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Optimization of business processes for inpatient care by introducing electronic health record

Relevance. Automation of healthcare is an acute issue in the era of global informatization. Timely, reliable and up-to-date information transfer is required to improve the quality and speed of medical care. The urgency of implementation of an electronic medical documentation is conditioned by the need for data standardization and providing immediate access to patients’ information.

Purpose of the study. The main purpose of this study is to optimize the workflow by creating a single format for the output of medical information systems. Next purpose is to reduce the number of documents to be filled and to avoid the transfer of unnecessary information and the re-entry of data.

Results. This study allowed the development of a health accounting template based on international standards and the state regulatory framework of the Republic of Kazakhstan. The relevant requirements and architecture are described. Since electronic health record (EHR) shall follow the HL7 V.3 standard, it should also follow the Clinical Document Architecture (CDA), because EHR consists of structured electronic medical documents.

Conclusion. In order to combine all the information on the patient’s health for the whole period of life, a single form of data output in the form of EHR is needed for all medical systems. The logical result of the study was the implementation of standards, regulatory framework, and the EHR structure. Information security issues should also be properly considered.

Keywords: e-health, electronic health record (EHR), IT in medicine.

Introduction. The development and modernization of health care system is recently under constant attention of both medical specialists and the state. One of the directions of development is the introduction of medical information systems (MIS). The State Program “Information Kazakhstan-2020” adopted in 2013 has introduced the term of “e-health” (electronic health) and identified the ways of further development of health informatics.

MIS existing in most of domestic health facilities do not provide solutions for acute problems in the field of management and delivery of medical care. At the same time, only 10% of health facilities in the RK use electronic health records (EHR) while EHRs have already replaced conventional paper documents by 50-60% in Europe and by nearly 70% in the US.

Materials and methods. The study was based on the data obtained from the information system “Electronic Medical History Documentation” implemented in Kazakh Research Institute of Oncology and Radiology and the analysis of HL7 standard templates for Clinical Document Architecture (CDA). Typical SEMD parameters were defined and the architecture for the use and integration with domestic medical information systems developed based on the analysis of data from cancer MIS and the paper versions of medical documentation in the forms approved by the Ministry of Healthcare of the RK.

The tools of the study included the methods of scientific cognition: observation, comparison, system analysis, as well as the methods of modeling, algorithmization, formalized analysis of information characteristics, unified modeling language (UML). The development tools for general and special purposes used in the course of the study included the Extensible Markup Language (XML) to form SEMD, Laravel and PHP – for creating web-application to work with SEMD, and SQL used to create and change databases.

Results and discussion. According to the Concept of e-Health Development in the Republic of Kazakhstan for 2013-2020 approved by the Order of the MoH of the RK №498, “by 2020, the implementation of e-health of the Republic of Kazakhstan shall ensure timely, relevant, reliable, and sufficient automated receipt of information to achieve a safe and sustainable healthcare system focused on patient needs [1]." For that purpose, all medical organizations and units of the MoH of the RK shall have high-speed and secure access to fully interoperable e-health systems based on paperless technology using EHRs.

The healthcare system of Kazakhstan is now changing its focus from the treatment of certain diseases to the protection and maintenance of health of a certain person. So, the e-health should also become “patient-oriented” [2]. The main element of the new e-health paradigm should be EHRs of Kazakhstani citizens instead of statistical reports and analytical information. The main idea of this technology is to ensure the availability of medical information from any medical organization in the country since the data will be stored in a unified format.

The second important feature is that the access to data will be secured in accordance with access policies and current legislation so that the patient himself shall decide who, when and how will see his EHR. EHR will store all the most important health data throughout the life of the person, and it will be quickly available from anywhere through any authorized information system. This EHR should be based on recognized health standards such as HL7 (ISO/HL7 27831) and DICOM. HL7 V.3 Clinical Document Architecture – CDA standard used in many countries of the world shall be followed to ensure the semantic interoperability of MISs involved in the transfer of structured clinical information. This standard defines the structure of electronic medical documents [3].
All participants of diagnostic and preventive processes will gain new opportunities through e-health:
- Patients can obtain data on their health status, can control access of medical staff to their personal archives;
- Doctors can receive “alarms” and other medical information about patients ensuring continuity of rendered medical care;
- Managers can get access to analytical information on all parts of healthcare system.

E-health innovation has different aspects. Reaching a fundamentally different, higher quality of clinical medicine and healthcare management in the medium term will require the presence of structured electronic medical documents (SEMD) and the means of interoperability providing opportunities to collect data in unified formats.

EHR is a document that integrates the most important vital characteristics of the patient’s health, its diagnoses, blood group, allergy information, etc. A CDA document consists of a Header (for computer reading) that includes metadata for searching and retrieving a document, and a Body (for human readings) that contains actual clinical data [4]. A CDA document can implement one of three levels of semantic detailing. The first level is quite simple: it is a machine-readable document header with a standardized set of structural elements. The title contains a unique ID of the SEMD, the type and title of the document, the date of creation, the level of confidentiality of the document, the language and the version number of the document.

CDA document should possess constancy and inalterability. Any changes are made in the next version of the document, not in the source document. Individual Identification Number (IIN) is used as a unique identifier of the patient and its unique number in the MIS. Object identifiers in OID format are used to uniquely identify the elements of EHR [5] in order to organize their maintenance and accounting. In first level CDA, only text and attached files (pdf, word, jpeg, etc.) can be transmitted in the body of the document. Such SEMD can only be read on a computer screen or in the printed form. Second level CDA has some structured sections in the body of the document and can also contain many nested subsections. Their number, sequence, hierarchy and obligatory nature depend on the type of medical document. Computer analysis of second level CDA allows searching for interesting sections of the patient's medical information throughout all the related documents. Special medical terms are also coded in the dictionaries. For example, a clinical diagnosis can be coded according to the International Classification of Diseases 10, and the drugs – according to the state drugs register.

SEMDs contain generalized information on medical cases of the patient [6]. Cases of hospitalization are described in a SEMD called “Inpatient Discharge Summary”, cases of treatment in an outpatient clinic – in a SEMD called “Outpatient Discharge Summary.” These are complex structured documents containing interrelated clinical information. “Inpatient Discharge Summary” contains significant historical data, the dynamics of changes in the patient’s condition from admission to discharge, as well as the final clinical diagnosis and information confirming the established diagnosis, including significant data of instrumental and laboratory studies, other diagnostic studies, and opinions of medical experts. Discharge Summary reflects the conducted treatment, as well as the recommendations on the necessary treatment and recovery after discharge. This document in XML format has a structured content divided into certain mandatory and optional sections.

In addition, there are SEMDs that contain the opinions of medical experts and the results of diagnostic and lab tests performed outside the hospital. The results of lab testing should be transferred from laboratory information systems (LIS) of various manufacturers.

**Conclusion.** Thus, we described the set of generalized properties required for any EHR so that it is suitable for transmission, complete, useful and effective and can maintain its integrity in all systems, countries and over time. EHR architecture neither prescribes what kind of information will be stored nor established how it should be managed. EHR architecture does not impose any restrictions on the types of data to be stored in the records. Such data does have to be copied on paper. Such details as “field sizes” necessary for physical databases are not fixed in EHR architecture. Information security shall also be given a special attention. The collection and dissemination of personal data in medical records should be carried out within the framework of the Law of the RK dated May 21, 2013 № 94-V “On personal data and its protection” [7]. The main purpose of EHR is to provide a documented record of medical treatment that supports current and future treatment performed by the same or other physicians. This information provides an opportunity for communication between physicians involved in the treatment of the patient. The patient and the doctor would both benefit from such a system.

**References**
The influence of screening on the main indicators of colorectal cancer (on the experience of the North Kazakhstan Region)

Relevance. World Health Organization (WHO) predicts about 20 mln. new cases of malignant neoplasms by 2020 and about 12 mln. of deaths which is due to the growth in numbers and aging of the world's population [1]. At present, the prevention and search for additional diagnostic resources for early detection of malignancies are of great importance in oncology due to a direct correlation between the cancer detection stage and its treatment outcome [2].

The experience of developed countries demonstrates that state screening programs increase the share of early detection of malignancies with subsequent reduction of mortality from oncological processes.

Purpose of this study is to assess the impact of colorectal cancer (CRC) screening on its early detection and the prevalence of advanced forms of colon malignancies.

Materials and Methods. This paper presents the results of CRC detection by stages in 2006-2011 (before screening) and 2012-2017 (during screening) in the North Kazakhstan Region.

CRC screening was carried out in accordance with the Order of the Ministry of Health of the Republic of Kazakhstan No. 665 «On Approval of the Rules for Conducting Preventive Medical Examinations of Target Populations» of 10.11.2009. The target group included men and women aged 50 to 70 with an interval of 2 years. In total, the target group in the North Kazakhstan Region in 2012-2017 included from 34,898 to 39,181 people. At attendance, the staff of the prevention department of out-patient clinics explained to the representatives of the target group the content of the first stage of screening – carrying out the hemoccult test.

Hemoccult test results were assessed by the paramedical personnel of out-patient clinics 3-10 minutes after deposition of faecal suspension on a special window of the test-card. Positive results of hemotest were to be confirmed by the doctors of the prevention department of the out-patient clinic.

In case of a positive hemotest, the patient was proposed to pass total colonofiberscopy. This procedure is offered in 9 medical centres of the North Kazakhstan Region.

The second stage of CRC screening activities was mainly included colonoscopy conducted in the regional centre using 4 video colonoscopes, and in the district centers of the region using 5 colonfiberoscopes.

Results. Table 1 shows the statistics of detected CRC cases by stages before screening, Table 2 – during the period of screening, 2012-2017.

Table 1 – Distribution of detected CRC cases by stages before screening, 2006-2011.

<table>
<thead>
<tr>
<th>Years</th>
<th>Stages I - II</th>
<th>Of them, during periodic health examination</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>70</td>
<td>9</td>
<td>70</td>
<td>20</td>
<td>160</td>
</tr>
<tr>
<td>2010</td>
<td>68</td>
<td>6</td>
<td>83</td>
<td>19</td>
<td>170</td>
</tr>
<tr>
<td>2009</td>
<td>63</td>
<td>5</td>
<td>76</td>
<td>19</td>
<td>158</td>
</tr>
<tr>
<td>2008</td>
<td>33</td>
<td>2</td>
<td>68</td>
<td>19</td>
<td>120</td>
</tr>
<tr>
<td>2007</td>
<td>63</td>
<td>2</td>
<td>84</td>
<td>25</td>
<td>172</td>
</tr>
<tr>
<td>2006</td>
<td>52</td>
<td>0</td>
<td>83</td>
<td>29</td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>342 (36.9%)</td>
<td>24 (2.5%)</td>
<td>464 (49.1%)</td>
<td>131 (13.9%)</td>
<td>944 (100%)</td>
</tr>
</tbody>
</table>

According to Table 1, the share of early detection of CRC before screening averaged to 36.9%, at that, only 2.5% of registered CRC cases were diagnosed during periodic health examinations. Besides, the advanced and disseminated forms of CRC (stages III and IV) averaged to 63% in the studied period before screening.
Table 2 – Distribution of detected CRC cases by stages during the period of screening, 2012-2017.

<table>
<thead>
<tr>
<th>Years</th>
<th>Stages I - II</th>
<th>Of them, during periodic health examination</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>120</td>
<td>23</td>
<td>21</td>
<td>15</td>
<td>156</td>
</tr>
<tr>
<td>2016</td>
<td>129</td>
<td>34</td>
<td>20</td>
<td>21</td>
<td>170</td>
</tr>
<tr>
<td>2015</td>
<td>97</td>
<td>44</td>
<td>62</td>
<td>23</td>
<td>182</td>
</tr>
<tr>
<td>2014</td>
<td>97</td>
<td>48</td>
<td>70</td>
<td>21</td>
<td>188</td>
</tr>
<tr>
<td>2013</td>
<td>92</td>
<td>35</td>
<td>63</td>
<td>21</td>
<td>176</td>
</tr>
<tr>
<td>2012</td>
<td>84</td>
<td>13</td>
<td>68</td>
<td>22</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>619 (59.2%)</td>
<td>197 (18.8%)</td>
<td>304 (29%)</td>
<td>123 (11.8%)</td>
<td>1046 (100%)</td>
</tr>
</tbody>
</table>

Table 2 shows that after the launch of CRC screening in 2012 in North-Kazakhstan Region the share of early stages of malignancies has been growing dynamically to reach the average of 59.2% in the last 6 years. At that, the number of patients detected during periodic health examinations has increased: from 2.5% before screening to 18.8% during the period of screening.

The share of advanced and disseminated forms of CRC (stages III and IV) has reduced during screening in comparison to pre-screening period. The share of patients detected at stages III and IV averaged to 63.1% in 2006-2011 vs. 40.7% in the period of screening what is 64.6% better.

Conclusions.

1. CRC screening is an efficient method of early detection of colon malignancies. During the screening, early detection of CRC has improved from 36.9% to 59.2%, that is, by 62.3% vs. the pre-screening period.

2. Due to a higher cancer awareness of the population and health care professionals during CRC screening, the share of detected disseminated forms of CRC had decreased from 63.1% to 40.7%.

References:


T790M mutation detection in EGFR gene for target therapy of non-small cell lung cancer

Relevance. Numerous research show high activity of EGFR gene and gene activated cascade in non-small cell lung cancer. The mutations related to sensitivity to tyrosine kinase inhibitors (TKI) and the mutations related to resistance to TKI, i.e., T790M mutation in exon 20, are of special interest in oncology practice.

