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PROGNOSTIC VALUE OF LIQUID BIOPSY IN CRC: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Liquid biopsy is a modern, quite appropriate, and promising method for diagnosing malignant neoplasms for oncology. The method allows us to determine the level of freely circulating tumor cells – micrometastases, tumor DNA, microRNA, and exosomes in blood plasma- and detect various genetic changes. A literature review of current scientific publications on liquid biopsy techniques, indexed in Medline, PubMed, and Medscape, was carried out as part of the work.*

The study aimed to *review is to assess the prognostic significance of liquid biopsy, to determine the place of the method in current recommendations, and its expediency from the point of view of the practice.*

Methods: *The information search was conducted in the Medline, PubMed, and Medscape databases, with a search depth of 8 years. Data from randomized controlled trials, clinical trials, reviews, systematic reviews, and meta-analyses were analyzed. The review includes full-fledged articles in the public domain and abstracts to obtain complete information on the problem.*

Results: *Liquid biopsy surpasses tissue biopsy in simplicity and speed of research, easy repeatability, and minimal invasiveness, as well as the possibility of dynamic monitoring of progression – the overall clonal transformation of the tumor and the emergence of resistance to treatment.*

The disadvantages of this method are low sensitivity, difficulty in correctly interpreting biomarkers and determining their specificity, and high risk of false positive and false negative results due to dormant tumor cells.

Conclusion: *At present, the Liquid biopsy method is relevant and in demand, but it needs to be tested on a validated sample of the main population, and in order to achieve effective clinical use, significant work needs to be done to standardize both pre-analytical and analytical procedures and generalize them for all components of liquid biopsy.*

Keywords: *Liquid biopsy, colorectal cancer, metastatic colorectal cancer, the validity of methods, tissue biopsy, the value of methods, micrometastases.*

Introduction: Approaches to cancer treatment have improved due to the increased specialists' knowledge about molecular disorders that stimulate tumors, which has led to even more effective targeted therapy development. Due to these achievements, testing molecular biomarkers for the stratification of cancer patients has become mandatory. First, a biopsy is performed – puncture of material from primary tumors for diagnosis pathomorphological confirmation. This approach is convenient for diagnostic purposes but excludes patient monitoring during the disease progression and possible relapse [1].

This approach has some advantages and limitations. The liquid biopsy method allows us to determine the level of freely circulating tumor cells – micrometastases, tumor DNA, microRNA, and exosomes in blood plasma- and detect various genetic changes [2]. All of the above allows us to study the literature and accumulated data on the liquid biopsy method as a diagnostic method from the point of view of prognostic significance, the place of the method in current recommendations, and practical expediency.

The study aimed to review is to assess the prognostic significance of liquid biopsy, to determine the place of the method in current recommendations, and its expediency from the point of view of the practice.

Materials and methods: Medline, PubMed, and Medscape databases were used to search for information. The search depth is eight years (2015-2022). Keywords used for selecting publications: liquid biopsy, colorectal cancer, metastatic colorectal cancer (mCRP), the validity of methods, tissue biopsy, the value of methods, micrometastases.

Type of articles for analysis: randomized controlled trials, clinical trials, reviews, systematic reviews, and meta-analyses. Full-fledged articles in the public domain and abstracts were selected to obtain complete information on the problem.

Information was collected according to the PRISMA 2020 scheme (Figure 1):

As a result of a keyword literature search, 78 sources were found. At the first stage of the analysis, 19 sources were eliminated, some were duplicated, and some did not correspond to the therapeutic area. Of the remaining 59 sources, 42 more were excluded, as they needed to reflect the purpose of the study entirely. As a result, 17 sources were used for this review article.

