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ADVANCES IN THE EARLY DIAGNOSIS OF LUNG CANCER

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Abstract: Lung cancer, especially the non-small cell lung cancer (NSCLC) subtype, remains one of the leading causes of death worldwide. Early detection is challenging due to the non-specific nature of the initial symptoms. However, advances in diagnosis, such as low-dose computed tomography (CT) and liquid biopsy, have shown great potential for improving early identification of the disease. Liquid biopsy, which analyzes circulating tumor DNA (ctDNA), has been increasingly used as a complementary tool to traditional tissue biopsy, especially in patients with difficulties in obtaining tissue samples. Although liquid biopsy has yet to replace the histopathological gold standard, it has proved effective in identifying actionable genetic mutations, allowing treatment to be personalized and therapeutic response to be monitored. In addition, accurate staging using the TNM classification and the integration of new therapies, such as immunotherapy and target therapies, have led to improvements in survival rates and patients' quality of life. However, lung cancer is still diagnosed at advanced stages in the majority of cases, highlighting the need for more effective screening strategies and ongoing medical education to promote early detection.

Keywords: Lung cancer, early diagnosis, non-small cell lung cancer (NSCLC), liquid biopsy, circulating tumor DNA (ctDNA), computed tomography, target therapies, immunotherapy, treatment personalization, TNM staging.

INTRODUCTION

Lung cancer represents one of the greatest threats to global public health, being the leading cause of cancer death, especially in developed countries such as the United States. It is estimated that in 2020, around 247,270 new cases of lung cancer were diagnosed in the US, with a distribution between 130,340 male cases and 116,930 female cases. The mor-

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tality associated with lung cancer is equally alarming, with more than 140,000 deaths predicted for the same year. However, due to the introduction of screening programs and the reduction in tobacco consumption, there has been a decrease in mortality rates, especially in men, with a 48% reduction in lung cancer mortality, and a 23% reduction in women. Despite this progress, lung cancer continues to be responsible for a high number of deaths, surpassing other neoplasms such as breast cancer and colorectal cancer (ALEXANDER; KIM; CHENG, 2020).

Globally, lung cancer is also one of the deadliest cancers, with a high incidence and mortality rate in India. Although the prevalence of lung cancer has increased in recent years, especially among men, epidemiological statistics on the disease in India are still limited, making early diagnosis and effective interventions difficult. According to the GLOBOCAN 2018 report, lung cancer accounted for 5.9% of all cancer cases in India, and was responsible for approximately 8.1% of cancer-related deaths in the country. Non-small cell lung cancer (NSCLC) is the predominant subtype, and its early detection has been a challenge. Driver mutations, such as the EGFR mutation and the ALK and ROS1 rearrangements, are common in patients with NSCLC and have proven to be important targets for targeted therapies. In recent years, advances in molecular diagnostics and personalized molecular therapy have played a crucial role in the management of patients with this condition (DESHPAND; CHANDRA; RAUTHAN, 2022).

Non-small cell lung cancer (NSCLC) is undoubtedly the most prevalent subtype of this neoplasm, and advances in treatment, such as surgery, radiation, chemotherapy, immunotherapy and targeted therapies, have led to an improvement in survival rates. However, many patients undergoing surgical treatment end up developing distant metastases or local recurrence, which makes controlling the disease an ongoing challenge. The introduction of molecular and immunotherapy therapies has shown remarkable progress, especially in patients with driver mutations such as EGFR and ALK rearrangement. These therapies, in combination with conventional treatments, have the potential to prolong overall survival and improve patients' quality of life. Personalization of treatment, taking into account the molecular characteristics of the tumour and the patient's clinical condition, has become essential for therapeutic success. Accurate subtyping of NSCLC, according to the most recent World Health Organization criteria, is fundamental for the development of appropriate therapeutic strategies (ALDUAIS et al., 2023).

METHODOLOGY

The methodology adopted in this literature review followed a systematic approach, aimed at analyzing the most recent advances in the early diagnosis of lung cancer. For the selection of studies, the inclusion criteria were articles published in the last five years, located in the PubMed database, using the descriptors "Lung Neoplasms" and "Diagnosis". The choice of these key terms was based on the relevance and scope they offer on the subject, making it possible to identify the most up-to-date and pertinent studies.

The inclusion criteria established that only articles in English that addressed the early diagnosis of lung cancer would be considered. In addition, the analysis was restricted to studies that addressed diagnostic techniques, advances in biomarkers, screening methods, and new therapeutic approaches aimed at the early detection of this neoplasm.