Purpose of the study: Comparative characteristic of T790M mutation detection methods from tumour biopsy material and circulating tumour DNA (ctDNA) of blood plasma. Determination of the most optimal and informative method of detection based on the study results.

Results: Tumour biopsy material and ctDNA of blood plasma were subjected to molecular-genetic testing to detect T790M mutation. The analysis was positive in the sample of paraffin block containing tumour cells, and negative – in the sample from blood plasma. It evidenced the lack of concordance of study results due to the limited sensitivity of detection method with ctDNA or DNA losses during extraction.

Conclusion: The T790M mutation detection from tumour biopsy material was found to be most informative due to lack of sensitivity of ctDNA method. ctDNA method could not be used for diagnostic purposes. To overcome these limitations, some changes should be introduced into the method of detection or the DNA extraction to increase sensitivity of mutation detection. Nowadays, tumour biopsy material is a most reliable source of DNA for the given method of mutation detection.

Keywords: lung cancer, T790M mutation, EGFR gene, ctDNA, tumour biopsy material.

Introduction. EGFR gene encodes the receptor of epidermal growth factor (EGF) which is a transmembrane protein from the receptor tyrosine kinase family. EGFR influences the proliferation, angiogenesis and elevation of metastatic cell activity [1, 2]. The mutations in EGFR gene lead to dimerization of receptor, autophosphorylation of its intracellular tyrosine kinase domain and activation of protein kinase pathways of MAPK and PI3K/AKT [3]. In turn, it activates the transcription factors regulating the synthesis of proteins and mRNA [4]. The definition of mutations in patients with non-small cell lung cancer (NSCLC) is vital since the presence or absence of mutations determines the choice of therapy and the disease prognosis. In patients with NSCLC, a majority of somatic EGFR gene mutations are localized in exons 18-21 which code the tyrosine kinase domain [5, 6]. Most important for oncological practice are the relevant mutations associated with the sensitivity to tyrosine kinase inhibitors (TKI): the deletions in exon 19 (del19) [3], the replacement of L858R in exon 21 [7, 8], as well as the mutations associated with the resistance to TKI, for example, T790M mutation in exon [7-9].

NSCLC treatment is complicated by the development of resistivity to TKI that in turn requires a timely identification of these mutations and the selection of appropriate therapy. When generation 1 & 2 EGFR TKIs (Gefitinib, Erlotinib, Afatinib) are used in the therapy of locally advanced or metastatic NSCLC with detected mutation in EGFR gene, the resistance to EGFR TKI therapy often develops after 8-12 months and is in most cases (up to 60%) caused by T790M mutation in EGFR gene [10, 11]. T790M mutation (the replacement of threonine amino-acid residue by methionine in 790 position) leads to inefficiency of the generations 1& 2 EGFR (12, 13) T790M mutation in EGFR gene allows identifying the group of patients with highest likelihood of apparent response to the therapy with Osmertinib [14].

The proposed case is unique since the mutations are traditionally determined only in tumour biopsy material. It significantly reduces the possibility of complete and precise diagnostics of mutations and the possible resistance of tumour cells to TKI therapy. In identification of the mutations, the sampling method is critical since only timely diagnostics can facilitate precise diagnostics of the disease.

It should be noted that the blood plasma ctDNA assay has several advantages vs. biopsy, such as: minimal invasiveness, opportunity for obtaining of material at any time (before, during, after treatment), lack of heterogeneity of the sample obtained. On the other hand, however, highly sensitive methods are required to analyse the tumour DNA mutations in blood plasma. There is a risk of false negative result due to the method sensitivity limitations.

Patient Data:

Patient K., 69 years old, was diagnosed in 2015 with “Peripheral cancer of the right lung upper lobe, STIII T3N3M0”. The patient received 6 courses of polychemotherapy in 2015, a course of chemoradiotherapy in 2016, and surgical rightward lobectomy in 2016. Histological conclusion №11235/15, 11276-80/15 of 2015: the lung papillary adenocarcinoma with vascular invasion. Molecular-genetic conclusion №62 (Rotor GENE 6000): an exon 19 del mutation in EGFR gene detected in the test sample. The disease progression: metastases to the lymph nodes of mediastinum and brain, stereotactic radiosurgery of the brain foci performed in April 2017. Stabilization of process observed during treatment with Erlotinib (Tarceva) and zoledronic acid (Zometa). Surgical treatment in the volume of right peripheral cancer of the right lung upper lobe, STIII T3N3M0”. The patient is registered since 2015. PET/CT in dynamics shows the contrast uptake in the right lung parenchyma, 5th and 6th ribs, bifurcation lymph nodes, and paratra-
The levels of oncomarkers are growing. PET/CT of 19/02/2018 vs. PET/CT of 25/10/2017: the increase in zones of consolidation in the right lung with an apparent increase of metabolic activity, suspected relapse of the disease. Mediastinal lymph nodes show a moderately elevated metabolism, with no new lymph nodes. The foci of hypermetabolism in 5-6 ribs rightward – without significant dynamics; thickening of the costal pleura rightward, with moderate elevation in metabolism. The oncologist's conclusion of 02/20/2018: the diagnosis of peripheral cancer of the right lung upper lobe ST III T3NMX0M0. The status in February 2018: II Clinical Group.

**Timeline:**

<table>
<thead>
<tr>
<th>Type of care</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polychemotherapy</td>
<td>2015</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>2016</td>
</tr>
<tr>
<td>Lobectomy, lymph node dissection</td>
<td>04/2016</td>
</tr>
<tr>
<td>Stereotactic radiosurgery</td>
<td>04/2017</td>
</tr>
<tr>
<td>Therapy with Erlotinib (Tarceva) and zoledronic acid (Zometa)</td>
<td>04/2017</td>
</tr>
<tr>
<td>Video-thoracoscopy, pneumolysis, thoracotomy, pneumonectomy</td>
<td>03/2018</td>
</tr>
</tbody>
</table>

**Diagnosis:** The material for analysis was the paraffin-embedded surgical material of tumour tissue and blood plasma of the patient. DNA from 10% formalin-fixed and paraffin-embedded tumour tissue was obtained by liquid-phase method using the Biolink DNA extraction kit according to the manufacturer’s instructions. DNA from blood plasma was obtained by solid-phase method of DNA sorption on magnetic particles by Applied Biosystems company. To identify the mutation, DNA was amplified by PCR in real-time mode by reagent sets for determination of T790M mutations of EGFR gene by Applied Biosystems company.

The mutation was detected using the reagent kit for determination of T790M mutations of EGFR gene by Applied Biosystems company. No mutation was detected during the diagnostics of free-circulating tumour DNA.

**Treatment:** The patient has received 6 courses of polychemotherapy in 2015, chemoradiotherapy in 2016, surgical treatment in 2015: lobectomy on the rightward, lymphadenectomy. stereotactic radiosurgery of the brain foci performed in April 2017. Treatment with Tarceva (Erlotinib) and Zometa (zoledronic acid). Surgical treatment in the volume of rightward thoracotomy, pneumonectomy, and pneumolysis in 2018.

**Results:** The result was positive in the paraffin block sample containing the tumour cells, and negative – in the sample obtained from blood plasma. There was no concordance of results due to the limitation of detection method sensitivity using ctDNA or to the loss of DNA during allotment (Figure 1).

**Discussion:** The blood plasma ctDNA assay has a number of disadvantages in comparison to the tumour tissue assay: circulating tumour DNA level may be low or undetectable depending on the time, the localization of tumour, and the presence of necrosis. Besides, in early stages of the disease or at limited seeding, the number of copies of circulating tumour DNA may be low [15]. It should be taken into account that the ctDNA in blood plasma was analysed post-surgery, when the tumour ctDNA level could be reduced due to the decrease in the tumour volume. Thus, a further improvement of methodology of molecular-genetic diagnostics is required to ensure efficient monitoring of tumour progression and timely application of appropriate targeted therapy.

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Expression of gene p53 and matrix metalloproteinase-9 in different histological types of uterine sarcoma

Introduction. Currently there is no doubt that the prognosis of almost all malignant neoplasms (MN), including female genital malignancies, is based on early diagnostics and timely start of treatment. Such prognosis shall include the assessment of invasive and metastatic tumour potential to allow future individualization of antineoplastic treatment. The ability of tumour cells for invasive growth and metastatic spread depends on the ability of the matrix metalloproteinase system to split the components of extracellular matrix. It is especially important in sarcomas that have a high frequency of relapse.

Purpose of the study: To determine the expression of p53 gene and MMP-9 in different histological types of uterine sarcoma in order to reveal possible interrelations.

Results: 38.9% patients with overexpression of mp53 gene had a relapse. 4 (33.3%) out of 40.0% patients with negative expression of p53 had a relapse. The maximum frequency of relapses was observed at low expression of p53 – mean value 0.0-6.0%. The expression of MMP-9 was detected in 58.6% cases. The high level of MMP-9 expression was noted in 63.6% cases of leiomyosarcoma, the middle and low levels – in endometrial stromal sarcoma (28.6% and 42.9%, respectively), and no expression – in undifferentiated sarcoma (72.7% cases).

Conclusion: Co-expression of the mutated p53 gene and MMP-9 established in tumour tissue indicates interrelation of their transcriptional activity and can be indicative of prognostic significance of the studied molecular genetic markers. The combination of overexpression mp53 even with a moderate expression of MMP-9 corresponds to the most unfavourable course of the process observed in undifferentiated uterine sarcoma. A high level of MMP-9 expression in the absence of mp53 gene expression corresponds to a more favourable prognosis for leiomyosarcoma. In case of endometrial stromal sarcoma, the overexpression of mp53 is observed at extremely low expression of MMP-9 and is also characterized by a more favourable prognosis.

Keywords: co-expression, molecular-biological marker, mutated p53, MMP-9, gene expression.
group of matrix metalloproteinases (MMP) which are contained both in tumour and stromal cells.

Among the large group of potential prognostic molecular markers, the special place is occupied by the MMP system since it is commonly known that the proteolytic processes play the key role in tumour development. They can endow the tumour cells with the ability for invasion and metastatic development [10].

A contradictory data of evaluation of the markers significance confirms the need for their further study for final clarification of clinical and morphological correlations with a view for their potential use in evaluation of the course and prognosis of tumour process, especially for such rare and aggressive tumour as the uterine sarcoma.

**Purpose of the study:** to determine the expression of p53 suppressor gene and MMP-9 at various histotypes of uterine sarcoma in order to identify possible interrelations.

**Materials and methods.** Immunohistochemical study of tumour tissue samples was conducted to detect the expression of mutated p53 and MMP-9 in 30 patients with histologically proved uterine sarcoma. The following histological types were presented: leiomyosarcoma (LMS) – 11 patients, undifferentiated sarcoma (UDS) – 12 patients, endometrial stromal sarcoma (ESS) – 7 patients. The age range was 51.7±1.5 years, median – 51.0 years. Distribution by stages: I stage (T1N0M0) was determined in 20 patients (66.7±8.8)%, II stage (T2N0M0) – in 6 patients (20.0±7.4)%, III and IV stages (T3N1M0-1) – in 2 patients (6.7±4.6)%. All patients received chemotherapy using polyclonal antibodies to MMP-9 (92kDa) (Thermo scientific company) was used to visualize the primary antibodies. DAB (diaminobenzidine) was used as a chromogenic substrate. The results were calculated using the Avtandilov’s ocular grid [11] in 10 freely selected visual fields with the magnification of 400x. The immunohistochemical marker was assessed by two parameters: the rate of expansion and the colour intensity. The marker expansion was calculated by the share of positively stained cells in the total number of cells in the vision field. The colour intensity was assessed using semi-quantitative scale: 1+ - weak, 2+ - moderate, 3+ - severe reaction.

The data was statistically processed using the STATISTICA 10.0 software package. Fisher’s exact method, Student’s t-test, method of the most reliable estimation for small number of observations, non-parametric criteria of Mann-Whitney and Kraskel-Wallis to compare the average data of selected groups were used to determine the reliability of data. The probability of differences between the neighbouring values was considered at the significance level of p<0.05.

**Results.** Immunohistochemical study of the tumour tissue was performed in 30 cases of uterine sarcoma to analyse the apoptosis regulation by amplification of the p53 gene and MMP-9. Let’s consider the influence of these factors on the disease course.

The analysis of clinical data showed that 11 (36.7%) out of 30 patients (follow-up) had the tumour recurrence. Among 18 patients with p53 gene over-expression, 7 (38.9%) patients had the relapse. Among 12 (40.0%) patients with negative p53 gene expression, 4 (33.3%) had the relapse. The statistical analysis didn’t reveal a probable effect of expression of that marker on the sarcoma recurrence (p = 0.767). It also corresponds to the results of other investigators [12]. At the same time, according to the literature, in the case of gene amplification, the disease prognosis is statistically worse in its over-expression. In high malignant tumours, the mutant p53 gene expression reaches 33.0% [13], and the disease relapse occurs within 28 months [13].

In 30 patients, the p53 gene expression level ranged from 0.0 to 100.0%. The median was 6.0%. The mean value distinct from zero (18 patients) comprised 20.0%. Taking into account the different range of values, it was decided to analyse this indicator in different ranges of expression – 0.0 to 6.0%, 6.0 to 20.0%, and above 20.0% (Figure 1).

![Figure 1](image-url) – The relapses rate depending on the mp53 gene expression level

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**Oncology and radiology of Kazakhstan, №2 (48) 2018**

**DIAGNOSTICS**

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**KazlOR**
In some studies, the criterion for separation of p53-positive and p53-negative tumours was 20.0%, in other studies – 10.0% [3].

