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RAMAN SPECTROSCOPY IN ONCOLOGY FOR PREDICTING MALIGNANT DISEASES: A LITERATURE REVIEW

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ABSTRACT

Relevance: *This literature review examines scientific publications on the efficacy of optical spectroscopy methods, including Raman spectroscopy (RS), for the early diagnosis of tumors in oncology.*

The study aimed to *summarize the existing data, analyze their effectiveness in studying cancer located in different organs through Raman spectroscopy, and assess their diagnostic potential in oncology.*

Methods: *The literature search covered publications from 2015 to May 2025 using keyword-based database queries. After removing duplicates, articles were screened via abstracts and full texts. The research team reviewed all selected papers. All authors agreed upon a final list of 22 articles, with relevant data synthesized into this review.*

Results: *Optical spectroscopy (OS) has proven to be an effective tool for diagnosing, monitoring, and predicting malignant tumors in experimental and clinical studies. Over the past 20 years, RS has demonstrated 90% accuracy and specificity in early cancer detection and advantages in bioavailability, speed, clarity, and multiplex analysis-key factors driving its growing interest in biological research. However, foreign and domestic literature analysis revealed a lack of standardized protocols for RS in cancer diagnostics, highlighting the need for optimized, systematic guidelines.*

While promising, RS remains underexplored and requires further research to translate findings into routine clinical practice.

Conclusion: *Recent advancements in optical spectroscopy, particularly Raman methods, contribute to deeper cellular-level insights into oncological mechanisms and improve predictive diagnostics.*

Keywords: *oncology, malignant tumors, optical spectroscopy, predictive diagnostics, Raman spectroscopy, infrared spectroscopy.*

Introduction: Spectroscopy is a vibrational research method that combines various complementary methods.

Optical spectroscopy, including RS (RS), surface-enhanced RS (SERS), diffuse optical tomography, infrared spectroscopy, fluorescence spectroscopy, magnetic resonance spectroscopy, and electrical impedance spectroscopy, is a modern and optimal method for non-invasive diagnostics of oncological diseases.

Currently, cancer remains one of the leading causes of death and morbidity in the world [1].

Cancer has been one of the most important health problems worldwide for many years. This disease is associated with a disruption of cell growth and division regulation, leading to the uncontrolled proliferation of cells and the formation of tumors. In addition, tumors are characterized by heterogeneity, since they consist of different types of cells and extracellular components, which complicates their treatment. Another important feature is metastasis, i.e., the spread of cancer cells throughout the body via the blood or lymphatic system, resulting in the formation of secondary tumors in other organs [2].

Raman Spectroscopy as a Research Tool in Medicine: Among the optical spectroscopy methods, RS is one of the most well-known in medical research. This method is based on the Raman effect, discovered in 1928 by C. V. Raman and K. S. Krishnan. RS is a new method for studying biological tissues such as tumors [3, 4].

As a non-invasive, real-time, in vivo tool, RS ensures high specificity, sensitivity, and multiplexing capabilities, providing high spatial and temporal resolution to characterize the molecular basis of cancer [5].

Analysis of the correlation between the intensity of vibrational light scattering and frequency enables the identification of unique spectral structures associated with different samples. It is based on inelastic scattering of photons, known as vibrational conjugate scattering. Spectra of nucleic acids, proteins, lipids, and carbohydrates with Raman functional groups can be used to assess the metabolic state of various cells and tissues, each with its unique composition [6]. Monitoring the intensity of inelastic light scattering as a function of frequency enables the acquisition of a unique spectroscopic signature for a tissue sample [7].

The study aimed to summarize the existing data, analyze their effectiveness in studying cancer located in different organs through Raman spectroscopy, and assess their diagnostic potential in oncology.

Materials and methods: A literature review was conducted using keywords to search and select articles in databases for the period from 2015 to May 2025. After removing duplicates, articles were selected by reviewing their abstracts and full texts. The research team's authors reviewed all articles. The final list of selected articles was compiled after obtaining consent from all authors. Of these, 20 articles were selected; the relevant available data were analyzed and summarized in a review article.

