of departments, faculty members and residents was conducted on February 19, 2016. The self-assessment stage was conducted in accordance with the Order of KazIOR dated February 23, 2016.
The provided health care covers all types of cancers and allows trainees to master practical and theoretical material on the basis of clinical and diagnostic centers. In addition to clinical centers for thoracic, abdominal, neuro-oncology and gynecology, the institute provides care to patients with various forms of malignant neoplasms in its departments which are exclusive in the country, such as the departments for head and neck tumors, bone and soft tissue tumors, oncology, and pediatric oncology. Each year, KazIOR performs more than 1,500 surgical interventions, many of which are organ- preserved and reconstruction-plastic; it is the only institute in the Republic that offers conformal radiation therapy. KazIOR widely utilizes modern principles of drug therapy for malignant tumors, including high-dose chemotherapy. Its clinic possesses the most advanced equipment for full and profound diagnostics and management of tumor processes. Modern laboratories of the institute offer all types of laboratory analysis, from general tests to molecular genetics. Telemedical network allows providing remote consultations and conducting clinical discussions with all regions of the Republic.

Accreditation had a positive impact on the organization of the educational process at KazIOR.

First, the educational and methodological complex was brought in line with international standards and the requirements of the Ministry of Education and Science.

Table 1 – Distribution of residents by specialties, the academic year 2018-2019

<table>
<thead>
<tr>
<th>Specialty</th>
<th>No.</th>
<th>1st year of study</th>
<th>2nd year of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>56</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>Radiology</td>
<td>32</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>15</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>103</td>
<td>49</td>
<td>54</td>
</tr>
</tbody>
</table>

In 2018, 74 residents of three specialties have successfully passed the Republican independent testing and final certification. They gained the diplomas and were employed by regional cancer centers and primary health care institutions of the Republic. KazIOR residents lead the rating of the Ministry of Healthcare in their results of Republican testing. The continued collaboration with regional health departments and regional oncology dispensaries is aimed at the formation of targeted areas for KazIOR residency.

The Strategic Plan and Comprehensive Plan of the Institute include ways to improve educational activities for the next 5 years in order to strengthen the human capacity of cancer service specialists.

Training of residents and advanced training of healthcare providers on the basis of domestic and foreign educational institutions, as well as conducting of master classes with the involvement of foreign experts on the most pressing challenges of the sector continue in the framework of the Comprehensive Plan 2018–2022.

Faculty members and staff of the postgraduate education department will continue their advanced training on educational issues and the application of new principles in teaching (PBL, CBL, RBL, TBL-training based on scientific second, a team of experienced and highly professional teachers with practical experience has been formed.

Third, faculty members have an opportunity to receive advanced training at the leading scientific and educational centers in far abroad and neighboring countries to the best advantage of the educational process and the level of knowledge of the residents. Thus, since September 2015, the teachers have participated in educational programs and made oral and poster reports at conferences held in England, Austria, Russia, Thailand, Korea, USA, France, and Japan.

The training infrastructure has been significantly improved. The new computer center offers high-speed Internet access and training rooms with appropriate technological infrastructure; the training rooms and rooms for residents have been refurnished.

The possibility of establishing differentiated payrolls and bonuses for the staff involved in the organization and conduct of education is quite important.

The residents are involved in the work of the “Journal Club” whose activities are displayed on the Institute website and in social networks. They also take an active part in the specialized councils of the institute (surgical, radiological, therapeutic, and the board of young scientists).

The whole educational complex is presented at the official website of the institute.

Currently, 103 residents undergo training at KazIOR (Table 1).

Under the Republican Budget Program 005, 698 specialists have completed advanced training in 2015-2018 on the following priority issues of cancer service: Early diagnostics and treatment of gynecologic malignancies; Selected problems of radiation therapy of patients with malignancies; Psychosocial assistance to cancer patients; Surgical treatment of lung, esophagus and stomach tumors; Oncogynecology, mammology and etc. (Table 2).

62 students have been trained abroad on the following topical issues of the cancer service: The use of high-tech radiation therapy in pediatric oncology; Cancer surgery; Minimally invasive surgical treatment of esophageal cancer and stomach cancer; Laparoscopic surgery of urinary tract organs; Bone marrow transplantation; High-dose chemotherapy and transplantation of hematopoietic stem cells; Modern methods of lymphomas treatment and diagnosis; Psychotherapy in complex rehabilitation of cancer patients; Resuscitation and intensive therapy in hematology, and etc.
KazIOR will continue to develop training programs and guidelines on the topical issues of cancer service with the purpose to improve the professional level in oncology of physicians and nurses of the primary health care system. Such issues include: Principles of prevention, diagnostics and treatment of breast cancer; Principles of prevention, diagnostics, treatment and rehabilitation of colorectal cancer; Principles of prevention, diagnosis, treatment and rehabilitation of lung cancer; Principles of prevention, diagnosis, treatment and rehabilitation of gastric cancer; Epidemiology of malignant tumors; Palliative oncology; Ultrasound diagnostics in oncology (for oncologists and ultrasound diagnostics physicians); Computer imaging and MRI in oncology (for oncologists and radiation diagnostics physicians).

Conferences and seminars on the prevention and early detection of malignant neoplasm in the form of webinars and other forms of distant learning, master classes, practical training for employees of examination rooms and primary oncological offices, as well as rural health posts, are regularly held to improve cancer alertness of primary care physicians.

KazIOR continues training general practitioners in the field organizing trips, thematic master-classes, training workshops, international conferences to exchange experience and introduce modern technologies in oncology (the training schedule for 2019 is presented at KazIOR website and available at the regional cancer centers).

Training, retraining and advanced training of radiation therapists and medical physicists and engineers are provided in the framework of the radiological service human resources development. Postgraduate training will be provided at the place of work in cancer centers.

The practitioners, faculty members and staff of the postgraduate education center are regularly updated on topical issues of cancer service, as well as methodologies and new principles of teaching applied at leading cancer and educational centers in CIS and abroad.

To bring the staffing of the cancer service in line with the standards, the healthcare departments of the regions and cities of Almaty and Astana shall promptly send specialists for retraining (including short-term) and take an active part in the distribution of university graduates and job fairs.

Faculty members and staff of KazIOR Department of Postgraduate Education will take part in international conferences with oral and poster reports in order to present the scientific and practical achievements in the educational process, raise their professional level and discuss future activities with specialists from leading centers of the world.

The residents will be further involved in scientific programs and present their oral and poster reports at the international and domestic conferences.

KazIOR is an active member of a number of international organizations. This enables teachers to keep abreast of current trends in prevention, early detection, and treatment and use this information in their educational activities which has a positive impact on the quality of teaching.

Tutors and clinical mentors from among KazIOR faculty members are the heads and doctors of clinical diagnostic centers. That is, they are directly involved in the treatment process, have direct access to medical and diagnostic procedures and are responsible for the final result.

In addition, the appropriate infrastructure, modern technologies for the provision of highly specialized assistance establish KazIOR as the leader of postgraduate education.

**Conclusion:** highly qualified personnel, the triunity of practice, education, and science, partner relations with leading scientific and clinical centers, the availability of appropriate infrastructure and modern technologies for providing highly specialized care are fundamental factors for the success of postgraduate education provided by KazIOR.

**Table 2 – Retraining and advanced training cycles**

<table>
<thead>
<tr>
<th>Programs</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residency</td>
<td>15</td>
<td>76</td>
<td>54</td>
<td>49</td>
<td>194</td>
</tr>
<tr>
<td>Master classes under the Republican Budget Program 005</td>
<td>50</td>
<td>50</td>
<td>125</td>
<td>100</td>
<td>325</td>
</tr>
<tr>
<td>Advanced training and retraining under the Republican Budget Program 005</td>
<td>171</td>
<td>71</td>
<td>98</td>
<td>358</td>
<td>698</td>
</tr>
<tr>
<td>Training abroad under the Republican Budget Program 005</td>
<td>27</td>
<td>9</td>
<td>26</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>Training at KazIOR</td>
<td>143</td>
<td>113</td>
<td>130</td>
<td>90</td>
<td>476</td>
</tr>
<tr>
<td>Sponsored master classes</td>
<td>615</td>
<td>838</td>
<td>833</td>
<td>1367</td>
<td>3653</td>
</tr>
<tr>
<td>Training on cancer alertness of the specialists of the primary health care system (offsite cycles – 1 week)</td>
<td>833</td>
<td>401</td>
<td>451</td>
<td>482</td>
<td>2167</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1839</td>
<td>1482</td>
<td>1663</td>
<td>2397</td>
<td>7381</td>
</tr>
</tbody>
</table>
Role of the Center for postgraduate education in training staff for the cancer service of the Republic of Kazakhstan

Relevance. Worldwide, lung cancer is the most common cancer and the main cause of death in the structure of oncopathologies. In the Republic of Kazakhstan, lung cancer is also the most common form of malignant neoplasms. It ranks second in incidence and first in the structure of mortality from oncopathologies.

Purpose of the study was to evaluate the possibilities provided by low-dose computed tomography (CT) in early diagnostics of lung cancer.

Results. This paper presents the results of low-dose CT examination of 908 patients conducted at the East Kazakhstan Regional Cancer Dispensary.

Conclusion. The obtained results prove a high informative value of low-dose CT examination in early diagnostics of lung cancer.

Keywords: lung cancer, low-dose computed tomography.

Relevance. According to GLOBOCAN 2018 global statistics, lung cancer is the most common cancer (11.6% of the total number of cases) in both sexes and the main cause of death in the structure of cancer pathology (18.4% of the total number of deaths from cancer). In 2018, 2.1 million new cases of lung cancer and 1.8 million fatal cases were reported [1].

