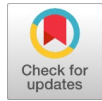


Problems in the Early Detection of Cancer

Rajabova Maftuna Rustamovna, Abdurashidova Kamola Turgunbayevna, Yusupov Bakhodir Karamatovich



Abstract: This article examines the analysis of existing challenges in early-stage cancer detection and approaches for their resolution. Additionally, the article discusses the probability of metastasis in early cancer detection based on actual tumour volume, as determined through diagnostic examination results. Numerous studies have demonstrated that early-stage detection and timely treatment of cancer significantly improve patients' survival outcomes. However, long-term survival indicators may not always correlate with treatment efficacy. This phenomenon is observed in certain patients as a result of slow disease progression or early diagnosis. While survival statistics appear to improve, actual mortality rates may remain unchanged. Despite decades of scientific research, only select early detection tests demonstrate proven efficacy in reducing cancer-related mortality rates. Nevertheless, such outcomes are sometimes achieved at the cost of detecting clinically insignificant tumour states in patient populations. Detection of cancer before metastasis and surgical resection of the tumour provides the opportunity for a complete cure. If the disease has metastasized, a combination of surgical intervention and systemic therapy (chemotherapy or immunotherapy) is employed; however, a complete cure may not always be achievable. Treatment efficacy is often dependent on the extent of metastatic disease burden. Therefore, cancer detection before the emergence of clinical manifestations and before the onset of metastasis represents the optimal therapeutic approach. In some instances, detection of metastasis at relatively early stages through screening may also enhance the efficacy of systemic therapy. If novel diagnostic tests cannot differentiate between biologically progressive and clinically insignificant tumours, early detection may lead to increased incidence rates without reducing cancer mortality. Detection of small tumours requires screening at short intervals; however, this increases the number of overdiagnoses, unnecessary tests, and false-positive results. In the context of biological heterogeneity in tumour growth rates, adapting the screening frequency to tumour kinetics plays a crucial role in balancing the benefit-to-harm ratio.

Keywords: Cancer, Metastasis, Screening, Liquid Biopsy, Medical Imaging, Artificial Intelligence (AI), The Tumour Volume Doubling Time (TVDT), Convolutional Neural Network (CNN), Deep Learning, Machine Learning.

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Nomenclature:

CNN: Convolutional Neural Network
TVDT: Tumour Volume Doubling Time
AI: Artificial Intelligence
CTCs: Circulating Tumour Cells

I. INTRODUCTION

Worldwide, cancer-related mortality and incidence rates are increasing. According to 2022 statistics, the number of new cancer cases reached 18.1 million, while cancer-related deaths accounted for 9.6 million. According to scientific projections, by 2030, up to 30 million people could die from cancer each year [1].

II. CHALLENGES IN CANCER DIAGNOSIS AND DETECTION

Early detection and timely treatment of cancer during its initial clinical stages significantly increase the patient's chances of survival. Numerous scientific studies have substantiated the effectiveness of early detection methods in improving predictive accuracy. However, longer patient survival does not necessarily mean that the treatment methods are more effective. In some cases, this is only associated with earlier detection of the disease or the increased identification of clinically slow-growing tumours. Therefore, although survival statistics may appear to improve, the actual time of death may remain unchanged. Despite several decades of scientific research, only a limited number of early detection tests have been proven to provide a clear benefit in reducing cancer-related mortality. However, this benefit comes at a certain cost, as in some cases, such cancer findings might never have become clinically apparent during the patient's lifetime. Additional fundamental research is required to improve early cancer detection methods; however, variations in tumour biology and the timing of metastasis complicate this process. Early detection test markers can be applied in clinical practice to shorten the time to diagnosis in patients. Additionally, it is used as a screening tool to detect asymptomatic cancer in individuals who appear healthy. Therefore, the term "early detection" is primarily discussed in the context of screening.

