肺癌的早期诊断技术

Core technical content

Abstract

* Usually submitted beforehand for approval
* Often made available in a meeting or conference catalogue (online or in print)
* Short and concise
* Not required for all conferences/posters
* Check guidelines
* May have separate sections or be a single paragraph
* Abstract Sections

Introduction

• 1-2 short paragraphs  
• Research background  
• Research question and hypothesis

• 1 paragraph for introduction1 paragraph describing purpose of research

Materials and Methods

* Materials used and methods applied (including statistics and significance cutoffs)
* Include relevant images, charts, graphs to help viewer understand your project Explain why you chose your methods
* Generally 2 paragraphs

Results

* Summary of results
* Figures and tables  
  Label clearly and with caption  
  Use figures and tables that look good to attract attention
* Sometimes caption text is only text in this section
* Relationship between results and research question
* More figures, less text and tables

Conclusions

* Review research question, results, and conclusions
* Bullet points acceptable/preferred
* Discuss why your results are interesting or significant

References

* List references
* Break into columns if needed
* Smaller font here to make everything fit
* Some conferences don’t require this section
* Relate to other research when possible
* What are the broader implications or applications?
* Future steps?
* May be additional sections depending on conference

Abstract

Introduction:

Lung cancer is the most common cause of cancer-related deaths in North America and other developed countries. According to the 2020 special report on lung cancer, this disease is the most commonly diagnosed cancer and the leading cause of cancer death in Canada [1]. The impact imposed is highlighted by statistics reporting a higher number of Canadians dying of lung cancer than colorectal, pancreatic, and breast cancers combined. For instance, approximately 30,000 Canadians will be diagnosed with lung cancer, with a projection of 21,000 death in 2020. Globally, the cancer burden is projected to double by 2050, with lung cancer at the top of the list [1].

People die from lung cancer because it is often not diagnosed until the cancer is at an advanced stage. Detailed pathogenesis, effective early detection, and suitable drugs help in the effective therapy of lung cancer. Thus, the earliest diagnosis of lung cancer is crucial, especially in screening high-risk populations (e.g., smokers, exposure to fumes, oil fields, toxic occupational places, etc.) with an urgent need to identify novel biomarkers.

Furthermore, accurate diagnosis is vital for the most suitable treatment of individual patients with lung cancer. Thus, there is an urgent need to identify sensitive and specific biomarkers for early diagnosis.

Currently, low-dose CT (LDCT) is routinely used for lung cancer screening. In addition, a trial (NELSON) has shown that this particular screening has a selectivity of 85% and a specificity of 99% compared to no screening [2]. A recent study showed that the overall false-positive rate reached 81% [3]. This very high number required additional imaging or testing to confirm the results.

This study will focus on 2 questions:

how to improve earliest diagnosis of lung cancer?

How to apply accurate diagnosis , suitable treatment of individual patients with lung cancer?

Materials and Methods

**Lung Cancer Staging**

**Classification**

Clinically, seven immune checkpoint inhibitor antibodies have been approved by the United States Food and Drug Administration (FDA) for the treatment of a variety of tumors: Ipilimumab that blocks cytotoxic T-lymphocyte antigen-4, and six antibodies that block PD-1/PD-L1 including pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab, and avelumab. These antibodies have achieved promising results in the treatment of recurrent SCLC. On the other hand, tumor vaccines, immunomodulators, cellular immunity, and other immunotherapy methods can play an increasingly important role in comprehensive tumor therapy. Reasonable treatment timing and optimal combined strategy are the hotspots of SCLC immunotherapy [17].

**NSCLC**

Over the last decade, tissue and/or blood biomarkers have helped guide patients’ treatment decisions with advanced NSCLC. Based on the detection of biomarkers, this has provided a channel for subgrouping patients. Evidence shows that treatment with targeted therapies has superior clinical outcomes than traditional cytotoxic chemotherapy [18,19]. A table of medical tests

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Newly diagnosed NSCLC patients are opted to take biomarker testing for determining optimal treatment. Practical guidelines such as the CAP/IASLC/AMP, ASCO, and National Comprehensive Cancer Network guidelines help select the most appropriate biomarkers and assays to use [20].

