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Precision medicine in oncology: role and prospects of mass spectrometry

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ABSTRACT

The aim of this review was to analyze the accumulated data on the use of mass spectrometry in diagnosing, treating, and prognosing cancer from the perspective of precision medicine.

Currently, universally accepted methods for early cancer diagnosis are not available, primarily due to low molecular specificity of pathological changes at early stages of cancer development. Additionally, the existing diagnostic modalities are notably limited in sensitivity. However, early detection is imperative for selection of the most suitable cancer treatment strategy and its successful implementation.

In the realm of oncology, mass spectrometry approaches show great potential for advancement and utilization. Mass spectrometry is becoming an indispensable tool in basic and applied research due to its sensitivity, specificity, and accuracy. It allows for efficient analysis of complex biological compounds, even at low concentrations. Moreover, contemporary mass spectrometry technology is capable of automating the analysis, thereby facilitating its diverse clinical applications in diagnosis, drug therapy selection, and even potential assistance to surgical oncologists in the operating room.

Considering all these characteristics and advantages, mass spectrometry methods for the analysis of biological samples can be defined as some of the most promising and dynamically developing tools in precision medicine, as they are capable of providing clinically valuable information based on omics technologies, taking into account personal characteristics of the patient.

Over the next decade, introduction of mass spectrometry-based methods into clinical practice based on the principles of precision medicine is expected to optimize selection of personalized treatment strategies for cancer patients and provide significant economic benefits by reducing morbidity, disability, and mortality.

This comprehensive review presents the analysis of 65 scientific publications, highlighting the results of clinical and experimental studies utilizing mass spectrometry methods for diagnosing cancer, investigating the underlying mechanisms of disease development, and evaluating the efficacy of therapeutic interventions. The review encompasses original articles published from January 1, 2018 to November 30, 2023.

The majority of studies back the potential of mass spectrometry as a valuable tool for cancer diagnosis and treatment monitoring. Broadening application of mass spectrometry techniques in the field of oncology holds significant promise and represents a relevant area for future research.

Keywords: mass spectrometric study, mass spectrometry, molecular profiling, cancer, tumor process, carcinogenesis, low-molecular-weight metabolites

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Прецизионная медицина в онкологии: роль и перспективы масс-спектрометрии

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РЕЗЮМЕ

Цель исследования – анализ накопленных данных о применении методов масс-спектрометрии в диагностике, лечении и прогнозировании течения онкологических заболеваний с позиций прецизионной медицины.

На сегодняшний день не существует общепризнанных методов ранней диагностики рака, так как патологические изменения на начальных стадиях развития обладают низкой молекулярной специфичностью, а существующие методы известны своей ограниченной чувствительностью. Однако именно возможность как можно более ранней диагностики является важным, если не определяющим, фактором адекватного выбора стратегии терапии онкологических заболеваний и ее успешного применения.

В этом контексте высокотехнологические подходы к профилированию молекулярного ландшафта тканей, использующие в своей основе метод масс-спектрометрии, имеют большой потенциал к развитию и применению в области онкологии. Современная масс-спектрометрия становится незаменимым инструментом в проведении фундаментальных и прикладных исследований за счет своей чувствительности, специфичности и точности, обеспечивающим эффективный анализ сложных биологических соединений даже в незначительных концентрациях. Важным свойством современных масс-спектрометрических технологий является возможность автоматизации аналитического процесса, что открывает перспективы широкого внедрения в клиническую практику на этапах постановки диагноза, выбора стратегии лекарственной терапии и даже сопровождения работы хирурга-онколога в операционной.

С учетом всех приведенных выше характеристик и преимуществ масс-спектрометрические методы анализа биологических образцов можно определить как один из наиболее перспективных и динамически развивающихся инструментов прецизионной медицины вследствие их способности на базе омиксных технологий предоставить клинически ценную информацию с учетом персональных особенностей пациента.

В ближайшее десятилетие можно ожидать, что внедрение методов, основанных на технологии масс-спектрометрии, в клиническую практику, стоящую на принципах прецизионной медицины, приведет к оптимизации процесса определения индивидуальных стратегий лечения онкологических больных и принесет значительный экономический эффект за счет снижения заболеваемости, инвалидности и смертности.

В настоящей обзорной статье представлен анализ 65 научных публикаций, посвященных результатам клинических и экспериментальных исследований, в которых методы масс-спектрометрического анализа применялись для диагностики онкологических заболеваний, выяснения механизмов их развития и оценки эффективности терапевтических воздействий. Обзор включает оригинальные статьи, опубликованные в период с 1 января 2018 г. по 30 ноября 2023 г.

Большинство исследований подтверждают, что масс-спектрометрия является перспективным инструментом в онкологической диагностике и мониторинге эффективности лечения. Расширение использования методов масс-спектрометрии в онкологии имеет большой потенциал и является актуальной задачей для дальнейших исследований.

Ключевые слова: масс-спектрометрическое исследование, масс-спектрометрия, молекулярное профилирование, рак, опухолевой процесс, канцерогенез, низкомолекулярные метаболиты

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.

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INTRODUCTION

World Health Organization (WHO) mortality data up to 2023 report that cancer is one of the leading causes of death around the world. In 2020, cancer caused the death of almost 10 million people, which means that one in six people died from cancer. The most common causes of cancer death in 2020 were lung cancer, colon and rectal cancer, liver cancer, stomach cancer, and breast cancer [1]. In countries where healthcare systems are effective, survival rates for many forms of cancer are increasing due to widespread availability of early diagnosis, quality treatment, and care for cancer patients [2]. Every year in the world, about 10 million new cancer diagnoses are made, which accounts for about 30% of the world population [3].

As early diagnosis improves disease prognosis, the discovery of sensitive biomarkers associated with carcinogenesis through precision medicine has become a priority in cancer research. The use of sensitive methods and the implementation of specific biomarkers for the treatment of cancer into clinical practice will allow early therapy to improve survival and preserve the quality of life of patients.

An innovative approach in healthcare is to understand the unique characteristics of each patient and apply this information to diagnosis, prevention, and treatment. Precision medicine makes it possible to more accurately determine the risk of developing diseases, select the most effective diagnostic methods, and provide personalized treatment recommendations. Precision medicine has the potential to significantly improve health outcomes, reduce unwanted side effects, and optimize healthcare costs. However, its widespread implementation requires joint efforts in the field of scientific research, development of new technologies, and ethical issues related to the use of personal patient data.

The concept of precision medicine is aimed at effective diagnosis and prescription of drugs taking into account the genotype. Metabolomics allows to combine the phenotypic characteristics and genotype of a particular person. Technologies for studying the molecular landscape using chromatography – mass spectrometry are used to search for molecular markers that may be associated with the development of tumors and their growth, which allows for differential diagnosis and verification of tumor diseases, predicting the effectiveness of proposed therapeutic strategies and monitoring the chosen treatment.

Oncogenesis is accompanied by global changes in the metabolic state, affecting both tumor tissues and the micro- and macroenvironment [1]. Advances in metabolomics make it possible to measure a wide range of cellular metabolites, providing an approach to identifying specific changes associated with tumor transformation of cells. Compared to genomic and proteomic changes, metabolic changes can be directly observed in relation to tumor cell states and are therefore a promising source of biomarkers for identifying cancer.

Differences in metabolomic expression can be used to monitor disease progression and search for promising therapeutic approaches. Empirical switching between drugs in search of the desired one with a satisfactory therapeutic response and the lowest toxicity profile is not ideal clinical practice. Thus, the search for biomarkers that provide an insight into the pathophysiology of the disease should help in personalizing diagnosis and stratifying treatment. In addition, mass spectrometry-based metabolomics has high potential for detecting molecular signatures of human diseases, and, ideally, the detected biomarkers

can be validated for use in routine clinical practice. The value of using high-throughput technologies, such as metabolomics, is the ability to develop predictive panels of biomarkers that can be used to identify patients who are less likely to benefit from therapy because they are at risk of developing adverse complications.

Mass spectrometry-based metabolomics provides an insight into molecular events occurring in a patient's cancerous tumor and in normal tissues. Metabolic reprogramming is considered as a hallmark of cancer that contributes to disease progression [4]. The differential metabolic demands of rapidly proliferating malignant cells compared to their non-transformed counterparts suggest that targeting metabolism may be a potential strategy for developing new cancer treatments [4]. A key step in developing new therapeutic approaches that exploit metabolic vulnerabilities is identifying metabolic changes that are relevant to a specific malignancy.

Changes in metabolites during tumorigenesis and standardization of data analysis have shown that mass spectrometry can be an effective tool for use in cancer epidemiology and translational research.

The aim of this review was to analyze the accumulated clinical data on the use of mass spectrometry in diagnosing, treating, and prognosing cancer from the perspective of precision medicine.

METHODS

The analysis of scientific publications of clinical trials and experimental studies was carried out in the PubMed electronic search system. The review includes original articles published from January 1, 2018 to November 30, 2023.

The query for searching for English-language publications included the words: mass spectrometry and (((cancer) or (tumors)) and (molecular profiling)). We identified 1,995 publications in English. At the first stage, articles were selected whose titles mentioned mass spectrometry methods in oncology, while review-type and duplicate publications were excluded. At the second stage, the abstracts of the publications were analyzed, and works where studies were performed on cell cultures or animal models were excluded. At the third stage, articles with full-text access were selected, resulting in a detailed analysis of 65 publications containing data on modern original research in the field of oncogenesis and molecular profiling. Description of the studies (type of biological material, methodological approach, study characteristics) is presented in Table.

RESULTS

Following the analysis, we can note a significant spread of molecular profiling methods in clinical practice. Research conducted in this area concerns various types of cancer, such as colorectal cancer, non-small cell lung cancer, gastric adenocarcinoma, prostate cancer, breast cancer, etc.

The results of the literature review indicate a significant contribution of molecular profiling methods to the study of cancer and their clinical application. In the discussion section, we reviewed several of the most interesting articles from those devoted to the use of mass spectrometry methods in oncology. The articles we selected are only part of the extensive work of researchers in this field and are a valuable contribution to the development of oncology and practical medicine.

Using mass spectrometry to identify biomarkers of tumorigenesis

During tumorigenesis, extensive changes in the metabolic state occur, which affect not only tumor tissues, but also their micro- and macroenvironment. Advances in metabolomics make it possible to measure a wide range of metabolites, allowing for the identification of specific metabolic changes associated with tumor processes. Cancer is a multifactorial disease, and understanding its basis requires not only an analysis of genetic predisposition, but also phenotypic characteristics of the body.