The analysis of data presented in Figure 1 shows that the maximum sarcoma relapse rate was observed at low p53 expression – in the range of 0.0 to 6.0% (p = 0.081). However, those indicators differed a little depending on the tumour histogenesis. In case of ESS, the relapses were observed when mp53 over-expression was over 6.0%. In case of UDS, the distribution of values was similar to the general group of patients, while in the group of LMS none of the patients with tumour recurrence had the mp53 over-expression.

The MMP-9 expression was presented in 17 (58.6%) out of 29 tumour samples. In one sample, MMP-9 was not detected. The tumour progression data was absent. Low level of expression (1+) was noted in 5 cases (17.6%), middle level (2+) – in 6 (35.3%) cases, high level (3+) – in 8 (47.1%) cases. No expression was observed in 12 (41.4%) patients.

The MMP-9 expression depending on the histological type of tumour is presented in the Table 1.

Table 1 – MMP-9 expression depending on uterine sarcoma histotype

<table>
<thead>
<tr>
<th>Histological type</th>
<th>MMP-9-9 indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0, %</td>
</tr>
<tr>
<td>Endometrial stromal sarcoma (ESS), n = 7</td>
<td>28.6</td>
</tr>
<tr>
<td>Leiomyosarcoma (LMS), n = 11</td>
<td>18.2</td>
</tr>
<tr>
<td>Undifferentiated sarcoma (UDS), n = 11</td>
<td>72.7</td>
</tr>
<tr>
<td>All sarcoma, n = 29</td>
<td>41.4</td>
</tr>
</tbody>
</table>

As presented in the Table, the high level of MMP-9 expression was noted in LMS in 63.6% of cases, middle and low levels were noted in ESS (28.6% and 42.9%, respectively), and no expression was observed in UDS what made 72.7% of cases (p=0.000 according to chi-square test).

The relapse rate depending on the histogenesis of tumour is presented in Table 2.

The relapse rate was noted in 11 out of 29 cases (37.9%); in 8 out of 17 (47.1%) cases in presence of MMP-9 expression, in 3 out of 12 (25.0%) in no expression of MMP-9.

As can be seen from Table 2, in case of LMS, the tumour relapse was observed at high level of MMP-9 expression, at the same time, no p53 gene mutation was noted.

In UDS, the disease recurrence was observed in the presence of mp53 expression, as well as in low and medium level of MMP-9 expression. In all cases of ESS relapses, the mp53 over-expression was noted, and only in one case – the middle level of MMP-9 expression was observed.

The analysis of interrelation between the mp53 gene and MMP-9 expression was performed (Figure 2). According to the data presented in the Figure, in elevation of the MMP-9 expression level, the distribution density shifts rightwards. As per the median test (chi-square), the dependence has the statistically significant value for the uterine sarcoma due regard to histogenesis (p=0.0123).
Within the analysis of correlation depending on the tumour histological type, it was revealed that in LMS this dependence was not observed, although the relapse rate was maximal (66.7%) in high MMP-9 expression (Table 2).

The statistically significant co-expression was observed in endometrial stromal sarcoma (p=0.008) and undifferentiated sarcoma (p=0.0006).

**Discussion.** The data obtained within the framework of the study, without taking into account the tumour histological forms, correlates with the literature data on the connection of changes in p53 gene and the expression of MMP-9, and their effect on the biological potential of the tumour. Not taking into account the tumour histological form, a high MMP-9 expression level and metastatic spread were observed in 7 cases with p53 gene expression. Among 6 patients with no p53 mutations in the tumour, only 2 had metastases, and 3 had a low or medium expression of MMP-9. Later, the influence of mp53 gene expression on MMP-9 expression was confirmed in LMS tumour tissue. The recovery of p53 wild-type lead to transcriptional inhibition of MMP-9 gene [10].

However, in our sample with the uterine LMS, a high level of MMP-9 expression was observed in the absence of mp53 expression.

**Conclusion.** Co-expression of the mutated p53 gene and MMP-9 established in tumour tissue indicates the interrelation of their transcriptional activity and can indicate the prognostic significance of the studied molecular genetic markers.

The combination of over-expression mp53 even with a moderate expression of MMP-9 corresponds to the most unfavourable course of the process observed in undifferentiated uterine sarcoma.

A high level of MMP-9 expression in the absence of mp53 gene expression corresponds to a more favourable prognosis for leiomyosarcoma.

In case of endometrial stromal sarcoma, the mp53 over-expression is observed at extremely low expression of MMP-9 and is also characterized by a more favourable prognosis of treatment outcomes.

Co-expression of mp53 and MMP-9 genes can be used as a prognostic factor in the course of the disease.

**References**


Role of SCCA tumour marker in the monitoring of chemoradiation therapy of head and neck cancer

Relevance. General examination and computed tomography are the only modern methods for evaluating the efficacy of treatment of patients with squamous cell carcinoma of the head and neck that help the oncologist in choosing the tactics of management of a patient after chemoradiotherapy is completed.

Purpose of the study: The authors analysed the sensitivity and the possibility of using the SCCA (squamous cell carcinoma antigen) to evaluate the efficacy of chemoradiotherapy of locally advanced squamous cell carcinoma of the head and neck. For that purpose, 30 patients with that pathology were examined for SCCA at the beginning of treatment and 1 month after its completion.

Results: Out of 30 examined patients with stages III, IVa, IVb head and neck cancer, 16 had elevated SCCA level in blood plasma (2.5 ng/ml). The diagnostic sensitivity of the SCCA marker was 53.3%. There was no statistically significant difference between mean SCCA levels in stage III and IV patients. Hence, the median in the group of patients with stage IV was 1.5 times higher. On average, after treatment, there was a decrease in the level of the SCCA marker on 1.64 ng/ml with its large spread from 1.35 ng/ml in the direction of growth to 3.38 ng/ml in the direction of decrease. During correlation analysis, the strongest relationship was found between the degree of tumour regression and the absolute change in the level of the SCCA marker (r = 0.6845; p = 0.003). There was also a relationship between the absolute change in the level of the SCCA marker and the time to death (r = 0.5942; p = 0.015).

Conclusion: The diagnostic sensitivity of the SCCA marker at III-IV stages of squamous cell carcinoma of the head and neck makes it impossible to use as a screening test. However, the monitoring of SCCA during chemoradiotherapy can reflect the efficacy of treatment, serve as an additional lab criterion when deciding on tactics for further management of the patient, and also serve as an additional prognostic factor.

Keywords: head and neck cancer, chronoradiotherapy, oncomarker, squamous cell carcinoma antigen, chemoradiotherapy.
The degree of tumour regression was assessed by RECIST criteria v.1.1 on the basis of computed tomography data.

The obtained data were collected in a Microsoft Excel 2016 sheet and processed statistically using “STATISTICS 12.0” software.

The obtained results were compared on the basis of log-rank criterion, p-criterion of significance of statistical differences. Besides, the Fisher’s exact test was used in order to determine the reliability of data obtained. In all cases, the difference was considered statistically significant at p<0.05.

The study was performed in the framework of the research and development work “Comparative analysis of algorithms for topometric preparation and planning of conventional and conformal radiotherapy on linear accelerators”, the theme code NAMS.04.14, the deadline 01.2014-12.2016; R&D “Development of a personalized control over the absorbed dose in radiation therapy of tumours of genitourinary system. Development of a package for the dosimetric estimation of the absorbed dose in radiation therapy of tumours of genitourinary system”, the theme code NAMS.02.17, the deadline 01.2017-12.2019.

Results and discussion. In order to pursue the objective, we analysed the results of chemoradiation treatment of patients with locally advanced squamous cell carcinoma of the head and neck after time-modulated administration of 5-fluorouracil in hypofractionation mode. The complete and partial tumour response to treatment amounted to 77.0%. At the same time, the stabilization and progression of the disease in the study group was 20.5% and 2.5%, respectively.

The survival rates are the most objective criteria for assessment of effectiveness of the treatment methods in malignant tumours. In our study, the two-year survival rate made in total 46.2 ± 8.3%, and the median survival composed 17.5 ± 3.6 months. Thus, the results of treatment of patients with locally advanced squamous cell carcinoma of the head and neck using the developed technique are compared with the literature data on classical chemoradiotherapy with cisplatin [6, 7].

SCCA marker assessment was started from the assessment of its sensitivity at the start of treatment. Thus, out of 30 examined patients with head and neck cancer of III, IVa, IVb stages, 16 patients had excessive values (2.5 ng/ml). Thus, the marker sensitivity was 53.3% what corresponded to the international data for these stages of the disease [4, 5]. Such sensitivity was too low to use as a screening method in squamous cell carcinoma of the head and neck.

There was no statistically significant difference between mean SCCA levels in patients with stages III and IV. However, the median in the group of patients with stage IV was 1.5 times higher.

Data on the oncomarker baseline level and the statistical indices are presented in Table 1.

Table 1 - Indices of SCCA oncomarker baseline level in blood plasma of patients with squamous cell carcinoma of the head and neck.

<table>
<thead>
<tr>
<th>Stage of the disease</th>
<th>Statistical indicators, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean value</td>
</tr>
<tr>
<td>III (n = 15)</td>
<td>3.74</td>
</tr>
<tr>
<td>IV (n = 15)</td>
<td>3.85</td>
</tr>
<tr>
<td>Total (n = 30)</td>
<td>3.79</td>
</tr>
</tbody>
</table>

If SCCA value was below the norm (14 persons), its level did not change significantly after radiotherapy and remained within the norm. Therefore, later we assessed the dynamics only in patients with an increased SCCA level – above 2.5 ng/ml before the treatment (Table 2).

As can be seen from the Table, the SCCA marker level has generally declined by 1.64 ng/ml. However, its large variation from 1.35 up to 3.38 has raised the need for a correlation analysis between the change of the oncomarker level and the efficacy of clinical treatment (Table 3).

Table 2 - SCCA oncomarker baseline level in blood plasma of patients with its increased level before the treatment.

<table>
<thead>
<tr>
<th>SCCA level</th>
<th>Statistical indicators, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean value</td>
</tr>
<tr>
<td>Before treatment (n = 16)</td>
<td>5.78</td>
</tr>
<tr>
<td>After treatment (n = 16)</td>
<td>4.14</td>
</tr>
<tr>
<td>Absolute difference of indices (n = 16)</td>
<td>1.64</td>
</tr>
<tr>
<td>Relative difference of indices (n = 16)</td>
<td>35.6 %</td>
</tr>
</tbody>
</table>

Table 3 - Correlation between the change of SCCA marker level and the treatment efficacy in patients with its increased level before the treatment.

<table>
<thead>
<tr>
<th></th>
<th>Degree of tumour regression</th>
<th>Time to death</th>
<th>Absolute change of SCCA level</th>
<th>Relative change of SCCA level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of tumour regression</td>
<td>1.0000 p = ---</td>
<td>0.6518 p = 0.006</td>
<td>0.6845 p = 0.003</td>
<td>0.5078 p = 0.045</td>
</tr>
<tr>
<td>Time to death</td>
<td>0.6518 p = 0.006</td>
<td>1.0000 p = ---</td>
<td>0.5942 p = 0.015</td>
<td>0.1598 p = 0.554</td>
</tr>
<tr>
<td>Absolute change of SCCA level</td>
<td>0.6845 p = 0.003</td>
<td>0.5942 p = 0.015</td>
<td>1.0000 p = ---</td>
<td>0.7724 p = 0.000</td>
</tr>
<tr>
<td>Relative change of SCCA level</td>
<td>0.5078 p = 0.045</td>
<td>0.1598 p = 0.554</td>
<td>0.7724 p = 0.000</td>
<td>1.0000 p = ---</td>
</tr>
</tbody>
</table>
The highest dependency was found between the degree of tumour regression and the absolute change of the SCCA marker level ($r = 0.6845$, $p = 0.003$). The relative change of that indicator to a lesser degree correlates with the immediate efficacy of treatment ($r = 0.5078$, $p = 0.045$). It should be also noted the dependency between the absolute change of the SCCA marker level and the time to death ($r = 0.5942$, $p = 0.015$). That could play a predictive role and influence the tactics of patients' management after chemoradiation therapy.

**Conclusion.** The diagnostic sensitivity of SCCA marker at stages III-IV of squamous cell carcinoma of the head and neck allows using it as a screening test. However, the monitoring of SCCA during chemoradiotherapy can reflect the treatment efficacy, serve as an additional lab criterion when deciding on further management of the patient, and also serve as an additional prognostic factor.

**References**
Combined treatment of lung cancer

Relevance. Lung cancer is leading in the structure of cancer morbidity and mortality in Russia and worldwide. The development of a combined method including optimal combination of surgical treatment, radiation and/or drug antitumour therapy is a priority that allows improving the treatment outcome. Special attention should be paid to intraoperative radiation therapy (IORT) that allows bringing a large single dose of radiation directly to the tumour or the zones of regional metastasis.

The aim of the study was to analyse the two-year results of combined treatment of patients with non-small cell lung cancer stage III with the use of IORT, chemotherapy and radiosensitization.

The results of combined treatment of 147 patients divided into 3 groups were studied in comparative aspect. The overall 5-year survival rate in the group of patients who received only surgical treatment with IORT was 29.2% (p<0.05). The inclusion in the combined treatment using IORT in a single dose of 15 G of preoperative chemotherapy with Paclitaxel/Carboplatin has authentically increased the overall 5-year survival rate to 39.2%. The additional use of radiosensitization with cisplatin has increased the overall 5-year survival rate to 47.9%.

Conclusion. The combined method including optimal combination of surgical treatment with radiation and/or drug antitumour therapy allows a significant and proven increase in the overall 5-year survival rate.