After malignant transformation, cancer initially remains small in size, asymptomatic, and undetectable by diagnostic methods. As the tumour increases in size, it may begin to present clinical signs, creating an opportunity for detection through early diagnostic tests. Although cancer cells are capable of metastasising at any stage, only a small proportion of them lead to macroscopic metastases. The primary cause of cancer-related deaths is associated with widespread metastatic disease. Because cancer often occurs in older



individuals, the risk of death from other causes is also high at any given time [2].

If, at the time of diagnosis, the cancer has not yet metastasized (the process in which cancer cells spread from their original site, or primary tumour, to other parts of the body, forming new tumours known as secondary lesions), the cancer can potentially be completely removed surgically, and the disease may be fully cured. In cases where metastasis has occurred, a combination of surgical intervention and systemic therapy (such as chemotherapy or immunotherapy) is applied; however, in some instances, the disease may already be incurable. The success of systemic treatment is often associated with the extent of metastatic disease at the time of diagnosis. The most favourable scenario for early detection is identifying the tumour before the onset of clinical symptoms and before metastasis occurs, thereby creating the opportunity for a complete cure. Alternatively, if screening detects a cancer that has already metastasized, identifying metastasis at a relatively early stage may enhance the effectiveness of systemic therapy.

When a tumour reaches a diameter of 1–2 mm, it develops characteristic angiogenesis—the formation of a capillary network that supplies it with blood. Therefore, it is considered that the process of metastasis may begin once the tumour reaches approximately 1 mm in diameter. The likelihood of metastasis is generally directly related to the tumour size at the time of diagnosis, with rapidly growing tumours having a higher probability of metastasis compared to those that grow more slowly [3]. Therefore, the probability of detecting tumours with a high likelihood of metastasis through screening is low, as such tumours tend to progress rapidly before clinical symptoms appear. This situation can be illustrated using breast cancer as an example, since this type of tumour is supported by comprehensive data characterising the growth of both primary tumours and metastases, as well as the availability of a mammography-based screening system. Each author profile, along with a photo (min 100 words), has been included in the final paper.

The tumour volume doubling time (TVDT) is a crucial kinetic indicator that reflects the biological growth rate of a tumour in breast cancer. This parameter ranges from 30 days to one year, with a median value of approximately 150 days.

According to research, the growth rate of metastatic cells is generally higher than that of the primary tumour, and their tumour volume doubling time may be up to twice as short as that of the primary tumour. Therefore, if the cancer is detected before the onset of clinical symptoms, it significantly reduces the likelihood of metastasis and increases the potential for radical, surgery-based treatment.

In particular, screening procedures must be repeated at sufficiently short intervals to detect rapidly growing tumours. For example, a tumour with a volume doubling time of 50 days would require only about 6 months to grow from the mammographic detection threshold (~5 mm) to the clinically diagnosable size (2 cm), which raises concerns about the adequacy of screening intervals for rapidly growing tumours. Thus, screening programs require an individualized approach with respect to the timing of screening intervals. For early-detectable and slow-growing tumours, the existing screening intervals may be adequate; however, they are less effective in identifying rapidly growing tumours. Thus, the tumour

volume doubling time (TVDT) is a crucial prognostic parameter for informing screening strategies in clinical decision-making. If new diagnostic tests cannot distinguish biologically progressive cancers from clinically insignificant ones, early detection may increase incidence without reducing cancer-related mortality. The detection of small tumours is primarily achieved through screening conducted at shorter intervals; however, this approach increases the frequency of screening. In the presence of biological heterogeneity in tumour growth rates, conducting screenings more frequently can lead to overdiagnosis, unnecessary testing, and the need to investigate false-positive results in a subset of the population. Adjusting the screening frequency to align with tumour growth kinetics plays a crucial role in balancing the ratio of benefits to potential harms. The potential to reduce mortality through early-stage disease detection depends on the growth rates of the primary tumour and metastases, as well as the evolution of the probability of metastasis along the tumour growth curve. From this perspective, the likelihood of metastasis relative to tumour size is a key factor determining the effectiveness of early disease detection. Although the capabilities of modern imaging technologies are continuously expanding, their limitations in detecting tiny tumours persist, and the actual effectiveness of these methods in screening largely depends on the early metastatic potential of the tumours [4].