In the Republic of Kazakhstan, lung cancer is also the most common form of malignancy; it ranks second in incidence and first in the structure of mortality from oncopathologies over the past twenty years. High incidence and mortality from lung cancer compared with the national average is observed in the East Kazakhstan region (35.6% and 25.5%, respectively) [2].

Clinical manifestations in lung cancer indicate the prevalence of the tumor process. The use of highly informative methods of examination is very important for early diagnostics of lung cancer in risk groups during the asymptomatic course of the disease [3].

According to the published results of two large randomized studies of lung cancer screening using low-dose computed tomography (LDCT) examination, the use of LDCT reduces the lung cancer mortality by 26% in the high-risk group [4,5]. However, despite this, not all countries who conduct screening have achieved such high rates [6]. According to some researchers, early diagnostics of lung cancer using LDCT requires major improvements both in the organization of the screening process and in the formation of risk groups [7].

Materials and methods. 908 residents of East Kazakhstan region (women – 56.6%, men – 43.4%; aged 18 to 89 years, average age – 54.7±12.6) underwent LDCT-examination of lungs using Revolution 128 (GE) computer tomograph with 1.25 mm slice thickness at 120kVp and 10mAs. The effective dose per patient did not exceed 1 μSv.

The results were interpreted by the physicians of the Kazakh Institute of Oncology and Radiology, Radiodiagnostics Department.

All examined subjects were questioned to define possible risk factors.

The findings were assessed in accordance with LUNG-RADS classification.

Findings and discussion. 30.2% of examined subjects had changes in the lungs according to LDCT results: pulmonary nodules of various shapes and sizes – 14.8%, 4.7% of them were suspicious of malignancy; multifocal lung lesion specific for a metastatic lesion – 0.4%; typical benign lesions – 0.6%; meta-tuberculosis changes – 4.6%; chronic bronchopulmonary diseases – 9.8%.

91 (10.1%) patients were recommended to undergo a follow-up dynamic CT after 3 to 12 months.

The analysis of questionnaires has shown harmful labor conditions in 25.8% of cases. Smokers accounted for 35.5% (of them, 86.3% men and 13.7% women); they had an average smoking history of 31.2 years and smoked an average of 0.86 packs of cigarettes per day.

Smokers accounted for 65.1% in the group of patients with detected lesions suspicious of malignancy.

The youngest patient (non-smoker) with a verified stage 3a lung cancer was 38 years old (born in 1980); the oldest patient with verified lung cancer was 72 years old (born in 1946).
Conclusions. The preliminary analysis of LDCT results has shown a high informative value of this method in the early diagnostics of lung cancer.

References:
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2. Pokazateli onkologicheskoy sluzhby Respubliki Kazakhstan za 2017 god (statisticheskiye materialy) [Indicators of the Cancer Service of the Republic of Kazakhstan for 2017 (statistical materials)]. – Almaty: Kazakh Institute of Oncology and Radiology, 2017 (in Russian);
Nodulocystic hidradenoma of the breast: a case review with imaging findings

Relevance. A nodulocystic hidradenoma is a neoplasm of sweat glands which is very rare in the breast. Its diagnostics is difficult; its imaging characteristics are not well studied and documented. Breast hidroadenomas present a diagnostic challenge to both pathologists and radiologists. Malignant transformation of benign nodular hidradenomas has also been reported. Complete surgical resection is a choice of treatment for this lesion.

Although we have found twenty-seven cases of clear cell hidradenomas of the breast reported in the literature till today, only four of those cases were diagnosed by both mammography and breast ultrasound. In two reported cases of nodular hidradenoma, false positive biopsy has led to a mastectomy. Malignant counterpart of hidradenoma is called hidradenocarcinoma.

To our knowledge, this paper is the first to report MR findings of nodulocystic hidradenoma of the breast.

Case report. We present a case of nodulocystic hidradenoma of the breast with mammography, tomosynthesis, ultrasound, and MRI results in a 24-year old woman.

Conclusions. Nodulocystic hidradenoma should be considered in differential diagnostics of a breast lump. However, there is no particular radiologic feature that could strongly predict the diagnosis of nodular hidradenoma. FNA and core biopsy may sometimes lead to a misdiagnosis, so the excision is usually needed for a definite histopathologic diagnosis.

Keywords: Nodulocystic hidradenoma, mammography, tomosynthesis, ultrasound, magnetic resonance imaging (MRI).

Background. A nodulocystic hidradenoma is a rare cutaneous adnexal-type neoplasm originating from sweat glands. It can occur anywhere in the body but is very rarely seen in the breast.

There is a lack of awareness among breast radiologists about this lesion due to its very low incidence and common removal without imaging assessment. Thus, the imaging characteristics of this tumor are not well established and documented. We present the first case of nodulocystic hidradenoma of the breast with mammography, tomosynthesis, ultrasound, and MRI results in a 24-year old woman, along with a literature review.

Case report. A 24-year old woman applied to the breast imaging center complaining of a palpable painful lump persistent for a few years. Over the last few months, it was growing in size with discoloration of the skin.

She had a strong family history of breast cancer with several female relatives with breast cancer from both paternal and maternal sides. The patient was not tested for breast cancer gene mutations.

Clinical data. During the physical examination, slight skin discoloration was noticed. On palpation, a mobile hard lump was detected in the upper outer quadrant of the left breast, mildly tender to palpation. Ipsilateral axillary lymph nodes were not enlarged on palpation.

Diagnosis. Targeted ultrasonography showed a complicated cyst measuring 3 centimeters in the left breast at the site of a palpable finding (Figure 1).

Ultrasound-assisted core biopsy revealed a low-grade papillary neoplasm of unknown origin but resembling of a papillary lesion of urothelial origin.

The patient then underwent digital breast tomosynthesis and contrast-enhanced breast MRI. CC and MLO views demonstrated a round high density circumscribed mass sized 2.5 centimeters with associated marker clip in the left breast at 3 o’clock located 15 centimeters from the nipple (Figure 2).

Breast MRI showed a round mass with circumscribed margins with a rim of solid enhancement up to 0.6 cm thick. Kinetic assessment of the solid component demonstrated its fast initial enhancement followed by plateau enhancement on the delayed portion of the curve (Figure 3).
A patient then underwent surgical excision of the lump. Final histopathologic results confirmed nodulocystic hidradenoma of the breast.

Pathology

Microscopic description: a relatively circumscribed intradermal cystic proliferation consisting of ribbons of monomorphic keratinocytes with eosinophilic cytoplasm and vesicular nuclei. No atypical cytomorphology or necrosis. Focal ductal differentiation, clear cells, and a vague papillary architecture. Stromal sclerosis and compressed fibrous tissue were also present. p63 and CK5/6 expressions were noticed.

Post-surgical healing course – without complications.

Discussion. Nodulocystic hidradenoma is a benign dermal tumor which arises from distal excretory ducts of eccrine or apocrine sweat glands [1, 2]. It is also known as clear cell hidradenoma, eccrine acrospiroma, nodular hidradenoma, or solid-cystic hidradenoma [3]. It may contain varying quantities of solid and cystic components and comprises approximately one-third of all hidradenomas [4]. This neoplasm usually occurs in the head, neck, upper body, and extremities. Its occurrence in the breast is rare [5, 6].

Clinically nodulocystic hidradenoma grows slowly; the reported duration of clinical symptoms ranges from 2 months to 15 years, with a mean duration of 2-3 years.

Such tumors may develop at any age but typically they develop between the third and seventh decades of life, usually peaking during the fifth decade [7].

Nodulocystic hidradenomas range in size from 0.7 to 8.0 cm, with an average size of 2.9 cm reported across the studies.

This tumor is more common among women than in men [8]. In our literature review, just six (22%) of the twenty seven cases were male.

Clinical findings often include a palpable mobile hard lump, usually tender on palpation, skin discoloration or ulceration, and nipple discharge if the tumor is located in the nipple areolar area [9, 10].

The preferable location if in the breast is the nipple areolar complex (around half of the lesions) and the axillary tail [11, 12].

Differential diagnostics includes primary breast carcinoma [13], metastatic carcinoma (renal cell carcinoma) [14], adenomyoepithelioma [12], and other benign skin tumors (eccrine spiradenoma, syringomatous squamous tumor, papillary syringocystadenoma, cylindroma, keratoacanthoma, trichoblastoma, trichilemmoma, etc.) [15, 16].

Imaging of a clear cell hidradenoma has been poorly described in the literature.

We have found twenty one articles reporting twenty seven cases of both malignant and benign clear cell hidradenomas of the breast in the literature to date. Seven articles were published in pathology or dermatology journals, eleven – in surgical and oncologic journals, and only three articles were published in radiology journals. Most of the articles provided a detailed description of histopathologic findings with very few authors briefly describing the radiologic appearance of the lesion. Due
to its rare occurrence in the breast and active surgical approach, very few cases have been reported based on radiological findings. To our knowledge, only four cases of benign breast hidradenoma have been diagnosed by both mammography and breast ultrasound [9, 10, 17, 18]. The imaging characteristics of nodular hidradenoma are summarized below.

**Ultrasound**

On ultrasound, it usually presents as a well-circumscribed complex cystic and solid mass with a variable solid portion. The fluid part of the lesion can be complicated due to hemorrhage or clear. Although in our case this tumor manifested as a complicated cyst on ultrasound- homogeneous, low-level echoes, without a discrete solid component, and with an imperceptible wall. Some articles report hypervascularity on Doppler flow.

**Mammography and digital breast tomosynthesis**

All articles describe nodular cystic hidradenomas as well-circumscribed, usually high-density round or oval masses on mammography.