**Keywords:** lung cancer, preoperative chemotherapy, surgery, intraoperative radiotherapy, radiosensitization, survival.

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**Relevance:** Lung cancer (LC) is leading in the structure of cancer morbidity and mortality in Russia and worldwide [1-3]. In 2015, the share of LC in Russia was 10.2% among all malignant neoplasms in both sexes. LC ranks first in morbidity (17.8%) and mortality (27.5%) in male population. In women, LC is the 10th in incidence (3.8%), but in the last 5 years the absolute number of women with LC has significantly increased [1]. Therefore, LC is one of the most important medical and socio-economic problems.

Non-small-cell lung cancer (NSCLC) is detected in up to 80% of cases of malignant lung tumours. Surgery remains the main method of its treatment and is the most effective in stages I-II of the disease. However, 68.4% of NSCLC patients at the time of presentation are diagnosed with locally advanced forms [1, 4, 5], and their results of treatment still remain unsatisfactory. Despite the constant improvement of surgical outcome, there is no observable increase in the survival rate of patients with stage III NSCLC [5, 6]. In this regard, the development of a method providing an optimal combination of surgical treatment, radiation and/or drug antitumour therapy is required to improve the treatment outcome [4, 7].

Currently, there is a research for new variants of radiotherapy in combined treatment of NSCLC with a special attention to intraoperative radiation therapy (IORT). It delivers a large single dose of radiation directly to the tumour or regional metastasis. The use of IORT in patients with LC can reduce local relapses by 10-12.5% vs. surgical treatment and improve the 5-year treatment outcome [4, 8].

**Purpose of the study:** to analyse the three years of experience in combined treatment of patients with stage III NSCLC using IORT, chemotherapy and radiosensitization.

---

**Material and methods:** The study included 147 patients with stage III NSCLC who underwent treatment in the Thoracic-Abdominal Department of the Oncology Research Institute of the Siberian Branch of the Russian Academy of Medical Sciences.

The patients were divided into three groups (two study groups and one control group): group I: chemotherapy, radical surgery, 15 Gy IORT with cisplatin radiosensitization (48 patients); group II: chemotherapy, radical surgery, 15 Gy IORT (51 patients); group III (control): ablative surgery, 15 Gy IORT (48 patients).

90 (61.2%) patients from both groups had the central clinical anatomical form of LC vs. the peripheral form in 57 (38.8%) patients. The final stage of the disease was established post-surgery in accordance with the international TNM classification (Edition 7, 2009): III A stage – in 133 (90.5%) patients, \(T_2N_2M_0\) – in 29 (19.7%) patients, \(T_2N_0M_0\) – in 68 (46.3%) patients, \(T_3N_2M_0\) – in 36 (24.5%) patients, and III B stage – in 14 (9.5%) patients (\(T_4N_0M_0\)). By histological structure, 92 (62.6%) patients had squamous cell carcinoma, 48 (32.6%) patients – glandular cancer, and the rest 7 (4.8%) patients had large-cell carcinoma.

At the first stage of combined treatment, the patients from the study groups received 2 courses of preoperative chemotherapy according to the scheme: paclitaxel 175 mg/m² IV on day 1, carboplatin AUC dose calculation – 6 IV on day 1. The interval between chemotherapy courses and surgical treatment was 3-4 weeks.

The second stage included Cisplatin-based treatment for the purpose of radiosensitization in group I according to the scheme: IV by drop infusion, 2 days pre-surgery, on the eve of surgery and 2 hours prior to the 6 mg/m² IORT dose on the day of surgery.
Surgical treatment was the main stage of combined treatment in all the study groups. Surgical treatment was the main stage of combined treatment in all the study groups. 49 (33.3%) patients underwent pneumonectomy, 56 (38.1%) patients underwent lung resection in the extent of lobectomy and bilobectomy. 13 (8.6%) patients underwent reconstructive plastic surgery, 29 (19.8%) patients – combined surgery.

The patients of all groups received IORT as a component of combined treatment using a small-size pulse betatron with 6 MeV average electron energy located directly in the surgery block. IORT was performed in a single dose of 15 Gy. Irradiation fields were formed using the removable collimators with straight or sloping 4x7 cm tubes. Each irradiation field included the radical part of the remaining lung lobe with bronchopulmonary lymph nodes during upper lobectomy, retropericardial region during lower lobectomy, tracheo-bronchial angle, area of the lower bifurcation lymph nodes, as well as paratracheal and paravenous cellular tissue during pneumonectomy.

The efficacy of the combined NSCLC treatment was compared based on the analysis of timing and frequency of relapses and metastases in the next three years. The curves of the observed survival were plotted by the Kaplan-Meier method. The significance of differences in survival between groups was assessed by the C-test F-criterion.

Results and discussion: Frequency and timing of relapses and metastases is one of the most important criterion of the efficacy of combined treatment for stage III NSCLC.

In Group I, the disease has progressed in 17 (35.4±6.9%) patients, mainly due to distant metastasis in 14 (29.2±6.5%) patients and in a lesser extent due to development of local recurrence in 3 (6.2±3.4%) patients. The disease-free period was 27±1.2 months. 31 (64.6±6.9%) patients had no relapses and metastases in 3 years.

In group II, the disease has progressed in 22 (43.1±6.9%) patients as distant metastases in 15 (29.4±6.3%) patients and loco-regional recurrences in 7 (13.7±4.8%) patients. The disease-free period was 23.8±1.3 months. 29 (56.9±6.9%) patients had no relapses and metastases in 3 years.

In the control group, the progression of NSCLC after treatment was reported in 30 (62.5±7.0%) patients, with local relapses in 10 (20.8±5.8%) patients and distant metastases in 20 (41.7±7.1%) patients. The disease-free period was 17.1±1.4 months. 18 (37.5±7.0%) patients had no relapses and metastases in 3 years.

The analysis of local relapses showed that most of the relapses in the regional lymphatic nodes (73.3±8.0%) and in the area of resected thoracic wall or diaphragm (20.0±7.3%), with a few cases (6.7±4.5%) of stump bronchus lesion. Distant metastasis most often affect the liver (48.7±5.6%), skeleton bones (30.8±5.2%), brain (11.5±3.6%), opposite lung (9.0±3.2%), adrenals (6.4±2.7%), pleura (5.1±2.4%), and others (2.6±1.8%).

Thus, the combined treatment in the study groups has significantly (p<0.05) increased the 3-year relapse-free period vs. the control group. The 3-year overall survival in the study groups with preoperative chemotherapy and IORT with radiosensitization was also higher compared to the control group (p<0.05).

Preoperative chemotherapy in the paclitaxel/carboplatin regimen statistically significantly reduces the number of local relapses by 7.1% and distant metastases by 12.3% vs. the control group of patients who underwent IORT without systemic chemotherapy (p<0.05). C-test was used (p=0.002) for statistically evaluation of reliability of the differences obtained.

Our findings are generally consistent with other studies in which the induction therapy has advantages in long-term survival.

The additional application of radiosensitization increases the loco-regional control of IORT and increases the duration of the disease-free period. Thus, IORT at a dose of 15 Gy with cisplatin radiosensitization (group I) allows a reliable (p<0.05) reduction of relapses by 7.5% and prolongs the relapse-free period by 3.2 months vs. the group of patients who received IORT in the dose of 15 Gy without radiosensitivity (group II). Thus, it can be concluded that radiosensitization raises the efficiency of a single-dose IORT.

The survival of patients with NSCLC (even with the same stage III) is largely determined by the lymphogenous spread of the tumour process. We have compared the overall 3-year survival depending on the level of regional lymphatic lesions to show a direct relationship between the involvement of regional lymph nodes in the tumour process and the treatment outcomes.

Thus, the survival rate of patients in the control group at N1 metastatic lesion of lymph nodes was 53.3±7.2% vs. 24.7±6.2% at N2 level. The combined treatment with preoperative chemotherapy (Group II) has significantly improved the survival rate at N1 and N2 level vs. the control group (p<0.05). Additional application of Cisplatin for the purpose of radiosensitization has improved the treatment outcomes at N2 vs. the patients who received IORT without radiosensitization (p<0.05).

Conclusions: The comparison of a large set of clinical data shows that combined treatment with preoperative chemotherapy with paclitaxel/carboplatin, major surgery and IORT with radiosensitization significantly improves the immediate and long-term outcome of treatment of patients with stage III NSCLC vs. the patients receiving only surgical treatment and IORT.

We link the decrease in the number of relapses and the increase in the duration of disease-free period in the study groups primarily to the damaging effect of IORT in a single dose of 15 Gy on possible tumour microfoci in the bronchial stump, the surrounding tissues and the lymphatic drainage channels, and with a rising radiosensitivity of tumour cells to ionizing radiation thanks to radiosensitizers. Preoperative paclitaxel and carboplatin chemotherapy also had a positive effect.

References


Comparative assessment of efficiency of different dose fractionation in radiation therapy of inoperable lung cancer

Relevance. The methods of X-ray therapy are developing; still its achievements remain simple in their structure. The difficulties in therapy of primary malignant tumour of lungs are connected with the local spread of the process, damage of lymph nodes and biological peculiarities of growth. Moreover, irradiation of damaged area by high doses is associated with a low tolerance of healthy tissues with no possibility to monitor the tissues of lungs and vital organs during radiation. This indicates the importance of calculation of the interval and time of radiation in the course of therapy of malignant lung tumour in further development of X-ray therapy. Today, the calculation of volumes and interval of one-time and total radiation in treatment is associated with many difficulties. In spite of the vast experience in X-ray therapy, there are no therapeutic indicators regarding a certain type of malignant tumour. Cardinal application of X-ray therapy shall rely on radiobiological basis of ionizing radiation [1-6].

The significant indicators for X-ray therapy planning include the reparation of normal tissues damaged by radiation and the resorption of tumour during treatment. Currently, there are no established requirements towards this process; different fraction indicators are not defined.

Materials and Methods. The results of X-ray therapy of 431 patients with malignant lung tumours were taken for the clinical analysis. 395 central malignant tumours of lungs were proven in 36 cases (8.3%) by cytology and morphology. The patients were classified by stage of the disease, localization and distribution of the lesion. In all groups, the patients were divided by age, duration of disease and the resorption of tumour during treatment. Currently, there are no established requirements towards this process; different fraction indicators are not defined.

Materials and Methods. The results of X-ray therapy of 431 patients with malignant lung tumours were taken for the clinical analysis. 395 central malignant tumours of lungs were proven in 36 cases (8.3%) by cytology and morphology. The patients were classified by stage of the disease, localization and distribution of the lesion. In all groups, the patients were divided by age, duration of disease and the resorption of tumour during treatment. Currently, there are no established requirements towards this process; different fraction indicators are not defined.

Results. The article provides direct and remote results of treatment of 431 patients with lung cancer. Different dose fractionation methods are assessed.

Conclusions. With the rapid growth of the tumour, the most effective methods are medium-fractionated irradiation by “split” course and the accelerated method of dose multifractionation. Dynamic dose fractionation is recommended for palliative radiotherapy.

Keywords: Radiation therapy, methods of fractionation; dynamic fractionation, multifractionation.

Relevance. The author reviews the efficiency of radiotherapy with different dose fractionation in inoperable lung cancer. Purpose: to improve the results of treatment of patients with lung cancer by improving dose fractionation.

Results. The article provides direct and remote results of treatment of 431 patients with lung cancer. Different dose fractionation methods are assessed.

Conclusions. With the rapid growth of the tumour, the most effective methods are medium-fractionated irradiation by “split” course and the accelerated method of dose multifractionation. Dynamic dose fractionation is recommended for palliative radiotherapy.

Keywords: Radiation therapy, methods of fractionation; dynamic fractionation, multifractionation.
condition were observed in 83% and 92.3% of the patients from those groups [7, 8].

In the study of the latest results of 425 patients with malignant lung tumours, the most efficient were the following methods of fraction radiation: fraction method with middle pauses (Group III), dynamic fractionation by Revesh (Group V), fractionation according to E. Magdon graph (Group VI), and accelerated multifractionation (Group VIII). Small fraction method was more efficient by average life expectancy vs the control group (Group I): 13.9, 13.8, 14.1, and 13.2 months vs 8.8 months. The statistical confidence of the differences was \( P < 0.2, P < 0.1 \). Life expectancy in Groups III, V, VI, and VII was 16.1%; 13.9%; 20.5%; 19.0% in comparison to the control group (Group I) with 3.5% what is 2 years more. The statistical difference is confident. \( P < 3; P < 1.2; P < 2 \).

The survival after X-ray therapy in patients with malignant lung tumours depended on the tumour distribution. The survival up to one year at stage II was 63.3%, up to 3 years – 27.3% and for more than 5 years – 18.2%. At stage III, the survival up to one year was 30.8%, up to 2 years – 10.6%, and up to 3 years – 3.6%. At stage IV, 10 patients have lived up to one year, and one patient – up to 2 years (4%).

The life expectancy was studied at different TDF, CRE. Medium life expectancy increased with the TFD (CRE – 1530-2200) – 14.1 months, at the dose of 40 Gy – 6.7 months \( (P < 0.1) \).

We’ve established the correction of life expectancy depending on the tumour regression. The life expectancy does not exceed 14.2±3.6 months at full tumour regression, and 3.9±0.9 months – at inefficient X-ray therapy \( (P < 3) \).

The life expectancy depending on the histological structure was as follows: one year at wide-cell malignant tumour – 35.2%, at adenocarcinoma – 37.2%; two years at wide-cell malignant tumour – 7%, at adenocarcinoma – 8.3%; 3 years at wide-cell malignant tumour – 3.2%, at adenocarcinoma – 2%.