In recent decades, medical research has actively studied non-invasive cancer screening methods based on the analysis of biological material, with special attention paid to identifying early stages of the disease. Some types of cancer, such as pancreatic cancer, do not show specific symptoms, making it difficult to diagnose early stages using conventional screening methods [51]. Pancreatic ductal adenocarcinoma (PDAC), which accounts for 90% of pancreatic cancers, is most often diagnosed at an advanced stage, resulting in the worst 5-year survival rate (7%) among all cancers. An international team of researchers from the Czech Republic, Germany, and Singapore have developed a lipidomic profiling approach to detect pancreatic cancer. The sensitivity and specificity of the method are more than 90%, which is superior to the

Table

Data on modern original research in the field of oncogenesis and molecular profiling

Title	Authors	Year, country	Methodological approach	No.
Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis	Mayerle J., Kalthoff H., Reszka R. et al.	2018, Germany	Biomarkers for the differential diagnosis of pancreatic adenocarcinoma and chronic pancreatitis were identified using gas and liquid chromatography – mass spectrometry in serum and blood plasma	[5]
Discrimination of papillary thyroid cancer from non-cancerous thyroid tissue based on lipid profiling by mass spectrometry imaging	Wojakowska A., Cole L.M., Chekan M. et al.	2018, Poland	Using high-resolution MALDI-Q-Ion Mobility-TOF-MS, a method has been developed for the differential diagnosis of papillary thyroid carcinoma based on the lipid profile of histological samples fixed in formalin	[6]
Identification of Potential Biomarkers and Metabolic Profiling of Serum in Ovarian Cancer Patients Using UPLC/Q-TOF MS	Yang W., Mu T., Jiang J. et al.	2018, China	Using ultraperformance liquid chromatography and quadrupole mass spectrometry with positive electrospray ionization, biomarkers of ovarian cancer were identified in blood serum, which can be used to diagnose the disease	[7]
A quantitative multimodal metabolomic assay for colorectal cancer	Farshidfar F., Kopciuk K.A., Hilsden R. et al.	2018, Canada	Using a multimodal approach using gas chromatography-mass spectrometry, a metabolomic profile was identified in blood serum that distinguishes colorectal cancer from the control group, including 48 metabolites	[8]
Molecular profiling of lung cancer specimens and liquid biopsies using MALDI-TOF mass spectrometry	Bonaparte E., Pesenti C., Fontana L. et al.	2018, Italy	Using mass spectrometry, which allows for multiplex genotyping, a panel capable of identifying the most common mutations in non-small cell lung cancer has been proposed	[9]
Comparing intestinal versus diffuse gastric cancer using a PEFF-oriented proteomic pipeline	Wippel H.H., Santos M.D.M., Clasen M.A. et al.	2018, Brazil	A method for differential diagnosis of diffuse and interstitial gastric cancer has been developed, based on comparison of proteomic profiles obtained by isobaric labeling of peptides, 10-step fractionation and reversed-phase nanochromatography in combination with mass spectrometry	[10]
Metabolomic prediction of treatment outcome in pancreatic ductal adenocarcinoma patients receiving gemcitabine	Phua L.C., Goh S., Tai D.W.M. et al.	2018, Singapore	Using gas chromatography / time of flight mass spectrometry (GC/TOFMS) for metabolomic profiling of histological samples, metabolic biomarkers have been proposed that predict resistance to gemcitabine in chemotherapy for pancreatic ductal adenocarcinoma	[11]
Proteomic Characterization of Prostate Cancer to Distinguish Nonmetastasizing and Metastasizing Primary Tumors and Lymph Node Metastases	Müller A.K., Föll M., Heckelmann B. et al.	2018, Germany	Using liquid chromatography with tandem mass spectrometry and subsequent quantitative determination, a proteomic signature of primary prostate cancer was revealed in which metastasis to the lymph nodes occurs	[12]
Designation of fingerprint glycopeptides for targeted glycoproteomic analysis of serum haptoglobin: insights into gastric cancer biomarker discovery	Lee J., Hua S., Lee S.H. et al.	2018, Korea	Biomarkers of gastric cancer (glycopeptides) were identified in blood serum using mass spectrometry. An analytical platform with a targeted glycoproteomic approach has been created for the detection of gastric cancer biomarkers in blood serum, including 3 glycopeptides that can be used to diagnose the disease	[13]
Expression of small leucine-rich extracellular matrix proteoglycans biglycan and lumican reveals oral lichen planus malignant potential	Lončar-Brzak B., Klobučar M., Veliki-Dalić I. et al.	2018, Croatia	Using the method of global protein profiling based on liquid chromatography with mass spectrometry, a method for the differential diagnosis of lichenoid disease and squamous cell carcinoma of the oral cavity has been developed. The small leucine-rich proteoglycans biglycan and lumican have been identified as important biomarkers of oral squamous cell carcinoma	[14]
Differential diagnosis between hepatocellular carcinoma and cirrhosis by serum amino acids and acylcarnitines	Zhang Y., Ding N., Cao Y. et al.	2018, China	A method for the differential diagnosis of hepatocarcinoma and liver cirrhosis has been proposed based on determining the profile of amino acids and acylcarnitines using mass spectrometry of whole blood samples dried on filter paper	[15]

Clinical Significance of Extracellular Vesicles in Plasma from Glioblastoma Patients	Osti D., Del Bene M., Rappa G. et al.	2019, USA, Italy	An increase in the level of extracellular vesicles in the blood plasma can help in the clinical diagnosis of glioblastoma: their decrease after resection, increase during relapse, as well as their proteomic profiling using mass spectrometry provide insight into the molecular profile of the tumor and can serve as a prognostic criterion for the response to therapy	[16]
Breast cancer detection using targeted plasma metabolomics	Jasbi P., Wang D., Cheng S.L. et al.	2019, USA, China	Using liquid chromatography with tandem mass spectrometry, a new panel containing 6 metabolites of potential biomarkers for the diagnosis of breast cancer was created	[17]
The decrease of some serum free amino acids can predict breast cancer diagnosis and progression	Eniu D.T., Romanciuc F., Moraru C. et al.	2019, Romania	Ultra-high performance liquid chromatography combined with mass spectrometry showed a significant decrease in the concentrations of arginine, alanine, isoleucine, tyrosine, and tryptophan in the blood serum of patients with confirmed breast cancer	[18]
Glycerophospholipids pathways and chromosomal instability in gastric cancer: Global lipidomics analysis	Hung C.Y., Yeh T.S., Tsai C.K. et al.	2019, Taiwan	Using liquid chromatography – mass spectrometry, it was found that chromosomal instability of gastric cancer is associated with changes in the lipid profile of tumors toward an increase in glycerolipids and glycerophospholipids	[19]
Metabolomics-Based Biosignatures of Prostate Cancer in Patients Following Radiotherapy	Nalbantoglu S., Abu-Asab M., Suy S. et al.	2019, USA, Turkey	Radiation metabolomics has been applied to search for metabolomic biomarkers of prostate cancer and tumor response to radiotherapy. The metabolome of blood serum of patients who underwent radiation therapy revealed predominance of aberrations in the metabolic pathways of nitrogen, pyrimidines, purines, porphyrins, and glycerophospholipids	[20]
Proteomics of Melanoma Response to Immunotherapy Reveals Mitochondrial Dependence	Harel M., Ortenberg R., Varanasi S.K. et al.	2019, USA, Israel	Proteomic analysis of melanoma samples using high-resolution liquid chromatography – mass spectrometry revealed a relationship between the metabolic state of melanoma and response to immunotherapy, which may form the basis for therapy adjustments	[21]
Reliable identification of prostate cancer using mass spectrometry metabolomic imaging in needle core biopsies	Morse N., Jamaspishvili T., Simon D. et al.	2019, Canada	Multidimensional metabolomic classifier for prostate cancer with potential for clinical application was developed	[22]
Proteomic signatures of 16 major types of human cancer reveal universal and cancer-type-specific proteins for the identification of potential therapeutic targets	Zhou Y., Lih T. M., Pan J. et al.	2020, USA	Using liquid chromatography with tandem mass spectrometry, the proteomic landscape of 16 major cancer types was presented, and universally expressed proteins specific to a particular tissue and cancer type were identified	[23]
Untargeted Metabolomics and Polyamine Profiling in Serum before and after Surgery in Colorectal Cancer Patients	Lee Y. R., An K. Y., Jeon J. et al.	2020, Korea	Liquid chromatography – mass spectrometry of blood serum in patients with colorectal cancer before and after surgery revealed differences in the metabolism of sphingolipids, arginine, proline, and steroid biosynthesis.	[24]
Metabolic Alterations Related to Glioma Grading Based on Metabolomics and Lipidomics Analyses	Yu D., Xuan Q., Zhang C. et al.	2020, China	Using gas chromatography – mass spectrometry, differential metabolites between various types of gliomas and paratumor tissues were studied. It was found that in high-grade gliomas the content of short-chain acylcarnitines is increased, and lysophosphatidylethanolamines are decreased	[25]
Stromal vapors for real-time molecular guidance of breast-conserving surgery	Vaysse P.M., Kooreman L.F., Engelen S.M. et al.	2020, Netherlands	Using mass spectrometry with rapid evaporative ionization, an intraoperative diagnostic method has been developed for rapid analysis of the border of a breast cancer tumor and healthy tissue using *in vivo* and real-time analysis based on electrosurgical vapors with a metabolomic profile	[26]
Histo-molecular differentiation of renal cancer subtypes by mass spectrometry imaging and rapid proteome profiling of formalin-fixed paraffin-embedded tumor tissue sections	Möginger U., Marcussen N., Jensen O.N. et al.	2020, Denmark	The combination of MALDI-MS imaging (MSI) and rapid LC-MS/MS-based microproteomics (15 min / sample) to analyze tissue sections can identify molecular features and correctly classify 100% of patients with renal oncocytoma, clear cell renal cell carcinoma, and chromophobe renal cell carcinoma	[27]

Table (continued)