On the other hand, the exclusion criteria were rigorously defined to guarantee the quality and accuracy of the selection. Articles that did not meet the inclusion requirements were

excluded from the analysis, such as studies not published in the last five years, articles that were not available in the PubMed database or that were not accessible in full, as well as research that only addressed therapeutic aspects with no direct link to early diagnosis. Studies that did not specifically deal with lung cancer or that did not present data relevant to the topic in question were also excluded.

The article selection process was carried out in two stages. Firstly, an initial screening was carried out based on the titles and abstracts, discarding articles that clearly did not meet the established criteria. In the second phase, the selected articles were read in full, with a detailed analysis of their methodologies, results and conclusions, in order to extract the most relevant information for synthesizing knowledge about advances in the early diagnosis of lung cancer. The entire process was rigorously recorded, guaranteeing the reproducibility of the study and transparency in the article selection process.

RESULTS AND DISCUSSION

The data analyzed shows that the majority of lung cancer cases continue to be diagnosed in symptomatic phases, with non-specific clinical manifestations such as persistent cough, dyspnea and fatigue, which often delay initial clinical suspicion. Hemoptysis, although present in only one fifth of cases, stands out for its higher positive predictive value (2.4%-7.5%), reinforcing its role as a warning sign. Imaging tests, such as computed tomography (CT), remain the mainstay for detection and staging, and are complemented by invasive methods such as bronchoscopy with biopsy, fine needle aspiration biopsy (FNAB) and mediastinoscopy. For peripheral lesions, image-guided transthoracic biopsy shows diagnostic superiority, while EBUS-TBNA is preferred in adenopathies and central tumors. In patients with suspected resectable disease (stages I or II), dispensing with biopsy prior to surgery emerges as a viable strategy, emphasizing the importance of accurate staging based on the IASLC TNM classification, revised in its 8th edition for greater prognostic accuracy (ALEXANDER; KIM; CHENG, 2020).

Although liquid biopsy does not replace the gold standard of histopathology, it has become a complementary tool, especially in scenarios where tissue is unavailable or invasive procedures are contraindicated. Studies such as NILE show that the incorporation of ctDNA increases the detection of biomarkers by 48% compared to tissue analysis alone, with agility in obtaining results. (ALEXANDER; KIM; CHENG, 2020) Tests such as Guardant360 CDx and FoundationOne Liquid CDx, approved by the FDA, validate the clinical usefulness of this approach in identifying mutations such as EGFR, ALK and ROS1, which are essential for targeted therapies. (DESHPAND; CHANDRA; RAUTHAN, 2022). However, the variable sensitivity of ctDNA (60%-85%) for specific mutations requires caution when interpreting negative results, reinforcing the need for tissue confirmation when feasible. Molecular dynamics, such as the early elimination of mutations in ctDNA (observed in the AURA3 study), correlate with therapeutic outcomes, highlighting its potential for monitoring treatment response (ALEXANDER; KIM; CHENG, 2020).

A recent study reinforces the effectiveness of liquid biopsy as an initial molecular screening tool, with the potential to speed up diagnosis and therapeutic choice even in the early symptomatic stages of the disease. By enabling the rapid identification of actionable genetic alterations, liquid biopsy would facilitate the early initiation of targeted treatments, especially in patients with difficulties in obtaining tissue samples. Its application on the front line suggests relevant benefits for diagnostic management in challenging clinical contexts, expanding the possibility of early interventions based on molecular profiling (CHALASANI et al., 2024).

The findings reiterate the urgency of overcoming the challenges of late diagnosis, given the unequivocal impact of early staging on overall survival. The reliance on non-specific symptoms, such as cough and fatigue, underlines the need for greater clinical readiness for early investigation in high-risk populations, even in the absence of classic signs. The integration of advanced imaging methods, such as CT and PET-CT, with targeted invasive techniques (EBUS-TBNA, transthoracic biopsy) represents an advance in diagnostic accuracy and staging, in line with IASLC guidelines (ALEXANDER; KIM; CHENG, 2020).