Results:

Raman Spectroscopy in Oncology: New approaches to understanding disease pathogenesis may lead to the discovery of biological markers that will allow better monitoring of disease progression and improve prognosis. RS is a research and diagnostic tool that helps uncover the molecular basis of diseases and provides objective, quantitative molecular information for diagnosis and treatment evaluation. G.W. Auner and co-authors reviewed the use of RS for the detection of brain, ovarian, breast, prostate, and pancreatic cancer, as well as circulating tumor cells [8]. Domestic authors have described the use of electrical impedance spectroscopy for the early detection of skin malignant melanoma, specifically by analyzing electrical conductivity and impedance waves in the damaged layer of the skin compared to the healthy layer [9].

Raman Spectroscopy in Neuro-Oncology: The primary task during surgery is to distinguish between tumor and healthy tissue, as well as to identify tumor cells that have infiltrated beyond a clear pathological border. Determining the residual tumor load is of great importance, as complete resection is a favorable prognostic factor. In an experimental study by Marco Riva and co-authors, single-point RS was performed on biopsy samples of healthy and tumor-affected tissue from 63 patients with stage II-IV gliomas, as classified by the World Health Organization (WHO), who underwent surgery using neuronavigation. Raman spectral analysis of the active functional groups of nucleic acids, proteins, and lipids enabled a detailed characterization of biopsies from neoplastic and normal brain tissue. Averaged Raman spectra showed differences in molecular signatures between neoplastic and normal samples. A literature review of Raman scattering revealed 137 peak types, of which 60 peaks are known to have high specificity, and 19 new peaks useful for differentiating glioma from healthy tissue were identified. Analysis of these new bands may contribute to the further development of real-time tissue analysis, improving the accuracy and efficiency of neurosurgical interventions. This study makes a significant contribution to the application of this technology in oncological brain surgery [5].

Additionally, a domestic literature review describes the regulation of 2-hydroxyglutarate (2-HG) during tumor tissue division at the cellular level using magnetic resonance spectroscopy, a non-invasive method for diagnosing gliomas of the central nervous system [10].

Raman Spectroscopy in Hematology and Oncohematology: Diagnostics and treatment of hematological and oncological diseases are currently possible only through a combination of scientific advances and methods. For example, rapid detection of acute leukemia is essential for accurate and timely clinical decisions. The success of immunotherapy in hematological malignancies has created new diagnostic challenges, including the need to assess the immune status. In addition, despite the recent introduction of high-throughput genetics, which has revolutionized this field, many challenges remain to be addressed. Therefore, the development of new technologies that can overcome barriers such as inaccessibility, lengthy diagnostic times, and the need for highly trained personnel remains relevant.

Medical applications of mass spectrometry (MS), a molecular spectroscopy technique that provides detailed information on the chemical structure, phase, crystallinity, and molecular interactions of a sample, have been studied for several decades. Due to the rapid assessment of the metabolic state of cells in vivo, MS is of particular interest in hematology and oncology. The study of normal hematopoietic stem/progenitor cells and their progeny is associated with several challenges, including limited sample availability and difficulties in preserving their original state and functions. Due to the complex behavior of these cell populations, functional assays that measure cellular activity are often necessary for a comprehensive evaluation of hematopoietic cells. In addition, single-cell resolution and label-free protocols, another key feature of PCa hematology, provide important insights into the heterogeneity of stem and mature cell populations, as well as for assessing the developmental stages and activation status of cells [11].

Raman Spectroscopy in Cartilage Cancer: A study by F. Niccoli et al. in 10 patients with chondrosarcoma, a common primary bone tumor, demonstrated that it is challenging to distinguish between benign tumors (enchondroma) and chondrosarcoma grade 1 (CS1), as these two tissue types share common biochemical components. However, unlike standard procedures, the use of machine learning (ML) methods for multivariate analysis can enhance the classification of enchondroma in the form of CS1. This article presents the results of the best methods for improving multivariate analysis using ML algorithms. To differentiate the RS signals, two main methods were employed to distinguish between tissues, cells, and the extracellular matrix (ECM): principal component analysis (PCA) and linear discriminant analysis (LDA). PCA (an unsupervised method) includes projecting features onto a hyperplane that contains most of the variance (approximately 95%) of the data and its orthogonal complement. LDA (supervised method) is used to find a subspace of features that optimizes the separation of the analyzed cartilage tissues. For this purpose, the supervised method based on PCA+LDA algorithms is highly scalable and can be applied not only to large data sets, but also to cancer tissue of any type [12].