Title	Authors	Year, country	Methodological approach	No.
Ion mobility mass spectrometry of human melanoma gangliosides	Sarbu M., Clemmer D.E., Zamfir A.D. et al.	2020, Romania	The combination of mass spectrometry with ion mobility separation revealed high frequency of gangliosides GD3 and GM3 as well as de-N-acetyl GM3 (d-GM3) and de-N-acetyl GD3 (d-GD3) when profiling them in human melanoma, which complements the existing list of biomarkers associated with this type of cancer	[28]
Identification of plasma lipid species as promising diagnostic markers for prostate cancer	Chen X., Zhu Y., Jijiwa M. et al.	2020, China, USA	Plasma lipid profiling using liquid chromatography electrospray ionization and tandem mass spectrometry identified a five-lipid panel of potential biomarkers to distinguish prostate cancer from benign prostatic hyperplasia. A combination of lipid biomarkers provides a new diagnostic strategy for patients with prostate cancer	[29]
Serum lipidomic biomarkers for non-small cell lung cancer in nonsmoking female patients	Noreldeen H.A., Du L., Li W. et al.	2020, Egypt, China	Untargeted lipidomic profiling of serum, based on ultra-high performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry, showed changes in the lipid profile in women with non-small cell lung cancer. Levels of unsaturated fatty acids decreased and those of saturated fatty acids and lysophosphatidylethanolamines increased, indicating changes in the metabolism of fatty acids and phosphatidylethanolamines. The developed serum combination lipid biomarker can be used for early diagnosis of non-small cell lung cancer	[30]
A serum lipidomic strategy revealed potential lipid biomarkers for early-stage cervical cancer	Cheng F., Wen Z., Feng X. et al.	2020, China	A panel of lipid biomarkers, including phosphatidylcholine and phosphatidylethanolamine, was developed by ultra-high-pressure liquid chromatography with quadrupole time-of-flight tandem mass spectrometry for the effective diagnosis of cervical cancer and squamous intraepithelial lesions	[31]
Liquid Chromatography-Mass Spectrometry-Based Tissue Metabolic Profiling Reveals Major Metabolic Pathway Alterations and Potential Biomarkers of Lung Cancer	You L., Fan Y., Liu X. et al.	2020, China	Untargeted metabolomics analysis based on liquid chromatography – mass spectrometry of lung carcinoma tissue and distal healthy lung tissue revealed an increase in lysophospholipids and a decrease in the content of 3-phosphoglyceric acid, phosphoenolpyruvate, 6-phosphogluconate and citrate in tumor tissue. It has been shown that during carcinogenesis, energy, purine, amino acid, lipid, and glutathione metabolism is disrupted.	[32]
Classification of thyroid tumors based on mass spectrometry imaging of tissue microarrays; a single-pixel approach	Kurczyk A., Gawin M., Chekan M. et al.	2020, Poland	The matrix laser desorption ionization method in the analysis of tissue microchips made it possible to identify high molecular similarities between different types of malignant neoplasms of the thyroid gland. Tumors with follicular morphology, such as adenoma, follicular cancer, and the follicular variant of papillary cancer, turned out to be especially similar in molecular structure	[33]
Study on the Diagnosis of Gastric Cancer by Magnetic Beads Extraction and Mass Spectrometry	Zhu N., Xing X., Cao L. et al.	2020, China	Using matrix-assisted laser desorption / ionization time-of-flight mass spectrometry, it was found that the expression of two peptide peaks with molecular weights of 2,863 Da and 2,953 Da was significantly increased, and the expression of two peptide peaks with molecular weights of 1,945 Da and 2,082 Da was decreased in the serum of patients with stomach cancer	[34]
Rapid estimation of tumor cell percentage in brain tissue biopsy samples using inline cartridge extraction mass spectrometry	Pekov S. I., Bormotov D.S., Nikitin P.V. et al.	2021, Russia	A study of 58 glial tumors was conducted to assess the percentage of tumor cells using the mass spectrometry method, which showed the possibility of automating routine tissue screening and its implementation in clinical practice during surgical interventions	[35]

Large-scale and high-resolution mass spectrometry-based proteomics profiling defines molecular subtypes of esophageal cancer for therapeutic targeting	Liu W., Xie L., He Y. H. et al.	2021, China	The study performed a proteomic analysis of 124 paired esophageal cancer tumors and corresponding adjacent non-tumor tissues, which identified two subtypes of esophageal cancer that are associated with patient survival and predicted potential drugs for one of the molecular subtypes	[36]
Early Breast Cancer Detection Using Untargeted and Targeted Metabolomics	Wei Y., Jasbi P., Shi X. et al.	2021, USA	In the current study, plasma samples from breast cancer patients and healthy controls were analyzed by untargeted liquid chromatography and quadrupole time-of-flight mass spectrometry, identifying 33 altered metabolites that provided accurate classification of early-stage breast cancer	[37]
The Colorectal Cancer Lipidome: Identification of a Robust Tumor-Specific Lipid Species Signature	Ecker J., Benedetti E., Kindt AS. et al.	2021, Germany	Using direct infusion electrospray ionization techniques coupled with tandem mass spectrometry and high-resolution mass spectrometry, significant differences in lipid composition were found between tumor and normal tissue in colorectal cancer. Glycerophospholipids showed a wide range of variation between patients, while the quantitative composition of glycero- and sphingolipids was more stable. There was also a significant increase in lipogenic enzyme activity and an association of triglyceride metabolic profile with postoperative disease-free survival and lymphovascular invasion in colorectal cancer	[38]
Proteomic profiling identifies signatures associated with progression of precancerous gastric lesions and risk of early gastric cancer	Li X., Zheng N. R., Wang L.H. et al.	2021, China	Using liquid chromatography and tandem mass spectrometry of blood serum, the proteomic landscape of precancerous lesions of the stomach and gastric cancer was determined, proteomic characteristics were determined, including proteomic subtypes and individual proteins associated with the progression of precancerous lesions of the stomach and the risk of early development of this disease	[39]
Proteomic profiling of soft tissue sarcomas with SWATH mass spectrometry	Milighetti M., Krasny L., Lee A. T. et al.	2021, Great Britain	Mass spectrometry techniques have been applied to comprehensive proteomic analysis of different soft tissue sarcoma subtypes to identify unique proteomic signatures, identify biological processes and key protein networks within histological tumor subtypes, and identify potential candidate proteins associated with predicting patient outcomes	[40]
Mass-spectrometry-based proteomic correlates of grade and stage reveal pathways and kinases associated with aggressive human cancers	Monsivais D., Vasquez Y.M., Chen F. et al.	2021, USA	Mass spectrometry was used to determine differential patterns of protein expression associated with the grade or stage of development of seven types of cancer – invasive breast carcinoma, colon adenocarcinoma, lung adenocarcinoma, clear cell renal cell carcinoma, serous ovarian tumor, uterine corpus carcinoma, and childhood glioma. The study showed that each cancer type had a proteomic signature that was different from those of other cancer types. Differentially expressed proteins and mRNAs were identified for late cancer development for each of the seven tumor types	[41]
Comprehensive Metabolomics and Lipidomics Profiling of Prostate Cancer Tissue Reveals Metabolic Dysregulations Associated with Disease Development	Lima A.R., Carvalho M., Aveiro S.S. et al.	2021, Portugal	Untargeted mass spectrometry and nuclear magnetic resonance techniques have been applied to prostate cancer research. The results revealed significant changes in the levels of 26 metabolites and 21 types of phospholipids in prostate cancer tissue, indicating dysregulation of 13 metabolic pathways associated with cancer development	[42]
Interim clinical trial analysis of intraoperative mass spectrometry for breast cancer surgery	Basu S.S., Stopka S.A., Abdelmoula W.M. et al.	2021, USA	Ambient ionization mass spectrometry was used to rapidly analyze the lipid profile of invasive breast carcinoma for potential application in breast-conserving surgery	[43]
Imaging Mass Spectrometry-Based Proteomic Analysis to Differentiate Melanocytic Nevi and Malignant Melanoma	Casadonte R., Kriegsmann M., Kriegsmann K. et al.	2021, Germany	Imaging mass spectrometry determined differences in the proteomic profile between malignant melanomas and melanocytic benign nevi with an overall accuracy of > 98%	[44]

Table (continued)

Title	Authors	Year, country	Methodological approach	No.
Intraoperative Mass Spectrometry Platform for IDH Mutation Status Prediction, Glioma Diagnosis, and Estimation of Tumor Cell Infiltration	Brown H.M., Alfaro C.M., Pirro V. et al.	2021, USA	To determine the extent of surgical intervention and increase the degree of safe resection, assessing the infiltration of tumor cells using desorption mass spectrometry with electrospray ionization, the isocitrate dehydrogenase mutation status was determined intraoperatively in patients with glioma	4527]
Metabolomic Profiling of Blood-Derived Microvesicles in Breast Cancer Patients	Buentzel J., Klemp H.G., Kraetzner R. et al.	2021, Germany	Using mass spectrometry and targeted metabolomic profiling of blood-derived microvesicles, it was shown that a combination of eight metabolites distinguishes breast cancer patients from healthy controls, there are differences between the molecular subtypes of breast cancer, and microvesicle biomarkers are a prognostic factor for overall survival	[46]
Lipidomic Signatures for Colorectal Cancer Diagnosis and Progression Using UPLC-QTOF-ESI+MS	Răchieriu C., Eniu D.T., Moiş E. et al.	2021, Romania	Using high-performance liquid chromatography – mass spectrometry, it was shown that several subclasses of lipids, including phosphatidylglycerols-phosphatidylethanolamines and phosphatidic acids, fatty acids and sterol esters, as well as ceramides, can be considered as specific markers for the development of colorectal cancer, dependent on lipogenesis and lipolysis	[47]
Global metabolomics profiling of colorectal cancer in Malaysian patients	Hashim N.A.A., Ab-Rahim S., Ngah W.Z.W. et al.	2021, Malaisia	High performance liquid chromatography – time of flight mass spectrometry identified 11 differential metabolites in blood serum, the levels of which were significantly different in patients with colorectal cancer. Using this panel allows to distinguish colorectal cancer with 80% accuracy	[48]
Lipidomic Profiling of Clinical Prostate Cancer Reveals Targetable Alterations in Membrane Lipid Composition	Butler L.M., Mah C.Y., Machiels J. et al.	2021, Australia	Using chromatography coupled with tandem mass spectrometry, significant differences in lipid composition were detected and spatially visualized in prostate cancer tumors compared to benign samples. The tumors were characterized by a higher proportion of monounsaturated lipids and elongated fatty acid chains in phosphatidylinositol and phosphatidylserine lipids	[49]
Integrated analysis of the faecal metagenome and serum metabolome reveals the role of gut microbiome-associated metabolites in the detection of colorectal cancer and adenoma	Chen F., Dai X. Zhou C.C. et al.	2022, China	Using mass spectrometry in combination with ultra-performance liquid chromatography, it was shown that reprogramming of the intestinal microbiome in patients with colorectal cancer is associated with changes in the serum metabolome. The model based on a panel of 8 gut microbiome-associated serum metabolites predicts colorectal cancer and colon adenomas with 84% and 93% accuracy, respectively	[50]
Lipidomic profiling of human serum enables detection of pancreatic cancer	Wolrab D., Jirásko R., Cífková E.et al.	2022, Czech Republic, Germany, Singapore, etc.	A three-phase biomarker study using comprehensive mass spectrometric determination of a wide range of serum lipids revealed statistically significant differences in long-chain sphingomyelins, ceramides, and (lyso)phosphatidylcholines between patients with pancreatic cancer and healthy controls	[51]
Proteogenomic analysis of lung adenocarcinoma reveals tumor heterogeneity, survival determinants, and therapeutically relevant pathways	Soltis A. R., Bateman N.W., Liu J. et al.	2022, USA	The use of molecular profiling technologies in the study of lung adenocarcinoma has identified three distinct cancer subtypes with unique characteristics, such as expression levels, mutations, proteomic regulatory networks, and therapeutic vulnerabilities	[52]