**MRI**

There have been a few case reports describing MRI characteristics of such tumors [19, 20]. In one case of planter eccrine acrospiroma, MRI revealed a homogeneously enhancing solid nodule. In another case of recurrent eccrine acrospiroma of the thigh, MRI showed a cystic mass with an enhancing mural nodule. However, the MR findings of nodulocystic hidradenoma of the breast have not been described before.

In our case, MRI presented a complex circumscribed mass with rim enhancement suggestive of malignancy.

Often, such neoplasms present a diagnostic challenge for both radiologists and pathologists [15, 21]. In our case, core biopsy has yielded low-grade papillary neoplasm possibly of urothelial origin that required an additional urologic investigation – CT urography, urine and blood tests.

These tumors are often misdiagnosed cytologically as benign cystic lesion [22] or as ductal carcinomas [6, 14, 23].

There were two cases of nodular hidradenomas reported where false positive biopsy results led to mastectomy [24, 25].

The malignant counterpart, hidradenocarcinoma, is a very rare tumor that can arise de novo or from a pre-existing hidradenoma [21]. Malignant transformation of nodular hidradenomas has also been reported in a few cases [26]. The malignant variants are typically aggressive with early metastases to lymph nodes, bones, and lungs [27, 28]. Benign and malignant versions are indistinguishable by imaging appearance [29-31].

Nodulocystic hidradenoma may recur after inadequate surgical excision [26, 15]. That is why a complete surgical excision with clear margins is the treatment of choice for these tumors.

**Conclusions.** To conclude, nodulocystic hidradenoma should be taken into account in differential diagnostics of a breast lump. However, there is no particular radiologic feature that could strongly predict the diagnosis of nodular hidradenoma.

FNA and core biopsy may sometimes lead to a misdiagnosis, so the excision is usually needed for a definite histopathologic diagnosis.

Awareness of these lesions among radiologists is essential for their prompt diagnostics and adequate management.

**References**

**SurePath® liquid-based cytology in molecular diagnostics of pancreatic ductal adenocarcinoma: a case report and literature review**

Relevance: Pancreatic ductal adenocarcinoma (PDAC) has an aggressively malignant nature, and its prognosis remains extremely poor in Kazakhstan as well as worldwide [1]. Cytological evaluation by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) techniques are widely used as routine clinical practice. However, this technique is not enough to diagnose PDAC for several reasons.

Purpose of the research: to evaluate the possibility to use KRAS mutations in SurePath® liquid-based cytology (SP-LBC) specimens obtained by EUS-FNA for PDAC diagnostics.

Results: PDAC was diagnosed using SP-LBC slide that contained a few suspicious malignant cells. The presence of a KRAS mutation (G12D) was confirmed by DNA extraction and PCR using SP-LBC and histological samples.

Conclusion: KRAS mutation in SP-LBC specimen obtained by EUS-FNA can accurately identify PDAC. SP-LBC is a useful technique for collecting high-quality cellular samples for genetic analysis as well as conducting an exploratory evaluation of appropriate molecular diagnostics for PDAC. However, there is a need for more data on the use of SP-LBC in PDAC diagnostics.

Keywords: Pancreatic ductal adenocarcinoma; EUS-FNA cytology; KRAS mutation; SurePath® based LBC.

**Introduction.** Pancreatic ductal adenocarcinoma (PDAC) has an aggressively malignant nature, and its prognosis remains extremely poor in Kazakhstan as well as worldwide [1]. Cytological evaluation by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is used to define an optimal therapeutic strategy [2, 3]. EUS-FNA has replaced conventional diagnostic approaches in many countries. However, in some situations, these approaches do not allow to diagnose PDAC, i.e., when cellular samples have a limited number of cell populations [4].

A semi-automated technique of Liquid-Based Cytology (LBC) has recently gained popularity as a method of collecting and processing both gynecologic and non-gynecologic cellular specimens [5-8]. Although the cost of material (LBC slides) and the preparation time for LBC are bigger than those required for conventional smears, LBC has several advantages like rapid and proper fixation and fewer cases of air-drying of artifacts [9]. Two LBC systems, ThinPrep® based LBC (TP-LBC) and SurePath® based LBC (SP-LBC), are currently used worldwide. These systems have gradually replaced conventional smears as the primary test method in both gynecological and non-gynecological screening programs [10]. LBC preparations are increasingly being used in non-gynecological cytology due to their high cell-recovery rates. Several authors have examined pancreatic cytology using SP-LBC. TP-LBC uses filtration, while SP-LBC uses density gradient centrifugation (cell enrichment) with a sampling device and collection vials for the preparation of the final slide. Therefore SP-LBC provides much higher diagnostic accuracy for cervical glandular neoplasms than TP-LBC [11]. Moreover, residual SP-LBC samples can be used for further immunocytochemistry examination and molecular analysis [12, 13].

In the presented study, we examined Kirsten-ras (KRAS) mutations in SP-LBC specimens and checked whether they could be used for PDAC diagnosis.

**Materials and methods.**

**Case information.** A 50-year-old man with back pain was referred to the Kurume University Hospital for examination. Abdominal CT has shown a pancreatic tail tumor – a mass 52 32 mm with low-to-high density – and liver metastases (Figure 1A). Serum tumor markers such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were increased (CA19-9 – 2590 U/mL, CEA – 7.0 ng/mL). Endoscopic ultrasonography has revealed a 22-mm mass in the pancreatic tail (Figure 1B). The clinical symptoms, imaging and lab results have shown a suspected case of pancreatic head cancer cT3 cN1 cM1, stage IV. On the basis of SP-LBC treatment of EUS-FNA cellular specimen, the patient was indeterminately diagnosed with PDAC.

**SP-LBC protocol.** The specimens were stored in vials filled with a preservative solution (CytoRich® Red Preservative, Becton Dickinson). Each vial was centrifuged at 1,500 rpm for 5 min on the day of sampling, and CytoRich® Red was decanted. Then, the vials were centrifuged again with distilled water. After decanting the vials, 0.5 ml of fresh distilled water was added, and the sediment was stirred. A 0.5-ml sample was then dispensed into the settling chamber, and preserved cells were allowed to rest on the slide for at least 10 min. Approximately 1 ml of 95% ethanol was added to the settling chamber. The slide rack was inverted, and excess sample was discarded. The settling chamber was carefully removed, and the LBC slides were immediately fixed in 95% ethanol. After overnight fixation, the slides were finally stained by conventional Papanicolaou staining.
DNA extraction and KRAS mutation analysis. The covered glass of the SP-LBC slide was removed for genetic analysis. Genomic DNA was purified using the QIAamp DNA FFPE Tissue kit (Qiagen, Hilden, Germany) as per the manufacturer’s instructions. Subsequently, mutations in the KRAS codons G12D, G12V, G12C, G12R, G12S, G12A, and G13D in the KRAS wild-type gene were examined using fluorescence resonance energy transfer-based preferential homoduplex formation assay (F-PHFA; Riken Genesis Co., Ltd., Tokyo, Japan) according to the manufacturer’s instructions.

Tissue specimens were routinely fixed in 10% buffered neutral formalin and embedded in paraffin. Paraffin-embedded tissues were sliced into thin sections of 8-μm thickness, and 2-3 sections were used for DNA extraction using QIAamp DNA FFPE Tissue kit, according to the manufacturer’s instructions. KRAS mutation analysis was next performed using the same F-PHFA assay, which was used for LBC specimens.

Results. Cytological and histological findings of pancreatic cancer. Cytological diagnosis by EUS-FNA was “indeterminate”; however, histopathological examination of the tumors proved it to be tubular adenocarcinoma (Figure 2). SP-LBC treated slides from the pancreatic tail tumor revealed several clusters and isolated cells with a necrotic background. Cytological analysis of tumor cells showed small and bland nuclei with abundant cytoplasm. Some of the clusters were composed of cells with enlarged nuclei and prominent nucleoli, and the malignant cells were suspected to be adenocarcinoma cells (Figure 3). Finally, the cytological diagnosis was “indeterminate” for the tumor cells presented on the SP-LBC slide.

Molecular diagnosis for SP-LBC sample. We used a EUS-FNA cellular specimen on the basis of which a patient was indeterminately diagnosed with PDAC. The cytological sample obtained from the SP-LBC slide was subjected to DNA extraction and PCR reactions, and have confirmed the KRAS mutation (G12S). KRAS mutation was also examined using histological tissue sample for double check, and we also confirmed the KRAS mutation (G12S).
**Discussion.** In the presented study, KRAS mutation in an SP-LBC specimen obtained by the EUS-FNA was used to accurately identify PDAC. A literature review of the PubMed database (2010–2018) was performed to identify several major genes involved in the development and progression of neoplastic diseases identified by LBC. These articles are summarized in Table 1. Recently, many molecular diagnostic studies using TP-LBC and SP-LBC were made concerning breast [14], uterine cervix [15], lung [16], thyroid gland [17], and urinary bladder [18] cancers. In gynecology, the improvement of sample adequacy using TP-LBC was attributed to the ability of that technique to remove obscuring elements from cervical specimens. In addition, LBC has also facilitated molecular testing for human papillomavirus (HPV) from the same cervical cytology specimens. Molecular diagnostics using LBC had higher sensitivity compared to cytology. It also allowed identifying BRF, EGFR, and KRAS mutations in LBC samples. Among them, EGFR status was an important factor for molecular targeted therapy of lung cancers; thus, molecular diagnostics using LBC has facilitated the choice of therapeutic strategy in several diseases. However, few studies have been made on cytological diagnostics of PDAC using LBC [12]. Moreover, no one reported the use of DNA extracted from LBC samples for the examination of PDAC.