**Conclusion.**

1. Time division of the radiation dose in the treatment of patients with inoperable malignant tumours of lungs is relevant when using pre-tested fractioned and multifractionated regimens.
2. Life expectancy is directly linked to all the regimens of dose fractionation and the tumour regression: life expectancy is increased at full tumour regression.
3. Stable tumour regression is reached at high received dosage of 60-80 Gy \( (\text{TDF} – 86-116; \text{CRE} – 1530-2000 \text{REU}) \).
4. Timely radiation at middle fractionation with a middle pause, accelerated multifractionation, and “dynamic” regimen are efficient at quick tumour development.
5. Dynamic fractionation as palliative X-ray therapy is efficient at malignant tumours complicated by atelectasis. This method of treatment is well tolerated by the patients.
6. The speed of tumour development, the time of its twofold increase and decrease have a prognostic value.

**References:**

Immediate and long-term results of combined treatment of patients with recurrent thoracic esophageal cancer

Relevance. Metastases in cervical and supraclavicular lymph nodes are found in 7-12% of cases after surgical treatment of esophageal cancer. At present, a certain tactic of treatment of this cohort of patients has not been worked out.

Purpose of the study: improving the results of treatment of patients with recurrent esophageal cancer after surgical treatment.

Results: 25 patients who received combined therapy for esophageal cancer recurrence in cervical lymph nodes underwent cervical node dissection after classical cervical lymph nodes teleirradiation. Special mention should be made of their life expectancy: 10 (40%) of 25 patients survived after two years, and 5 (20.0%) have been living for three years.

Keywords: metastases, cervical lymph nodes, radiotherapy, lymph node dissection.

Introduction. Currently, the optimal management of the recurrent esophageal cancer in the neck lymph nodes remains controversial.

The literature demonstrates a variety of lymphogenous metastases of esophageal cancer, the possibility to disrupt the sequence of its metastasis, and the fact that the assignment of lymph nodes to this or that metastasis stage is purely conditional. Therefore, the question of removing the supraclavicular and cervical lymph nodes as one block remains open as for the thoracic oesophagus cancer.

Some authors treat them as regional lymph nodes and call for their mandatory removal with bilateral cervical-supraclavicular lymph node dissection [3F] [1, 2]. Others remove supraclavicular lymph nodes only in case of an apparent metastatic lesion [3, 4]. The disadvantages of single-step 3-field lymph node dissection include: 1) the injury rate of the operation and its duration; 2) unsatisfactory short-term outcomes – post-surgical lethality ranges from 18.5 to 26.6%; 3) low 3-year and 5-year lifetime (14% and 6%, respectively) [5].

Other authors consider these lymph nodes as distant and do not recommend surgery for such patients, limiting the treatment to external-beam radiotherapy. Unfortunately, the immediate clinical outcome of radiation therapy does not exceed 20%, and only 5% of treated patients survive a one-year period [6, 7].

The presence of esophageal cancer metastasis in the neck lymph nodes is not always a sign of a bad condition of the patient. In some cases, the detection of recurrent esophageal cancer or distant metastases enables a re-treatment with a quite persistent positive outcome. The clinicians interpret such metastases as a reflection of extensive lymphogenous dissemination. This is certainly true for stomach cancer but does not seem to be always true for esophageal cancer. The authors’ own observations and the world literature data suggest that cervical lymph nodes metastases in esophageal cancer are conventionally regional.

Purpose of the study was to improve the immediate and long-term treatment outcomes of recurrent esophageal cancer. This purpose was achieved by combined treatment without preventive bilateral cervical-supraclavicular lymph node dissection. We did not perform preventive bilateral cervical-supraclavicular lymph node dissection due to a low incidence of metastasis in the cervical lymph nodes (7% to 12%) and a high percentage of post-surgical complications after 3-field lymph node dissection [8, 9].

Materials and Methods. 25 patients with recurrent esophageal cancer in cervical and supraclavicular lymph nodes long after surgery were subjected to combined treatment. The first stage of combined treatment included external-beam radiotherapy with the “Rokus-M” gamma-therapeutic device for the lymph nodes of the neck affected by the metastatic process, as well as the zones of regional metastasis.

The paratracheal, cervical oesophagus and supraclavicular lymph nodes on both sides were exposed to radiation as one block from the open front figure field; the larynx was protected with a lead block. The radiation therapy was administered by a split course with the single dose of 2Gy daily, 5 times a week to the total dose of 40-46 Gy depending on the patient condition.

Deep cervical and cervical lateral lymph nodes were irradiated from two opposite fields using equalizing wedges and with spinal protection. The fractionation regime depended on the process prevalence and the general patient’s condition. The total dose was 40-46 Gy.

In addition to the classical fractionation, we used the multiple split-dose method with the interval of 4-6 hours (hyperfractionation) in four patients, taking into account the different rate of repair of radiation damage in the tumour and normal tissues. It allowed increasing the dose to the tumour within 10% of safety for healthy tissues.

The immediate positive effect of radiation treatment was achieved in 10 (40%) of 25 patients:

• 8 (33.3 %) had partial involution of the tumour;
• 2 (8.4 %) had complete involution of the tumour.

Surgical treatment was started 2-3 weeks after the reduction of radiation reactions. The average interval between the relapse and radical surgery was 2-2.5 months.
Standard operations to remove metastatic nodes of the neck included Fascial-Cervical Neck Fiber Resection (FCNFR) and the Crile operation. FCNFR was indicated at displaced, isolated metastatic lymph nodes not adherent to the anatomical neck formations. Crile operation was performed in case of multiple metastatic lymph nodes or metastases in the lymph nodes of the neck with limited displacement adherent to the anatomical formations of the neck.

The technique of the Crile operation and FCNFR was not described here as it has been described in sufficient detail in Medical Atlases and manuals. But it should be noted that during these operations the authors were not removing the contents of the submandibular triangle and did not perform parotid resection [10].

**Results.** The lifetime of 25 patients who underwent combined treatment for recurrent esophageal cancer in the lymph nodes of the neck is worth looking at: 10 (40%) of 25 patients survived a two-year period and 5 (20.0 %) lived for three years. It is important that all the patients could freely take food in a natural way starting from Day 3 after surgery and till the last days of their life, adding body weight; and some patients have added 5 kg.

**Description of a clinical case:**

Patient K., 54 years old, medical record 12/874, was admitted to the Thoracic Surgery Department of the West Kazakhstan Regional Oncology Center on 14.07.2012 with complaints of the mass in the left supraclavicular region. The disease history was 1 month. On November 23, 2011, he underwent esophagus resection of the Lewis type for stage III oesophagus cancer of the bronchial segment. At the admission: the general condition was satisfactory, an enlarged, mobile, lymph node not adherent to the skin and adjacent anatomical structures was defined in the left supraclavicular region. A puncture biopsy of the lymph node was performed. Cytological Conclusion 2012/4431: metastasis of squamous cell carcinoma. Symptoms of metastasis to other organs were not revealed in the X-ray, an enlarged, mobile, lymph node not adherent to the skin and adjacent anatomical structures was defined in the left supraclavicular region. A puncture biopsy of the lymph node was performed. Cytological Conclusion 2012/4431-8: metastasis of squamous cell carcinoma. Symptoms of metastasis to other organs were not revealed in the X-ray, endoscopic, ultrasound study. The external-beam gamma therapy was performed on the area of the metastatic node and the zone of regional metastasis in the classical fractionation mode: 2 Gy. within 5 days before the total boost dose - 46 Gy. Two weeks after irradiation, 10.12.2012 the Fascial-Cervical Neck Fiber Resection was performed on the left side of the neck. Post-surgical period – without complications. Histological conclusion 2012/1256: metastasis of epidermoid cancer without keratinization with the phenomena of degree II radiation pathomorphosis. The patient was discharged in a satisfactory condition. During the last visit on 27.06.16 the disease did not progress.

**Conclusions.** Thus, the presence of esophageal cancer metastasis in lymph nodes of the neck is not always a sign of a bad condition of the patient. The significant improvement in long-term treatment outcome can be achieved in case of early recognition and combined treatment of recurrent esophageal cancer. This method of treatment can be used in specialized oncological institutions.

**References**

CLINICAL CASE

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Clinical cases: surgical treatment of lip cancer with reconstruction of advanced defects

Relevance. Treatment of lip cancer includes not only wide excision of the tumour, but also a simultaneous reconstruction. Reconstructive surgery is a plastic surgery, the purpose of which is to restore lost anatomy and functions. But, unfortunately, with wide excision of the lip without reconstruction extensive defects, as well as good long-term results, they are extremely problematic from an aesthetic and functional point of view, representing in particular permanent salivation, difficulty in chewing, leakage of food from the oral cavity and speech defect.

Aim: Demonstration the results of our clinical cases, with simultaneous reconstruction of the upper or lower lip cancer with advanced post-surgical defects was closed by local tissues.

Results: In the clinical cases described by us, the main method of treating lip cancer was surgical with a simultaneous reconstruction of the defect. The presented clinical case reviews the use a skin-mucosal flap in the reconstruction of the upper and lower lips in patients with SCC. In all cases, tumours are radically removed, have good prognostic, aesthetic and functional results.

Conclusions: There is no “gold standard” for reconstructions of extensive defects in the upper and lower lips, especially in squamous cell carcinoma. In the clinical case No.1, we propose this method as another version of the reconstruction. Clinical cases No. 2 and 3 are known in oncology and have good long-term functional and aesthetic results. According to our clinical cases, the quality of life all patients, does not suffer.

Keywords: lip cancer, reconstruction of lips, simultaneous reconstruction, squamous cell carcinoma.

Introduction. Lip cancer is a malignant neoplasm affecting the vermilion border of the lips. This tumour is easily accessible visually, and its early diagnosis is not particularly difficult. Nevertheless, practice shows that there are also forms of cancer of this localization that are difficult to diagnose at early stages, which indicates diagnostic errors. Patient visit at the late stages Т₁ и Т₂ is 2935.5% [1].

Lip cancer is a fairly common malignant neoplasm, and errors in diagnosis are not uncommon. Lip cancer accounts for almost 3% of all malignant neoplasms and 12% of malignant neoplasms of the head and neck, and occupies the 8-9th place in frequency. Among all lip malignant neoplasms, the lower lip cancer is 95%, the upper lip cancer is 2-3% [2]. Squamous cell carcinoma (SCC) mainly affects the lower lip and accounts for 90% of cases, mainly on the red lip. Basal cell carcinoma (BCC) is more common on the skin of the upper lip. Rarer types: adenocarcinoma, melanoma, lymphoma and sarcoma [3]. Lip carcinomas often appear on the premalignant lesion background, such as radiation dermatitis, chronic cheilitis, leucoplakia and xeroderma pigmentosum. Thus, the diagnosis and treatment knowledge of these premalignant lesions is necessary to avoid their degeneration into a tumour.

Lip malignant neoplasm is more common in white men over 50 years, probably due to the exposure to sun in combination with increased use of tobacco, alcohol and the presence of viral oncogenes, especially in patients with immune deficiency [4, 5].

Initially, the tumour appears as a papule or a plate which develops in the exophytic or ulcerative form. In these cases, a biopsy or scraping is required to confirm the diagnosis of carcinoma. Patients with stage T2 have regional metastatic lymph nodes in 8% of cases, with a significant increase at the late stage [6].

The most common treatment methods are surgical intervention, radiation therapy and cryotherapy (freezing with liquid nitrogen). At that, the treatment efficiency is close to 100% at early stages. The choice of treatment method depends on the stage and size of the tumour, the age of the patient and the general state of health, although this form of cancer is more curable than malignant neoplasm of other locations of the head and neck. According to some authors, the frequency of relapse varies from 5 to 35%, the mortality reaches 15% [3, 7]. The regular case monitoring is important. The five-year survival rate is reduced to 50% with cancer metastasis to the regional lymph nodes [8].

The lip cancer treatment includes not only extensive excision of the primary site but also a one-stage reconstruction. Reconstructive operations are plastic surgical interventions whose purpose is to restore lost anatomy and functions. The successful reconstruction depends on careful preoperative planning, knowledge of anatomy and the use of various surgical techniques. Tumours identified at early stages have good prognostic, aesthetic and functional outcomes after surgery compared to the treatment of extensive tumours that alter the appearance and functionality of the lip. Unfortunately, total radical labial excisions without the reconstruction of extensive defects, although they give good long-term results, are extremely problematic from an aesthetic and functional point of view, since they result in permanent salivation, difficulty in chewing, leakage of food from the oral cavity and speech defect.

One-stage reconstruction surgery was the method of choice for the treatment of patients with malignant neoplasm of the lip in the clinical cases presented below. Local tissues were used for simultaneous reconstruction of extensive post-surgical defects of the upper or lower lip.
Patient information.

№1. Patient P., a woman aged 51 years, was admitted on 27.03.2017 to the Center of tumours of bones, soft tissues and melanomas of the Kazakh Institute of Oncology and Radiology (KazIOR). Complaints at admission: the absence of the upper lip right segment with ulcerous defects along the edges bleeding on contact, and the upper gum exposure in the region of anterior incisive teeth, periodic local pain.

According to oral information provided by the patient, she was ill since 2000, from the time when the mass first appeared on the skin of the upper lip on the right. In connection with the mass growth, in 2004, she went to a doctor in a private clinic in Taraz where an operation was performed under local anaesthesia: excision of the skin tumour of the nasolabial fold area on the right (a case record was not provided). The continued tumour growth was noted in the post-surgical period. The rapid tumour growth has been noted since January 2017. In February 2017, she was treated in the Regional Oncological Dispensary in Taraz, did not receive special treatment because of severe anaemia, but only hemostimulation therapy.