Profiling of Urine Carbonyl Metabolic Fingerprints in Bladder Cancer Based on Ambient Ionization Mass Spectrometry	Li Y., Jiang L., Wang, Z. et al.	2022, China	Metabolic fingerprint profiling of carbonyl compounds in bladder cancer based on the N,N-dimethylethylenediamine desorption, separation, and ionization mass spectrometry platform identified 9 potential biomarkers for early non-invasive diagnosis	[53]
N-Glycan and Glycopeptide Serum Biomarkers in Philippine Lung Cancer Patients Identified Using Liquid Chromatography–Tandem Mass Spectrometry	Alvarez M.R.S., Zhou Q., Tena J. et al.	2022, Philippines	Using ultra-high performance liquid chromatography coupled with triple quadrupole mass spectrometry, specifically expressed glycoproteins were identified in the serum of lung cancer patients	[54]
Integrating age, BMI, and serum N-glycans detected by MALDI mass spectrometry to classify suspicious mammogram findings as benign lesions or breast cancer	Blaschke C.R., Hill E.G., Mehta A.S. et al.	2022, USA	Using matrix-assisted laser desorption / ionization, serum N-glycans were identified that have diagnostic potential for the differential diagnosis of benign tumors and invasive breast cancer	[55]
Deep mining and quantification of oxidized cholesteryl esters discovers potential biomarkers involved in breast cancer by liquid chromatography-mass spectrometry	Wang X., Li H., Zou X., Yan X. et al.	2022, China	Using quadrupole time-of-flight mass spectrometry combined with reversed-phase liquid chromatography, an increased content of oxidized cholesteryl ester was determined in serum samples from patients with breast cancer	[56]
Identification of prediagnostic metabolites associated with prostate cancer risk by untargeted mass spectrometry-based metabolomics	Östman J.R., Pinto R.C., Ebbels T.M. et al.	2022, Sweden, Great Britain	Untargeted metabolomic profiling based on high-resolution mass spectrometry of blood plasma has identified a number of phospholipids and some free fatty acids that are positively associated with the risk of developing common and non-aggressive prostate cancer	[57]
MALDI Mass Spectrometry Imaging highlights specific metabolome and lipidome profiles in salivary gland tumor tissues	Sommella E., Salviati E., Caponigro V. et al.	2022, Italy	Laser desorption / ionization mass spectrometry imaging was used to identify lipid and metabolic markers of parotid neoplasms: glycerophospholipids, glutamate metabolism, and nucleotides were markedly increased in tumor tissues, while sphingomyelins and triacylglycerols were decreased	[58]
Coated Blade Spray-Mass Spectrometry as a New Approach for the Rapid Characterization of Brain Tumors	Bogusiewicz J., Gaca-Tabaszewska M., Olszówka, D. et al.	2022, Poland, Canada	Coated blade spray mass spectrometry coupled with high-resolution mass spectrometry has developed a method for the differential diagnosis of meningioma and glioma based on differences in the lipid profile of surgical biopsies	[59]
Metabolomic profile of prostate cancer-specific survival among 1812 Finnish men	Huang J., Zhao B., Weinstein S. J. et al.	2022, China, USA	A prospective, untargeted metabolomic analysis identified prediagnostic serum metabolites associated with the molecular basis of prostate cancer progression and patient survival	[60]
Blood plasma metabolome profiling at different stages of renal cell carcinoma	Maslov D.L., Trifonova O.P., Lichtenberg S. et al.	2022, USA, Russia	Mass spectrometry of blood plasma revealed an association between changes in the levels of certain amino acids and the progression of kidney cancer	[61]
Molecular pathological diagnosis of thyroid tumors using spatially resolved metabolomics	Huang L., Mao X., Sun C. et al.	2022, China	Using metabolomic analysis with spatial resolution, a molecular diagnostic method has been developed to distinguish benign adenomas and malignant papillary carcinomas of the thyroid gland	[62]
Proteomic signatures of infiltrative gastric cancer by proteomic and bioinformatic analysis	Zhang L.H., Zhuo H.Q., Hou J.J. et al.	2022, China	Using high-performance liquid chromatography and tandem mass spectrometry, 20 differentially expressed proteins were identified that can be used as prognostic markers in infiltrating gastric cancer	[63]
Identifying cancer cell-secreted proteins that activate cancer-associated fibroblasts as prognostic factors for patients with pancreatic cancer	Luo Q., Liu J., Fu Q. et al.	2022, China	Liquid chromatography – tandem mass spectrometry was used to identify 6 proteins secreted by pancreatic cancer cells that promote cancer cell migration and invasion to evaluate the prognosis of 3-year postoperative survival	[64]

Table (continued)

Title	Authors	Year, country	Methodological approach	No.
Salivary Lipids of Patients with Non-Small Cell Lung Cancer Show Perturbation with Respect to Plasma	Hwang B.Y., Seo J.W., Muftuoglu C. et al.	2023, Turkey	Using nanoflow ultra-high performance liquid chromatography – electrospray ionization – tandem mass spectrometry, 27 salivary lipids and 10 plasma lipids were isolated as candidate markers for non-small cell lung cancer. The study showed that changes in the distribution of salivary lipid profile may be more informative markers than changes in blood plasma	[65]
Data-Independent Acquisition Mass Spectrometry Analysis of FFPE Rectal Cancer Samples Offers In-Depth Proteomics Characterization of the Response to Neoadjuvant Chemoradiotherapy	Stanojevic A., Samiotaki M., Lygirou V. et al.	2023, Serbia, Greece, the Netherlands, Spain	Using mass spectrometry, proteins were isolated in biopsy samples of rectal cancer tumors – prognostic markers of a favorable outcome of non-adjuvant chemoradiation therapy for selecting the optimal volume of surgical intervention and choosing the optimal treatment strategy	[66]
Serum Proteomic Profiles of Patients with High and Low Risk of Endometrial Cancer Recurrence	Pietkiewicz D., Zaborowski M.P., Jaz K. et al.	2023, Poland	Using matrix laser desorption / ionization – time-of-flight mass spectrometry of blood serum, protein biomarkers were isolated to stratify patients with low and high risks of developing relapses for more clinically based treatment and intensification of first-line therapy	[67]
Kinase Inhibitor Pulldown Assay Identifies a Chemotherapy Response Signature in Triple-negative Breast Cancer Based on Purine-binding Proteins	Wang J., Saltzman A.B., Jaehnig E. et al.	2023, USA	Using chromatography – mass spectrometry, an approach based on the quantitative determination of kinase inhibitors has been developed to predict the effectiveness of non-adjuvant chemotherapy for triple-negative breast cancer	[68]
Lung adenocarcinoma and squamous cell carcinoma difficult for immunohistochemical diagnosis can be distinguished by lipid profile	Yamashita T., Takanashi Y., Uebayashi A. et al.	2023, Japan	Using liquid chromatography and tandem mass spectrometry, a method has been developed for the differential diagnosis of lung adenocarcinoma and squamous cell carcinoma of the lung by analyzing the lipid profile of a biopsy specimen	[69]
Proteomic and Metabolomic Analysis of Bone Marrow and Plasma from Patients with Extramedullary Multiple Myeloma Identifies Distinct Protein and Metabolite Signatures	Dunphy K., Bazou D., Henry M. et al.	2023, Israel, Finland	Using chromatography – mass spectrometry methods, the proteome of mononuclear cells of bone marrow cells and blood plasma was studied, and a method was developed for the differential diagnosis of multiple myeloma and extramedullary multiple myeloma by analyzing the metabolomic profile of blood plasma	[70]

existing marker glycoprotein CA 19-9, especially at an early stage.

A colorectal cancer study [50] developed a diagnostic panel including eight serum metabolites associated with the gut microbiome to predict colorectal cancer and colorectal adenoma, which showed high performance and specificity values in targeted and untargeted metabolomic analyses.

A study on bladder cancer [53] considered the use of mass spectrometry of urine to search for metabolites containing carbonyl groups for diagnosis. The work identified nine potential biomarkers that can be used as a non-invasive and less expensive alternative to traditional cystoscopy.

Mass spectrometry-based techniques and approaches can be an invaluable tool in the operating room as they allow for a rapid analysis of biological materials. Differentiation of cancerous and healthy tissues, as well as tumor classification based on its histologic and molecular features using rapid evaporative ionization mass spectrometry (REIMS) is shown in the article [26]. This method is based on the analysis of aerosols generated when tissue is cut with an electrocautery blade or other instruments and then sent to a mass spectrometer. This tool, also known as the smart knife (iKnife), has been widely used in the surgical differentiation of healthy and cancerous tissues [59].

The possibility of using ambient mass spectrometry to assess the percentage of tumor cells in the tissues of glial brain tumors is presented in the article [35]: a quick and accurate assessment of the percentage of tumor cells in clinical practice and neurosurgery plays an important role for diagnosis and surgical intervention. The researchers trained the system to estimate the percentage of tumor cells with an accuracy of about 90% using a cassette embedding method, which allows for samples to be analyzed without preliminary preparation and machine learning methods. The use of such techniques can automate routine tissue screening and tumor cell percentage assessment, speeding up estimation of tumor cell percentage during neurosurgery.

In cancer research, mass spectrometry-based proteomic approaches are used to initially identify potential new prognostic, diagnostic or therapeutic markers, opening new opportunities for subsequent research. The ability to conduct proteomic studies on formalin-fixed and paraffin-embedded tissues [10, 12, 23] provided an opportunity for retrospective proteomic studies on selective cohorts with long-term follow-up.

Biological materials obtained during autopsies of patients with cancer are of great interest for research because they provide an adequate assessment of the quality of clinical diagnosis and contribute to the development of optimized approaches to therapy [71]. Implementation into clinical practice of advanced methods for assessing protein expression and conducting advanced translational multi-omics studies allows for the most comprehensive understanding of the pathogenetic processes in cancers associated with changes in the molecular, metabolic, and genetic landscapes [72].

Using mass spectrometry to determine the treatment strategy and evaluate therapy effectiveness

Patients with cancer undergo clinical staging, which influences the choice of optimal treatment and prognosis of the disease. Treatment options may include various combinations: follow-up, surgery, and / or radiation therapy. Thus, initial risk stratification in patients with carcinogenesis is important to achieve optimal therapeutic results and maintain the quality of life. Predictive biomarkers of a risk of complications or late effects of treatment are needed for clinical decisions on treatment selection.

A proteomic study of 116 melanoma tumors found that the response to immunotherapy was associated with enriched mitochondrial lipid metabolism. High levels of mitochondrial metabolism resulted in increased antigen presentation and interferon signaling. In addition, knockout of genes associated with beta oxidation reduced the sensitivity of melanoma to T cell killing. These results indicate an important role of mitochondrial lipid metabolism in response to immunotherapy and may have implications for the development of new treatment strategies for melanoma.