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Organ</th>
<th>LBC</th>
<th>Target gene</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nishimura R*</td>
<td>2016</td>
<td>Japan</td>
<td>Breast</td>
<td>Thin-Prep</td>
<td>HER2</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Tewari P</td>
<td>2018</td>
<td>Ireland</td>
<td>Uterine cervix</td>
<td>Thin-Prep</td>
<td>Human papillomavirus</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Malapelle U</td>
<td>2012</td>
<td>Italy</td>
<td>Lung</td>
<td>Thin Prep</td>
<td>EGFR/KRAS</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>Rossi ED</td>
<td>2013</td>
<td>Italy</td>
<td>Thyroid gland</td>
<td>Thin Prep</td>
<td>Braf (V600E)</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>Mian C*</td>
<td>2010</td>
<td>Italy</td>
<td>Urinary bladder</td>
<td>Thin-Prep</td>
<td>Chromosomes 3, 7 and 17 Loss of 9p21 locus</td>
<td>18</td>
</tr>
</tbody>
</table>

* Molecular diagnostics was made using FISH method

**Conclusions.** KRAS mutation in an SP-LBC specimen obtained by the EUS-FNA can accurately identify PDAC. SP-LBC is a useful technique for collecting high-quality cellular specimens for genetic analysis as well as conducting an exploratory evaluation of appropriate molecular diagnostics for PDAC. However, there is a need for more data on PDAC diagnostics using SP-LBC.

**Acknowledgment.** We would like to thank Editage (www.editage.jp) for English language editing.
17. Rossi E.D., Martini M., Capodimonti S. et al. BRAF (V600E) mutation analysis on liquid-based cytology-processed aspiration biopsies predicts bilaterality and lymph node involvement in papillary thyroid microcarcinoma // Cancer Cytopathol. - 2013. - Vol.121. - P.291-297;
Primary liver cancer: a clinical case

Relevance: Primary liver cancer is a common malignant neoplasm. According to the official statistics of the Republic of Kazakhstan, in 2016 liver cancer ranked 14th in the structure of oncological morbidity republic-wide, and 9th in Kyzylorda region. The incidence of primary liver cancer in the Republic of Kazakhstan was 4.9‰. The incidence in Kyzylorda region (7.4‰) was 1.5 times higher than the national figures.

Among malignant tumors, primary liver cancer is a severe organ disease, and the choice of its treatment method is challenging. A radical method is surgery though most of the patients cannot stand anatomical resection of the liver. The average life expectancy after radical surgery is 22.6 months.

The article provides the results of a clinical case of liver cancer after radical surgical treatment.

Results: In the subscribed case, surgical treatment of primary liver cancer stage III with germination in the right kidney has allowed to stabilize the patient’s condition and to achieve almost 10 years of survival with a tendency of further improvement.

Conclusion: Early liver cancer can be cured by radical surgical treatment.

Keywords: liver cancer, cirrhosis, surgical treatment.

Introduction. Liver cancer is a severe malignant pathology [1]. Its development is especially influenced by chronic viral hepatitis B, C, D and alcohol abuse. Rare etiological factors include oral contraceptives, radiopaque substances, mycotoxins, i.e. aflatoxins found in food products. Malignancy occurs when liver cirrhosis reaches 80%. Hepatocellular liver cancer ranks 8th worldwide in frequency. Primary liver cancer accounts for 80-90% of all malignant tumors. The incidence of hepatocellular liver cancer in young people is growing [2]. In the Republic of Kazakhstan, in 2016, liver cancer ranked 14th in incidence in both sexes, 10th in men, and 15th in women. Per 100 000 of primary cancer cases, liver cancer accounted for 5.9% in men vs. 4.0% in women. That means liver cancer incidence in men is 1.5 times more often than in women [3].

The treatment of primary liver cancer is a complex issue. Surgery mortality accounts for 18.3-22.8%. Life expectancy after final surgery is 22.6 months [1].

Materials. The presented clinical case demonstrates good results after combined final surgery for liver cancer. Patient data.

Patient A., born in 1962 (case history No. 747), was admitted to the surgical department of Kyzylorda Cancer Center on March 26, 2009. Patient A., 47 year old, complained of pain in the right rib, overall weakness, weight loss in the last 2-3 months by 9-10 kg, and the loss of appetite. The patient could not associate the disease with any other conditions from his medical history.

Anamnesis Vitae: no infectious hepatitis, no tuberculosis. No injuries. No drug allergy. No transfusion of blood or its components in the past.

Clinical manifestations.


Diagnostics. Complete blood count at admission (March 27, 2009): White blood cells – 8.9x10^9/L; Erythrocytes – 3.3 x10^12/L; Hemoglobin – 87.00 g/L; Platelet count – 0.91; Lymphocytes – 18.08%; Monocytes – 11.51%; Eosinophils - 4.95%; Basophils - 0.66%; Neutrophils - 64.8%.

Urinalysis: Amount (ml) – 10.00; color – yellowish; specific gravity – 1012; pH – 6.5; epithelium – 3-4; protein – 0.099; sugar – not found.

Biochemical analysis: Total protein – 85.10 mmol/L; Urea – 5.70 mmol/L; Glucose – 3.96 mmol/L; ALT (Alanine aminotransferase) – 0.48 IU/L; AST (Aspartate Aminotransferase) – 117.40 IU/L; Total bilirubin – 19.5 mmol/L; Coagulation profile: PTI – 83%, APTT – 58.9, Fibrinogen – 3.2 g/L, Creatinine – 72 µmol/L; Electrolytes: calcium – 1.02/L, potassium – 4.3 mmol/L, sodium – 140 mmol/L. IFA (March 27, 2009): Hepatitis B and C – negative. Oncological markers: CEA – 2.68 IU/ml, CA19-9 – 58.63 IU/ml, AFP – 1017 ng/L. Ultrasound examination (March 26, 2009): The formation in liver. nephroptosis (degree 1). Gastrofibroscopy (March 27, 2009) – no pathologies. Chest radiography (March 30, 2009) – normal. CT (February 02, 2009): the formation in the dextral part of the liver.

Before surgery, the patient received hepatoprotectors and vitamins IV, single infusions of saline and other liquids to support the balance of red cell mass and acid bases.

Clinical diagnosis: malignant hepatoma extended into the right kidney, ST III, T3N0M0. Moderate anemia.
Treatment: Thomas Starzl laparotomy was conducted on April 08, 2009 by Professor B.B. Baimakhanov. The size of tumor in the dextral liver side – 15.0x15.0 cm. The tumor has penetrated the kidneys. The conducted nephrectomy included an extended rightward hemihepatectomy and adrenal glandectomy. External drainages were established on the choledochal duct, under the dextral diaphragm, and on the ventricle by Pikovsky method.

The patient was admitted in serious condition to the intensive care unit where he received the relevant antibacterial and infusion therapy, vitamins, 5 infusions of red cell mass, 9 infusions of fresh plasma, protein preparations, hepatoprotectors.

Complete blood count (April 30, 2009): White blood cells – 7.9x10x9/L; Erythrocytes – 3.5x10x12/L; Hemoglobin – 108.00 g/L; Platelet count – 0.91; Lymphocytes – 18%; Monocytes – 11.51%; ESR – 52 h/mm.

Urinalysis: Amount (ml) – 10.00; color – yellowish; specific gravity – 1005; pH – 6.5; epithelium – 2-4; protein – 0.115, sugar – not found, erythrocytes – 3-4.


Histology results No.679: hepatocellular carcinoma, with metastases to the outer kidneys operculum.

On May 04, 2009, the patient was discharged in satisfactory state for outpatient follow-up at the place of residence.

The patient remained under constant follow-up control. Ultrasound examination (August 11, 2015): the state after liver resection. Diffusive changes in the left side of the liver. The liver volume returned to the previous normal level. Chronic pyelonephritis of the left kidney. Hydrocalycosis. AFP – 2.89 ng/L (August 11, 2015).

In November 2018, the patient was examined out patiently. No complaints. Weight gain of 12 kg. Overall condition – satisfactory.

Results. The results of final combined surgery were assessed in connection with the recovery of a person suffering from liver cancer. In spite of Stage III of the disease and kidney penetration, the conducted combined surgery gave good results, having improved the patient’s quality of life.

Discussion. In spite of high post-operative mortality reported in the medical literature (average life expectancy – 22.6 months), in the described case the patient has lived for about 10 years after surgery and shows the possibility of continuing life in the future.

Conclusions. This clinical case shows the possibility of complete recovery of a patient in case of a timely surgery conducted at an early stage of primary liver cancer.

References:
Results of using high-dose ifosfamide in disseminated soft tissue sarcomas in Kazakh Institute of Oncology and Radiology

Soft tissue sarcoma (STS) is one of the most adverse forms of tumors from the point of diagnosis and treatment due to its relatively rare occurrence and diversity of histological types.

Surgery is the main treatment for STS.

After local excision as an independent treatment, the frequency of local recurrence is 38.8 to 81.1% [1-4]. STS removal within its pseudocapsules results in tumor recurrence in about 90% cases; extensive local removal of tumor results in 40% recurrence; radical local tumor excision – in 10-15% recurrence [5-7]. Thus, surgical treatment for STS often results in local recurrence what has caused the search for new methods and treatment regimens for STS [3, 8].

The complex treatment of STS on the limbs has expanded the scope of organ-preserving surgery and significantly reduced the local recurrence rate.

Chemotherapy based on doxorubicin and its analogs is now used to increase the 5-year survival of patients with primary and recurring STS. Adjuvant chemotherapy has increased the 5-year survival of STS patients from 53 to 87% [9, 10]. However, disseminated non-operable STS requires independent chemotherapy.

Purpose of the study was to evaluate the effectiveness of high-dose ifosfamide chemotherapy in disseminated non-operable STS.