Raman Spectroscopy in Colon Cancer: About 30% of colorectal cancer (CRC) cases are caused by mutations in inherited genes. Approximately 15% are caused by malfunctioning repair genes, while another 80–85% are caused by mutations in the adenomatous polyposis coli (APC) gene. CRC can also develop as a result of inflammatory bowel disease.

Uncontrolled cell growth, a hallmark of cancer development, requires a continuous supply of nutrients. Carbohydrates and fats play an important role in tumor growth. Changes in lipid metabolism are a primary factor in the development of various diseases, including cancer. Therefore, this class of compounds is of increasing interest in clinical trials as biological markers to determine the role of lipidomics in cancer research. Among them (FA) - saturated (palmitic acid (PA, 16:0)), unsaturated (linoleic acid (LA, 18:2), eicosapentaenoic acid (EPA, 20:5)), and their potential in the diagnosis and treatment of colorectal cancer has been identified.

Evidence of lipid reprogramming in cancer cells was first described in the 1920s as the Warburg effect [13]. However, there is now a widespread trend towards the opposite of the Warburg effect: researchers have discovered that different types of cancer cells have unique metabolic characteristics, and some can synthesize adenosine triphosphate via oxidative phosphorylation [14].

In general, lipids can be characterized as a diverse group of compounds using LIPID MAPS [15]. K. Beton-Maysur et al. analyzed PA, LA, and EPA acids in normal (CD-18 Co) and malignant (Caco-2) human colon cells using Raman imaging and spectroscopy [14]. In addition, excessive intake of saturated fatty acids (SFAs), including PA, may increase the risk of obesity and digestive disorders. Many research groups have also proven a correlation between excessive PA intake and cancer development. Lipid analysis showed that PA may affect the aggressiveness of cancer cells [16].

This study demonstrated the possibility of visualizing the internal structures of individual cells (endoplasmic reticulum, mitochondria, lipid droplets, and nucleus) and analyzing fatty acid metabolism using Raman microscopy and cluster analysis. The distribution and metabolism of fatty acids in different cellular compartments were monitored by spectroscopic analysis of the intensity ratios of characteristic bands (I1656/I1444, I1444/I1256, I1444/I750 and I1304/I1256). The results showed LA to be the most effective membrane penetrator, having a significant impact on cell viability. Specifically, LA inhibits the growth of Caco-2 cancer cells while stimulating the proliferation of normal CCD-18 Co cells. PA, on the contrary, exhibits the opposite effect. The obtained data confirm the effectiveness of using Raman imaging to study the molecular mechanisms of colon carcinogenesis and to assess the effect of various fatty acids on cell metabolism [16].

Raman Spectroscopy in Lung Cancer: Lung cancer is the leading cause of cancer death worldwide. Due to its high mortality rate, the development of effective non-invasive diagnostic methods for this disease remains an urgent problem. Traditional diagnostic methods (computed tomography, sputum cytology, biopsy, and bronchoscopy) are often insufficient for early detection of the disease, as they are expensive, time-consuming, and may have insufficient sensitivity. On the other hand, these methods are less invasive and more convenient for the patient, without compromising the diagnostic accuracy. Vibrational spectroscopy, particularly Raman and Fourier transform infrared spectroscopy (FTIR), has been developed, enabling the detection of molecular-level changes with high sensitivity. These methods are non-invasive, non-destructive, do not require reagents, and leave no residues, providing detailed information on the composition and structural conformation of specific molecules [17–19]. FTIR spectroscopy measures the absorption of infrared light by a sample, revealing information about molecular vibrations, chemical bonds, and functional groups. On the other hand, RS measures the inelastic scattering effect and provides additional information about the molecular structure of a biological sample [20].

For RS, 1 µL of plasma from each individual was pipetted onto an aluminum foil attached to a glass slide and air-dried for 5 minutes. Aluminum foil was chosen due to its advantages, including high reflectivity, stability, flexibility, low background noise, and low cost. This makes it the most suitable base material for enhancing the Raman effect. FTIR spectroscopy was performed by attenuated total reflection (ATR) using a special crystal in direct contact with the sample [21].