The results of a study by scientists from the USA and Turkey indicate an association of metabolic pathways of purines, pyrimidines, nitrogen, and porphyrins with radiosensitivity or radioresistance [20]. The work involved metabolomic profiling of patients with prostate cancer who underwent radiation therapy, which is important for identifying their new metabolomic status and assessing the consequences of radiation. It was shown that bilirubin can be used

as a reference value for prostate cancer patients receiving radiotherapy, as its level may be associated with treatment-induced liver toxicity. The change in the porphyrin pathway and its associations with bilirubin and phosphoric acid during radiation therapy are of particular interest. This may have practical implications in selecting optimal treatment strategies and monitoring the effectiveness of radiation therapy in patients with this type of cancer.

A study [16] assessing the role of patient plasma extracellular vesicles for early diagnosis of glioblastoma and as a prognostic tool for optimal clinical management showed that extracellular vesicle concentrations were increased in plasma of glioblastoma patients compared to healthy controls. After tumor resection, a decrease in the number of extracellular vesicles to the level of healthy people was observed. During relapse, an increase in the number of extracellular vesicles in plasma was revealed.

A team of scientists using high-resolution mass spectrometry-based proteomic profiling identified molecular subtypes of esophageal cancer [36]. The study performed a proteomic analysis of 124 paired esophageal cancer tumors and corresponding adjacent healthy tissues. The proteomic analysis revealed a catalog of proteins, phosphosites, and pathways that are dysregulated in esophageal cancer. Proteomic molecular subtyping identified two cancer subtypes associated with patient survival. In addition, several promising drugs specific to the malignant subtype of esophageal cancer were predicted and tested, which may open new treatment prospects.

An interesting approach, including the use of proteomic methods in patients with prostate cancer, is the combined use of mass spectrometry and immunohistochemistry methods aimed at differential separation of non-metastatic and metastatic primary tumors and detection of metastases in lymph nodes [12]. One of the serious problems that specialists faced when assessing the risk and prognosis of prostate cancer was the inability to use standard prognostic schemes (prostate-specific antigen (PSA) concentration, Gleason / ISUP score, etc.) for accurate prediction of the biological course and metastatic potential of the tumor process [12]. The approach proposed by the authors [12] made it possible to compare the proteomic composition of tissues affected by various prostate tumors (non-metastatic primary, metastatic primary, secondary) with each other, with healthy prostate tissue or with benign hyperplasia. The results showed that zones of prostate cancer have measurable and significantly different biological markers compared to healthy tissue and also demonstrated several proteins that are likely to be involved in the tumorigenesis of differentially various tumors [12].

Using mass spectrometry in basic cancer research

Mass spectrometry-based methods are also used in basic research to search for molecular mechanisms of oncogenesis. Using this powerful tool in tandem with proteomic analysis enables to study protein characteristics on a large scale, including their expression levels, specific post-translational modifications, and protein – protein interactions. All this allows for the most complete understanding of the factors initiating carcinogenesis and cellular metabolism in oncology at the protein level. Quantitative proteomics makes significant contributions to the fundamental understanding of the molecular pathogenesis of cancer, providing researchers with comprehensive information about protein interactions and signaling pathways, altered metabolites and gene regulation in cancer cells. The above is also true for lipidomic, metabolomic, and glycomic analysis methods.

Indeed, many studies published in recent years provide important insights into cancer biology. Thus, recent work has substantiated the relationship between the occurrence and progression of colorectal cancer and the specific effects of the lipid environment [50]. It is important to note that the authors took into account the already known relationship between colorectal cancer, diet, metabolic disorders, and gut microbiome status.

When studying brain tumors, it was shown that primary glioblastomas, as well as those developed from astrocytomas, are enriched with mono- and diunsaturated phosphatidylcholines, while the content of saturated and polyunsaturated phosphatidylcholines and phosphatidylethanolamines decreases. These changes are apparently associated with the availability of polyunsaturated fatty acids and the activation of de novo lipid synthesis and beta-oxidation pathways under anaerobic conditions in the tumor center [75].

Other studies have carried out a detailed study of the significance of lipid markers that are valid

for subtyping non-small cell lung cancer regardless of tissue morphology and immunohistochemical markers [69], the role of aberrant glycosylation in tumorigenesis [54], and the contribution of low-molecular-weight metabolites (initiators, intermediates and products of various biochemical reactions) to the development of tumors [61]. Although all of the above advances relate primarily to the basic cancer research, in the future, these and other discoveries will allow for the identification of new cancer biomarkers and lead to the development of new therapeutic strategies.

Summarizing the results of modern research aimed at studying the possibility of using mass spectrometry for diagnosing and predicting the course of cancer from the perspective of precision medicine, we can say that the use of omics research methods based on mass spectrometry in oncology is of great fundamental and practical importance. Metabolomics studies are aimed at identifying and quantitative (or semi-quantitative) assessment of metabolites of different classes, understanding their nature and mechanisms of formation. Understanding the molecular biology of tumors is important for the discovery of new biomarkers of the tumor process, as well as for early detection or subtyping of the tumor. Expanding the use of mass spectrometry-based methods in oncology will help increase the clinical value of biomarkers and find specific metabolites for various cancers, which is a key point in the search for new therapeutic targets, and will contribute to the development of new pathogenetically grounded preventive measures and recommendations for the clinical management of cancer patients.

CONCLUSION

Cancers are some of the most serious problems of modern healthcare [76, 77]. Despite some progress in the diagnosis and development of approaches to treatment and prognosis of cancer in recent years, there is still an urgent need for the discovery of new cancer biomarkers. Efforts in this direction have been made using various approaches, including new high-tech and knowledge-intensive methods, such as genomics, transcriptomics, metabolomics, and proteomics [78].

Identification of molecules of interest and total screening of the molecular landscape in these methods is carried out using mass spectrometry, which has come a long way in recent decades, and today is a powerful technology thanks to the unprecedented level of sensitivity and specificity of the analysis, which is used in clinical practice for analyzing biological samples.

While nucleic acid-based methods of analysis have the advantage of amplification potential, but lack the “effector” component, omics technologies and proteomics, in particular, are considered to be more relevant in the context of application in oncology, since the proteome is directly involved in the implementation of biological effects [79]. Detection of quantitative and / or qualitative modifications of proteins characterized by low abundance in biological samples requires the use of highly sensitive and specific analytical methods. Liquid chromatography in tandem with mass spectrometry is the most widely used method for comprehensive protein identification and quantification.

The use of mass spectrometry in oncology research is not limited to the proteomic analysis and affects other areas of omics research (lipidomics [80], metabolomics [81], glycomics [82]).

Following the literature review, it was found that many publications of recent years describe various approaches and technologies for using mass spectrometry for analyzing biological samples. Mass spectrometry was initially used in clinical toxicology laboratories for specialized identification of target compounds (1950s) [78]. However, already in 1957, the development and use of a portable clinical mass spectrometer for direct, continuous quantitative analysis of four gases in patient’s exhaled breath was reported in assessing the function of external respiration [83].

With the development of new ionization sources and mass analyzers in the 1990s, mass spectrometry has made a transition from a complex analytical tool used almost exclusively by experienced scientists in research laboratories to a more robust and versatile technology suitable for a wide range of applications, including clinical ones [84, 85]. Finally, in recent years, mass spectrometry in combination with gas chromatography and liquid chromatography has become a routine clinical laboratory technology that can provide critical information about clinical samples [86]. The development of electrospray ionization (ESI) and matrix-assisted laser desorption ionization (MALDI) technologies has revolutionized the use of mass spectrometry, allowing researchers to study larger biological

molecules, such as glycoconjugates, proteins, and nucleic acids [87, 88]. The development of ESI has greatly facilitated the use of mass spectrometry in clinical analyzes of biological fluids, such as blood and urine [87], while the development of MALDI has led to advances in molecular imaging technologies for biological tissue sections for the diagnosis of cancer [88].

Ambient mass spectrometry-based methods, which do not involve chromatographic separation, are extremely promising due to their rapidity [89], while desorption electrospray ionization mass spectrometry (DESI-MS) allows for rapid imaging of biological tissues [90, 91].

The discovery of new cancer biomarkers has changed current practice in oncology [92, 93]. Tumor genome and transcriptome profiling are now established tools for the discovery of new biomarkers, but changes in proteome expression are more likely to reflect changes in tumor pathophysiology. Mass spectrometry is a powerful method that allows to carry out proteomic studies in personalized medicine, and the overlay of proteomic data on the results of genomic and transcriptomic studies allows us to move into the new field of proteogenomics, which demonstrates a growing potential in understanding cancer biology [94]. All this makes clinical proteomics and proteogenomics some of the most promising areas of molecular clinical research, including large-scale study of proteins, their expression, functions and structure, as well as application of the results obtained for the development of approaches to diagnosis, treatment, and monitoring of the effectiveness of cancer therapy. The implementation of all these methods is impossible without the use of mass spectrometry.

In the meantime, metabolomics is also one of the most promising omics technologies, which comprehensively analyzes low-molecular-weight molecules (metabolites) in biological systems [95, 96]. Since metabolites are initiators, intermediates, and products of various biochemical reactions, significant metabolic changes most accurately reflect the physiological and pathological processes occurring in the human body, including the occurrence and development of cancer [97, 98]. Numerous studies have demonstrated the ability of mass spectrometry-based approaches for detecting the results of metabolomic profiling for cancer diagnosis to predict the effectiveness of proposed therapeutic strategies and quickly monitor the progress of treatment [61, 99].

Finally, the latest mass spectrometry-based methods can be an invaluable tool in the operating room, as they can quickly analyze biological materials while the oncologist is working, which will allow for adjustment of the surgical strategy [59]. Indeed, the ability to accurately differentiate between cancerous and healthy tissue within a short time, as well as to classify a tumor based on its histologic and molecular features is an extremely valuable tool when performing operations with cancer resection [101]. The most prominent representative of such approaches to the use of mass spectrometry in oncology is REIMS based on the analysis of aerosols generated when the tissue is cut with an electrocautery blade or another instrument and then placed in a mass spectrometer [102]. This tool, also known as the smart knife (iKnife), has been widely used in the surgical differentiation of healthy and cancerous tissues. [103]. The iKnife is not the only technology for rapid analysis of such small volumes of biological samples. Alternative methods include paper spray (PS) ionization and probe electrospray ionization (PESI), which involve ionization of selected analytes by applying high voltage to the probe, installed directly into the mass spectrometer [73, 74]. In the CBS-MS approach, analytes are extracted from a biological matrix using a specially designed sword-shaped probe coated with immobilized sorption particles. After extraction, the probe is inserted into the mass spectrometer interface, where a drop of desorption solvent is placed on the surface of the blade to release analytes, and high voltage is applied to ensure ionization and analysis of the extracted substances [104]. All of the described approaches, in addition to high accuracy and rapidity of the results obtained, allow for the standardization of diagnostic procedures, which is necessary for the use of these methods for precision medicine in clinical practice.

Therefore, mass spectrometry-based technologies are rapidly moving from laboratory to clinical use in the direct analysis of biological samples of tissues and body fluids. At the same time, there is parallel search for new ways of using them, which can have a significant positive impact on the development of approaches to the study of the pathogenetic features of carcinogenesis at the molecular level, as well as to the diagnosis and treatment of cancer

patients. It can be expected that in the next decade, mass spectrometry and technologies based on direct analysis of tissue samples will continue to be implemented into clinical practice and, after approval by regulatory authorities, will become routine methods in oncology.