Results: The treatment of disseminated non-operable STS with ifosfamide has resulted in a complete response in 9 (29%) cases, partial response – 15 (48.4%), progression – 4 (12.9%), and death – in 3 (9.7%) cases. Out of 31 STS patients, 3 had lung mts regression, 1 – main foci regression, 1 – lung mts stabilization, and in 2 cases death might have been caused by pancytopenia and acute kidney deficiency possibly caused by the collapse of the tumor with chemotherapy.

Conclusion: high-dose ifosfamide treatment has significantly expanded the capacity of drug treatment of disseminated non-operable STS, especially rhabdosarcoma, synovial sarcoma, as well as malignant tumors of peripheral nerve shells and undifferentiated pleomorphic STS.

Keywords: Soft tissue sarcoma, ifosfamide, doxorubicin.

Introduction. Soft tissue sarcoma (STS) means a heterogeneous group of diseases which includes more than 50 histological subtypes of tumors. STSs are relatively rare and account for 0.2-2.6% of all human malignancies [11-13].

The incidence rate is 1.7‰ in men and 1.6‰ in women. In 60% of cases, STS affects the limbs, of them, 66% of cases affect lower limbs [14-17]. Various authors report frequent hematogenous metastasis in case of STS (24-52.6%), while lymphogenous metastasis is less frequent (2.9-10%) [9, 18-20].

In 2017, 373 new STS cases (1.3% of all malignant neoplasms) were diagnosed in the Republic of Kazakhstan, of them, men – 52%, women – 48%. STS ranked 20th in cancer incidence and 19th in cancer mortality [18].

STS is mainly treated surgically but chemotherapy (CT) is required in case of disseminated non-operable disease [9]. The median survival of patients with disseminated STS amounts to 11 months but approximately 25% of patients live up to 3 years. It could be attributed to tumor biology and/or the CT ineffectiveness [13].

Neoadjuvant, adjuvant, and therapeutic CT is used since recently to increase the 5-year survival of patients suffering from primary and recurrent STSs with generalized tumor process. Doxorubicin and its analogs are the main CT drugs.

CT is currently used as a part of complex treatment, as well as an independent method of treating patients with STS metastases to other organs.

CT with doxorubicin in dosages from 70 to 80 mg/m2 delivers an objective response of 10 to 15% with most frequent partial responses. Monotherapy with ifosfamide produces similar results as doxorubicin: the response rate ranges from 7 to 41% (average – 25%). Ifosfamide is dose-dependent, with a minimum efficacy threshold at a dosage of more than 6 g/m2 and a significantly higher efficacy at doses above 10 g/m2 [11].

Comparative studies of monotherapy with doxorubicin and combination therapy with doxorubicin and ifosfamide have been conducted since 1993. In Europe, monotherapy with doxorubicin is recognized as a standard in both adjuvant therapy and the treatment of disseminated forms. The US lean toward combined tactics; the advantages of both schemes are argued for more than 30 years.

Thus, the latest publication of the European Organization for Research and Treatment of Cancer (EORTC) of 2014 contained the results of a multicenter phase III study aimed to compare the efficacy of doxorubicin at a dose of...
75 mg/m² and a combination of the same dose of doxorubicin with ifosfamide at a dose of 10 g/m². The study included 228 patients with locally advanced and disseminated forms of STS. The toxicity was predictably higher in the combination group; PFS was twice higher in the combination group (7.4 months vs. 4.6 months). The immediate efficacy (60% vs. 31%) and overall survival (14.3 months vs. 12.8 months) were also in favor of the combination, but statistical significance was not achieved [12, 21].

Materials and methods. Center for Bone, Soft Tissue Tumors and Melanomas of the Kazakh Institute of Oncology and Radiology has been administering high-dose chemotherapy (HDCT) with ifosfamide since 2014. For four years, this therapy was given to 31 patients with disseminated STS (excluding patients with extrasosseous Ewing sarcomas/PNET) in the following cases: 7 (22.6%) cases of rhabdomyosarcoma, 6 (19.4%) – undifferentiated sarcoma, 5 (16.1%) – each of synovial sarcoma and malignant tumors of the peripheral nerve shells, 3 (9.7%) – lipoblastic lipoma, 2 (6.45%) – pleomorphic and leiomyosarcoma, 1 (3.2%) – fibrosarcoma (Table 1). The gender ratio was 1:1, that is, men – 16, women – 15. The average age of patients was 39.7 years (22-71 years). See Table 2 for the distribution of the patients by tumor localization. On average, all patients received 4 courses of systemic polychemotherapy. Median follow-up was 14.7 months.

Table 1 – Distribution of STS patients by histological types

<table>
<thead>
<tr>
<th>Histological type</th>
<th>No. of patients</th>
<th>Efficacy (%)</th>
<th>Positive response to treatment</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma</td>
<td>7</td>
<td>22.6%</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
<td>6</td>
<td>19.4%</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>5</td>
<td>16.1%</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Malignant tumors of the peripheral nerve shells</td>
<td>5</td>
<td>16.1%</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Undifferentiated lipoblastic lipoma</td>
<td>3</td>
<td>9.7%</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Pleomorphic sarcomas</td>
<td>2</td>
<td>6.45%</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>2</td>
<td>6.45%</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>1</td>
<td>3.2%</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 – Distribution of STS patients by tumor localization

<table>
<thead>
<tr>
<th>Tumor localization</th>
<th>No. of patients</th>
<th>Abs. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbs and body surface</td>
<td>21</td>
<td>67.7%</td>
</tr>
<tr>
<td>Retroperitoneal space</td>
<td>3</td>
<td>9.7%</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3</td>
<td>9.7%</td>
</tr>
<tr>
<td>Small pelvis area</td>
<td>3</td>
<td>9.7%</td>
</tr>
<tr>
<td>Thorax and abdominal cavity</td>
<td>1</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Results and Discussion. According to global data, the efficacy of doxorubicin monotherapy varies from 10 to 15%. In our study, the efficacy of ifosfamide amounted to 77.4% (complete and partial response). HDCT with ifosfamide was more efficient for rhabdomyosarcomas (Figure 1). Three out of 31 STS patient showed regression of metastatic foci in the lungs, 1 – regression of the primary focus, 1 – stabilization of metastatic foci in the lungs, and 2 cases resulted in death associated with pancytopenia and acute renal failure, possibly associated with the tumor destruction due to the performed CT (Table 3).
Table 3 – HDCT results in STS patients

<table>
<thead>
<tr>
<th>Effect</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>9</td>
<td>29%</td>
</tr>
<tr>
<td>Partial response</td>
<td>15</td>
<td>48.4%</td>
</tr>
<tr>
<td>Progression</td>
<td>4</td>
<td>12.9%</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

**Conclusion.** The introduction of high-dose ifosfamide treatment has significantly expanded the capacity of drug treatment of disseminated STS. Ifosfamide was most effective in treating rhabdomyosarcoma and synovial sarcoma; over 50% of responses were also positive in malignant tumors of the peripheral nerve sheaths and undifferentiated pleomorphic STS. The obtained positive results – a complete response in 29% of cases and a partial response in 48.4% of cases – have proven the advantage of HDCT with ifosfamide in treating disseminated STS.

**References:**
1. Pokazateli onkologicheskoy služby Respiblik Kazakhstan za 2017 god [Indicators of the Cancer Service of the Republic of Kazakhstan for 2017]. – Almaty: Kazakhstan Institute of Oncology and Radiology, 2018. – Tables 1.2, 1.7 (in Russian);
Angiogenesis is one of the main conditions for tumor growth and metastasis in colon cancer. Experimental studies show the dependence of colon cancer recurrence frequency from the primary tumor vascular density [1]. Vascular endothelial growth factor (VEGF) is one of the main factors for angiogenesis. VEGF induces proliferation and migration of vascular endothelial cells and leads to the formation of new capillaries; it increases vascular wall permeability, thus creating the necessary conditions for better access of oxygen and nutrients to the tumor cells [2]. VEGF activates the relevant receptors (VEGFR-1, -2 and -3), and their signal passes through various signaling pathways including Akt (protein kinase B) and ERK [3]. Therefore, VEGF signaling pathway does not only promotes angiogenesis but also plays an important role in such cellular processes as reproduction, migration, tumor cells invasion and the inhibition of apoptosis [4].

A number of studies conducted in the 1990s have shown a prognostic meaning of the level of VEGF in the serum and tumor tissue of colon cancer patients. Higher VEGF expression was related to a worse prognosis [5, 6]. Today, Kazakhstan has approved three targeted drugs that affect angiogenesis: Bevacizumab, sunitinib, and sorafenib.

**Inhibitors of vascular endothelial growth factor (VEGF)**

**Bevacizumab.** Bevacizumab blocks VEGF A what results in a rapid decrease of microvascular bed density. It also normalizes the structure and function of the altered vessels to improve the penetration of chemotherapeutic drugs into the tumor and inhibits its neovascularization [2, 7, 8]. The importance of Bevacizumab in first-line chemotherapy for metastatic colorectal cancer has been shown in four key randomized studies.

In the first study, Bevacizumab has supplemented chemotherapy with irinotecan and 5-fluorouracil/Leucovorin in the IFL regimen. It has significantly increased the frequency of objective response, the time to progression, and the median life expectancy from 15.6 to 20.3 months [9].

In the study NO16966, the patients received a combination of FOLFOX (Oxaliplatin + 5-fluorouracil (5-FU) + calcium folinate (Leucovorin)) or XELOX (Capecitabine + Oxaliplatin) with or without the addition of Bevacizumab. The combination with Bevacizumab has reliably increased the time to progression [10]. The subgroups analysis has shown a significant gain only from the addition of Bevacizumab to the XELOX regimen vs. no statistically significant difference in time to progression in patients treated with FOLFOX. It was noted that half of the patients had to terminate therapy for reasons not related to the disease progression. Among patients who managed to complete treatment before progression, the addition of Bevacizumab has increased the median time to progression regardless of the treatment regimen [11].