The rise of liquid biopsy redefines diagnostic paradigms, offering a non-invasive window into the tumor's molecular profile. Its value transcends the mere detection of mutations, extending to the identification of therapeutic resistance mechanisms, such as amplifications of HER2 or mutations in EGFR C797S, critical for real-time therapeutic adjustments. (ALEXANDER; KIM; CHENG, 2020) In the context of personalized therapies, the ability of tests such as Guardant360 CDx to identify actionable alterations in multiple genes (ALK, ROS1, BRAF) expands treatment options, particularly in patients with advanced NSCLC. (DESHPAND; CHANDRA; RAUTHAN, 2022) However, technical limitations, such as the moderate sensitivity of ctDNA and the influence of tumor burden on detectability, require contextualized interpretation, avoiding false reassurance in the face of negative results. (ALDUAIS et al., 2023)

Recent advances in the early diagnosis of lung cancer, especially the non-small cell lung cancer (NSCLC) subtype, represent a paradigm shift in the oncological approach. The combination of high-resolution imaging techniques, such as low-dose computed tomography (LDCT), and the development of molecular biomarkers, such as circulating tumor DNA (ctDNA), has significantly increased the sensitivity and specificity of early detection. Recent clinical trials, such as NELSON and NILE, reinforce the effectiveness of these strategies, demonstrating significant reductions in lung cancer mortality among high-risk populations (DE KONING et al., 2020; GANDARA et al., 2021).

Liquid biopsy is emerging as a promising complementary tool, allowing not only the early identification of actionable mutations, but also the dynamic monitoring of therapeutic response and the detection of emerging resistance. Tests such as Guardant360 CDx and FoundationOne Liquid CDx, already approved by regulatory agencies such as the FDA and EMA, have an established role in clinical practice, although there are still limitations in terms of sensitivity in tumors with low tumor burden (PASQUALE et al., 2023).

In addition to the technical aspects, there is a need for more effective population screening strategies, with clear guidelines and standardized protocols that incorporate individual risk factors in addition to smoking, such as family history, occupational exposures and predisposing genetic alterations (NATIONAL COMPREHENSIVE CANCER NETWORK, 2023). Continued medical education and population awareness are also crucial to overcoming the diagnostic delay, since many patients still arrive at health services in advanced stages of the disease.

Harmonization between liquid and tissue biopsy is emerging as an ideal strategy, balancing the agility of the former with the reliability of the latter. Consensus recommendations international and regulatory agencies such as the FDA and EMA emphasize this complementarity, especially in scenarios of disease relapse or progression. (DESHPAND; CHANDRA; RAUTHAN, 2022) Furthermore, the incorporation of biomarkers such as blood BMT, associated with response to immunotherapy, illustrates the continued expansion

of liquid biopsy applications, although its methodological standardization remains a challenge. (ALEXANDER; KIM; CHENG, 2020)

In summary, the advances discussed not only refine diagnosis, but also catalyze the transition to precision oncology. The prioritization of less invasive approaches, without neglecting histopathological accuracy, combined with the continuous education of professionals on warning signs and new technologies, is the way to reduce the mortality associated with lung cancer. Future efforts should focus on validating integrated protocols and democratizing access to these innovations, ensuring equity in the application of scientific knowledge.

CONCLUSION

Lung cancer is still the leading cause of cancer death worldwide, with its high prevalence strongly linked to smoking, as well as environmental and genetic factors. Understanding the mechanisms behind the development of the disease, as well as accurately identifying risk factors - such as active and passive smoking, exposure to chemical agents and family history - is essential for creating effective prevention and early diagnosis strategies. Although many cases are detected at advanced stages, advances in imaging techniques, such as positron emission tomography (PET) and computed tomography (CT), have enabled more precise staging, facilitating more assertive therapeutic decisions.

As far as treatment is concerned, there have been significant advances, especially for non-small cell lung cancer (NSCLC). Surgery, chemotherapy, radiotherapy and, more recently, immunotherapy and targeted therapies have provided better results. Personalization of treatment, based on the molecular profile of the tumour, has increased survival rates and improved patients' quality of life, reinforcing the importance of continued research into biomarkers and innovative therapies. However, overall survival is still low, which highlights the need for more effective treatments and, above all, earlier diagnosis.

Given this scenario, it is essential that clinical research continues to search for new biomarkers, develop more precise therapies and improve screening strategies. In addition, public policies focused on reducing smoking and exposure to carcinogens are indispensable for reducing the incidence and mortality of the disease. The future of lung cancer treatment depends on the integration of multidisciplinary approaches, combining technological and therapeutic advances, always with the aim of offering more personalized and efficient medicine.

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