REFERENCES

1. https://www.who.int/ru/news-room/fact-sheets/detail/cancer
2. https://www.who.int/ru/health-topics/cancer#tab=tab_1
3. Al-Zhoughbi W., Huang, J., Paramasivan G.S., Till H., Pichler M., Guertl-Lackner B. et al. Tumor macroenvironment and metabolism. *Seminars in Oncology*. 2014;41(2):281–295. DOI: 10.1053/j.seminoncol.2014.02.005
4. Beatty A., Fink L.S., Singh T., Strigun A., Peter E., Ferrer C.M. et al. Metabolite profiling reveals the glutathione biosynthetic pathway as a therapeutic target in triple-negative breast cancer. *Molecular Cancer Therapeutics*. 2018;17(1):264–275. DOI: 10.1158/1535-7163.MCT-17-0407.
5. Mayerle J., Kalthoff H., Reszka R., Kamlage B., Peter E., Schniewind B. et al. Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis. *Gut*. 2018;67(1):128–137. DOI: 10.1136/gutjnl-2016-312432.
6. Wojakowska A., Cole L.M., Chekan M., Bednarczyk K., Maksymiak M., Oczko-Wojciechowska M. et al. Discrimination of papillary thyroid cancer from non-cancerous thyroid tissue based on lipid profiling by mass spectrometry imaging. *Endokrynologia Polska.* 2018;69(1):2–8. DOI: 10.5603/EP.a2018.0003.
7. Yang W., Mu T., Jiang J., Sun Q., Hou X., Sun Y. et al. Identification of potential biomarkers and metabolic profiling of serum in ovarian cancer patients using UPLC/Q-TOF MS. *Cellular Physiology and Biochemistry*. 2018;51(3):1134–1148. DOI: 10.1159/000495492.
8. Farshidfar F., Kopciuk K.A., Hilsden R., McGregor S.E., Mazurak V.C., MacLean A. et al. A quantitative multimodal metabolomic assay for colorectal cancer. *BMC Cancer*. 2018;18(1): 1–12. DOI: 10.1186/s12885-017-3923-z.
9. Bonaparte E., Pesenti C., Fontana L., Falcone R., Paganini L., Marzorati A. et al. Molecular profiling of lung cancer specimens and liquid biopsies using MALDI-TOF mass spectrometry. *Diagnostic Pathology*. 2018;13(1):1–9. DOI: 10.1186/s13000-017-0683-7.
10. Wippel H.H., Santos M.D. M., Clasen M.A., Kurt L.U., Nogueira F.C.S., Carvalho C.E. et al. Comparing intestinal versus diffuse gastric cancer using a PEFF-oriented proteomic pipeline. *Journal of Proteomics*. 2018;171:63–72. DOI: 10.1016/j.jprot.2017.10.005.
11. Phua L.C., Goh S., Tai D.W.M., Leow W.Q., Alkaff S.M.F., Chan C.Y. et al. Metabolomic prediction of treatment outcome in pancreatic ductal adenocarcinoma patients receiving gemcitabine. *Cancer Chemotherapy and Pharmacology*. 2018;81:277–289. DOI: 10.1007/s00280-017-3475-6.
12. Müller A.K., Föll M., Heckelmann, B., Kiefer S., Werner M., Schilling O. et al. Proteomic characterization of prostate cancer to distinguish nonmetastasizing and metastasizing primary tumors and lymph node metastases. *Neoplasia*. 2018;20(2):140–151. DOI: 10.1016/j.neo.2017.10.009.
13. Lee J., Hua S., Lee S.H., Oh M.J., Yun J., Kim J.Y. et al. Designation of fingerprint glycopeptides for targeted glycoproteomic analysis of serum haptoglobin: insights into gastric cancer biomarker discovery. *Analytical and Bioanalytical Chemistry.* 2018;410:1617–1629. DOI: 10.1007/s00216-017-0811-y.
14. Lončar-Brzak B., Klobučar M., Veliki-Dalić I., Sabol I., Kraljević Pavelić S., Krušlin B. et al. Expression of small leucine-rich extracellular matrix proteoglycans biglycan and lumican reveals oral lichen planus malignant potential. *Clinical Oral Investigations*. 2018;22:1071–1082. DOI: 10.1007/s00784-017-2190-3.
15. Zhang Y., Ding N., Cao Y., Zhu Z., Gao P. Differential diagnosis between hepatocellular carcinoma and cirrhosis by serum amino acids and acylcarnitines. *International Journal of Clinical and Experimental Pathology*. 2018;1(3):1763.
16. Osti D., Del Bene M., Rappa G., Santos M., Matafora V., Richichi C. et al. Clinical significance of extracellular vesicles in plasma from glioblastoma patients. *Clinical Cancer Research.* 2019;25(1):266–276. DOI: 10.1158/1078-0432.CCR-18-1941.
17. Jasbi P., Wang D., Cheng S.L., Fei Q., Cui J.Y., Liu L. et al. Breast cancer detection using targeted plasma metabolomics. *Journal of Chromatography B*. 2019;1105:26–37. DOI: 10.1016/j.jchromb.2018.11.029.
18. Eniu D.T., Romanciuc F., Moraru C., Goidescu I., Eniu D., Staicu A. et al. The decrease of some serum free amino acids can predict breast cancer diagnosis and progression. *Scandinavian Journal of Clinical and Laboratory Investigation.* 2019;79(1–2):17–24. DOI: 10.1080/00365513.2018.1542541.
19. Hung C.Y., Yeh T.S., Tsai C.K., Wu R.C., Lai Y.C., Chiang M.H. et al. Glycerophospholipids pathways and chromosomal instability in gastric cancer: Global lipidomics analysis. *World Journal of Gastrointestinal Oncology.* 2019;11(3):181. DOI: 10.4251/wjgo.v11.i3.181.
20. Nalbantoglu S., Abu-Asab M., Suy S., Collins S., Amri H. Metabolomics-based biosignatures of prostate cancer in patients following radiotherapy. *OMICS: A Journal of Integrative Biology*. 2019;23(4):214–223. DOI: 10.1089/omi.2019.0006.
21. Harel M., Ortenberg R., Varanasi S.K., Mangalhara K.C., Mardamshina M., Markovits E. et al. Proteomics of melanoma response to immunotherapy reveals mitochondrial dependence. *Cell*. 2019;179(1):236–250. DOI: 10.1016/j.cell.2019.08.012.

22. Morse N., Jamaspishvili T., Simon D., Patel P.G., Ren K.Y.M., Wang J. et al. Reliable identification of prostate cancer using mass spectrometry metabolomic imaging in needle core biopsies. *Laboratory Investigation.* 2019;99(10):1561–1571. DOI: 10.1038/s41374-019-0265-2.
23. Zhou Y., Lih T.M., Pa J., Höt N., Don M., Cao Y.Hu. et al. Proteomic signatures of 16 major types of human cancer reveal universal and cancer-type-specific proteins for the identification of potential therapeutic targets. *Journal of Hematology & Oncology*. 2020;13:1–15. DOI: 10.1186/s13045-020-01013-x.
24. Lee Y.R., An K.Y., Jeon J., Kim N.K., Lee J.W., Hong J. et al. Untargeted metabolomics and polyamine profiling in serum before and after surgery in colorectal cancer patients. *Metabolites*. 2020;10(12):487. DOI: 10.3390/metabo10120487.
25. Yu D., Xuan Q., Zhang C., Hu C., Li Y., Zhao X. et al. Metabolic alterations related to glioma grading based on metabolomics and lipidomics analyses. *Metabolites*. 2020;10(12):478. DOI: 10.3390/metabo10120478.
26. Vaysse P.M., Kooreman L.F., Engelen S.M., Kremer B., Olde Damink S. W., Heeren R.M. et al. Stromal vapors for real-time molecular guidance of breast-conserving surgery. *Scientific Reports*. 2020;10(1):20109. DOI: 10.1038/s41598-020-77102-1.
27. Möginger U., Marcussen N., Jensen O.N. Histo-molecular differentiation of renal cancer subtypes by mass spectrometry imaging and rapid proteome profiling of formalin-fixed paraffin-embedded tumor tissue sections. *Oncotarget*. 2020;11(44):3998. DOI: 10.18632/oncotarget.27787.
28. Sarbu M., Clemmer D.E., Zamfir A.D. Ion mobility mass spectrometry of human melanoma gangliosides. *Biochimie*. 2020;177: 26–237. DOI: 10.1016/j.biochi.2020.08.011.
29. Chen X., Zhu Y., Jijiwa M., Nasu M., Ai J., Dai S. et al. Identification of plasma lipid species as promising diagnostic markers for prostate cancer. *BMC Medical Informatics and Decision Making*. 2020;20:1–10. DOI: 10.1186/s12911-020-01242-7.
30. Noreldeen H.A., Du L., Li W., Liu X., Wang Y., Xu G. Serum lipidomic biomarkers for non-small cell lung cancer in nonsmoking female patients. *Journal of Pharmaceutical and Biomedical Analysis*. 2020;185:113220. DOI: 10.1016/j.jpba.2020.113220.
31. Cheng F., Wen Z., Feng X., Wang X., Chen Y. A serum lipidomic strategy revealed potential lipid biomarkers for early-stage cervical cancer. *Life Sciences*. 2020;260:118489. DOI: 10.1016/j.lfs.2020.118489.
32. You L., Fan Y., Liu X., Shao S., Guo L., Noreldeen H.A. et al. Liquid chromatography–mass spectrometry-based tissue metabolic profiling reveals major metabolic pathway alterations and potential biomarkers of lung cancer. *Journal of Proteome Research*. 2020;19(9):3750–3760. DOI: 10.1021/acs.jproteome.0c00285.
33. Kurczyk A., Gawin M., Chekan M., Wilk A., Łakomiec K., Mrukwa G. et al. Classification of thyroid tumors based on mass spectrometry imaging of tissue microarrays; a single-pixel approach. *International Journal of Molecular Sciences*. 2020;21(17):6289. DOI: 10.3390/ijms21176289.
34. Zhu N., Xing X., Cao L., Zhang Y., Zhang T., Li Z. et al. Study on the diagnosis of gastric cancer by magnetic beads extraction and mass spectrometry. *BioMed Research International*. 2020;2020:2743060. DOI: 10.1155/2020/2743060.
35. Pekov S.I., Bormotov D.S., Nikitin P.V., Sorokin A.A., Shurkhay V.A., Eliferov V.A. et al. Rapid estimation of tumor cell percentage in brain tissue biopsy samples using inline cartridge extraction mass spectrometry. *Analytical and Bioanalytical Chemistry*. 2021;413:2913–2922. DOI: 10.1007/s00216-021-03220-y.
36. Liu W., Xie L., He Y.H., Wu Z.Y., Liu L.X., Bai X.F. et al. Large-scale and high-resolution mass spectrometry-based proteomics profiling defines molecular subtypes of esophageal cancer for therapeutic targeting. *Nature Communications*. 2021;12(1):4961. DOI: 10.1038/s41467-021-25202-5.
37. Wei Y., Jasbi P., Shi X., Turner C., Hrovat J., Liu L. et al. Early breast cancer detection using untargeted and targeted metabolomics. *Journal of Proteome Research*. 2021;20(6):3124–3133. DOI: 10.1021/acs.jproteome.1c00019.
38. Ecker J., Benedetti E., Kindt A.S., Höring M., Perl M., Machmüller A.C. et al. The colorectal cancer lipidome: identification of a robust tumor-specific lipid species signature. *Gastroenterology*. 2021;161(3):910–923. DOI: 10.1053/j.gastro.2021.05.009.
39. Li X., Zheng N.R., Wang L.H., Li Z.W., Liu Z.C., Fan H. et al. Proteomic profiling identifies signatures associated with progression of precancerous gastric lesions and risk of early gastric cancer. *EBioMedicine*. 2021;74. DOI: 10.1016/j.ebiom.2021.103714.
40. Milighetti M., Krasny L., Lee A.T., Morani G., Szecsei C., Chen Y. et al. Proteomic profiling of soft tissue sarcomas with SWATH mass spectrometry. *Journal of Proteomics*. 2021; 241:104236. DOI: 10.1016/j.jprot.2021.104236.
41. Monsivais D., Vasquez Y.M., Chen F., Zhang Y., Chandrashekar D.S., Faver J.C. et al. Mass-spectrometry-based proteomic correlates of grade and stage reveal pathways and kinases associated with aggressive human cancers. *Oncogene*. 2021;40(11):2081–2095. DOI: 10.1038/s41388-021-01681-0.
42. Lima A.R., Carvalho M., Aveiro S.S., Melo T., Domingues M.R., Macedo-Silva C. et al. Comprehensive metabolomics and lipidomics profiling of prostate cancer tissue reveals metabolic dysregulations associated with disease development. *Journal of Proteome Research*. 2021;21(3):727–739. DOI: 10.1021/acs.jproteome.1c00754.
43. Basu S.S., Stopka S.A., Abdelmoula W.M., Randall E.C., Gimenez-Cassina Lopez B., Regan M.S. et al. Interim clinical trial analysis of intraoperative mass spectrometry for breast cancer surgery. *NPJ Breast*