Then, the efficiency studies of Bevacizumab in the adjuvant treatment of colon cancer were initiated. The NSABP (National Surgical Adjuvant Breast and Bowel Project) C-08 study included more than 2,600 patients with stage II–III colon cancer. The regimens “FOLFOX ± Bevacizumab” were compared. During the median follow-up of 36 months, no reliable improvement in survival without signs of disease was noted (75.5% in the non-Bevacizumab group vs. 77.4% in the Bevacizumab group; p = 0.15; risk ratio (RR) = 0.85) [12]. Similar results were obtained in AVANT (Randomized, three-arm multinational Phase III trials).
study to investigate with XELOX or FOLFOX4 vs. FOLFOX4 alone as adjuvant treatment for colon cancer) study with a similar design [13].

Three main conclusions can be drawn from the results of Bevacizumab clinical studies. First, sooner or later the patients develop tumor resistance to conducted treatment; moreover, some tumors are apparently not sensitive to Bevacizumab. Considering Bevacizumab as a targeted drug requires finding biomarkers for it. Still, the available clinical signs do not allow predicting who of the patients has or will develop resistance to the drug [14]. Some of the mentioned clinical signs in retrospective and often non-randomized studies could be effectively used to predict the response to adding Bevacizumab to chemotherapy. The most interesting signs include some blood plasma markers (VEGF, soluble VEGF receptors), markers in the tumor tissue (VEGF D), arterial hypertension, and lactate dehydrogenase (LDH) level. However, prior to the practical application of these markers, their significance shall be confirmed in prospective and randomized studies. Therefore, today it is not possible to recommend using any factors to select patients for Bevacizumab therapy. Secondly, monotherapy with Bevacizumab is not efficient enough. It requires its combined use with cytostatics while it does not seem to matter with which chemotherapy drug it should be combined. Thirdly, the inclusion of Bevacizumab in the adjuvant therapy of patients with colon cancer has proved to be inefficient. It might be due to the lack of a substrate for Bevacizumab action, an altered vascular network in micrometastases, in patients who received adjuvant treatment.

**Aflibercept.** Unlike Bevacizumab, Aflibercept is a “trap” for several growth factors – all VEGF isoforms (A and B), as well as a placenta growth factor (PIGF).

In 2011, the results of a randomized Phase III placebo-controlled study to on assessment of the efficacy of Aflibercept 4 mg/m² in second-line treatment of patients with metastatic colon cancer in combination with FOLFIRI (irinotecan + fluorouracil + Leucovorin) were presented. The addition of an anti-angiogenic drug was shown to improve the median life expectancy (13.50 months vs. 12.06 months; RR = 0.817; p = 0.0032), the median time to progression (6.90 months vs. 4.67 months; RR = 0.758; p = 0.00007), as well as to increase the frequency of achieving an objective response (19.8% vs. 11.1%; p = 0.0001) in comparison with the “FOLFIRI + placebo” combination. Diarrhea, asthenia, stomatitis, arterial hypertension, proteinuria, and neutropenia were the most often adverse effects caused by treatment. The subgroup analysis has shown the greatest gain in overall survival in patients with ECOG 0 status (RR = 0.768), in patients younger than 65 years (RR = 0.796), in patients with a history of arterial hypertension (RR = 0.714), and in patients with isolated liver damage (RR = 0.649) [15]. Interestingly, the drug was effective in patients regardless of whether they had received Bevacizumab in the first-line chemotherapy. The median life expectancy among patients who had previously received Bevacizumab was 12.5 months in the group receiving Aflibercept vs. 11.7 months in the group receiving placebo (RR = 0.862) [16]. Thus, a randomized study is required to determine optimal tactics for this category of patients – a continuation of Bevacizumab therapy after progression or a transfer to Aflibercept. Such a study is expected to be registered shortly.

**Regorafenib.** This drug binds and inhibits 2nd and 3rd type VEGFR tyrosine kinases, c-kit, PDGFR, and Raf-kinase leading to the depression of the tumor angiogenesis and the termination of the tumor cells proliferation.

In February 2012, the results of a Phase III comparative study of Regorafenib and placebo were presented in 760 patients with metastatic colon cancer refractory to standard therapy. Regorafenib has shown a statistically significant increase in the median life expectancy compared with placebo: 6.4 months vs. 5.0 months (calculated RR = 0.773; 95% CI 0.635–0.941; p = 0.0051). The median time to progression in the Regorafenib group was 1.9 months vs. 1.7 months in the placebo group (calculated RR = 0.493; 95% CI 0.418–0.581; p <0.000001). The objective response was 1.6% and 0.4%, respectively. Disease control was achieved in 44% of Regorafenib cases and 21% of placebo cases (p <0.000001). Such complications as the hand-foot syndrome (17%), asthenia (15%), diarrhea (15%), hyperbilirubinemia (8%) and arterial hypertension (7%) were more frequent in the Regorafenib group [17].

The use of other receptor tyrosine kinase inhibitors to VEGF did not increase the life expectancy of patients.

**Ramucirumab.** Ramucirumab is a human monoclonal antibody IgG-1 that targets the extracellular domain VEGFR-2 which is the main mediator of the VEGF pathway. By binding to VEGFR-2, Ramucirumab prevents all VEGF ligands from binding to VEGFR-2 and inhibits the VEGF pathway. Unlike Aflibercept and Bevacizumab, Ramucirumab prevents VEGF from interacting with the receptor by binding to VEGFR-2 rather than VEGF [18, 19].

Phase II study with the FOLFOX regimen and Phase III study with the FOLFIRI regimen in patients with metastatic colon cancer are still ongoing. In addition, despite the negative results of joint use of angiogenesis inhibitors and anti-EGFR drugs, a Phase II study of a combination of Cetuximab and Ramucirumab was initiated [20]. IMC-18F1 is a monoclonal antibody that selectively blocks VEGF-1. VEGF is thought to bind directly to VEGFR-2, while VEGF-1 plays an important role in regulating the activity of VEGFR-2 [21].

A Phase II study is currently underway with IMC-18F1 drug in patients with metastatic colon cancer. Even if its results turn out to be negative, an assessment of clinical efficacy of such drugs as Aflibercept, Ramucirumab, and IMC-18F1 is very important. Since their clinical effect is likely to vary, it will help to understand the role of various components of the VEGF system in colon cancer pathogenesis.

Thus, antibodies to VEGF are most efficient in blocking angiogenesis in patients with metastatic colon cancer, while the inhibitors of receptor tyrosine kinases to VEGF have proven ineffective. An exception is the encouraging results of the study on the use of Regorafenib.
Inhibitors of the signaling pathway from the epidermal growth factor receptor (EGFR)

EGFR hyper-expression is observed in 60–92% of colon cancer cases. After stimulation of the receptor, the signal from the epidermal growth factor is transmitted through a number of intracellular protein molecules, including RAS-RAF-MEK-ERK and PI3K-Akt-mTOR, to the cell’s genome and affects cellular processes such as differentiation, proliferation, migration, angiogenesis, and apoptosis [22, 23]. This receptor can be blocked by monoclonal antibodies, two of them, Cetuximab and Panitumumab, being already used in clinical practice. However, a mutation in the KRAS protein gene disrupts this pathway, and the use of monoclonal antibodies to EGFR becomes ineffective. Therefore, the effect of EGFR inhibitors is observed only in patients without such a mutation. The KRAS gene mutation frequency is 40% [24-26].

Cetuximab is a chimeric monoclonal antibody to the outer EGFR domain. In contrast, Panitumumab is a fully human immunoglobulin. The inhibition of EGFR receptors not only in the tumor, but also in the normal tissues of the body, determines the development of a number of specific adverse effects during therapy with EGFR inhibitors such as skin toxicity, diarrhea, and hypomagnesemia. A clear correlation has been established between the severity of skin toxicity and the efficacy of anti-EGFR antibody therapy. Patients receiving Panitumumab who developed degree 3-4 skin toxicity had a longer time to progression vs. the patients who developed degree 1-2 skin toxicity and the patients who received only chemotherapy (11.3, 6.1, and 8.7 months, respectively) [27].

In the CRYSTAL study (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer – Cetuximab in combination with irinotecan as a first-line therapy for metastatic colorectal cancer), in the absence of a KRAS mutation the use of Cetuximab has increased the time to progression by 1.5 months, the overall survival rate – by 3.5 months, and the frequency of achieving the objective response – by almost 1.5 times [28]. In the OPUS study (Oxaliplatin and Cetuximab in First-Line Treatment of mCRC – Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer), in the group of patients with wild type KRAS protein the addition of Cetuximab to the FOLF-OX regimen has increased the time to progression, but not the life expectancy [29]. A meta-analysis of these CRYSTAL and OPUS studies (845 patients with the wild KRAS phenotype) has revealed that the addition of Cetuximab increased the probability of achieving an objective response by more than twice in comparison with the patients who received only chemotherapy (p <0.0001) [30].

In the COIN (Continuous or NIntermittent) study conducted by the Medical Research Council (MRC), in contrast to the results of previous studies, the use of a combination of Cetuximab with Oxaliplatin-containing chemotherapy regimens did not lead to an increase in survival without progression and the overall survival, although the objective response was significantly higher (64% vs. 57%, p = 0.049) [29]. The negative COIN data has contributed to the emergence of the hypothesis that Oxaliplatin-based regimens were not optimal for co-administration with Cetuximab. The subsequent analysis of that study has shown a lack of gain from Cetuximab only in the XELOX group. This was due to higher toxicity which resulted in a greater reduction of doses of chemotherapeutic drugs and, consequently, reduced the regimen efficacy.