Historical studies based on long-term follow-up of patients with various types of cancer who were treated solely with primary surgery provide critical clinical insights into the late occurrence of metastases. Analysing such data through multiscale computational models and simulating the progression of tumour disease offers an opportunity to develop individualised screening strategies. “Early cancer detection is being explored through blood tests known as “liquid biopsy,” which identify circulating tumour cells (CTCs) and circulating DNA (ctDNA). However, the accuracy of these tests, particularly in detecting small tumours, is currently insufficient for screening purposes. While the effectiveness of ctDNA-based tests may improve with technological advances, the fundamental biology of ctDNA release may limit their potential for early disease detection. Because the release of DNA into the bloodstream through apoptosis depends on cell death, it may be limited in invasive tumours that evade programmed cell death and metastasise early. Modelling studies suggest that slow-growing tumours may have a higher ctDNA burden compared to fast-growing tumours of the same size. The complex dynamics of tumour progression make it challenging to accurately predict the balance between early disease detection and overdiagnosis (as well as overtreatment). Additionally, if liquid biopsies do not provide precise information about tumour localisation, their practical value may be limited. Therefore, after an abnormal result is detected in a blood test, additional imaging and invasive procedures, including a complete biopsy, are required to determine the origin of the tumour [5].

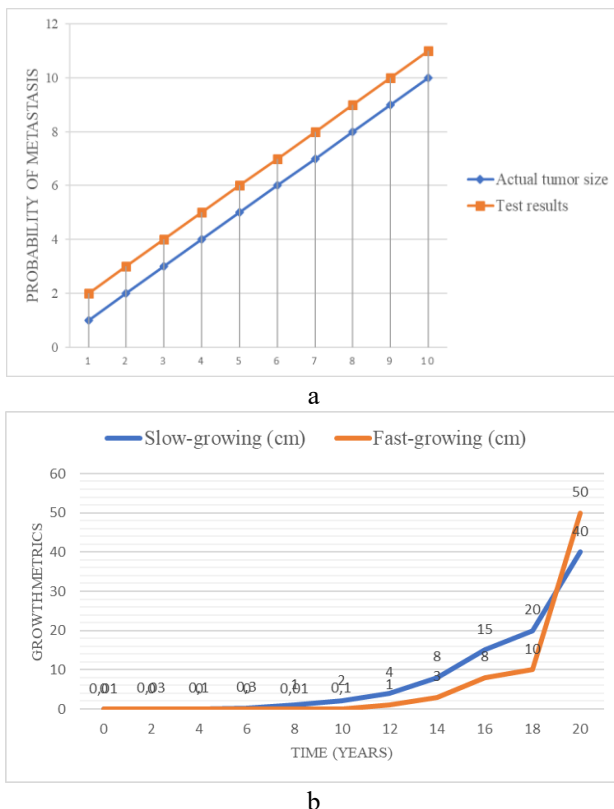
Evaluating the clinical utility of liquid biopsies in early disease detection largely depends on the results of empirical studies. Even if their



sensitivity for detecting small primary tumours is insufficient, they may still help assess the metastatic potential of tumours identified through other methods. Scientific research has demonstrated that the cellular composition of tumours is heterogeneous, and only specific subpopulations are capable of initiating metastasis. Therefore, identifying molecular markers associated with metastasis in tumours detected through screening can help avoid overtreatment and improve patient prognosis. Additionally, modelling the dynamics of biomarkers related to cancer progression offers an opportunity to develop personalised screening and treatment strategies [6].

