New Insight of Oncology: Cancer Concept without Tumor

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Abstract: This article presents an analysis of current trends in the field of oncology, as an industry that was influenced by both scientific discoveries and the very order of civilization development as a whole. The key technological breakthroughs that have had an impact on oncology in the medium and long term perspective, as well as changes in the structure and approaches to the treatment of oncological diseases, which, in their turn, can determine the foresight of oncology development for the coming decades, are outlined. The TNM (tumor, lymph node, and metastasis) Classification of Malignant Tumors has been critically reassessed through the prism of the achievements in modern molecular biology. In this context, we are inevitably moving towards a new paradigm of oncological science "cancer without a tumor", where the tumor itself becomes a symptom of a systemic "oncological disease". The concept of "cancer without a tumor" has been proposed for the first time. This article is intended to engage professional communities in the oncology field in a discussion of understanding the transformation of the modern concept of oncological diseases.

Keywords: Oncology, TNM, Systemic disease, Cancer without tumor, Cancer concept, Molecular biology.

INTRODUCTION

Cancer is the second leading cause of death in the world following to heart diseases [1]. This is an extensive and heterogeneous class of systemic diseases, which, one way or another, affects all human organs. It should be emphasized that the number of cancer patients is growing and this trend will continue in the coming years [2]. The higher the life expectancy, the higher the risk of developing cancer.

Despite the difficult period that humanity is going through, there is an ambitious task set for the medical community, aimed at reducing mortality from malignant neoplasms and increasing life expectancy.

Modern oncology is one of the most dynamically developing areas of medicine [3]. Globally, in recent decades, there has been significant progress in science in the field of biology and pharmaceutical industry; artificial intelligence and digitalization technologies are being actively introduced, - communication tools have made medicine a single global industry. The COVID-19 pandemic had a significant impact on scientific trends as well [4,17].

The solution of specific clinical problems becomes possible due to the translation of the fundamental science achievements. Innovative technologies make it possible to permanently move towards solving health problems. Bioinformatics, genomics, metabolomics, proteomics, transcriptomics are vivid examples of the atomization in modern molecular biology, allowing you to look even deeper into the causes of tumor development, to "reveal" previously unknown data on the unique nature of the human body.

In this article, we would like to discuss the topic of modern oncology transformation based on the results of significant fundamental discoveries in the recent decades. At the same time, we did not aim to detail any specific studies, but to determine the trends that followed these studies - what vector of development we have eventually received.

HISTORICAL BACKGROUNDS AND DIGRESSION

Historians associate the origin of oncology with the name of Hippocrates (460-370 BC) who described a woman with bloody discharge from the nipples and who was also the first to introduce the term "cancer". The word comes from the ancient Greek καρκίνος, meaning crab and tumor. In the days of ancient medicine, it was believed that it was necessary to “excise a pathological tumor in the area where it borders healthy tissues,” although even at that time both Hippocrates and the Roman physician Galen (129-216) assumed that cancer was a systemic disease. Lack of fundamental knowledge, limitations associated with scientific and

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technological progress, restrained the oncology development only within the framework of descriptive medicine [4-6,5].

Oncology received a new impetus to development with the advent and development of surgery. In Europe, until the 16th century, there was no significant progress in the surgical treatment of malignant tumors.

Ambroise Pare (1510-1590) first drew attention to the relationship between a primary breast tumor and the presence of a tumor in the axillary region, proposed the surgical removal of tumors having "non-ulcer skin over the mammary gland" [6,7]. Hermann Boerhaave (1668–1738) suggested that inflammation could lead to cancer. This idea is widely accepted today [7].

Henri Francois Le Dran (1685-1770) suggested that breast cancer is a local tumor that spreads through the lymphatic vessels. The 19th century was marked by new advances in surgical oncology. In 1809, the world's first successful operation for a tumor in the abdominal cavity was performed. The American surgeon Ephraim McDowell (1771-1830) who revealed an ovarian tumor in a patient, is considered to be the founding father of abdominal surgery. In 1829, Joseph-Claude Antelme Recamier (1774-1852) first introduced the term "metastasis" into practice. In 1838, German pathologist Johannes Müller (1801-1858) demonstrated that a cancerous tumor is made up of cells. His work "On the structural details of malignant tumors" is the first use of microscopic examination in pathological anatomy [7,9].