Clinical data. The skin and mucous membrane is absent in the area of the upper lip. They are destroyed by the tumour, an open defect of 1.5x2.0 cm with a bare gum area and anterior superior incisive teeth. There are crater-like ulcers along the edges with a lesion of the upper part of the gum and a leading edge of the nose to the right up to 1.5 cm, bleeding on contact (Figure 1a, b, c).

Diagnostics. The computer tomography of the facial skeleton dated 28.03.2017: diffuse thickening of the nasal vestibule soft tissues on the right side, up to 0.7 cm, 3.0 cm long. A skin defect of the upper lip on the right, 2.0x1.3 cm in size. Conclusion: status after surgical treatment for lip skin cancer, relapse, necrosis.


28.03.2017 she was consulted by a cardiologist, diagnosis: Hypertension of the 3rd degree, risk 3. The cardiac risk is high. There are no contraindications to the special treatment.

The patient was diagnosed with “St.II (T N M) upper lip skin cancer on the right side. Condition after non-radi- cal surgical treatment (2004). Continued growth. Necrosis”.

Treatment. 04.04.2017 the patient underwent an operation under general anaesthesia in the extent of “Wide excision of the upper lip skin tumour with resection of the gingival part of the anterior incisor on the right, resection of the lower third of the nasal septum, the nasal vestibule on both sides and removal of the front upper incisors. A plastic reconstruction of defect of the mucosa by the tensor fascia latae site from the outer surface of the middle third of the thigh to the right. A plastic reconstruction of the upper lip defect with dermis fat graft from the nasolabial region to the left and the buccal region to the right” (Fig. 2a, b, c).
Post-surgical histological examination No. 0.16930-34 dated 11.04.2017: basal skull (metatypical) carcinoma of the upper lip skin with lymphoid infiltration of the stroma. Tumour cells were not found at the edge of the resection. The patient received antibacterial therapy and daily dressings after surgery; the sutures were removed 11 days after surgery and she was discharged home on Day 13 (Figure 3).

Figure 3 - Patient P., 51 years, Day 13 after surgery.

No 2. Patient T., a man aged 64 years, was admitted the 17th of September 2017 to the Center of tumours of bones, soft tissues and melanomas of KazIOR. Complaints at admission: the total absence of the lower lip and the presence of a mass on the skin of the lower lip on the left site, constant drooling.

According to oral information provided by the patient: he was ill since 2010, when there was a mass on the vermilion border of the lower lip on the right. After repeated traumatisation of the mass, he noted bleeding and tumour growth.

In June 2013, he applied to the Regional Oncological Dispensary in Taraz where the scraping was made. Cytological Conclusion No 39 dated 04.06.2013: squamous cell carcinoma

The treatment was carried out in the Regional Oncological Dispensary in Taraz:
- 04.02-18.02.2014 - the 1st course of radiotherapy on “Rum17” apparatus, the total boost dose 14 Gy, D3150-BFL, the total boost dose 23 Gy.
- 04.03-26.03.2014 - the 2d course of radiotherapy, the total boost dose 42 Gy

In April 2016 he noted the repeated growth of the lower lip tumour.
- 17.08-01.09.2016 - the 3rd course of radiation therapy for the tumour relapse area, the total boost dose 20 Gy.
- 21.09-07.10.2016 - the 4th course of radiation therapy for the tumour relapse area, the total boost dose 44 Gy. The patient noted the post-radial burn on the vermilion border of the lower lip, bleeding and soreness.
- 15.12.2016 - operation under general anaesthesia in volume “the excision of the lower lip mass”. Histological Conclusion: squamous cell carcinoma

In August 2017 he noted the appearance of a mass along the post-surgical cicatrix on the skin of the lower lip on the left.

Clinical data. The skin and mucous membrane of the lower lip are absent - the condition after the operation, the open defect is 3,5х1,5 cm with the bare portion of the gum and lower teeth. There is a solid, painful mass with d-1.0 cm along the edge of the post-surgical scar on the skin of the lower lip on the left, and a constant drooling (Fig. 4a).

Diagnostics. 18.10.2017 he was consulted by a cardiologist, the patient was diagnosed with: "Hypertension of the 2d degree, risk 2". There are no contraindications to the special treatment.


Ultrasound of the neck dated 18.10.2017. Conclusion: echo signs of salivary adenitis of the submaxillary glands from both sides. Single lymph nodes of the neck on both sides with preservation of differentiation, more data for lymphadenopathy.

The patient was diagnosed with “St1(T1N0M0) lower lip cancer”. Condition after 2 courses of radiation therapy (the total boost dose 79 Gy 2014) Relapse (2016). Condition after 2 courses of radiation therapy (the total boost dose 66 Gy 2016) Continued growth. Condition after surgical treatment (2016). Relapse”.

Treatment. 19.10.2017, the operation was performed under the general anaesthesia in the extent of: “The excision of the post-surgical scar with the excision of a recurrent tumour of the lower lip skin with the plastic reconstruction of the defect by the skin-mucous graft from the nasolabial fold on the left; c – Day 7 after surgery.

No 3. Patient L., a man aged 57 years, was admitted on 01.03.2018 to the Center of tumours of bones, soft tis-
sues and melanomas of KazIOR. Complaints at admission: on the presence of an ulcerative defect on the skin, vermil- ion border and mucosa of the lower lip on the right, bleed- ing on contact, ulcerative defect of the chin area.

According to oral information provided by the pa- tient: he was ill since 2017, when the mass with a gradu- al growth in the dynamics appeared on the lower lip on the right. He was examined in the Regional Onco- logical Dispensary of Novosibirsk in October 2017. Sur- gical treatment was recommended. In January 2018 he applied to the Regional Oncological Dispensary at his place of residence in Semey. He was directed for treat- ment to KazIOR.

**Clinical data.** Crater-like ulcerative defect with the size of 4.0x3.0 cm, on the vermillion border of the lower lip on the right with spreading to the skin and mucosa of the lower lip, there is a vermillion border in the centre; the mu- cosa of the lower lip is absent - destroyed by the tumour, bleeding on contact. Tumour-shaped solid mass with d=3.0 cm in the thickness of the soft tissues of the chin region, there is a decay of 1.0x0.5 cm with a saccharine discharge in the centre of which (Fig. 5a, b, c).

**Diagnostics.** Ultrasound of the cervical lymph nodes dated 02.03.2018: enlarged lymph nodes of the submandibular regions (right: up to 27.3x22x19.7 mm V = 6.19 cm³, left - up to 20.4x18.3x15.3mm V = 2.98 cm³) and upper third of the neck to the right (up to 15.4x14.1x10.5 mm V = 1.19 cm³), echograph- ically characteristic for mts, with sites of infiltration and oedema in soft tissues along the periphery of the nodes. Enlarged lymph nodes of the upper third of the neck to the left (up to 15.6x12.7x8.3 mm V = 0.86 cm³) - differentiate between mts and lymphad- enitis.

Based on clinical data, past medical history, localization and cytological data, the patient was diagnosed with “St.III (T3N0M0) lower lip cancer. Mts in the lymph nodes of the chin area. Necrosis”.

**Treatment.** 06.03.2018, the operation was carried out under the general anaesthesia, in the extent of “Two-sided cervical lymphodissection 1, 2, 5a of the zones on the left, 1, 2, 5a of the zone to the right with removal of the soft tis- sues of the oral cavity bottom. Drainage”, “Resection of the lower lip on the right with excision of the tumour. Plastic re- construction of the defect by a skin-mucous graft from the nasolabial fold on the right” (Fig. 6a, b). Histological Con- clusion No 0.14166-95 dated 14.03.2018: Keratinizing squa- mous cell carcinoma G1 of the lower lip with ulceration and purulent inflammation. Tumour cells were not found at the edges of resection. Cancer metastases in 7 of the 12 exam- ined lymph nodes. Salivary gland of normal structure.

Post-surgical period was without complications. The patient received antibacterial therapy, daily dressings, and was discharged home on Day 9 after surgery (Figure 6b).
**Results.** Surgical treatment with one-stage reconstruction of the defect was the method of choice for lip malignant neoplasms in the described clinical cases. In all cases, tumours were radically removed with good prognostic, aesthetic and functional results.

**Discussion.** Surgical excision of the lip tumour at early stages does not create special problems for reconstruction. The lip reconstruction to close extensive defects requires the utmost care to preserve it as naturally as possible and function. It should be remembered that lips are an extremely important part of the face not only from the aesthetic point of view, but also in relation to some important functions. They play a major role in nutrition, speech and expression facial expressions. For these reasons, at the lip reconstruction, all three layers must be considered: the skin, muscles and mucous membrane. Commis sure is crucial to avoid saliva leakage and ensure proper intake of food, so it is necessary to restore the structure in places with more serious damage. The task of reconstruction in the area with the greatest defect is the use of skin flaps to restore the complete structure of the lips, especially local flaps, which provide excellent consistency in terms of texture, colour and thickness. The reconstruction may be complicated, when the lip is involved because of lesions of neighbouring structures, the tumour recurs or in primary-multiple skin cancer. The reconstruction should ensure adequate opening of the oral cavity and sufficient mucous membrane next to the commissure to avoid contracture. Various authors offer numerous reduction methods; we have used in these cases a skin-mucosal flap in the reconstruction of the upper and lower lips in patients with SCC. Although microsurgery is recommended at later stages of SCC, there is no “gold standard” for the reconstruction of extensive defects in the upper and lower lips, especially in the case of SCC. The restoration of large tissue loss is the most important problem of lip cancer surgery. We propose this method as another version of the reconstruction in the clinical case No. 1. Clinical cases No. 2 and 3 are known in oncology and have good long-term functional and aesthetic results. In the described clinical cases, the quality of life of patients does not suffer in post-surgical period.

**References**

Unilateral breastfeeding is a risk factor for breast cancer

Relevance. The problems of breastfeeding are covered unilaterally in domestic and foreign literature, only as advantages for normal physical and psychological development of children. However, even these advantages have not been applied in full force in recent years. Most children are transferred to artificial feeding very early and often unreasonably.

Purpose of the study: Epidemiological studies of breast cancer patients in Kyrgyzstan region (KR) and retrospective analysis to determine risk factors for breast cancer.

Results: The study has revealed a growth in incidence of breast cancer patients increased from 7.8‰ to 15.3‰ from 2002 to 2017. In collecting the anamnesis of patients with breast cancer, we noticed that even the many-breasted women and the women who were breastfeeding for up to one and more than 2 years were mostly feeding with one breast. That, unilateral breastfeeding was more common in the group of patients with breast cancer (42.1±4.6% vs. 2.0±1.0%, P<0.001).

Conclusion: 1. The main approach to reducing cancer should be based on preventing the disease, not on its treatment [1].
2. Unilateral feeding can be one of the leading risk factors for developing breast cancer along with many other risk factors for breast cancer.
3. There is a need to develop a strategy and regional and national policies to support and promote breastfeeding in order to reduce morbidity and mortality of young children, and the risk of breast cancer.

Keywords: unilateral feeding, morbidity, mortality, breast cancer, risk factors.
Main reasons for stopping breastfeeding:

I. Modern life conditions: wide advertising of baby food; early return of women to work; fear to loose sex appeal.

II. Disapproval of breastfeeding by relatives: advises from the relatives (mother, mother-in-law) to feed with artificial additions, even demand to feed with additional food when a child is crying or gains weight poorly; mother has to return to work by request of the relatives if she is the only source of income in the family.

III. Insufficient support of breastfeeding by medical workers: lack of systemic teaching how to breastfeed in medical colleges and universities; lack of systemic training of doctors, paediatricians, oncologists and mammologists of primary healthcare institutions on the issues of breastfeeding.

IV. Insufficient advertising of breastfeeding: insufficient advertising of breastfeeding via audio-visual, broadcasting and other mass media; insufficiency or lack of academic literature and non-fiction.

V. One-sided breast feeding and its reasons: one-sided deterioration of lactation after mastitis; cracked nipples; national peculiarities: breastfeeding by mother by inclining to a cradle, as it is convenient for her; one-sided feeding lying on her side, as it is convenient for her; false confidence that milk goes poorly on the one side; doubts in volume and quality of breast milk; formation of child habit to be fed on the one side based on own convenience, one-sided treatment by nipple improvement. Due to such reasons, milk generation decreases on the one side, and a stable hypogalactia develops.

Breastfeeding is efficient, convenient, favourable, warm and clean. Preparation to breastfeeding does not take time and additional funds. Mother's and child's disease incidence reduces at breastfeeding, and medical aid related costs decrease. It is necessary to develop a national program for support of breastfeeding to reduce disease incidence and mortality of new-borns and decrease probability of BMT.

Conclusion.

1. Prevention is the key way to reduce cancer incidence. This conclusion is topical and reasonable for BMT.
2. According to the data obtained in the course of the study, one-sided breastfeeding may be the main factor of threat among numerous factors of BMT threat.
3. A national program for support of breastfeeding shall be focused on both mothers and children in order to decrease BMT incidence.

References:

Perfusion computed tomography in gastric cancer diagnostics and treatment efficacy evaluation (literature review)

Introduction. Gastric cancer remains one of the most common causes of cancer deaths worldwide. Introduction of 320-slice multispiral computer tomographs, high-field MR scanners (3T) has provided high-quality visualizing images of organs and systems. New imaging methods provide not only imaging of the organ structure, but also allow assessing the metabolic and functional state of various organs and types of lesions. CT perfusion is one of these methods. It is since recently used to diagnose gastric cancer.