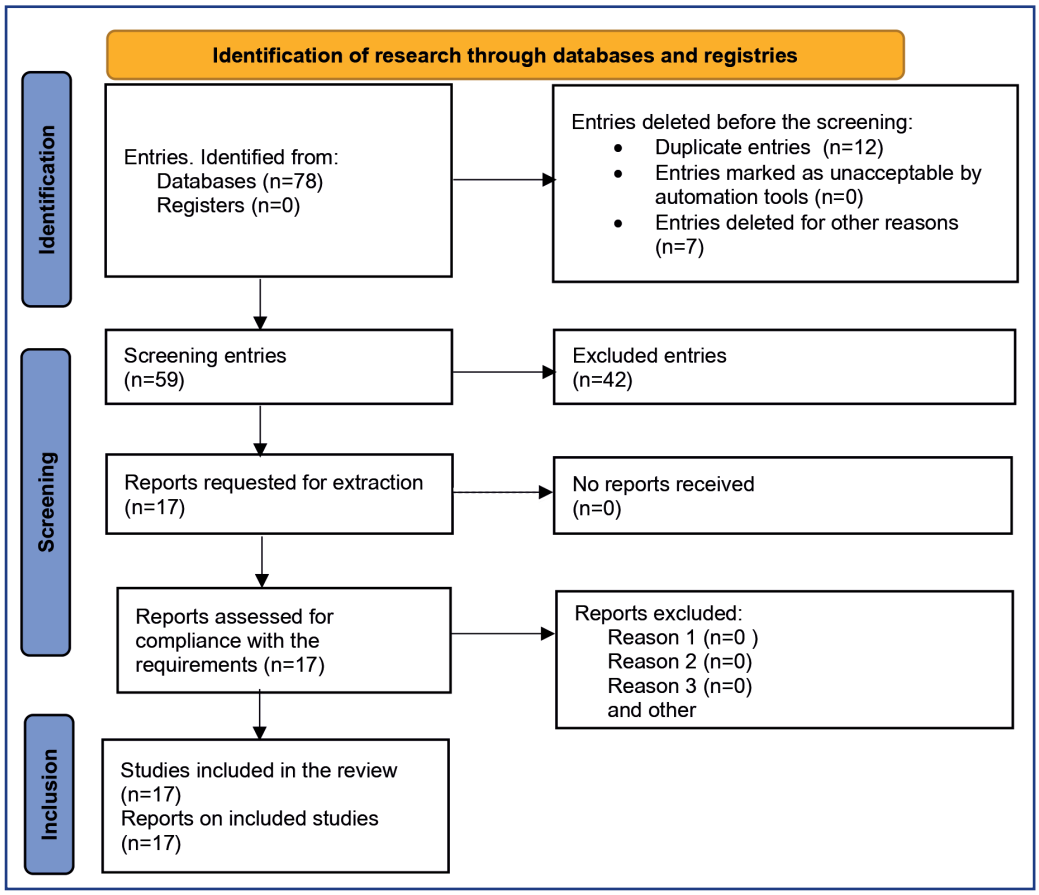

Figure 1 – Collecting information for a literature review

Results: Evaluation of the mutational profile of cancer is usually carried out using a fragment of a primary tumor or metastasis [1]. Obtaining a tissue biopsy requires surgical intervention, which significantly limits the possibility of taking a biopsy. Depending on the tumor's location, tumor tissue's availability may be problematic.

Moreover, heterogeneity within the tumor, especially spatial heterogeneity, can lead to unreliable biomarker detection results, especially when testing a single biopsy area [3-5]. In addition, multiple tumor foci complicate the characterization of the patient's cancer. The availability of tumor samples during long-term treatment of patients may be difficult, and, in addition, testing of archived tumor samples may be suboptimal due to the evolution of the tumor. Since it is necessary to conduct serial monitoring of tumor progression and development in patients, repeated use of tissue biopsy is only sometimes possible.

There is an urgent need to use more accessible materials implying non-invasive or minimally invasive procedures that allow systematic and real-time monitoring of molecular changes in the patient's cancer, including colorectal cancer.

There is some data in the literature studying the inclusion of RAS/BRAF liquid biopsy and the determination of circulating DNA (cDNA) in the work of cancer centers. So, Van't Erve I. et al.. studied liquid biopsies taken from 100 MCC patients to compare digital PCR analysis of cDNA with conventional RAS/BRAF mutation profiling of tumor tissue. The results of a liquid biopsy of tissue DNA and cDNA showed a 93% match, which underlines the potential clinical usefulness of a liquid biopsy for detecting primary resistance to anti-EGFR [6].

Pastor B. et al. found that circulating extracellular DNA (ecDNA) contains circulating tumor cDNA, which can be obtained from serial fluid biopsies, allowing tumor genome analysis throughout treatment. The authors have investigated that ecDNA and mutant cDNA can be potential biomarkers to predict the best treatment outcomes for MCC patients. The authors analyzed longitudinally collected plasma ecDNA from 43 MCC patients, prospectively included in the TEXCAN phase II study, using an advanced real-time IntPlex PCR method based on critical observations of a specific structure and size of the ecDNA. Qualitative mutations (KRAS, NRAS, BRAFV600E) and quantitative (total ecDNA concentration, mutant cDNA concentration, mutant cDNA fraction) parameters correlated with overall survival (OS) and progression-free survival (PFS), and shows that the levels of ecDNA before treatment and mutant

cDNA levels can identify MCC patients who need one or another targeted treatment [7].