The impetus for the development of experimental and clinical oncology was given by the theory of irritation by Rudolf Virchow (1821-1902), published in 1853. Virchow was the first to correctly describe the occurrence of cancer from normal cells (his teacher Müller suggested that cancer arises from cells, but from special cells, which he called blastema). In 1855, he proposed that cancer results from the activation of dormant cells (perhaps similar to those now known as stem cells) present in mature tissue [7-10].

In 1865, Carl Thiersch (1822-1895) demonstrated the epithelial origin of cancer, which put him in opposition to Rudolf Virchow's doctrine that cancer can originate from connective tissue [1-3,7]. At the end of the 19th century another significant for oncology historical event took place - in 1896, the world's first transplantation of a malignant tumor from adult dogs to puppies was performed by the founder of experimental oncology Mstislav Novinsky (1841-1914).

In the same period, surgeon William Stewart Halsted (1852-1922) *et al*. outlined the theory of cancer development, which was one of the key ones until the end of the 20th century and it became a basis for creating a classification of tumors according to the TNM system [11]. It was believed that solid tumors spread continuously over time, passing through a series of stages, from the site of the primary tumor through the lymphatic vessels to distant organs, giving an increasingly poor prognosis with each stage. A consequence of this view, limited by current knowledge, was the suggestion that tumor size or location, regional lymph node involvement and distant metastases are indicators of disease spread and they can be used to predict the disease outcome. Much later, in 1953, French surgeon Pierre Denoix (1912-1990) proposed to the International Cancer Union three factors (size and location of tumor, regional lymph node involvement and distant metastases) to be standardized and integrated into a prognostic system that could be used for all solid tumors with some adaptation to anatomical localization. His proposal for a common language for predicting solid tumors was adopted in the form of the TNM staging system, which is currently used worldwide [7,8,10,19].

In 1911 American pathologist Peyton Rous (1879–1970) proved that viruses cause cancer in chickens, for which he was awarded the Nobel Prize in 1966. In 1953, James Watson (b. 1928) and Francis Crick (1916-2004) described the double helical structure of DNA, starting modern age of genetics.

In 1956 in USA, Ming Chiu Li (1919-1980) first clinically demonstrated that chemotherapy could lead to a cure for metastatic malignant disease and in 1960 he published another important and original discovery: the use of combination chemotherapy with multiple agents for the treatment of metastatic testicular cancer [7,8].

In 1957-1958 Lev Zilber (1894-1966), George Svet-Moldavsky (1928-1982) and their collaborators established that the Rous sarcoma virus previously considered species-specific, can cause tumors not only in birds, but also in mammals, thereby proving the absence of strict species specificity of oncogenic viruses. The discovery of alpha-fetoprotein in the blood serum of mice with chemically induced hepatoma in 1962 by Garry Abelev (1928-2013) and the discovery in 1963 by Yuri Tatarinov (1928-2012) of this protein in the blood serum of a patient with primary liver cancer laid the foundation for the development of a

fundamentally new method for the immunological diagnosis of primary liver cancer, embryonic teratoblastomas and a number of other tumors [7,10].

In 1970, the first oncogene was discovered in the United States. In 1973, the first successful bone marrow transplantation was performed on a dog in Seattle, USA by Edward Donnal Thomas (1920-2012), which served as the basis for the subsequent development of methods for treating leukemia using bone marrow transplantation. In 1990, Thomas received the Nobel Prize for his work [8,10].

In the 1980s, the first WHO Cancer Control Program was developed. During the same period, Gianni Bonnadona (1934-2015) in Milan, Italy conducted the first study of adjuvant chemotherapy for breast cancer using cyclophosphamide, methotrexate and 5-fluorouracil which led to a reduction in cancer recurrence [5,11].

In 1994, scientists from the USA, Canada, UK, France, Japan jointly discovered a cancer suppressor gene *BRCA1*, the first known gene whose mutation predisposes to breast and ovarian cancer. Since 1994, active implementation of the achievements in gene therapy, immune system modulations and development of genetically engineered antibodies began to be used in cancer treatment [7,12].

