ANNOTATION

for the dissertation by Tlegenov Askar Shyndalyevich on the topic «OMICS - research of malignant and nodular neoplasms of the thyroid gland in Kazakhstan», submitted for the degree of Philosophy Doctor (PhD) in specialty
6D 110100 - Medicine.

Relevance of the topic

Among all organs of the endocrine system, the most common type of cancer is thyroid cancer (TC) (La Vecchia 2015). The various characteristic features of thyroid cancer and the annual growth of this disease around the world determine current days its general relevance, as well as differential diagnosis, especially at the early presurgery stage. (Jemal 2010). In the general structure of cancer incidence, thyroid cancer takes 10th place in the world, it takes 3.1% of all cases of primary malignant tumors, in Kazakhstan, thyroid cancer is at 18th place, where it takes 1.4% (Cancer Research International Agency).

In the most countries of the world, over the past two decades, there has been an increase of thyroid cancer cases both women and men. The reason for the increase of thyroid cancer cases is considered to be mainly papillary thyroid cancer (PTC) and it is the subject of scientific debate. It is most likely the significant part of the increase of thyroid cancer cases is coming from methods improving of thyroid cancer diagnostic (Davies 2013). It should be mentioned based on the data of pathological studies, the cases of thyroid cancer ranges from 0.01% to 35.6% (Boucek 2009) based on autopsy not connected with the thyroid cancer. This indicates the existence of a rather high quantity of unrecognized and, apparently, clinically insignificant thyroid tumors in the population. Low mortality from thyroid cancer indicates increase of sickness rate from accidentally detected cases. (Davies 2014). Changes of environmental state and contact with risk factors also considered possible as a real increase of sickness rate. For example, the number of tumors not only small ones but also large ones increases. (Pathak 2013). It is expected that if improvement of diagnostic methods were the only reason for the increase of thyroid cancer cases, then there would be a noticeable decrease in mortality from thyroid cancer, which is not noted in the studies. (Burgess 2002). Potential risk factors for thyroid cancer are ionizing radiation, increase of body mass index, condition of hormones, the reproductive system state, food factor and various other environmental factors (Peterson 2012).

The increasing incidence of thyroid cancer is an urgent problem of modern medicine and indicates the need to improve existing diagnostic measures and to develop new high-tech research methods with the introduction into practical thyroidology, which will correspond to modern trends in world science in

medicine. Differential diagnosis of thyroid neoplasms is currently carried out by performing fine-needle aspiration biopsy of thyroid nodules under ultrasound guidance. Fine needle aspiration biopsy followed by cytological examination is the main diagnostic procedure at the preoperative stage. However, despite the high diagnostic accuracy of this method, in a number of cases there are errors and difficulties associated with the interpretation of the material obtained (Kondratyeva 2007). Difficulties are associated primarily with the heterogeneity of the structure, as well as with the cytological and morphological variety of thyroid tumors. (De Lellis 2004). For example, only histological variants of PTC, in addition to the classic, in the 4th edition of the WHO Classification of tumors of endocrine origin, there are of 14 (Lloyd 2017).

Due to the presence - due to a number of objective and subjective reasons - urgent unresolved problems of diagnostics of thyroid nodules, scientists in many countries of the world are actively engaged in the search for new methods for diagnosing oncological diseases. Ones of the most advanced and promising approaches to solving such problems is highly productive molecular genetic methods. In the course of their development, molecular genetic methods were constantly supplemented by a variety of technologies that became available in the course of scientific and technological progress. An example of such very significant achievements is OMICS-technologies, which represent a whole complex of the most modern methods of research and identification of molecular genetic markers of oncological diseases. (Agretti 2012).

OMICS - technologies, first of all, it is "genomics" itself, as well as "transcriptomics" and "proteomics", which are highly developed to date. A relatively new direction in scientific research is "metabolomics", an actively developing science over the past decade. At present, it is difficult to imagine modern research that does not include high-tech molecular genetic methods that describe the properties of a biological object at the postgenomic levels. In-depth studies of the state of several systems at once allow a comprehensive approach to the study of the processes occurring in living cells, consistently reflecting the entire flow of information from genes to the phenotype of a biological object. Wherein the genomics can be the beginning of such studies, and metabolomics - a source of necessary additional information, a kind of "scientific mediator", since the metabolite profile is an important informative characteristic of the phenotype. It can be expected that the experience gained and the results of molecular genetic OMICS - studies will allow improve the diagnosis of thyroid cancer.

The use of highly effective methods based on OMICS technologies with the subsequent identification and implementation of new diagnostic biomarkers has great potential for improving the algorithm for diagnosing thyroid cancer,

especially at the early preoperative stage.