There are many different types of tissue- and blood-based assays available for biomarker testing, all with their advantages and disadvantages that clinicians should understand when deciding which assays to use. For example, plasma-based assays have many advan- tages over tissue-based tests because the test is non-invasive, fast, and easily repeatable over time. Still, they may be less sensitive than tissue-based assays and cannot serve as stand-alone testing for patients with NSCLC. For example, the most common targetable mutation (*EGFR*) testing has been part of the standard practice since 2011.

NSCLC serves as a model for the successful application of “precision medicine” or the concept of using advanced genetic analysis of a patient’s tumor to obtain an individualized therapy plan in contrast with cancer treatment regimens assigned in a definite manner, based mainly on the organ of origin. The NCI-MATCH Trial (Molecular Analysis for Therapy Choice) is an example of an advanced precision medicine clinical trial, where genomic sequencing of a patient’s tumor is performed. The cancer treatment regimen is derived based on the genomic findings, not the organ in which cancer originated. Further advances in precision medicine depend on the development of novel diagnostic assays, which are needed to provide feedback (preferably quantitative) to oncologists regarding the efficacy of therapy [21].

Checkpoint immunotherapy (CPI) in metastatic NSCLC and the emergence of pre- dictive biomarkers for CPI efficacy reinforces the importance of testing for both treatable genomic abnormalities and immune-related biomarkers. To this point, current national and international guidelines now recommend testing for alterations of the oncogenic targets *EGFR*, *ALK*, *ROS1*, *BRAF*, *RET*, *MET*, and *HER2*, along with immune biomarkers such as PD-L1 and tumor mutational burden (TMB) [22].

As highlighted above, both SCLC and NSCLC benefit from using biomarkers in early diagnosis and follow-up of a treatment and even choosing a treatment protocol.

**Traditional Diagnosis and Screening**

*6.3. Sputum Examination*

Another diagnostic procedure of lung cancer is the cytological examination of sputa, especially multiple samples, which helps detect central tumors from the larger bronchi (e.g., squamous- and small-cell carcinomas). In general, sputum samples failed to detect small adenocarcinomas (diameter ≤ 2 cm) that originated from the airway ramifications, such as small bronchi, bronchioles, and alveoli. This has become of greater importance because cigarette exposure changes (filters and decreased nicotine content) have increased adenocarcinomas and decreased squamous carcinomas. Sputum cytology’s sensitivity for early lung cancer is only in the 20–30% range from screening studies. Early studies showed that the ability to detect pre-malignant conditions depends on different factors such as the number and type of cells (deeper airways) [29]. Studies have also concluded that sputum cytology was insufficiently insensitive or accurate to be included in the routine workup of any patient suspected of having lung cancer [30].

Studies have shown that perhaps immunostaining could provide a more favorable outcome compared to sputum cytology. For example, an 8-year study at the Johns Hopkins hospital collected annual sputum specimens from individuals screened with known clinical outcomes. The sputum specimens were archived and screened for biomarkers that could indicate lung tumors in an early or pre-invasive stage [31]. As a result of this investigation, two monoclonal antibodies were studied to distinguish the pattern of marker expression. Results showed that positive staining with these antibodies predicted subsequent lung cancer approximately two years before clinical recognition of the disease based on chest X-ray and cytology. In addition, one of these antibodies (703D4) showed higher sensitivity and was later identified as recognizing the protein heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1 [32]. Following this study, the role of hnRNP A2/B1 overexpression for detecting pre-clinical lung cancer was studied in a large high-risk population, including 6000 Chinese tin miners who were heavy smokers and had an elevated lung cancer rate. This study indicated that the expression of hnRNP A2/B1 in epithelium cells from sputum was 2- to 3-fold more sensitive for early detection of lung cancer than standard chest X-ray and sputum cytology methods [31].