In the Poseidon study, published in October 2021, the authors conducted a prospective direct comparison of liquid and standard tissue biopsy (STB) in the exact center. This study was because some patients may have different results from standard molecular tissue studies during the first visit. A liquid biopsy can help circumvent these obstacles. The authors, in natural conditions, included in the study MCC patients with unknown RAS/BRAF status at the time of the first visit. The inclusion criteria were the presence of tumor tissue in the archive and the absence of previous anti-EGFR treatment. At the first visit, a plasma sample was taken from the patients for liquid biopsy and STB. The primary endpoint was comparing the time to the liquid biopsy results (T1) and STB (T2) using the Mann-Whitney U-test. The secondary endpoints were the correspondence between the methods, defined as a total percentage match, and the accuracy of the liquid biopsy in terms of specificity, sensitivity, and positive and negative prognostic value. As a result, the average value of T1 and T2 was 7 and 22 days, respectively ($p < 0.00001$), and the overall percentage correspondence between the liquid biopsy results and STB was 83%. The specificity and sensitivity of liquid biopsy compared with STB were 90% and 80%, respectively, with a positive prognostic value of 94% and a negative 69% for liquid biopsy. The obtained results allowed the authors to conclude that faster execution time, high consistency, and accuracy are the three critical points for introducing liquid biopsy into the routine management of MCC, mainly when the decision on first-line therapy is urgent. The request for biomaterial from the archive of external centers may take a long time [8].

A liquid biopsy is an ideal procedure, primarily confirmed by the impressive developments we have witnessed in recent years (Table 1).

Table 1 – Comparative characteristics of standard tissue and liquid biopsy methods

Standard tissue biopsy	Liquid biopsy
The Gold Standard	High interest among researchers
Availability for histological analysis and stag-ing	Limited ability to perform histological analysis
May be unavailable	Easily available It takes a shorter time to get the result Risk of false results (+/-)
Invasive method Patient dis-comfort (risk of clinical complications)	Minimal invasiveness
Depending on the collection and storage pro-cedures, preserved tissues can represent high-ly variable DNA of different qualities.	New DNA, not modified with preservatives, must follow a strict procedure for collecting, processing, and storing the material to avoid DNA degradation.
High DNA yield, risk of DNA degradation, cross-linking, and the amount of DNA varies depending on sampling methods.	The quantity and quality of DNA depend on the pre-analytical and analytical processes.
The localized analysis does not allow us to characterize the intra- and inter-tumor hetero-geneity (metastasis) characteristic of most tu-mors, especially in the late stages and with multiple tumor localization.	Allows, in principle (if it is possible to isolate and analyze a sufficient amount of DNA to identify both intra- and inter-tumor heterogene-ity and multiplicity of tumor sites.
Not applicable to sequential monitoring.	Applicable to sequential monitoring
Fixed time to get the result.	Sampling of the material can be performed at any time during therapy or observation of the patient.
Dynamic observation of the molecular chang-es of the tumor is impossible.	Dynamic observation of tumor evolution (sig-nificant for the short half-life of circulating tu-mor DNA).

Many authors discuss intra-tumor heterogeneity and its significance in CC. For example, F. Fabbri et al. demonstrated for the first time the possibility of analyzing pure circulating tumor cells (CTC) at the molecular level and avoiding mixing with lymphocytes using the DEPArray platform (Menarini Silicon Biosystem, USA) based on dielectrophoresis as well as the KRAS mismatch between CTC and primary tumor tissue after 100% extraction of uninfected cells and sequencing. In a cohort of 40 patients with metastatic CC, 21 patients had more than three CTC in a 7.5 ml blood sample. An additional analysis of KRAS in 16 patients showed only a 50% correspondence between the assessment of primary tumor tissue and CTC [9].

The RAS CC study using the OncoBEAM™ system (Sysmex Inostics, Germany) showed that the overall consistency of standard and liquid biopsies results was 96.4%. Of 55 patients with a positive RAS mutation in tumor tissue, 53 also had a RAS mutation in ecDNA [10]. With the same analysis, an additional study with a cohort of 236 patients with mCRP showed an 89% correlation of the RAS mutation between tumor biopsy and ecDNA [11]. Another study evaluating the clinical usefulness of ecDNA involving 140 MCC patients showed slightly different results. Only a moderate correspondence (accuracy 72-87%) was observed between plasma samples and tumor tissue, possibly due

to the higher frequency of KRAS mutation in plasma samples [12].