In 2006, the US Food and Drug Administration approved the first human papillomavirus vaccine to prevent infections that cause cervical cancer and in 2017 the first adoptive cell immunotherapy, also known as T-cell therapy using chimeric antigen receptors, was approved (CARs).

In 2009, as part of the study of the logistics of lymphogenous metastasis, Shamil Gantsev (b. 1951) in Russia was the first to identify previously undescribed tertiary lymphoid structures in breast cancer. In subsequent years, a massive layer of versatile studies of these structures was carried out from a macroscopic description to an in-depth morphological description, having received the name "postnatal lymph nodes" and the process of their formation–“neolymphogenesis”. The results of the study of this phenomenon were included in the monograph "Atlas of Lymphatic System Cancer-Sentinel Lymph Node, Lymphangiogenesis, and Neolymphogenesis", published in 2020 by a global publishing company Springer Nature [13-15].

In 2018, James Allison (b. 1948) and Tasuku Honjo (b. 1942) were awarded the Nobel Prize in Physiology or Medicine for their developments in the field of immuno-oncology. They have developed a fundamentally new approach to cancer therapy, different from the previously existing radiotherapy and chemotherapy, which is known as "checkpoint inhibition". Their research is focused on how to eliminate the suppression of immune system by cancer cells. James Allison of the Anderson Cancer Center at the University of Texas, USA showed, for the first time, that an antibody that blocks the CTLA-4 complex on the surface of T-lymphocytes, introduced into the body of animals with a tumor, leads to activation of an antitumor immune response. Japanese immunologist Tasuku Honjo from Kyoto University discovered the PD-1 receptor on the surface of lymphocytes, the activation of which leads to suppression of immune activity. The research of these two scientists led to the emergence of a new class of anti-cancer drugs based on antibodies. The first such drug, ipilimumab, an antibody that blocks CTLA-4, was approved in 2011 for melanoma treatment. An anti-PD-1 antibody, nivolumab, was approved in 2014 against melanoma, lung, kidney and several other types of cancer [2].

Thus, modern oncology has come a long way in its history from a macrodescription of a tumor with primitive approaches to treatment aimed only at physical cytoreductive effects, to the definition of some molecular mechanisms of development in a tumor, where the tumor cell is the center and functional unit in an inextricable biological connection between the body and carrier.

These trends are compelling us to significantly reassess our approaches to understanding the fundamental concepts of oncological diseases.

CANCER CONCEPT WITHOUT TUMOR

From TNM to Molecular Diagnostics

Staging rules are described in the seventh edition of the American Joint Committee on Cancer Staging Guidelines by American Joint Committee on Cancer (AJCC) released in 2009. It was revised in 2017 by AJCC. Key changes in the principles of tumor staging were discussed at the XXII annual National Comprehensive Conference Cancer Network (NCCN), March 25, 2017 in Orlando, USA. Since 1959, the TNM system adhered to the principle of describing the anatomical distribution of the lesion: primary tumor (T), regional lymph nodes (N), and distant metastases (M). The AJCC Expert Group concluded that advances in molecular biology, laboratory diagnostics and other

areas of medicine have called into question the existence of a purely anatomical approach to the principles of tumor staging. Non-anatomical factors such as genomic profiles and molecular targets are increasingly coming to the forefront in identifying patient populations with different molecular characteristics, prognoses and treatment approaches. The Expert Group recognized that the current 8th revision classification should be based on the anatomical factors of TNM with the need to include biological markers [7,11,18].

Today, the disadvantages of the TNM staging system are obvious, primarily due to the fact that since its inception it has been a surgical system assuming that all patients would undergo surgery and would not receive any other therapy. Initially, the TNM system did not take into account the prescription of drug therapy. Therefore, the survival changes associated with these treatments are not reflected in the stages. It is quite difficult to stratify the system by stages in order to incorporate new treatments within each stage. In addition, continuous work is underway with the addition of new biomarkers. They are predictors of tumor development with the staging system [11,18].