Cancer. 2021;7(1):116. DOI: 10.1038/s41523-021-00318-5.
44. Casadonte R., Kriegsmann M., Kriegsmann K., Hauk I., Meliss R.R., Mueller C.S. et al Imaging mass spectrometry-based proteomic analysis to differentiate melanocytic nevi and malignant melanoma. *Cancers*. 2021;13(13):3197. DOI: 10.3390/cancers13133197.
45. Brown H.M., Alfaro C.M., Pirro V., Dey M., Hattab E.M., Cohen-Gadol A.A. et al. Cooks R.G. Intraoperative mass spectrometry platform for IDH mutation status prediction, glioma diagnosis, and estimation of tumor cell infiltration. *The Journal of Applied Laboratory Medicine*. 2021;6(4):902–916. DOI: 10.1093/jalm/jfaa233.
46. Buentzel J., Klemp H.G., Kraetzner R., Schulz M., Dihazi G.H., Streit F. et al. Metabolomic profiling of blood-derived microvesicles in breast cancer patients. *International Journal of Molecular Sciences*. 2021;22(24):13540. DOI: 10.3390/ijms222413540.
47. Răchieriu C., Eniu D.T., Moiş E., Graur F., Socaciu C., Socaciu M.A. et al. Lipidomic signatures for colorectal cancer diagnosis and progression using UPLC-QTOF-ESI+ MS. *Biomolecules*. 2021;11(3):417. DOI: 10.3390/biom11030417.
48. Hashim N.A.A., Ab-Rahim S., Ngah W.Z.W., Nathan S., Ab Mutalib N.S., Sagap I. et al. Global metabolomics profiling of colorectal cancer in Malaysian patients. *BioImpacts: BI*. 2021; 11(1):33. DOI: 10.34172/bi.2021.05.
49. Butler L.M., Mah C.Y., Machiels J., Vincent A.D., Irani S., Mutuku S.M. et al. Lipidomic profiling of clinical prostate cancer reveals targetable alterations in membrane lipid composition. *Cancer Research*. 2021;81(19):4981–4993. DOI: 10.1158/0008-5472.CAN-20-3863.
50. Chen F., Dai X., Zhou C.C., Li K.X., Zhang Y.J., Lou X.Y. et al. Integrated analysis of the faecal metagenome and serum metabolome reveals the role of gut microbiome-associated metabolites in the detection of colorectal cancer and adenoma. *Gut*. 2022;71(7):1315–1325. DOI: 10.1136/gutjnl-2020-323476.
51. Wolrab D., Jirásko R., Cífková E., Höring M., Mei D., Chocholoušková M. et al Lipidomic profiling of human serum enables detection of pancreatic cancer. *Nature Communications*. 2022;13(1):124. DOI: 10.1038/s41467-021-27765-9.
52. Soltis A.R., Bateman N.W., Liu J., Nguyen T., Franks T.J., Zhang X. et al. Proteogenomic analysis of lung adenocarcinoma reveals tumor heterogeneity, survival determinants, and therapeutically relevant pathways. *Cell Reports Medicine*. 2022;3(11). DOI: 10.1016/j.xcrm.2022.100819.
53. Li Y., Jiang L., Wang Z., Wang Y., Cao X., Meng L. et al. Profiling of urine carbonyl metabolic fingerprints in bladder cancer based on ambient ionization mass spectrometry. *Analytical Chemistry*. 2022;94(27):9894–9902. DOI: 10.1021/acs.analchem.2c01890.
54. Alvarez M.R.S., Zhou Q., Tena J., Lebrilla C.B., Completo G.C., Heralde III F.M. et al. N-Glycan and glycopeptide serum biomarkers in philippine lung cancer patients identified using liquid chromatography-tandem mass gpectrometry. *ACS Omega*. 2022;7(44):40230–40240. DOI: 10.1021/acsomega.2c05111.
55. Blaschke C.R., Hill E.G., Mehta A.S., Angel P.M., Laronga C., Drake R.R. Integrating age, BMI, and serum N-glycans detected by MALDI mass spectrometry to classify suspicious mammogram findings as benign lesions or breast cancer. *Scientific Reports*. 2022;12(1):20801. DOI: 10.1038/s41598-022-25401-0.
56. Wang X., Li H., Zou X., Yan X., Cong P., Li H. et al. Deep mining and quantification of oxidized cholesteryl esters discovers potential biomarkers involved in breast cancer by liquid chromatography-mass spectrometry. *Journal of Chromatography A*. 2022;1663:462764. DOI: 10.1016/j.chroma.2021.462764.
57. Östman J.R., Pinto R.C., Ebbels T.M., Thysell E., Hallmans G., Moazzami A.A. Identification of prediagnostic metabolites associated with prostate cancer risk by untargeted mass spectrometry-based metabolomics: A case-control study nested in the Northern Sweden Health and Disease Study. *International Journal of Cancer*. 2022;151(12):2115–2127. DOI: 10.1002/ijc.34223.
58. Sommella E., Salviati E., Caponigro V., Grimaldi M., Musella S., Bertamino A. et al. MALDI Mass Spectrometry Imaging highlights specific metabolome and lipidome profiles in salivary gland tumor tissues. *Metabolites*. 2022;12(6):530. DOI: 10.3390/metabo12060530.
59. Bogusiewicz J., Gaca-Tabaszewska M., Olszówka D., Jaroch K., Furtak J., Harat M. et al. Coated blade spray-mass spectrometry as a new approach for the rapid characterization of brain tumors. *Molecules*. 2022;27(7):2251. DOI: 10.3390/molecules27072251.
60. Huang J., Zhao B., Weinstein S.J., Albanes D., Mondul A.M. Metabolomic profile of prostate cancer-specific survival among 1812 Finnish men. *BMC Medicine*. 2022;20(1):1–13. DOI: 10.1186/s12916-022-02561-4.
61. Maslov D.L., Trifonova O.P., Lichtenberg S., Balashova E.E., Mamedli Z.Z., Alferov A.A. et al. Blood plasma metabolome profiling at different stages of renal cell carcinoma. *Cancers*. 2022;15(1):140. DOI: 10.3390/cancers15010140.
62. Huang L., Mao X., Sun C., Li T., Song X., Li J. et al. Molecular pathological diagnosis of thyroid tumors using spatially resolved metabolomics. *Molecules*. 2022;27(4):1390. DOI: 10.3390/molecules27041390.
63. Zhang L.H., Zhuo H.Q., Hou J.J., Zhou Y., Cheng J., Cai J.C. Proteomic signatures of infiltrative gastric cancer by proteomic and bioinformatic analysis. *World Journal of Gastrointestinal Oncology*. 2022;14(11):2097. DOI: 10.4251/wjgo.v14.i11.2097.
64. Luo Q., Liu J., Fu Q., Zhang X., Yu P., Liu P. et al. Identifying cancer cell-secreted proteins that activate