**Lung Tissue Biopsies**

**7. Lung Tissue Biopsies**

The gold standard for cancer confirmation is a biopsy of the tissues. Lung tissue biopsy samples must have adequate tissue material to identify the subtype of lung cancer by histopathology procedures. The initial biopsy is critical to confirm early diagnosis, avoiding repeating the biopsy with increased risk of complications and a delay in treat- ment initiation. Many commonly used procedures in diagnosing lung cancer include fiber optic bronchoscopy with or without transbronchial needle aspiration, endobronchial ultrasonography, image-guided trans-thoracic needle aspiration, mediastinoscopy, pleural fluid analysis (thoracentesis), thoracoscopy, and surgical approaches. These procedures are costly, prone to complications, and there is a possible need for more samples [36].

**Transition to Biomarker Applications**

In practice, the cornerstones of lung cancer assessment are radiology and tissue biopsies, as discussed earlier. Between missing early diagnosis, cost, and their risks, especially thoracic oncology biopsies, introducing the use of techniques as simple as a blood test provides a much safer and faster option. A review at the MD Anderson Cancer Center assessing cancer biopsies showed more than 17% adverse effects for thoracic biopsies [45].

*8.2. Blood Circulating Antigens*

A number of antigens found in blood have been assessed over the years as potential biomarkers of lung cancer. The most studied biomarkers include CYFRA 21-1, carcinoem- briogenic antigen (CEA), neuron specific enolase (NSE), and squamous cell carcinoma antigen (SCC-Ag). The following table is provided as an illustration of the sensitivities and specificities reported by clinical trials (Table 2).

As shown in Table 2, variations are observed across the different types of lung cancers. These variations could have originated in the cancer stage at the moment of blood collection and/or other methodologies used for the analysis, such as differences in the ELISA kits from different suppliers, including the threshold of the antigen values set by the company. Taken together, it appears that a unique antigen biomarker is not valuable for diagnostic and likely, a multi-antigen approach should be considered in combination or not with other biomarkers.

*8.2. Blood Circulating Antigens*

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**Liquid Biopsies Use in Lung Cancer**

Factors Contributing to Disparities in Lung Cancer Screening

**Race and Ethnicity Model**A table with numbers and text

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Definition of abbreviations: AI/AN = American Indian/Alaskan Native; API = Asian/Pacific Islander; SEER = surveillance, epidemiology, and end results. \*Weighted percent, population adjusted; from 2015 National Health Interview Survey, United States (27).†Age-adjusted per 100,000; SEER 21 Area Registry, 2012–2016 (2).

Current screening guidelines do not align similarly for black and white individuals. Racial differences in both smoking patterns and age at diagnosis contribute to racial disparities in screening eligibility. Screening provides an opportunity for earlier stage at diagnosis for all racial/ethnic groups (3, 12); however, black smokers have lower rates of lung cancer screening than white smokers (39). Black participants in the LDCT arm of the NSLT study had greater reduction in both lung cancer and all-cause mortality than white participants, despite low participation (4.4% black vs. 90.9% white) (8). In a more diverse screening population with a higher percentage of black individuals (69.6%), lung cancer screening detected a larger percentage of cancers than the NSLT study (2.6% vs. 1.1%), with the majority being early-stage lung cancer (7). Despite having greater lung cancer incidence, black smokers are less likely to be eligible for screening (40, 41), as the current lung cancer screening guidelines with the 30 pack-year inclusion criteria exclude a higher proportion of high-risk black smokers because of their lower average cigarette per day consumption compared with white smokers. This reduced cigarette smoking behavior has led researchers to suggest that expansion of lung cancer screening eligibility to individuals with any smoking history (42) or 20 to 29 pack-year smoking history (41, 43) would increase the proportion of screening-eligible black patients. Black smokers are also at greater risk of developing lung cancer at an earlier age, with the highest difference in age- adjusted incidence between black and white smokers noted in the 50- to 54-year-old age range, earlier than the currently recommended minimum screening age of 55 years (10). Reducing the minimum age criteria to 50 years, as done in the NELSON trial, would further increase the number of eligible black smokers (41).