In the study by H. Hano et al., 36 participants were recruited, including 18 patients with non-small cell lung cancer and 18 healthy participants. The information was obtained by combining Raman and FT-IR measurements in a single spectroscopic instrument. This instrument combines the two methods, enabling simultaneous measurements of a sample using two spectroscopic methods in a single location. Data fusion strategies can be divided into three types: low-level, mid-level, and high-level fusion. In low-level data fusion (LLDF), matrices from multiple data sources are directly combined to create a comprehensive dataset covering the full range of measured variables. Mid-level data fusion (MLDF) addresses the problem of high dimensionality. This method reduces data complexity by selecting or pruning features prior to data fusion, thereby preserving important information and enhancing model training efficiency. High-level data fusion (HLDF) combines the predicted results of models created for each data source, leveraging the strengths of each model to enhance the accuracy of predictions. In this study, the peak at 624 cm-1 in RS indicates C-C bond bending in phenylalanine and lipids. The peak at 966 cm-1 corresponds to the deformation of the CH3 group in the amino acids' tryptophan, valine, and proline. Of particular importance is the peak at 1125 cm-1, which indicates the stretching of the CC, CO, and CN bonds in lipids, glycogen, and proteins. The peak observed at 1587 cm-1 corresponds to the stretching of the C=C bond in tryptophan, while the amide I bands between 1632 and 1668 cm-1 correspond to changes in the secondary structure of the protein (α-helix and β-sheets) [22].

In FTIR spectroscopy, the vibration bands at 1055-1070 cm^{-1} indicate symmetric vibration of the PO^{-2} group in phospholipids, and the intense absorption band at 1699 cm^{-1} indicates stretching of the C=O bond in the amide I group.

These spectral markers enable the detection of changes in proteins and lipids at the molecular level in the diagnosis of lung cancer. Amide I bands indicate changes in protein structure, while phosphate and carbonyl group vibrations serve as important biological markers in the diagnosis of cancer. This study demonstrates the potential of Raman and FTIR spectroscopy in detecting malignant lung tumors using modern data fusion techniques [22].

Conclusion: According to the literature review, RS is one of the most widely used and proven methods in various fields of oncology.

Furthermore, numerous experimental studies have convincingly demonstrated the effectiveness of this method in characterizing biological tissues. However, to successfully transfer this technology into clinical practice, it is necessary to address several key challenges, including the creation of a comprehensive spectral database and the development of robust tissue classification methods that are thoroughly tested for compliance with established diagnostic standards. Solving methodological problems will enable RS to fully realize its potential and transition from the realm of research to everyday clinical practice, as well as establish a worthy place among modern diagnostic tools.

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АҢДАТПА

ҚАТЕРЛІ АУРУЛАРДЫҢ БОЛЖАУШЫЛАРЫН АНЫҚТАУ ҮШІН ОНКОЛОГИЯДАҒЫ РАМАН СПЕКТРОСКОПИЯСЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Мақалада онкологиядағы ісіктерді ерте диагностикалау үшін оптикалық спектроскопия әдістері соның ішінде Раман спектроскопиясы (РС) тиімділігі бойынша ғылыми жарияланымдарға әдеби шолу берілген.*

Зерттеу мақсаты *– бұл әдебиеттік шолу бар деректерді жинақтау, Раман спектроскопиясы арқылы әртүрлі мүшеде орналасқан қатерлі ісікті зерттеуде тиімділігін талдау және олардың онкологиядағы диагностикалық әлеуетін бағалау болып табылады.*

Әсілдері: *Әдеби шолу 2015 жылдан бастап 2025 жылдың мамыр айына дейінгі кезеңге арналған дерекқорлардағы мақалаларды іздеу және таңдау түйінді сөздерді қолдану арқылы жүзеге асырылды. Көшірмелерді жойғаннан кейін мақалалар олармен байланысты аннотациялар мен толық мәтіндерді қарау арқылы тексерілді. Барлық мақалалар зерттеу тобының авторларымен тексерілді. Іріктеу жасалған мақалалардың соңғы тізімі барлық авторлармен келісілгенге дейін жүргізіліп, 22 мақала іріктеліп алынды, қолда бар тиісті деректер сарапталып, шолу мақаласы түрінде жинақталды.*