cancer-associated fibroblasts as prognostic factors for patients with pancreatic cancer. *Journal of Cellular and Molecular Medicine*. 2022;26(22):5657–5669. DOI: 10.1111/jcmm.17596.
65. Hwang B.Y., Seo J.W., Muftuoglu C., Mert U., Guldaval F., Asadi M. et al. Salivary lipids of patients with non-small cell lung cancer show perturbation with respect to plasma. *International Journal of Molecular Sciences*. 2023;24(18):14264. DOI: 10.3390/ijms241814264.
66. Stanojevic A., Samiotaki M., Lygirou V., Marinkovic M., Nikolic V., Stojanovic-Rundic S. et al. Data-independent acquisition mass spectrometry analysis of FFPE rectal cancer samples offers in-depth proteomics characterization of the response to neoadjuvant chemoradiotherapy. *International Journal of Molecular Sciences*. 2023;24(20):15412. DOI: 10.3390/ijms242015412
67. Pietkiewicz D., Zaborowski M.P., Jaz K., Matuszewska E., Światły-Błaszkiewicz A., Kluz T. et al. Serum proteomic profiles of patients with high and low risk of endometrial cancer recurrence. *International Journal of Molecular Sciences*. 2023;24(19):14528. DOI: 10.3390/ijms241914528.
68. Wang J., Saltzman A.B., Jaehnig E.J., Lei J.T., Malovannaya A., Holt M.V. et al. Kinase inhibitor pulldown assay identifies a chemotherapy response signature in triple-negative breast cancer based on purine-binding proteins. *Cancer Research Communications*. 2023;3(8):1551–1563. DOI: 10.1158/2767-9764.CRC-22-0501.
69. Yamashita T., Takanashi Y., Uebayashi A., Oka M., Mizuno K., Kawase A. et al. Lung adenocarcinoma and squamous cell carcinoma difficult for immunohistochemical diagnosis can be distinguished by lipid profile. *Scientific Reports*. 2023;13(1):12092. DOI: 10.1038/s41598-023-37848-w.
70. Dunphy K., Bazou D., Henry M., Meleady P., Mietttinen J.J., Heckman C.A. et al. Proteomic and metabolomic analysis of bone marrow and plasma from patients with extramedullary multiple myeloma identifies distinct protein and metabolite signatures. *Cancers*. 2023;15(15):3764. DOI: 10.3390/cancers15153764.
71. Kocsmar E., Schmid M., Cosenza-Contreras M., Kocsmar I., Foll M., Krey L. et al. Proteome alterations in human autopsy tissues in relation to time after death. *Cellular and Molecular Life Sciences*. 2023;80(5):117. DOI: 10.1007/s00018-023-04754-3.
72. Cao L., Huang C., Zhou D.C., Hu Y., Lih T.M., Savage S.R. et al. Proteogenomic characterization of pancreatic ductal adenocarcinoma. *Cell*. 2021;184(19):5031–5052. DOI: 10.1016/j.cell.2021.08.023.
73. Pekov S.I., Sorokin A.A., Kuzin A.A., Bocharov K.V., Bormotov D.S., Shivalin A.S. et al. Analysis of phosphatidylcholines alterations in human glioblastomas *ex vivo*. *Biomeditsinskaia Khimiia*. 2021;15(3):241–247. DOI: 10.18097/PBMC20216701081.
74. Torres-de la Roche L.A., Acevedo-Mesa A., Lizarazo I.L., Devassy R., Becker S. et al. Hormonal Contraception and the Risk of Breast Cancer in Women of Reproductive Age: A Meta-Analysis. *Cancers*. 2023;15(23):5624. DOI: 10.3390/cancers15235624.
75. Onyije F.M., Dolatkhah R., Olsson A., Bouaoun L., Deltour I., Erdmann F. et al. Risk factors for childhood brain tumours: A systematic review and meta-analysis of observational studies from 1976 to 2022. *Cancer Epidemiology*. 2024;88:102510. DOI: 10.1016/j.canep.2023.102510.
76. Zhang J., Sans M., Garza K.Y., Eberlin L.S. Mass spectrometry technologies to advance care for cancer patients in clinical and intraoperative use. *Mass Spectrometry Reviews*. 2021;40(5):692–720. DOI: 10.1002/mas.21664.
77. Zhang L.H., Zhuo H.Q., Hou J.J., Zhou Y., Cheng J., Cai J.C. Proteomic signatures of infiltrative gastric cancer by proteomic and bioinformatic analysis. *World Journal of Gastrointestinal Oncology*. 2022;14(11):2097. DOI: 10.4251/wjgo.v14.i11.2097.
78. Elmallah M.I., Ortega-Deballon P., Hermite L., Pais-De-Barros J. P., Gobbo J., Garrido C. Lipidomic profiling of exosomes from colorectal cancer cells and patients reveals potential biomarkers. *Molecular Oncology*. 2022;16(14):2710–2718. DOI: 10.1002/1878-0261.13223.
79. Sommella E., Salviati E., Caponigro V., Grimaldi M., Musella S., Bertamino A. et al. MALDI Mass Spectrometry Imaging highlights specific metabolome and lipidome profiles in salivary gland tumor tissues. *Metabolites*. 2022;12(6):530. DOI: 10.3390/metabo12060530.
80. Blaschke C.R., Hill E.G., Mehta A.S., Angel P.M., Laronga C., Drake R.R. Integrating age, BMI, and serum N-glycans detected by MALDI mass spectrometry to classify suspicious mammogram findings as benign lesions or breast cancer. *Scientific Reports*. 2022;12(1):20801. DOI: 10.1038/s41598-022-25401-0.
81. Fowler K.T., Hugh-Jones P. Mass spectrometry applied to clinical practice and research. *British Medical Journal*. 1957;1(5029):1205. DOI: 10.1136/bmj.1.5029.1205.
82. Cotter R.J. Time-of-flight mass spectrometry for the structural analysis of biological molecules. *Analytical Chemistry*. 1992;64(21):1027A–1039A. DOI: 10.1021/ac00045a002.
83. Bryden W.A., Benson R.C., Echelberger S.A., Phillips T.E., Cotter R.J., Fenselau C. The tiny-TOF mass spectrometer for chemical and biological sensing. *Johns Hopkins APL Technical Digest*. 1995;16(3):296–310. DOI: 10.1007/978-94-015-9534-6_10.
84. Rifai N., Horvath A. R., Wittwer C.T., Hoofnagle A. Principles and applications of clinical mass spectrometry: small molecules, peptides, and pathogens. Elsevier, 2018.
85. Raćkowska E., Bobrowska-Korczak B., Giebułtowicz J. Development and validation of a rapid LC–MS/MS method for determination of methylated nucleosides and nucleobases in urine. *Journal of Chro-*

matography B. 2019;1128:121775. DOI: 10.1016/j.jchromb.2019.121775.
86. Drake R.R., McDowell C., West C., David F., Powers T.W., Nowling T. et al. Defining the human kidney N-glycome in normal and cancer tissues using MALDI imaging mass spectrometry. *Journal of Mass Spectrometry*. 2020;55(4):e4490. DOI: 10.1002/jms.4490.
87. Takats Z., Strittmatter N., McKenzie J.S. Ambient mass spectrometry in cancer research. *Advances in Cancer Research*. 2017;134:231–256. DOI: 10.1016/bs.acr.2016.11.011.
88. Jarmusch A.K., Pirro V., Baird Z., Hattab E.M., Cohen-Gadol A.A., Cooks R.G. Lipid and metabolite profiles of human brain tumors by desorption electrospray ionization-MS. *Proceedings of the National Academy of Sciences*. 2016;113(6):1486–1491. DOI: 10.1073/pnas.1523306113.
89. Tillner J., Wu V., Jones E.A., Pringle S.D., Karancsi T., Dannhorn A. et al. Faster, more reproducible DESI-MS for biological tissue imaging. *Journal of the American Society for Mass Spectrometry*. 2017;28(10):2090–2098. DOI: 10.1007/s13361-017-1714-z.
90. Kaushal A., Kaur N., Sharma S., Sharma A.K., Kala D., Prakash H. et al. Current update on biomarkers for detection of cancer: comprehensive analysis. *Vaccines*. 2022;10(12):2138. DOI: 10.3390/vaccines10122138.
91. Khan H., Shah M.R., Barek J., Malik M.I. Cancer biomarkers and their biosensors: A comprehensive review. *TrAC Trends in Analytical Chemistry*. 2023;158:116813. DOI: 10.1016/j.trac.2022.116813.
92. Luo Q., Liu J., Fu Q., Zhang X., Yu P., Liu P. et al. Identifying cancer cell-secreted proteins that activate cancer-associated fibroblasts as prognostic factors for patients with pancreatic cancer. *Journal of Cellular and Molecular Medicine.* 2022;26(22):5657–5669. DOI: 10.1111/jcmm.17596.
93. Zhu Z. J., Qi Z., Zhang J., Xue W.H., Li L.F., Shen Z.B. et al. Untargeted metabolomics analysis of esophageal squamous cell carcinoma discovers dysregulated metabolic pathways and potential diagnostic biomarkers. *Journal of Cancer*. 2020;11(13):3944. DOI: 10.7150/jca.41733.
94. Pinu F.R., Beale D.J., Paten A.M., Kouremenos K., Swarup S., Schirra H.J. et al. Systems biology and multi-omics integration: viewpoints from the metabolomics research community. *Metabolites*. 2019;9(4):76. DOI: 10.3390/metabo9040076.
95. Schmidt D.R., Patel R., Kirsch D.G., Lewis C.A., Vander Heiden M.G., Locasale J.W. Metabolomics in cancer research and emerging applications in clinical oncology. *CA: Cancer Journal for Clinicians.* 2021;71(4):333–358. DOI: 10.3322/caac.21670.
96. Pandey N., Lanke V., Vinod P.K. Network-based metabolic characterization of renal cell carcinoma. *Scientific Reports.* 2020;10(1):5955. DOI: 10.1038/s41598-020-62853-8.
97. Mollica V., Santoni M., Matrana M.R., Basso U., De Giorgi U., Rizzo A. et al. Concomitant proton pump inhibitors and outcome of patients treated with nivolumab alone or plus ipilimumab for advanced renal cell carcinoma. *Targeted Oncology*. 2022;17(1):61–68. DOI: 10.1007/s11523-021-00861-y.
98. Maslov D.L., Trifonova O.P., Lichtenberg S., Balashova E.E., Mamedli Z.Z., Alferov A.A. et al. Blood plasma metabolome profiling at different stages of renal cell carcinoma. *Cancers*. 2022;15(1): 140. DOI: 10.3390/cancers15010140.
99. Rankin-Turner S., Heaney L.M. Applications of ambient ionization mass spectrometry in 2020: An annual review. *Analytical Science Advances*. 2021;2(3–4):193–212. DOI: 10.1002/ansa.202300004.
100. Genangeli M., Heeren R.M., Porta Siegel T. Tissue classification by rapid evaporative ionization mass spectrometry (REIMS): comparison between a diathermic knife and CO 2 laser sampling on classification performance. *Analytical and Bioanalytical Chemistry.* 2019;411:7943–7955. DOI: 10.1007/s00216-019-02148-8.
101. St. John E.R., Balog J., McKenzie J.S., Rossi M., Covington A., Muirhead L. et al. Rapid evaporative ionisation mass spectrometry of electrosurgical vapours for the identification of breast pathology: towards an intelligent knife for breast cancer surgery. *Breast Cancer Research*. 2017;19(1):1–14. DOI: 10.1186/s13058-017-0845-2.
102. Gómez-Ríos G.A., Tascon M., Reyes-Garcés N., Boyacı E., Poole J., Pawliszyn J. Quantitative analysis of biofluid spots by coated blade spray mass spectrometry, a new approach to rapid screening. *Scientific Reports.* 2017;7(1):16104. DOI: 10.1038/s41598-017-16494-z.
103. St. John E.R., Rossi M., Pruski P., Darzi A., Takats Z. Intraoperative tissue identification by mass spectrometric technologies. *TrAC Trends in Analytical Chemistry.* 2016;85:2–9. DOI: 10.1126/scitranslmed.3005623.
104. Shamraeva M.A., Bormotov D.S., Shamarina E.V., Bocharov K.V., Peregudova O.V., Pekov S.I. et al. Spherical sampler probes enhance the robustness of ambient ionization mass spectrometry for rapid drugs screening. *Molecules.* 2022;27(3):945. DOI: 10.3390/molecules27030945.

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