Current screening guidelines are projected to capture a higher proportion of eligible white smokers with lung cancer, potentially further exacerbating the disparity gap in lung cancer survival (40). Risk models that incorporate race/ethnicity, such as the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial model (PLCOM2012) and the Lung Cancer Death Risk Assessment Tool (LCDRAT) demonstrate improved accuracy in predicting lung cancer risk compared with the NLST criteria (42, 44, 45). Future lung cancer screening guidelines should consider expanded eligibility criteria or risk-based approaches to address equity in screening eligibility (45).

Environmental and  
Occupational Exposures

Environmental factors other than tobacco also confer an increased risk for development of lung cancer and are considered by the National Comprehensive Cancer Network in their consensus-based guideline category 2 recommendations. These category 2 recommendations require a minimum 20 smoking pack-years and age 50 years, along with additional risk factors and PLCOM2012 risk calculator assessment (53) for lung cancer screening eligibility. Radon is present in soil, concentrated in enclosed spaces such as mines and homes, and has been identified by the U.S. Environmental Protection Agency as the second leading cause of lung cancer after cigarette smoking (54). Secondhand smoke and other environmental hazards such as asbestos, chromium, arsenic, and air pollution also play a role in lung cancer risk, exacerbated by concurrent smoking (55). Environmental and occupational  
exposures are often more common in underrepresented minority populations and those with lower socioeconomic status (56), potentially contributing to existing disparities in lung cancer incidence. Screening with LDCT for asbestos-exposed workers yields detection of lung cancer at localized disease rates similar to those in the NLST (57), and lung cancer risk prediction tools, such as the Bach model, that incorporate asbestos exposure demonstrate improved performance over USPSTF eligibility criteria in national datasets (42, 58). In considering these environmental factors, challenges arise because of lack of patient awareness of exposure and low exposure in the general population; however, targeted occupational screening questions could be considered for high-risk individuals with subsequent referral for screening.

HIV

Lung cancer is the leading cause of non– AIDS-defining cancer deaths, and lung cancer incidence in HIV-positive patients is significantly higher than the general population (5). In addition, age of lung cancer onset in HIV-positive patients is  
25 to 30 years earlier than the general population, with average age of diagnosis between 38 and 57 years, compared with 70 years in the general population (5). Most of lung cancer cases occurring in HIV-positive patients present at late stage, with only 15% presenting at local, resectable stage, and, as a result, median survival is between 3.5 and 6.3 months (5, 59). HIV-infected patients have an estimated 52% excess lung cancer risk when compared with noninfected individuals (60). These high lung cancer rates have been attributed to high smoking prevalence among HIV-infected individuals, with smoking prevalence ranging from 25% to 80%, two to three times higher than the general population (5, 61). Prior studies also implicate the chronic inflammatory state and immunosuppressive treatment regimens in this population as well as a potential oncogenic role of the HIV virus (61). Current lung cancer screening guidelines perform poorly in individuals living with HIV (62). A modified Lung Cancer Policy Model that mirrors the distinctive aspects of lung cancer screening in HIV-infected individuals appears to provide similar mortality reduction in HIV- infected persons with a CD41 cell count of >500 cells/ml, as in the general population (63). Because of the high incidence and mortality associated with lung cancer in HIV-infected patients, lung cancer screening should be considered in this high- risk group and must be accompanied by smoking cessation programs, although further work should be done to determine appropriate screening eligibility criteria (59).