No such inverse correlation was noted in the “FOLFOX + Cetuximab” group. The results of the Scandinavian randomized study NORDIC VII (Phase III trial of Cetuximab with continuous or intermittent fluorouracil, Leucovorin, and Oxaliplatin (Nordic FLOX) vs. FLOX alone in the first-line treatment of metastatic colorectal cancer) in which Cetuximab was studied in combination with the 5-fluorouracil stream regimen in the first-line therapy has made additional intrigue [31]. The addition of Cetuximab did not improve the survival rates but was not associated with higher toxicity.

Another randomized trial PRIME (Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) has compared the combination of “FOLFOX + Panitumumab” with the FOLFOX regimen as the first-line treatment of patients with metastatic colon cancer. In patients without KRAS mutation, the addition of Panitumumab has reliably increased the median time to progression from 8.0 to 9.6 months (p = 0.02) and the frequency of objective response from 48% to 57% (p = 0.02) [32]. The life expectancy tended to increase from 19.7 to 23.9 months (p = 0.07).

Based on the results of these studies with Cetuximab and Panitumumab, the best chemotherapeutic “partners” for them are the regimens which include irinotecan or FOLFOX, but not XELOX or Nordic FLOX (5-fluorouracil + folinate + Oxaliplatin (Eloxatin®)).

Joint inhibition of the VEGFR and EGFR pathways

Combined blockade of several key receptors (the combined use of Bevacizumab and Cetuximab/Panitumumab) has not been successful. In two randomized Phase III studies, the combination of two targeted drugs has statistically significantly reduced the median time to progression. Among patients with the wild KRAS gene type, the median time to progression and life expectancy did not differ. It shows a negative influence of the combination of EGFR inhibitors with Bevacizumab; its mechanism is still unknown [33, 34].

HER2-inhibitors

The human epidermal growth factor receptor 2 (HER2) is an oncogenic factor and a well-known therapeutic target in breast and stomach cancer. The functional and genomic analysis of xenografts obtained from the patients has shown that a subgroup of approximately 5% of metastatic colorectal cancer (CRC) tumors is due to HER2 amplification or mutation. HER2 amplification is considered as an oncogenic factor, prognostic biomarker and a clinically acceptable target in CRC, taking into account the specificities of HER2 testing in this type of tumor. Although the role of HER2 as a biomarker for prediction in CRC remains uncertain, its importance as a therapeutic goal has been established. Indeed, independent studies have confirmed a substantial clinical benefit in patients receiving therapy fo-
cused on biomarkers targeting HER2, with an impact on the response rates and duration that was favorably distinguished from immunotherapy and other examples of precision oncology. HER2-oriented therapeutic strategies could change the treatment paradigm for the clinically significant subgroup of patients with metastatic CRC.

HER2 is the only member of the EGFR family that does not bind ligands; it is activated by heterodimerization with other ligand-bound receptors [35], with the strongest mitogenic signals generated by HER2-HER3 heterodimers. HER2 overexpression usually caused by gene amplification allows activating HER2 even in the absence of a ligand associated with other partners [36]. Overexpression or amplification of HER2 has been observed in 13–20% of breast cancer cases [37], in 7–34% of stomach cancer cases [37], and in 1.9–14.3% of lung cancer cases [38]. Different levels of HER2 hyper-expression have been recorded in CRC, at that, the rate of membrane expression varied from 2% to 11% [39]. Those factors could be explained by a number of factors including small populations under study, various antibodies for immunohistochemistry (IHC), the analysis of individual subgroups of patients with heterogeneous clinical-pathological characteristics of CRC, and the use of various assessment systems [40]. More recent studies have consistently shown that HER2 overexpression amounts to approximately 2% of all mCRC [40] increasing up to 5% at stage III [9] or IV of KRAS exon 2 wild-type tumors.

The predictive role of HER2 in CRC remains uncertain. Earlier studies proposed a negative prognostic effect of HER2 hyperexpression [41] but later no correlation between HER2 amplification and the outcome has been established. However, in one of the largest studied cohorts (1,645 patients with stages I-IV CRC), OS tended to worsen in 26 patients (1.6%) with HER2-positive disease compared with patients with HER2-negative disease [37]. HER2 was also identified as a poor prognostic indicator in the PETACC-8 study among patients with stage III colon cancer. HER2 changes were present in 66/1,689 patients (3.9%), and both NGS, FISH, and HER2 mutational status determined by NGS were associated with a shorter time to relapse (Hazard Ratio (HR) 1.9, 95% CI 1.1–3.2; P = 0.03) and a shorter overall survival (HR 1.7, 95% CI 0.9–3.2; P = 0.045). Such predictive value remained after correction for age, treatment, RAS mutation, histological extent, tumor location, pT and pN condition, obstruction or bowel perforation, as well as vascular or lymphatic invasion.

The assessment of a potential prognostic effect of HER2 amplification in CRC is hindered by a low frequency of such changes what could also potentially explain the controversial research findings on that issue. However, according to the available data, a negative prognostic effect of HER2 is less pronounced than in other changes, such as the BRAF mutation.

HER2 amplification is a clinically significant genetic change in mCRC as confirmed by the HERACLES and MyPathway studies. This biomarker can be screened using established diagnostic tools. It is found in a significant 5% of patients with wild-type KRAS mRDC and can potentially be a predictor of the lack of effect of monoclonal antibodies against EGFR. HER2-targeted therapy favorably differs from new therapeutic strategies for mCRC, such as BRAF-directed therapy and immunotherapy with control point inhibitors. HER2 amplification shows a frequency similar to the frequency of tumors with a high level of MSI (MSI-H) (5%) [40] and lower than in BRAF mutations (10%); however, compared with BRAF-targeted combinations (ORR 16–21%; median PFS 4.2 months [40]), the responses achieved so far in clinical studies with HER2-directed therapy are higher (ORR 30–38%) and longer (median PFS 5.2 months [6]), resembling the results obtained with control point inhibitors for MSI-H tumors. The toxicity of HER2-directed combinations is also less than BRAF- or MSI-H-directed therapeutic agents [42]. Thus, HER2-directed therapy appears to combine the advantages of precision medicine (rapid and deep induction of tumor contraction) with immunotherapy (long-term response and better tolerance). Although no data from Phase III studies with HER2-targeted drugs is available, randomized studies will require a long time to achieve results in such a selected population [42]. A strong underlying biological rationale [42], consistent action at a therapeutic level [42], and a favorable comparison with other approaches of precision medicine confirm the need for conditional approval of drugs targeting HER2 for their clinical use by regulatory authorities.

**BRAF inhibitors**

BRAF-targeted treatment of mCRC has changed rapidly over the past 4 years, with the new opportunities emerging at a high speed. New drugs like Wnt or cyclin-dependent kinase inhibitors in combination with BRAF inhibitors are currently being evaluated in Phase I and II studies. The introduction of targeted therapy at an early stage of the disease, with or without chemotherapy, is also under assessment. Changes in the BRAF-mt treatment scenario are expected in the coming years. The results of using the new drugs targeted at the MAPK pathway are also expected. E.g., new molecules specifically targeting both BRAF, and C-RAF or ERK (downline mediators of the MAPK pathway) have proven their safety and efficacy in preclinical models, and the development of Phase I has begun (NCT02607813; NCT02711345).

Nevertheless, the resistance to targeted therapy is developing almost systematically, and its characterization and overcoming are the subjects of ongoing studies. A pre-clinical study published by Oddo et al. [43] has shown reactivation of the MAPK pathway in resistant cells: the mutations or amplifications of KRAS, EGFR, MAP2K1 or BRAF were reported. KRAS mutations were also observed in circulating DNA plasma in a resistant patient report. A group of authors has also tested in vitro combinations in those resistant cells to show that the combined inhibitors of ERK, BRAF and EGFR could overcome the acquired resistance. Clinical trials are currently required to study such combinations in an attempt to improve the results of treatment of CKPP BRAF-mt, but safety profiles can be a problem. Similarly, Alhornian et al. have reported the emergence of KRAS amplification, BRAF amplification, and MEK1 mutation in the matched post-treatment biopsies of patients receiving targeted BRAF therapy [44]. These
changes lead to a resistance that can be reversed with ERK inhibitors. MET amplification has also been described as a mechanism of resistance to BRAF inhibition which could be reversed by double inhibition of BRAF and MET (Vemurafenib and Crizotinib) [45].

BRAF-mt tumors have played a major role in the era of the CRC molecular classification based on gene expression profiling. CRC consortium has proposed four different subtypes based on gene expression signatures. BRAF mutations have been observed in all four subtypes [46]. However, there is a clear enrichment of CMS1 (MSI immune subtype) characterized by greater immune infiltration and worse survival after relapse, similar to the classic CRC BRAF-mt. Prior to this classification, a 64-gene expression signature with 96% sensitivity and 86% specificity was identified for BRAF-mt CRC [47]. However, the same signature has been found in the BRAF-WT CRC subgroup which also had a worse survival rate similar to the classic BRAF-mt CRC. Consequently, all tumors with this genetic signature have been identified as BRAF-like CRC. There are many ongoing studies to confirm this and propose new treatments. Vecchione et al. [48] have recently reported that RANBP2 (a gene encoding a protein that regulates the organization of microtubules in the mitotic spindle) is necessary for the survival in these tumors. In vitro and in vivo studies have shown a possible significant efficacy of Vinorelbine, as a microtubule disruptor, in these tumors. A prospective study to prove this hypothesis will start soon in the framework of the European MoTricColor project.