Material and methods. The conducted literature review has covered the PubMed database for the period of 2008-2018. Search was performed by keywords “Perfusion CT, gastric cancer”. Of the 25 sources, only 14 scientific publications met the established selection criteria.

Literature review. A review of the literature about perfusion CT of gastric cancer is provided. Study of intra-tumour hemodynamics, or so-called tumour perfusion, is necessary to understand the status of cancer. The parameter for non-invasive preoperative evaluation of tumour perfusion has not been developed yet.

Conclusion. CT perfusion parameters can serve as indicators of the degree of malignancy and prognostic evaluation of gastric cancer. They allow evaluating the efficacy of neoadjuvant chemotherapy in patients with advanced gastric cancer. Perfusion CT of gastric cancer requires further study.

Keywords: Perfusion, gastric cancer, CT.

Relevance. Gastric cancer (GC) is one of the most common malignant neoplasms in the world and one of the most common causes of cancer deaths worldwide. For several decades, GC is leading in the structure of cancer mortality in the Republic of Kazakhstan. For example, in 2014, GC ranked second in the structure of cancer mortality [2]. Computed tomography (CT) plays one of the leading roles in the diagnosis of GC. Today, this method is one of the leading methods to determine the prevalence of a tumour within the stomach wall and involvement of adjacent organs in the process, as well as to detect distant metastases [1, 3, 4]. The new 320-slice multispiral computer tomographs and high-field MR scanners (3T) provide high-quality images of organs and systems. New methods of radiological imaging not only deliver images of organ structure but also allow assessing the metabolic and functional state of various organs and the types of lesions. These new methods of visualization include: diffusion MRI, magnetic resonance spectroscopy, positron emission tomography (PET-CT) and perfusion CT and MRI. They assess not only structural but also functional data. The data provided by the mentioned visualization methods is called “biomarkers” as it allows analysing the biological behaviour of normal and involved tissues [5]. There are several scientific papers related to perfusion CT with GC.

Materials and methods. The literature review was conducted based on the scientific research data available in PubMed database for the period of 2008-2018. The search words included “Perfusion CT, gastric cancer”. A total of 25 literature sources were revealed, of which 11 publications were excluded as not fitting the selection criteria (all works that did not include patients with GC were excluded). The literature review included 14 literature sources meeting the selection criteria.

Literature review. The study of intra-tumour hemodynamics known as tumour perfusion is necessary to understand the course of cancer. The parameter for non-invasive preoperative evaluation of tumour perfusion has not yet been developed.

The early study of CT perfusion in GC was made by Satoth A. et al. (2010). The paper describes 50 cases of patients who underwent surgery for GC. Perfusion CT was performed on 16-slice computer tomograph. Blood flow velocity (ml/min/100 g) was measured and compared with histopathological characteristics. Its correlation with microvessel density and stromal tumour structure was evaluated, and the correlation of vessels and stromal tissue was calculated. The authors concluded that a reduced value of the blood flow velocity obtained on perfusion CT may reflect the progression of the process in gastric cancer. The perfusion of the tumour was decreasing with the increase in tumour stage and the degree of malignancy, and therefore perfusion CT could be the best method for assessing the malignancy of GC [6]. Zhang H. et al. (2008) came to the same conclusions [7].

Another early work (2010) to study CT perfusion in GC was a prospective study performed on a 64-slice computer tomograph in 35 patients with GC. The patients were divided into three subgroups depending on the tumour location; the control group consisted of 24 patients without gastric pathology. Four parameters of CT perfusion were studied, such as perfusion, peak increase, time to peak and...
blood flow volume. The results showed that the blood flow was significantly higher in the GC group, compared with that in the control group. It was noted that the threshold value of the blood flow volume (8.6 ml x 100 g⁻¹) corresponds to a sensitivity of 88.6% and a specificity of 62.9% for the GC diagnosis. Perfusion CT was able to evaluate tumour vascularization and was used to diagnose GC [8].

Yao J. et al. (2011) have studied tumour vascularization and angiogenesis of gastric tumours by analysing blood flow volume on perfusion CTs. The authors analysed the correlation between the parameters measured on perfusion CTs, microvessel density and vascular endothelial growth factor (VEGF), determining them in tumour tissue on histological sections after surgery for GC. The blood flow value on CT perfusion sections significantly correlated with the density of microvessels in the tumour (the Pearson correlation coefficient was 0.420, p=0.001), which may reflect angiogenesis in gastric adenocarcinoma. However, no correlation was found between VEGF expression and perfusion CT-parameters, and there was also no correlation between the group of patients having positive VEGF expression with patients without VEGF expression in the gastric tumour [9]. On perfusion CTs, blood volume was significantly increased with gastric adenocarcinoma as compared with the normal stomach (19.75 +/- 14.74 vs. 13.59 +/- 11.46 ml/100 g, whole stomach, P = 0.004). There were no significant differences in perfusion parameters between groups of patients with or without lymph node metastases, and there were no significant differences in perfusion between early and late forms of gastric cancer. Perfusion CT is a technique for quantifying tumour vascularity and angiogenesis in gastric adenocarcinoma [10].

At present, four main parameters are studied when performing perfusion CT in GC: blood flow velocity, blood flow volume, mean transit time, and capillary bed permeability surface.

Such parameters as blood flow velocity, blood flow volume and the surface area of permeability in study groups are statistically significant for comparing the three degrees of differentiation of gastric adenocarcinoma (low-, medium-, and highly-differentiated). The values of blood flow velocity, blood flow volume and permeability surface can serve as indicators of the degree of GC malignancy [11]. The same conclusions were made by Sun Z.Q. et al. (2015). They showed that the perfusion image of the stomach on CT sections had a high potential for clinical use as functional imaging technology. The values of blood flow velocity, blood flow volume and permeability surface served as indicators of GC malignancy and prognostic assessment. The parameter of average transit time did not show significant differences in the compared groups [12].

Lee D.H. et al. (2018) have also noted that the evaluation of CT perfusion parameters could help to determine histological subtypes of GC. However, in a preoperative perfusion CT scan of 46 patients with GC, the permeability surface (p=0.001) and the mean transit time (p=0.032) for a poorly differentiated carcinoma were significantly higher than the same parameters at other histological types of GC [13].

The capacity of CT perfusion in the differentiation of macroscopic forms of GC between Bormann II and Bormann III types was assessed by Lee J. et al. (2016). Such parameters as blood flow velocity, blood flow volume, arterial blood flow velocity and clearance (permeability surface) were measured. It was found that blood flow velocity, blood flow volume, arterial blood flow velocity did not differ significantly in the groups at the ulcer level, whereas the clearance in stomach area with ulcer defect in the Bormann III type was significantly higher than in the Bormann II type (p=0.00). More proximally and distally to the ulcerative defect in the gastric wall on the lesion side, there were no significant differences in the groups in all studied parameters in CT perfusion studies of the stomach. The authors suggest that such a parameter as clearance (permeability) has a definite diagnostic value for GC differentiation between Bormann II and Bormann III types [14].

CT perfusion has established itself as a method of qualitative and quantitative evaluation of the efficacy of neoadjuvant chemotherapy in GC. Thus, the decrease in tumour size after neoadjuvant therapy has significantly correlated with the blood flow velocity and permeability of the surface on perfusion CTs. Neoadjuvant therapy was more effective for patients with higher initial values of blood flow velocity and surface permeability in the stomach tumour. There were no significant differences between a decrease in the gastric tumour size with parameters such as blood flow volume and mean transit time. Patients with a positive response to chemotherapy showed a decrease in perfusion parameters such as blood flow velocity, blood flow volume and surface permeability, while mean transit time increased in the course of the treatment [15]. Sun Z. et al. (2017) have revealed the significant differences in blood flow velocity and blood flow volume in patients with advanced forms of GC before and after chemotherapy (p<0.001). Those two parameters correlated with the pathomorphological response of the tumour (r=0.660, p<0.001; r=0.706, p<0.001). The authors derived the criteria for the chemotherapy efficacy. Thus, the decrease in blood flow velocity by 12.1% during treatment (P=0.005) was considered as the criterion for the efficacy of chemotherapy in advanced GC. Sensitivity and specificity were derived for this criterion, which were 82% and 84% respectively. Thus, the decrease in blood flow volume by 32.8% during treatment (P=0.002) was considered as another predictive criterion for the efficacy of chemotherapy in advanced GC. Sensitivity and specificity for that criterion were 82% and 89% respectively. Blood flow velocity and blood flow volume were important for the evaluation of tumour microcirculation and neoadjuvant chemotherapy efficacy in patients with advanced forms of GC [16]. Other researchers have derived sensitivity (69%) and specificity (58%) for surface permeability as a predictive factor in the efficacy of chemotherapy in GC [17]. When studying CT perfusion in GC in low-dose regimen, Sun Z. et al. (2018) have revealed the significant differences in blood flow velocity and blood flow volume before and after three courses of chemotherapy. Those two parameters correlated with the clinical response (p <0.01). Sensitivity and specificity of the rate of decrease in blood flow volume was significantly higher than for the rate of tumour size reduction during treatment. Low-dose CT-perfusion allowed evaluating the efficacy of tumour microcirculation and neoadjuvant chemotherapy in patients with advanced GC forms [18, 19].

**Conclusion.** CT perfusion is an important method that allows evaluating tumour microcirculation and can be used to diagnose GC. CT-perfusion parameters can serve as indicators for the degree of malignancy and prognostic evaluation of GC course and allows evaluating the efficacy of neoadjuvant chemotherapy in patients with advanced forms of GC. However, the interpretation of perfusion CT imaging in GC is not well understood, has conflicting data in different researchers and requires further investigation.
References


Pancreatic neuroendocrine neoplasia: Modern views (literature review)

Relevance. The article reviews the literature on modern issues of classification, diagnostics and treatment of pancreatic neuroendocrine tumours (PNT). According to modern views all PNTs with clinical manifestations (in the form of the syndromes caused by products of specific hormones; increases in level of hormones in blood of patients without clinical manifestations; in the form of signs of availability of volume education in different departments of a pancreas) and/or revealed by radiological methods (more than 5 mm) are malignant in their biology as they have high metastatic potential.

Purpose of this overview is to systematize and familiarize with the modern aspects of diagnostics and treatment of PNTs.

Results. The author shows that many PNTs are non-functioning, that is, they don’t release various gastrointestinal hormones and polypeptides in blood and therefore are not associated with indicative clinical manifestations. PNT diagnostics is a hard task and influences the choice of treatment and the remote results.

Surgery is the only available method of radical and adequate treatment of functioning hormonal pancreatic tumours. Modern authors suggest surgery also for non-functioning PNTs. Extensive distal excision or pancreato-duodenectomy are more common. Big sizes of tumours are not considered as a contraindication to surgery nowadays. Post-surgical complications are less than 1 case per 100 000 population [4].

All pancreas gland (PG) tumours with the annual incidence of 1 per 100 000 population [4] account for approximately 2-5% of all tumours of this type [1]. According to the latest data, non-functioning PNTs make up more than 60% of all neuroendocrine tumours of PG [4].

The growing interest to neuroendocrine tumours is explained by their growing incidence worldwide in the last 30-35 years. Modlin I.M. et al. [1] propose a 5-fold increase over 30 years (from 1.09 cases per 100 000 population in 1973 to 5.25 cases per 100 000 in 2004) likely associated with relevant improvement of diagnostics due to the use of immunohistochemical tests and the improvement of imaging techniques.

Today, this group of tumours includes high-differentiated malignant NETs, the so-called pancreatic neuroendocrine cancer (carcinoma, PNCs). PNTs are heterogeneous epithelial malignancies developed from the pancreas neuroendocrine cells (Langerhans islets) [2, 3]. They account for approximately 2-5% of all pancreas gland (PG) tumours with the annual incidence rate less than 1 case per 100 000 population [4].

A significant part of PNTs belongs to non-functioning tumours when various secretions of gastrointestinal hormones and polypeptides are not secreted into the blood and, as a result, not accompanied by attributed clinical manifestations. The tumours associated with clinical syndromes caused by abnormal hormone production are considered as the functioning (syndromic) PNTs. They include the insulino- ma, gastrinoma, glucagonoma, VIPoma and other less common neoplasms. In a number of cases, the non-functioning tumours are detected accidentally and belonged per se to the incidentaloma [5, 6]. Non-functioning (non-syndromic) PNTs are not associated with clinical syndromes of hormonal hyper-production but can also secrete the peptide hormones or biogenic amines in an amount insufficient to cause corresponding symptoms and paraneoplastic syndromes. Mass formations less than 5 mm in diameter are usually non-functional are referred to as neuroendocrine microadenomas. According to the latest data, non-functioning PNTs make more than 60% of all neuroendocrine tumours of PG [4].

The frequency of tumour development is not gender-dependent; they are found at different ages with a peak detection at the age of 30-60 years. PNTs have a distinct neuroendocrine differentiation manifested in the morphological structure and immunohistochemical expression of synaptophysin, and in a majority of cases – the chromogranin A. PNTs are mainly slowly growing tumours with overall 5-, 10- and 20-year survival rates in 33%, 17% and 10%, respectively [4]. In aggressive and rapidly growing PNCs, the life expectancy of patients rarely exceeds 1 year [4, 7]. It is worth emphasizing that the surgical treatment of PNTs significantly improves the specified survival rates.