Discussion: Liquid biopsy may be of great practical importance for treating patients. Accurate and continuous molecular characterization of CC is crucial for the correct and timely use of molecular-targeted therapies.

KRAS and NRAS mutations differ significantly between sporadic CC lesions, and the status of these mutations in tumor metastases is unpredictable [13].

Liquid biopsy can detect KRAS mutations in ecDNA in cases where the mutation has not been determined by biopsy of the primary tumor. It may be a fundamental step in choosing therapy since tumor cells with KRAS mutation resist treatment with monoclonal antibodies against EGFR [13]. Achieving effective clinical use of liquid biopsy requires significant efforts to standardize and generalize pre-analytical and analytical procedures for all components of liquid biopsy. Much has already been done in this area. The need for standardization of pre-analytical procedures includes the selection of blood collection tubes, the time between blood collection and plasma treatment, and procedures for extraction/isolation of liquid biopsy components. Standard procedures should be approved accordingly for their characterization and quantification. Moreover, standardization should maximize the yield of liquid biopsy markers.

The liquid biopsy technique can provide a critical clinical understanding of the molecular subtypes of the tumor, especially when the discrepancy of KRAS mutations between primary and recurrent or metastatic tumors after resection can reach about 20% [14].

As mentioned above, the method of liquid biopsies can determine the exact characteristics of cancer heterogeneity (tumors and metastatic sites) and its evolution. In this process, a necessary step is to accumulate data from extensive clinically validated studies to evaluate and demonstrate the effectiveness of several markers detected during liquid biopsy (including exosomes, cDNA) in clinical settings and positive results of choosing therapy options in patients [15]. In addition, the complementarity of several components of liquid biopsy, potentially originating from different populations of tumor cells, has yet to be studied.

In 2020, efforts were made to standardize pre-analytical workflows for liquid biopsy in the context of the Horizon 2020 SPIDIA4P consortium project of the European Union, indicating the existing demand and proven workflow [16].

Conclusion: Morbidity, mortality, age of diagnosis, nonspecific symptoms, and intra-tumor heterogeneity in CC demonstrate that there are still opportunities to improve clinical management and treatment outcomes of patients. A liquid biopsy can be a tool that adds a new perspective to clinical routine and confidence in clinical decision-making.

A standard tissue biopsy is crucial for the pathological evaluation of a tumor during a tumor biopsy and displays the current pathological status of a particular lesion. Liquid biopsy is ideal for the longitudinal monitoring of a common disease by molecular characterization with the additional possibility of understanding the spatial and temporal heterogeneity of the CC [17].

A liquid biopsy can improve diagnosis, prognosis, and treatment response by providing valuable information about a patient's disease to aid clinical decision-making.

The great potential of liquid biopsy in oncology is just beginning to be effectively studied in research. In recent years, impressive data have begun to appear in the literature, highlighting the potential clinical use of liquid biopsy. It tends to develop since many current clinical studies include serial blood collection as a biomaterial for tumor research, determining prognosis, and therapy options. Moreover, the constant improvements in precise and susceptible technologies we have observed in recent years will open up even more opportunities to study several components secreted by tumors simultaneously.

The use of DNA and CTC can offer new methods of diagnosis, prediction, and subsequent response to treatment, and, most importantly, liquid biopsy platforms are aimed at providing the necessary information to improve patient outcomes. However, issues such as pre-analytical variables, the rarity of CTC and cDNA in samples, analytical validity, clinical validation, cost-effectiveness, and regulatory approval must be addressed before clinical use.

Summing up the above, liquid biopsy is an easily repeatable and minimally invasive method that can and should be used to detect early metastases and relapses and determine the characteristics of the tumor phenotype, its heterogeneity, and minimal residual disease.