On the other hand, these objects appear to be heterogeneous if we go further in the transcriptome classification of colorectal BRAF-mt tumors [49]. The analysis of the gene profile BM1 and BM2 has allowed identifying two subgroups from uncontrolled clustering, BM1 shows the activation of the KRAS/AKT pathway, mTOR deregulation and epithelial-mesenchymal transition, while BM2 is characterized by cell cycle deregulation (high level of CDK1 and low level of cyclin D1). BM1 has a worse prognosis, and a different treatment approach is recommended compared to BM2. For example, inhibition of BRAF/MEK/PI3K can be of great benefit to BM1 compared to inhibition of CDK1, which can be of great benefit to BM2. These results may offer a new perspective for CRC BRAF-mt allowing to classify and select the best treatment beyond the BRAF/EGFR blockade.

Finally, partial overlapping of mutations between MSI and BRAF is common in this population. In the era of cancer immunotherapy, anti-PD1 drugs have been approved for MSI tumors including mCRC. However, the role of these antibodies in mCRC MSI BRAF-mt remains unclear. Therefore, the best sequence (target therapy or checkpoint inhibitors) may be studied in the future.

Conclusion. All the foregoing necessitates the research aimed at a comprehensive study and immunohistochemical characterization of colorectal cancer. Some mCRC patients can achieve tumor regression and improve their long-term survival prospects thanks to more active use of modern cytostatic regimens in conjunction with targeted drugs.

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LITERATURE REVIEW

Whole-body MRI capacity in diagnostics, staging, and assessment of treatment efficiency of lymphomas: a literature review

Relevance. Lymphomas make up to 5-6% of all malignant neoplasms in adults and up to 10% of oncological diseases in children. Due to a quite favorable overall prognosis in early detection of lymphomas, the prevention of long-term complications associated with their therapy and diagnostics remains relevant and acute. Radiological methods (CT, PET/CT 18-FDG, MRI) play an important role in the initial staging of lymphomas, the assessment of treatment efficiency and the detection of recurrences.

During treatment and subsequent dynamic control, the patients with malignant lymphomas undergo multiple cycles of CT and PET-CT studies thus accumulating quite a high dose of ionizing radiation, even in the case of low-dose CT, which may contribute to an increased risk of secondary tumors in the future. It increases the interest in MRI as a radiation-free method of the staging of malignant lymphomas and dynamic observation during treatment, an alternative to CT and/or PET.

The purpose of the study was to assess the capacity of whole-body MRI in diagnosing, staging, and assessment of the efficiency of lymphoma treatment.

Results. Whole-body MRI is a highly sensitive method of primary staging and assessment of treatment efficiency of malignant lymphomas, as the efficiency of conventional MRI in malignant lymphomas is equal to CT with contrast enhancement. Moreover, MRI using DWI mode is highly comparable with the results obtained by PET/CT–18FDG and is an excellent alternative for patients with lymphomas as it is free of ionizing radiation and intravenous contrasting.

Conclusion. The obtained results give reason to consider MRI as a method having an identical capacity with CT and PET/CT in diagnosing, staging and assessment of the efficiency of lymphoma treatment.

Keywords: whole-body MRI, lymphoma.

Introduction. Lymphomas are the tumors originating from lymphoid tissue located outside the bone marrow [1]. Lymphomas account for 5-6% of all malignancies in adults, and up to 10% of cancer diseases in children [2]. Malignant lymphoma is the most common primary hematopoietic malignant tumor, as well as one of the most treatable forms of cancer. The two main categories of lymphomas include Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The exact initial diagnostics of lymphoma is decisive for proper treatment planning and prognosis. Radiology methods (CT, PET-CT with F-18, MRI) play an important role in the initial staging of lymphomas, evaluating the effectiveness of therapy and detecting recurrence of the disease [3-8].

Materials and Methods. The conducted literature search was conducted on the PubMed database for the last 15 years (2003-2018) by keywords «Whole-body MRI, Lymphoma». This literature review includes 30 literature sources matching the selection criteria – these are full-text scientific articles containing the analysis of whole-body MRI results in lymphomas in comparison with other methods of radiation diagnosis, such as CT and PET-CT.

Literature review. CT is the most widely used radiology method for lymphoma staging due to its wide availability and a relatively low cost. Main CT-criterion indicating the lesion of lymph nodes is the change in their size. Pathologically changed lymph nodes are longer than 15 mm and/or wider than 10 mm [9, 10]. Total sensitivity and specificity of CT at node lesions above 15 mm in size reaches 87.5 and 85.6%, respectively [10-12]. It should be noted that the main limitation for the initial staging of malignant lymphomas using CT is the low level of informativity of this method with nodal lesions smaller than 10-15 mm in size. It increases the probability of false positive conclusions in case of a benign lymph nodes’ hyperplasia and lymphadenopathies of another genesis in children [13].

In lymphomas, morphological changes can fall significantly behind rapid functional changes; therefore, CT is not an ideal diagnostic tool in assessing early response to systemic therapy [8, 9, 10, 12]. In addition, CT is not applicable to the re-staging of lymphoma after completion of a course of treatment due to low informativity of this method in defining persisting viable tumor cells in large residual tumor masses [9, 11, 12]. PET-CT with F-18 is based on the fixation of positron decay of radiopharmaceutical drug which actively accumulates in foci with increased glucose consumption. Any foci with increased F-18 consumption in relation to the background tissue in the absence of benign hypermetabolic disorders is considered positive for malignant lymphoma. A meta-analysis of several prospective studies has shown that PET sensitivity and specificity in the staging of malignant lymphomas and the assessment of their response to treatment leave behind the sensitivity and specificity of contrast CT [14, 15]. The main factor defining the intensity of 18F accumulation in a tumor is the histological type of the tumor. HL and aggres-

UDC: 616-006.44

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Oncology and radiology of Kazakhstan, №1 (51) 2019
sive types of NHL are known for their high level of glycolysis that means a high intensity of the drug accumulation in tumor foci. Moderate and low levels of glycolysis and the relevant low intensity of $^{18}$F accumulation in the tumor tissue are typical for indolent NHL. PET is an efficient method for detecting a lymphomatous lesion regardless of its size, as well as to detect active tumor cells in the residual tumor masses after completion of the course of treatment [14, 16, 17]. Several large-scale studies have proven PET-CT to be a more accurate method of staging and re-staging of malignant lymphomas than contrast CT [18, 19]. A disadvantage of PET, and especially PET-CT, is their relatively high cost that makes both methods most costly in radiation examination [20].

During treatment and future dynamic follow-up, patients with malignant lymphomas have to undergo multiple cycles of CT and PET-CT examinations. As a result, they accumulate a significant dose of ionizing radiation, even in case of a low-dose CT. It can promote the risk of secondary tumors in the future [6-8, 10]. These reasons raise interest in MRI as an option without radiation burden. MRI creates an alternative to CT and/or PET for the staging of malignant lymphomas and dynamic follow-up during treatment [10, 21]. The main advantage of the whole-body MRI is the possibility to obtain a whole picture of the pathological process spread in the body (lesions of lymph nodes of bone marrow and other organs) within one examination. Recent studies show that the whole-body non-contrast MRI protocols including diffuse-weighted images (DWI) can be used for the initial staging of lymphomas [7, 22-28]. Magnetic resonance diffusion is a method that allows determining the translational movement of intracellular water molecules in the tissues. DWI MRI has high potential in assessing malignant lymphomas. Quantitative measurement of the degree of diffusion (according to the distribution maps of the true or apparent diffusion coefficient (ADC)) can help distinguish malignant and benign lymph nodes [5, 8, 24-28]. In staging of malignant lymphomas, DWI is a valuable addition to the standard MRI protocols. DWI allows visualizing and measuring of the extra-, intra-and transcellular movement of water molecules due to their intrinsic thermal energy. The degree of freedom of movement of water molecules depends on several characteristics of the tissue such as cell packing density, the number of water molecules in the extracellular space, the concentration of protein and peptide molecules, the viscosity of the medium, and the presence of tissue necrosis. Limited diffusion is characteristic for most malignant tumors including malignant lymphomas. The use of DWI allows obtaining high contrast between the lesion focus and the background tissues which facilitates the detection of pathological foci [24-29]. Starting from 2008, many publications were devoted to incomplete and small studies of the results of using whole-body MRI for lymphomas. According to preliminary data, MRI sensitivity and specificity in detecting node lesions in malignant lymphomas reach 98-99%, in extra-node lesions – 91-99%. According to preliminary results of a range of incomplete studies, DWI can be potentially used (analog to PET) to differentiate clusters of viable tumor cells from foci of fibrosis or necrosis in tumor masses remaining after treatment [20].

**Conclusions.** A quite positive general prognosis at early detection of lymphomas actualizes the topic of prevention of long-term complications related to the conducted therapeutic and diagnostic procedures. All modern methods of anatomical visualization (Ultrasound, CT, and MRI) have a limited capacity of detecting metastases as they mainly rely on low-sensitive “size-anatomical” criteria. A hybrid PET-CT has high diagnostic accuracy and is gaining popularity as a method of visualization, initial staging, and assessment of evaluating the efficacy of treatment of aggressive malignant lymphomas. CT and PET-CT currently used to diagnose malignant lymphomas are associated with exposure to significant ionizing radiation therefore attempts shall be made to reduce the exposure rate. Whole-body MRI and DWI (especially, with ADC) seem to be an effective alternative to CT and PET. A direct comparison of DWI and PET results is required to define if functional information obtained from DWI can replace PET. MRI can be especially useful for certain groups of patients like children, pregnant women, individuals with increased risk of complications from the administration of contrast agents. Moreover, MRI can become a method of choice for patients with an F-18 negative lymphoma. The value of diffuse-weighted MRI and ADC is not yet established finally. Today, PET is still required to evaluate the response to treatment. Whole-body MRI, being a relatively new radiation-free method of initial staging and evaluation of response to treatment in malignant lymphomas, becomes a widely available diagnostic option. Complex use of routine MRI with DWI and ADC can significantly increase the accuracy of diagnosis and is the subject of ongoing research.

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