Materials and Methods. The peculiarities of the clinical picture, diagnostics and treatment of patients with various PNTs forms are reviewed based on the available papers of 38 domestic and foreign authors. The studies cover in total more than 15 000 patients who underwent examination and treatment in surgical and cancer hospitals of different countries worldwide.
The classifications are presented below:

**International WHO classification of PNTs (2010)**
(D. Klimstra et al.) [15]

Pancreatic neuroendocrine microadenoma Neuroendocrine tumour (NET)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ki-67 index, %</th>
<th>Mitotic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PNT G1</td>
<td>Less than 3</td>
<td>Less than 2</td>
</tr>
<tr>
<td>2. PNT G2</td>
<td>3-20</td>
<td>From 2 up to 20</td>
</tr>
<tr>
<td>3. PNT G3</td>
<td>More than 20</td>
<td>More than 20</td>
</tr>
</tbody>
</table>

**TNM classification of PG PNTs in line with ENETS**
(G. Rindi et al., 2006) [12]

| TX - Tumour cannot be assessed |
| T1 - Tumour is limited to the gland and less than 2 cm |
| T2 - Tumour is limited to the gland and have size of 2-4 cm |
| T3 - Tumour is limited to the gland and more than 4 cm or adhere to duodenum or bile ducts |

According to modern views, all PNTs with clinical manifestations (in the form of syndromes due to production of specific hormones, hormones level elevation in the blood of patients without clinical manifestations; in signs

Table 2 – PNTs classification by stages according to ENETS (G. Rindi et al., 2006) [12]

<table>
<thead>
<tr>
<th>Стадия</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Notes:**
- Ki-67 proliferation index is based on evaluation of more than 500 cells in the regions of the highest nuclear tracer labelling. The mitotic index is based on evaluation of mitoses in 50 fields of vision at high magnification (0.2 square mm) in the regions of the greatest density and is expressed as mitosis in 10 HPF (2 square mm). The grade is determined based on the highest score. For Ki-67 index evaluation, it is recommended to count with use of the printed image.
of space-occupying mass presence in various parts of pancreas gland) and/or detected by the radiation study methods (more than 5 mm) are malignant in their biology, since they have a high potential for metastasis. It is worth to emphasize that the PNTs clinical course and manifestations may be more or less malignant, depending on availability of production of biologically active substances (hormones and peptides) and development of the relevant syndromes.

The etiology and pathogenesis of malignant NETs, as well as other carcinomas, are associated with the accumulation of somatic mutations in oncogenes and anti-oncogenes. In 10-20% of cases, a high-differentiated PNTs can be associated with genetically determined hereditary syndromes, such as multiple endocrine neoplasia of the first type (MEN-I), von Hippel-Lindau syndrome (VHL), neurofibromatosis of the first type, tuberous sclerosis, glucagon-cell dysplasia and neoplasia [4]. The neuroendocrine tumours can occur sporadically or as a manifestation of the hereditary syndrome of multiple endocrine neoplasias (MEN). The MEN-I gene mutations, underlying the syndrome of multiple endocrine neoplasias of type I (MEN-I), have become the most known. This syndrome is a hereditary, autosomal dominant disease with a high degree of penetrance, and characterized by development of thyroid gland adenomas, neuroendocrine tumours of the gastro-pancreatoduodenal zone, and the pituitary gland tumours [22]. According to recent data, for PNTs are indicative the specific genetic disorders, such as MEN I, DAXX and ATRX genes mutations, as well as genes of mTOR TSC2, PTEN and PIK3CA signalling pathway. Besides, the PNCs genetic disorders are very different from those observed in PNTs and mainly represented by the mutations of genes involved in the cell cycle, such as TP53, RB1 and CDKN2A (p16) [4].

Clinical picture and diagnostics. Commonly, considerable difficulties are related to the diagnostics of syndrome of multiple endocrine neoplasias (MEN), including PNTs [22]. The diagnostic potential of most modern methods of preoperative topical diagnostics exceeds 50-60%, and various versions of their combined application enable localizing up to 80-95% of NETs and their distant metastases [23].

The following algorithm for NET diagnostics is currently recommended [24]:

1st stage – the case history (anamnesis), physical examination, assumption of the disease probability on the basis of clinical data;

2nd stage – laboratory diagnostics: hormonal profile study - biochemical blood test for determination of chromogranin A level, serotonin, neuron-specific enolase, calcitonin, as well as specific markers for various NET types (serum calcium, parathyroid hormone, pancreatic polypeptide, prolactin in women, gastrin, glucagon, insulin, calcitonin, etc.), and ectopic hormones (adenocorticotropin hormone, somatostatin, neurotensin, etc.). 24-hour urine test to determine the excretion of the serotonin metabolite of 5-hydroxyindole-acetic acid;

3rd stage – instrumental diagnostics: for imaging of tumours the ultrasound (ultrasound study) [25], computer (CT) [21] and magnetic resonance imaging (MRI) tomography are used [26, 27]; the radioisotope methods of examination (in a number of complicated cases it is recommended the application of selective adrenal glands angiography and positron emission tomography), gastroscopy, colonoscopy, lesion biopsy or surgical biopsy are used to obtain the tumour tissue samples. The topical diagnostics are use for detection of adenomas or hyperplasia of the endocrine part of potential “target organs” (pituitary, parathyroid, pancreatic and adrenal glands);

4th stage – morphological study of tumour tissues and mandatory immunohistochemical study with determination of marker expression of neuroendocrine differentiation (chromogranin A and synaptophysin) and exocrine differentiation (CK-pan 19, epithelial-membrane antigen). For hormonal-active NET, the specific markers (gastrin, glucagon, insulin, calcitonin, somatostatin, etc.) are determined. The NET proliferative potential should be identified by staining for Ki-67 proliferation marker. A more detailed morphological diagnostics is presented below.

The syndromic diagnosis requires definition of the level of tumour-secreted hormones (insulin, C-peptide, proinsulin, gastrin, glucagon and VIP) along with the review of the disease clinical picture. In patients with non-functional or malignant tumours, the level of chromogranin A is determined. Hormonal profile of possible “target organs” – the pituitary and parathyroid glands (STH, ACTH, prolactin, parathyroid hormone) – shall be studied to exclude the MEN-1 syndrome. Currently, functional tumours of PG are divided into two groups: orthoendocrine which secret hormones specific to physiological function of the islets, and pararendocrine which secret not specific hormones. Pararendocrine tumours also include certain rare tumours, secreting other peptides and prostandins [21, 28, 29].

Orthoendocrine tumours. Insulinoma is a tumour formed by beta-cells of Langerhans islets. It secretes an excessive amount of insulin what is manifested by hypoglycaemic symptom complex [30]. Glucagonoma (Malleson’s tumour) is a tumour formed by alpha-cells of Langerhans islets that secretes glucagon. Glucagonoma commonly reaches a considerable size. Alpha-cell formations are malignant in a predominant majority of cases. Glucagonomas are associated with a complicated symptom complex. It most often includes dermatitis, diabetes, anaemia, and weight loss [28]. Somatostatinoma formed by delta-cells of Langerhans islets is registered extremely rare [23]. It is often accompanied with cholelithiases, diabetes, diarrhoea or steatorrhea, hypochlorhydria, anaemia, and weight loss.

Pararendocrine tumours. Gastrinoma (Zollinger-Ellison syndrome) is a tumour formed by G-cells which are either not found in physiological conditions of PG or are found in small amounts only in the mucous membrane of large excretory ducts. This type of NET ranks second among all hormone-active PG neoplasms after insulinoma [5]. In 1955, American surgeons Zollinger and Ellison have described the syndrome named Zollinger-Ellison syndrome with a specific complex of symptoms: severe recurrent peptic ulcer of the duodenum, hypersecretory activity of mucous membrane of the stomach and endocrine gastrin-producing tumours (in PG or another location) [5, 31]. VIPoma (Werner-Morrison syndrome) is a PG tumour that produces vasoactive intestinal peptide (VIP) and accounts for about 5% of all hormone-producing pancreas tumours. In 1958, Werner and Morrison have described the syndrome of watery diarrhoea in a patient with a non-beta-cell tumour of PG. This disease is sometimes called “pancreatic chola” [5]. Corticotropinoma is a hormonal PG tumour. Ectopic secretion of the ACTH-like hormone

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can be observed in many organs and tissues, including PG. The clinical symptoms in this case are presented by glucocorticoid hypercorticism [23]. Paratirinoma is a PG tumour. Hypercalcemia is a rare phenomenon and a leading sign of endocrine tumours of PG.

Currently, morphological diagnostics of PNTs is impossible without IGH analysis which allows confirming the epithelial and neuroendocrine nature of the tumour, distinguishing individual subtypes of NETs, clarifying the hormonal status, as well as determining the place of development of the primary tumour within the study of metastases without an identified primary focus [20]. Two main markers recommended for confirmation of neuroendocrine nature of the tumour are: chromogranin A – one of the most distinctive nonspecific markers associated with dense secretory granules, and synaptophysin – a marker of small vesicles. It is important to note that the chromogranin A expression may or may not be present in low-differentiated forms, and the presence of synaptophysin is mandatory for diagnostics of a NET [20]. IHC staining for keratin is used to confirm epithelial nature of the NET. The majority of NETs show positive expression when staining with antibodies to pancytokeratin (AE1/AE3) and antibodies to low molecular weight cytokeratins (CK8, CK18, CAM 5.2) [32]. In the study of metastases of highly differentiated NETs without an identified primary focus, two main IHC markers are recommended for diagnostic purposes: CDX2 and TTF1 [32, 33]. Diagnostic markers presented in a number of recent studies make it possible to differentiate primary tumours of gastrointestinal tract and PG: ISL1, PDX1, PAX6 and NESP55 [32, 34, 35]. During intraoperative revision, Chernousov A.F. et al. [28] has mandatory performed the intraoperative ultrasound scan (IOUSS), and, if necessary, the endoscopic transillumination. If the diagnosis is not clear, a biopsy of PG and liver formations is performed under ultrasound control followed by histological and immunohistochemical tests. Radiation methods for diagnostics of “target organs” shall be used to exclude the MEN syndrome along with hormonal studies and the review of the family history. For this purpose, a number of authors use MRI of pituitary gland, ultrasound examination and, if necessary, the scintigraphy of parathyroid glands, and the CT of adrenal glands [28].

According to Chernousov A.F. et al. [28], in a majority of patients (92%) with hormone-active NETs the syndromic diagnosis was established on the basis of clinical picture review. The sensitivity of sampling with fasting conductin in organic hyperinsulinsim amounted to 99%. In 87% of patients with persistently recurring ulcer due to the Zollinger-Ellison syndrome, the calcium-loaded test has facilitated the confirmation of the diagnosis “gastrinoma”. The sensitivity of non-specific marker of NET – chromogranin A – has amounted to 77%, with the specificity of 90%.

Treatment of neuroendocrine tumours. Currently, surgery is the only available method of radical and adequate treatment of all types of NETs [36-40]. NET therapy includes the removal of the primary focus of tumour and the metastases [41] with an exception of multiple gastrinomas and non-functioning tumours up to 2 cm [22]. Given the high incidence of multiple lesions and nesidioblastosis of PG, the surgeons more often perform extended operations in MEN-1 syndrome compared to sporadic tumours. In the case of surgical treatment of two endocrine organs, many authors [22, 23, 30, 42] recommand starting with a surgery for a clinically most evident syndrome or a neoplasm with a higher malignancy. The next important issue is the extent of surgical intervention on PG in MEN-1, taking into account the multiple lesions and nesidioblastosis. Most authors prefer resection [18, 22, 23, 36] that accounts for 61% of all interventions [22]. Postoperative complications make 30%, the overall mortality is 4.7% [28]. The five-year survival rate of patients with PNTs is about 60-100% with localized process, 40% - in a locally advanced process, 25% - under a metastatic process, and 80% – at all stages of the disease [24]. Median survival of patients with low-differentiated NET is about 10 months [24]. In case of MEN-1, the relapse of clinical symptoms is noted in 16% of patients, 5-year survival of patients after radical and cytoreductive interventions is 100% and 64%, respectively [28]. According to modern views, the patients with non-functional PNTs are subject to surgical treatment. As most of these tumours are malignant, an extensive distal or pancreateoduodenal resection is commonly made [22, 28, 43]. Large tumour size is not a contraindication to surgery operation and, if necessary, a pancreateoduodenal resection (PDR), central resection, or distal resection of the pancreas gland is performed. In non-functioning malignant NETs, an extended and even combined resection of PG (with removal of neighbouring organs) is recommended [21, 23, 37]. In case of a functioning tumour, the somatostatin analogues (ACC) shall be prescribed before the procedure to prevent a crisis. Cytoreductive surgery as an alternative to loco-regional therapy is particularly applicable for patients with non-treatable carcinoid syndrome, refractory insulinoma, glucagonoma, or VIPoma, in patients with non-functional NETs without disease progression for 6 months and in patients suffering from the general disease burden. Besides, the retrospective studies have shown higher overall survival in case of removal of liver metastases. Liver transplantation is not generally recommended but can be a choice for certain patients with carcinoid syndrome or other functioning tumours with multiple liver metastases in case of their refractivity to systemic therapy. In advanced tumour processes, metastases and relapses of the NET, cytoreductive methods of treatment are used to reduce the tumour mass: surgical tumour resection, RF ablation, embolization and chemoembolization of metastases in the liver. A combination of somatostatin analogues and interferon preparations is used to enhance the antiproliferative and antisecretory effect of NET with carcinoid syndrome [24].

Conclusion. Thus, the key tasks of PNT treatment are: the removal of primary tumour, the inhibition of tumour growth, the suppression of hormonal expression, and the improvement of quality of life of patients. Currently, surgical treatment is a method of choice and the only way to achieve recovery. The rational and comprehensive use of a modern range of surgical and therapeutic methods allows a considerable prolongation of life and the improvement of life quality of patients with metastatic forms of PNTs.

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