However, the main thing that needs to happen is not the renovation of the archaic TNM system, but the gradual abandonment of this outdated model. First of all, we need to accept the fact that cancer is not a disease of an anatomical organ, but a disease of the system as a whole. And the anatomical location of the tumor, when it is detected, is primarily connected to our limited methods of detecting the disease than to the nature of the tumor itself. Already at the time of its discovery, all patients are at the risk of metastasis, while some patients, depending on the molecular characteristics of the tumor and the host organism, have a better prognosis for metastasis upon detection than the rest. Carcinogenesis is not determined by what stage the patient is at, at the time of discovery, but rather by the molecular (genomic and proteomic) characteristics of the tumor and the host. From this point of view, treatment should be determined by the molecular biology of the tumor and/or host, and not by the location of the tumor at the time of diagnosis. It is possible that in near future we will see in our clinics not the specialized departments belonging to a specific anatomical entity, such as the department of head and neck tumors, the department of oncoproctology and so on, but the departments that combine tumors with certain biomarkers, for example, tumors with disorders in the *Her2-neu* gene. This seems to be a natural classification that will take place once the proportion of surgical treatment of cancers decreases with simultaneous increase in the proportion of biological therapy [12,16,19].

From Standard to Personalized Oncology and Back to Standard Oncology

Innovative path of knowledge from the standards of general oncology to personalized oncology has every chance to not only completely change the way cancer is treated, but also to turn the entire medical practice upside down. Instead of separating patients into categories of disease, precise, personalized medicine focuses on prevention, diagnosis and treatment based on the unique biochemical characteristics of each individual patient. The determining factor in the choice of treatment options is the characteristics of the tumor of each patient,rather than the part of the body that is affected, and the type of cancer that affects hundreds of other people. A personalized approach changes the very essence of medicine, usually offering treatments that can help the widest range of people. But such "comprehensiveness" has a possibility that it will not help in this particular case or even harm. After all, each person has a whole set of molecular genetic features that significantly affect health. Meanwhile, introduction of new approach is a multifactorial task. And in the process of developing oncological thought, one cannot reject conventional way of cancer research that goes from the particular to the general, making it possible to identify the main patterns of the emergence, existence, development and treatment of cancer, based on the experience of the scientific community of oncologists.

Oncomorphology is very important for modern oncology. Through development of oncomorphology, oncology has received a new round of development. At the moment, in the arsenal of morphological diagnostics there is a huge variety of various tools for making or clarifying an oncological diagnosis. Due to the discovery of hundreds of immunohistochemical markers and a wide range of molecular genetic studies, we obtain a detailed tumor profile that allows us to take into account all known characteristics of an aggressive disease, a lot of information about the microenvironment and hormonal status of the tumor. Based on the results obtained, the most effective individual treatment regimens are already being developed today [19] We can definitely say that the development of oncology and the life expectancy of patients suffering from malignant neoplasms in the future will directly depend on the level of personalized morphological diagnostics.

The systemic nature of oncological diseases has become a fundamental postulate on which modern oncologists rely in understanding the concept of this group of diseases, which is confirmed by clinical practice - a progressive decrease in the share of local methods of treatment (for example, in Russia in 2020, the share of surgical treatment was only 34.5%), in clinical guidelines, more and more attention is paid to the biological profile of the tumor rather than its topography. At the same time, looking even further into the future, we would like to note that the challenge for oncologists will be to understand the mechanisms of an earlier period of development of “oncological disease”, the stage of “cancer without a tumor”, when histological realization has not yet occurred - an ideal period for preventive measures. This aspect is likely to form the basis of cancer prevention in the future, where primary prevention will be of key importance. The preventive and prognostic orientation of personalized medicine requires more and more targets for influencing biological systems and a “portrait” of a healthy as well as a sick person.

CONCLUSION

Achievements of modern science dictate new approaches to understand the term "cancer". A modern doctor must first of all understand the concept of the disease. From a morphological point of view, a tumor is an accumulation of pathological cells. Original meaning of “cancer” is a group of diseases associated with abnormal cell growth that can penetrate or spread to other parts of the body. "Cancer" in this context is more of a collective concept. Our current understanding on the systemic nature of neoplastic diseases brings us importance not of the tumor itself but of the condition that manifests itself as a morphological substrate, in the development of tumor which may be called "oncological disease". This is a fundamental point. In this perspective, the tumor itself goes into the category of a “symptom” of an oncological disease and a new definition of “cancer without a tumor” proposed by us is revealed.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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REFERENCES

[1] Lipsick J. A history of cancer research: Carcinogens and mutagens. Cold Spring Harb Perspect Med 2021; 11(3). https://doi.org/10.1101/cshperspect.a035857

[2] Fisher B. Biological research in the evolution of cancer surgery: a personal perspective. Cancer Res 2008; 68(24): 10007-10020. https://doi.org/10.1158/0008-5472.CAN-08-0186

[3] Gantsev SK, *et al*. Oncology: Textbook for medical students. Moscow: GEOTAR-Media 2022; pp. 19-40.