III. THE PROGRESSION OF TUMOUR DISEASE IN EARLY DETECTION OF THE DISEASE

The progression of tumour disease is the primary factor determining the likelihood of detecting metastases at the time of existing screening tests. For example, mammographic screening can detect tumours as small as 5 mm in diameter, whereas clinically detectable breast tumours are typically 2 cm or larger. If a tumour has an average volume doubling time of 150 days, it would take approximately 8 years to reach a size capable of metastasis (greater than 1 mm) and an additional 3 years to grow to a size detectable by mammography.



[Fig.1: (a) Probability of Metastasis Based on the Primary Breast Tumour Size; (b) Log-Linear Growth of the Primary Tumour and Metastases Over Time] [7]

IV. MATH

Before we examine the mathematical calculation of the probability of metastasis based on the size of the primary breast tumour, we need to consider the following. In this graph, two sets of x and y values are presented in a linear

form, where each x -point (ranging from 1 to 10) corresponds to its respective y -value.

x represents the variable for tumour size, ranging from 1 to 10.

$y_1(x)$ - represents the probability of metastasis based on the actual tumour size.

$y_2(x)$ - represents the probability of metastasis as determined based on the results of examinations.

In Figure 1a, the blue line represents the actual tumour size, which is calculated as follows:

In Figure 1a, the blue line represents linear growth, increasing by 1 unit at each stage.

Here:

Starting point: $y_1(x)=1$

For each x , the slope is: $\Delta_y=1$

The probability of metastasis, based on the actual tumour volume, is calculated using the following formula.

$$y_1(x) = x \quad \dots (1)$$

The orange line in Figure 1a represents the probability of metastasis determined based on examination results, which is calculated as follows:

In Figure 1a, the orange line is consistently 1 unit higher than the corresponding values of the blue line [8].

Here:

Starting point: $y_2(x)=2$

For each x , the slope is: $\Delta_y=1$

The probability of metastasis determined based on examination results is calculated using the following formula:

$$y_2(x) = x + 1 \quad \dots (2)$$

The benefit-to-risk ratio of early-stage disease detection can be optimized by considering the biological heterogeneity of tumor growth kinetics. Therefore, fundamental studies aimed at identifying the growth and metastatic patterns of tumours with various localisations are essential. Research on early-stage disease detection should primarily focus on developing technologies capable of identifying small tumours with early metastatic potential and diagnostic tests that can detect occult metastases that may already be present at the time of diagnosis. However, the main challenge in demonstrating the usefulness of such screening tests is determining their actual impact on clinical outcomes. It is insufficient to rely solely on proxy indicators, such as an increase in the proportion of early-stage disease among newly detected tumours (stage shift) or the observation of longer survival times in screen-detected tumours. Because such outcomes may arise due to lead-time bias or length-time bias [9], lead-time bias occurs in situations where a cancer detected through screening would have become clinically apparent before metastasis occurred, or when incurable metastases were already present at the time of screening. In both cases, early-stage detection of the disease does not lead to any significant improvement in quality of life or overall survival. Length-time bias refers to the tendency for slow-growing, relatively low-risk tumours to be detected more frequently through screening, which can lead to overdiagnosis and overtreatment.

Randomized controlled clinical trials are necessary to evaluate the actual health benefits of various early

detection methods. However, such trials are costly and time-consuming, and given the large number of existing and emerging tests, conducting such trials for each one is practically impossible. Therefore, the research community should develop strategies to enable the early prioritisation of tests with a low likelihood of effectiveness and direct resources toward those that are most clinically promising.

Additionally, several challenges can arise in the early detection of cancer, including issues related to imaging studies for lung and colorectal cancer detection. Among these challenges is the complexity of tumour morphology and its heterogeneous nature, which makes accurate diagnosis and classification difficult. Additionally, the availability of labelled data for training machine learning models remains limited, which hinders the development of robust algorithms. At the same time, overfitting and limited generalization capabilities pose significant obstacles to translating research findings into clinical practice [10].