Aim: to improve the comprehensive diagnosis of thyroid cancer by determining the spectrum of metabolites and BRAF gene mutations at the preoperative stage

Tasks

1. Determine the mass spectra of metabolites from blood plasma samples from patients with benign and malignant thyroid neoplasms and control subjects, followed by identification of metabolites and determination of test parameters;

2. Analyze the frequency of BRAF gene mutation in patients with thyroid cancer;

3. Determine the possibility of using detection of the BRAF gene mutation as a molecular genetic marker of thyroid cancer.

4. Improve the algorithm for complex diagnosis of thyroid cancer by determining the spectrum of metabolites and BRAF gene mutations at the preoperative stage

Scientific novelty

On the own clinical and diagnostic material:

For the first time in the framework of domestic thyroidology at the modern evidence level, in order to improve the preoperative diagnosis of thyroid cancer, metabolic and molecular genetic indicators have been established and analyzed.

1. At the scientific and methodological level, the possibility of using high-tech OMIKS - the study of the spectrum of metabolites in the blood plasma for the diagnosis of malignant neoplasms of the thyroid gland was demonstrated.

2. The possibility of using a new high-tech molecular - genetic method for analyzing BRAF gene mutations in FNAB material for the diagnosis of thyroid malignant neoplasms has been shown.

3. The effectiveness of the use of modern highly effective OMICS technologies has been demonstrated, which proves the experimental hypothesis and shows the need to introduce fundamentally new approaches to the diagnosis of thyroid cancer, especially at the early preoperative stage.

Practical significance

The first stage on the study of the spectrum of metabolites was carried out within the framework of research work (number 0116RK00041) at the Kazakh National Medical University named after S.D. Asfendiyarov in 2016.

1. The practical significance of the work performed lies in the possibility of introducing OMICS technology into practical thyroidology.

2. Identified specific metabolites as biomarker candidates for the diagnosis of malignant neoplasms of the thyroid gland.

3. The approved method for determining the BRAF mutation in patients with malignant neoplasms of the thyroid gland in Kazakhstan has shown its high efficiency and the possibility of using it for diagnosis at an early preoperative stage.

4. Improved the approach to the diagnosis of malignant neoplasms of the thyroid gland based on the use of high-tech OMICS studies.

Key Points to defend

1. Violation of the spectrum of metabolites in thyroid cancer can be effectively used for diagnosis. In this case, the following metabolite candidates may be more specific: M129T312, M206T234, M87T21, M72T15.

2. The appearance of a BRAF gene mutation indicates the possible development of thyroid cancer and can be effectively used for diagnosis. Mutation of the BRAF gene in the washes of puncture needles for thyroid cancer is more specific and sensitive.

3. Analysis of the results of the spectrum of metabolites and genetic mutation of the BRAF gene in patients with thyroid cancer has made it possible to improve the diagnostic algorithm

Approbation of the thesis

In the course of the study, the current results were reported at 3 international conferences, of which 2 were foreign:

- International XIV Scientific and Practical Conference "Ecology. Radiation. Health "28 August 2019, Semey" Omics - research of malignant and nodular neoplasms of the thyroid gland in Kazakhstan "(oral presentation);

- 26 th Annual Meeting of International Congresson Nutrition and Integrative Medicine ICNIM 2018, Jule21-22. 2018, Japan «Molecular and genetics studies of thyroid gland cancer and clinical experience of using AHCC» (poster report);

- 26 th Annual Meeting of International Congress on Nutrition and Integrative Medicine ICNIM 2018, Jule21-22. 2018, Japan «Study of the metabolism spectrum of malignant thyroid formations and prospects of using AHCC in the treatment» (poster report)

Published works

In the course of the dissertation research, 12 works were published based on the materials and results. Of these, 6 abstracts (2 in English) presented at international conferences, of which 2 are foreign; 6 articles (1 in English) of which 3 in journals recommended by the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, 1 in a foreign indexed journal of the Scopus database, 1 article in a journal with an impact factor indexed in the RSCI database, 1 article in a republican specialized journal; 1 copyright certificate.

Scope of the dissertation and its structure

The first chapter provides a review of the literature on the research topic, including etiology, pathogenesis, diagnostic methods. Among other things, publications on the application of molecular genetic and other studies and their relationship with the pathology under study were examined. The second chapter contains information on materials and methods of research with the presentation of the results in the third chapter. In subsequent chapters (4 - 6), a discussion and a diagnostic algorithm are provided. The manuscript is accompanied by 16 figures, 29 tables, 5 supplement. The bibliographic list contains 180 literary sources, including historical references to original research in Russian and foreign languages.