Results

**Lung Cancer Staging**

**NSCLC**

Checkpoint immunotherapy (CPI) in metastatic NSCLC and the emergence of pre- dictive biomarkers for CPI efficacy reinforces the importance of testing for both treatable genomic abnormalities and immune-related biomarkers. To this point, current national and international guidelines now recommend testing for alterations of the oncogenic targets *EGFR*, *ALK*, *ROS1*, *BRAF*, *RET*, *MET*, and *HER2*, along with immune biomarkers such as PD-L1 and tumor mutational burden (TMB) [22].

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**Classification**

**Traditional Diagnosis and Screening**

**Lung Tissue Biopsies**

**Transition to Biomarker Applications**

**Liquid Biopsies Use in Lung Cancer**

Factors Contributing to Disparities in Lung Cancer Screening

Race and Ethnicity

Rurality

Environmental and  
Occupational Exposures

HIV Infection

Access to Care

Patient-Level Barriers

Conclusions

The early diagnosis of lung cancer remains a challenge because most of the available techniques and methodologies currently in use can detect cancer in advanced stages when treatment and a cure may not be efficient to control the disease. Thus, although significant progress happened over the last years, early diagnosis is still not accurate.

Lung cancer is mainly diagnosed by bronchoscopy and biopsies. In the case of bronchoscopy, it appears that the experience of the bronchoscopist is crucial for an accurate diagnosis. Although bronchoscopy is a minimally invasive technique with discomfort for the patients, complications can arise, especially if biopsies are taken from the suspicious tissue. Then, screening for early lung cancer development is required for an early therapy that can improve the outcome of the disease.

In recent years, the search for biomarkers in human fluids has been an attractive methodology that has progressed in the right way. For instance, studies have shown that sputum, blood, and urine samples can answer the demand for biomarkers. Most of the published biomarkers are detected by PCR, metabolomics, or by other molecular biology techniques that will provide fast results for early intervention. In addition, the use of urine samples has proven that the detection of a metabolite in lung cancer is feasible, and it can be performed in a matter of hours. In summary, we believe that the trend in the development of more reliable tests for early diagnosis of lung cancer should be focused on biomarker discovery that will alleviate the discomfort of the patients, as well as the burden for the health authorities, as the techniques and methodologies currently in use are expensive.

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Conclusions

Racial differences in smoking behaviors, lung cancer incidence, age at presentation, and mortality should be considered in lung cancer screening guidelines. Black individuals have higher incidence, earlier presentation, and increased mortality of lung cancer than white individuals, despite lower overall cigarette consumption. Lung cancer screening has maximum benefit when combined with smoking cessation and should be emphasized in all populations. Current lung cancer screening eligibility guidelines using the 30-pack-year criterion exclude a large percentage of high-risk, light-smoker black individuals. Revisions to screening guidelines should consider racial/ ethnic variation in cigarette smoking, additional risk factors, and overall level of risk. Individuals with HIV have a disproportionately high burden of lung cancer morbidity and mortality, and thus HIV status should be considered in screening eligibility guidelines. Consideration of screening for those with known occupational exposures also deserves further discussion. Improving access to high-quality healthcare systems, both financially with insurance coverage and geographically with access to high-volume screening facilities, is essential to address the high incidence and mortality of lung cancer. Implementation of lung cancer screening and smoking cessation  
programs requires addressing community beliefs regarding the importance of smoking cessation and risks of lung cancer. Outcomes for high-risk  
individuals and patients with lung cancer will equalize once disparities in lung cancer screening eligibility and access to care are considered. We call on professional organizations caring for patients with lung cancer to address the disparities discussed in this review and translate them into actionable policy recommendations. n

* Classification of patient
* Apply suitable methods for different disease stage

References

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Lung cancer survival has only marginally improved over the last several decades, but the availability of screening and early detection by low-dose CT and advances in targeted treatments and immunotherapy will likely decrease mortality rates and improve patient survival outcomes in the near future.