According to the studies by Gerlinger, Litjens, Yamashita, and their colleagues:

The research conducted by Gerlinger and his team highlighted significant intratumoral heterogeneity in lung cancer, which complicates the accurate diagnosis and classification of the disease. Researchers identified distinct genetic mutations in different regions of the same tumour, which makes the development of unified diagnostic criteria challenging [11].

Litjens and his colleagues highlighted the scarcity of large annotated datasets for training machine learning models in medical imaging. This limitation hinders the development of robust algorithms and their subsequent validation across diverse patient populations. Yamashita and his colleagues demonstrated that deep learning models trained on limited datasets often exhibit overfitting, which reduces their ability to generalize to new, unseen data. This issue is particularly evident in lung cancer imaging, where variability in tumour appearance can lead to a decline in model performance under clinical conditions [12].

Table I: Advantages and Limitations of Large-Scale Studies on Cancer [13]

No	Researchers	Advantages	Disadvantages
1	TCGA Consortium	It has mapped the genetic and molecular landscape of cancer, providing a foundation for personalized treatment.	Research is expensive and complex, and its implementation in clinical practice has not been fully realised.
2	Gerlinger et al.	It revealed the genetic heterogeneity of tumours and highlighted the limitations of biopsy samples.	Heterogeneity complicates diagnosis, and standardized approaches have not been developed.
3	Hanahan and Weinberg	It transformed the key hallmarks of cancer biology into a theoretical model, paving the way for scientific research.	The model is general and theoretical; it does not fully align with real clinical scenarios.
4	Litjens et al.	It identified the capabilities and methodological challenges of artificial intelligence in image analysis.	It requires large and annotated datasets; the model does not adapt well to other conditions.
5	Yamashita et al.	It analyzed the stability and overfitting issues of models trained on limited data.	The model adapts poorly to new cases and has limited

			applicability in clinical practice.
6	Esteva et al.	It brought image-based diagnosis using CNNs closer to clinical application.	It relies solely on imaging; other clinical indicators are not taken into consideration.
7	Beck et al.	The possibility of predicting outcomes from histological images using artificial intelligence has been established.	Data quality is sensitive; retraining with new data is required.
8	Kather et al.	Genetic alterations have been successfully identified from routine tissue images.	It only works for certain types of cancer and has lower accuracy compared to genomic tests.
9	Liu et al.	It only works for certain types of cancer and has lower accuracy compared to genomic tests.	Data is not always available; its implementation in practice is limited.
10	Topol E.	It introduced medical artificial intelligence to the public and promoted collaboration between physicians and AI.	Theoretical approaches do not yet fully translate into practical applications; they are often optimistically assessed.

V. CONCLUSION

Early-stage cancer detection is a crucial factor in improving patient survival rates and quality of life. Advancements in screening and diagnostic technologies are creating significant opportunities in this field. However, challenges such as overdiagnosis, biological heterogeneity, and insufficient assessment of metastatic potential limit the clinical effectiveness of these approaches. Kinetic parameters, such as tumour volume doubling time (TVDT) and the probability of metastasis, highlight the need to individualise screening strategies. While liquid biopsy and ctDNA-based methods are promising, their low sensitivity in detecting small tumours limits their clinical applicability.

Although artificial intelligence and deep learning technologies hold significant potential for improving diagnostics, their clinical implementation faces challenges, including the need for annotated data, image quality issues, and limitations in generalisation and validation. Therefore, any technology aimed at early detection must be evaluated with consideration of clinical benefit, biological rationale, technical reliability, and epidemiological balance. Future research should focus on refining screening approaches at the molecular and personalized levels.

DECLARATION STATEMENT

I must verify the accuracy of the following information as the article's author.

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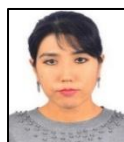
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