Нәтижелері: *Онкологияда оптикалық спектроскопия (ОС) қатерлі ісіктерді диагностикалау, бақылау және болжау үшін тәжірбиеде және клиникалық зерттеулерде тиімді құрал болып табылатынын көруге болады. Эксперименталды зерттеулердің нәтижелерінде көретін болсақ соңғы 20 жылда РС әдістер қатерлі ісіктердің ерте диагностикасында 90% дәлдігі және арнайылығын көрсетті, сонымен қатар биологиялық жетімділікте қолжетімділігімен тиімді, яғни спектроскопияға қызығушылықтың артуының оның биологиялық матерaлды зерттеуде жылдамдылығы, нәтиженің айқындылығы мен мультикомплексті болуы себеп болып табылады. Шетелдік және отандық әдебиеттерді талдауда қолданылған Раман спектроскопиясын онкологиялық ауруларды диагностикалауда бірыңғай әдістемелер туралы егжей-тегжейлі техникалық деректер жоқ екенін көрсетті, бұл пайдалануды реттейтін хаттамаларды жүйелі оңтайландыру қажеттілігін көрсетеді.*

РС әлі де жақсы түсінілмеген және кеңірек зерттеу қажет ететін және алынған нәтижелерді күнделікті тәжірибеге енгізуде ықпалы зор зерттеу әдістері болып табылады.

Қорытынды: *РС соңғы жылдары ОС-да әдістерінің медицина саласында дамуы онкологиялық аурулардың пайда болу механизмінің жасушалық деңгейде терең зерттеуге және оның болжаушыларын анықтауға көмектеседі.*

Түйін сөздер: *онкология, қатерлі ісіктер, оптикалық спектроскопия, болжаушылар, Раман спектроскопиясы, инфрақызыл спектроскопиясы.*

АННОТАЦИЯ

РАМАНОВСКАЯ СПЕКТРОСКОПИЯ В ОНКОЛОГИИ ДЛЯ ВЫЯВЛЕНИЯ ПРЕДИКТОРОВ ЗЛОКАЧЕСТВЕННЫХ ЗАБОЛЕВАНИЙ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *В статье представлен обзор научных публикаций, посвященных эффективности методов оптической спектроскопии, включая Рамановскую спектроскопию (РС), для ранней диагностики опухолей в онкологии.*

Цель исследования *– представляет собой сбор существующих данных, анализ эффективности исследования злокачественных новообразований, расположенных в различных органах, с помощью Рамановской спектроскопии, и оценку её диагностического потенциала в онкологии.*

Методы: *Поиск литературы проводился по публикациям с 2015 года по май 2025 года по ключевым словам в базах данных. После исключения дубликатов статьи отбирались на основе анализа аннотаций и полных текстов. Все публикации были проверены авторами исследования. Окончательный список из 22 статей был согласован всеми авторами, после чего соответствующие данные были проанализированы и систематизированы в виде обзора.*

Результаты: *Оптическая спектроскопия (ОС) является эффективным инструментом для диагностики, мониторинга и прогнозирования злокачественных опухолей как в экспериментальных, так и в клинических исследованиях. Результаты экспериментальных работ показали, что за последние 20 лет РС продемонстрировала 90% точность и специфичность в ранней диагностике рака, а также преимущества в биодоступности, скорости, четкости и мультиплексном анализе, что обуславливает растущий интерес к этому методу в биологических исследованиях. Однако анализ зарубежной и отечественной литературы выявил отсутствие единых стандартизированных методик применения РС в диагностике онкологических заболеваний, что подчеркивает необходимость разработки оптимизированных систематических протоколов.*

Несмотря на перспективность, РС остается недостаточно изученной и требует дальнейших исследований для внедрения полученных результатов в клиническую практику.

Заключение: *Современные достижения в области оптической спектроскопии, в частности Рамановских методов, способствуют углубленному изучению механизмов возникновения онкологических заболеваний на клеточном уровне и совершенствованию их предиктивной диагностики.*

Ключевые слова: *онкология, злокачественные опухоли, оптическая спектроскопия, предиктивная диагностика, Рамановская спектроскопия, инфракрасная спектроскопия.*

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