[4] Nagai H, Kim YH. Cancer prevention from the perspective of global cancer burden patterns. J Thorac Dis 2017; 9(3): 448-451. https://doi.org/10.21037/jtd.2017.02.75

[5] GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2024; 403(10440): 2100-2132. Erratum in: Lancet 2024; 403(10440): 1988.

[6] Karamanou M, Diamantis A, Androutsos G. Oncologic conceptions of Ambroise Paré (1509-1590), father of surgery. J BUON 2009; 14(2): 149-155.

[7] Wagener DJTh. The History of Oncology. 1st ed. Bohn Stafleu van Loghum 2009; ISBN: 978-90-313-6143-4.

[8] DeVita VT Jr, Chu E. A history of cancer chemotherapy. Cancer Res 2008; 68(21): 8643-8653. https://doi.org/10.1158/0008-5472.CAN-07-6611

[9] Lipsick J. A History of Cancer Research: Tumor Suppressor Genes. Cold Spring Harb Perspect Biol 2020; 12(2). https://doi.org/10.1101/cshperspect.a035907

[10] McAleer S. A history of cancer and its treatment: Presidential Address to the Ulster Medical Society. Ulster Med J 2022; 91(3): 124-129.

[11] Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM Classification of Malignant Tumors. 8th ed. Wiley-Blackwell 2016.

[12] Shams M, Abdallah S, Alsadoun L, Hamid YH, Gasim R, Hassan A. Oncological Horizons: The Synergy of Medical and Surgical Innovations in Cancer Treatment. Cureus 2023; 15(11). https://doi.org/10.7759/cureus.49249

[13] Gantsev SK, Gantsev KS, Kzyrgalin SR. Atlas of lymphatic system in cancer: Sentinel lymph node, Lymphangiogenesis and Neolymphogenesis. Switzerland: Springer Nature 2020; pp. 33-57. https://doi.org/10.1007/978-3-030-40967-8_4

[14] Gantsev SK, Ishmuratova RS, Frolova VY, Kzyrgalin SR, Umezawa K, Islamgulov DV, Khusnutdinova EK. The role of inflammatory chemokines in lymphoid neoorganogenesis in breast cancer. Biomedicine & Pharmacotherapy 2013; 67(5): 363-366. https://doi.org/10.1016/j.biopha.2013.03.017

[15] Gantsev SK, Kzyrgalin SR. Postnatal induced neolymphangiogenesis in malignant neoplasms. Herzen Journal 2017; 6(4): 66-71. https://doi.org/10.17116/onkolog20176466-71

[16] Haltaufderheide J, Wäscher S, Bertlich B, Vollmann J, Reinacher-Schick A, Schildmann J. "I need to know what makes somebody tick …": Challenges and Strategies of

Implementing Shared Decision-Making in Individualized Oncology. Oncologist 2019; 24(4): 555-562. https://doi.org/10.1634/theoncologist.2017-0615

[17] González-Montero J, Valenzuela G, Ahumada M, Barajas O, Villanueva L. Management of cancer patients during COVID-19 pandemic at developing countries. World J Clin Cases. 2020; 8(16): 3390-3404. https://doi.org/10.12998/wjcc.v8.i16.3390

[18] Imran A, Qamar HY, Ali Q, Naeem H, Riaz M, Amin S, Kanwal N, Ali F, Sabar MF, Nasir IA. Role of Molecular Biology in Cancer Treatment: A Review Article. Iran J Public Health 2017; 46(11): 1475-1485.

[19] O'Sullivan B, Brierley J, Byrd D, Bosman F, Kehoe S, Kossary C, Piñeros M, Van Eycken E, Weir HK, Gospodarowicz M. The TNM classification of malignant tumours-towards common understanding and reasonable expectations. Lancet Oncol 2017; 18(7): 849-851. https://doi.org/10.1016/S1470-2045(17)30438-2

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