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АҢДАТПА

КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІК КЕЗІНДЕГІ СҰЙЫҚТЫҚТЫ БИОПСИЯНЫҢ БОЛЖАМДЫҚ МАҢЫЗЫ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Сұйық биопсия (FB) онкология үшін қатерлі ісіктерді диагностикалаудың заманауи, өте өзекті және перспективалы әдісі болып табылады. Бұл әдіс қан плазмасындағы еркін айналымдағы ісік жасушаларының – микрометастаздардың, ісік ДНҚ-ның, микроРНҚ-ның және экзосомалардың деңгейін анықтауға, сондай-ақ әртүрлі генетикалық өзгерістерді анықтауға мүмкіндік береді. Жұмыс шеңберінде Medline, PubMed, Medscape индекстелген сұйық биопсия әдістемелеріне арналған өзекті ғылыми жарияланымдарға әдеби шолу жүргізілді.*

Зерттеудің мақсаты *– сұйық биопсияның болжамды маңыздылығын бағалау, әдістің қазіргі ұсыныстардағы орнын, практика тұрғысынан орындылығын анықтау болып табылады.*

Материалдар мен әдістері: *Ақпаратты іздеу үшін 8 жылдық терең тарихы бар Medline, PubMed, Medscape дерекқорлары пайдаланылды. Рандомизацияланған бақыланатын зерттеулердің, клиникалық зерттеулердің, шолулардың, жүйелі шолулардың және мета-талдаулардың деректері талданды. Шолуға еркін қол жетімді толық мақалалар да, мәселе бойынша толық ақпарат алу үшін дерексіз мақалалар да кірді.*

Ақпаратты өңдеу үшін Excel кестесі пайдаланылды, оның ішінде кейінгі талдау үшін ақпарат бар.

Нәтижелері: *СБ қарапайымдылығы мен зерттеу жылдамдығы, жеңіл қайталануы және төмен инвазивтілігі, сондай-ақ прогрессияны динамикалық бақылау мүмкіндігі ісіктің жалпы клондық трансформациясы және емдеуге төзімділіктің пайда болуы бойынша тіндік биопсиядан асып түседі.*

Бұл әдістің кемшіліктері төмен сезімталдық, биомаркерлерді дұрыс түсіндірудің және олардың ерекшелігін анықтаудың күрделілігі, дормантты ісік жасушаларының болуына байланысты жалған оң және жалған теріс нәтижелердің жоғары қаупі болып саналады.

Қорытынды: *қазіргі уақытта СБ әдісі өзекті және сұранысқа ие, бірақ оны негізгі популяцияға тексерілген үлгіде сынау қажет, ал тиімді клиникалық қолдануға қол жеткізу үшін аналитикалық және аналитикалық процедураларды стандарттаумен оларды сұйық биопсияның барлық компоненттері үшін жалпылау үшін маңызды жұмыс жасалуы керек.*

Түйінді сөздер: *сұйық биопсия, колоректальды қатерлі ісік, метастатикалық колоректальды қатерлі ісік, әдістердің жарамдылығы, тіндік биопсия, әдістердің құндылығы, микрометастаздар.*

АННОТАЦИЯ

ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ЖИДКОСТНОЙ БИОПСИИ ПРИ КРР: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Жидкостная биопсия является современным, достаточно актуальным и перспективным методом диагностики злокачественных новообразований для онкологии. Данный метод в качестве диагностической концепции позволяет определять циркулирующие факторы, производных опухоли, которые в последствии позволят определить прогноз опухоли, и определить тактику ведения.*

Цель исследования *– оценить прогностическую значимость жидкостной биопсии, определить место метода в современных рекомендациях, целесообразность с точки зрения практики.*

Методы: *Был проведен поиск информации в базах данных Medline, PubMed, Medscape. Были проанализированы данные рандомизированных контролируемых исследований, клинических исследований, обзоров, систематических обзоров, и мета-анализов. В обзор вошли как полновесные статьи в свободном доступе, так и абстракты, для возможности получения пол-ной информации по проблеме.*

Результаты: *Жидкостная биопсия превосходит тканевую биопсию по минимальной инвазивности, а соответственно более низком риске осложнений от процедур забора материала, возможности выявления как внутри – так и межопухолевой гетерогенности и множественность участков опухоли, что позволяет наблюдать за опухолью в динамике и мониторировать общую клональную трансформацию опухоли и возможную резистентность к лечению.*

Недостатками данного метода принято считать низкую чувствительность, сложность правильной интерпретации биомаркеров и определения их специфичности, высокий риск ложноположительных и ложноотрицательных результатов из-за присутствия дормантных опухолевых клеток.

Заключение: *В текущее время метод жидкостной биопсии актуален, востребован, но его требуется апробировать на валидированной выборке к основной популяции, а для достижения эффективного клинического использования предстоит выполнить важную работу по стандартизации как преаналитических, так и аналитических процедур и обобщить их для всех компонентов жидкостной биопсии.*

Ключевые слова: *жидкостная биопсия, колоректальный рак, метастатический колоректальный рак (мКРР), валидность методов, тканевая биопсия, ценность методов, микрометастазы.*

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