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Blood Based Multi-Cancer Early Detection Tests in Lung Cancer Screening

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Abstract

Lung cancer is responsible for the most cancer-related deaths worldwide. While the implementation of low dose CT (LDCT) screening for high-risk individuals has been shown to improve outcomes and reduce mortality by 20%, there is still room for improvement in screening (de Koning et al, 2020). Multi-cancer early detection (MCED) tests aim to detect early-stage cancer with the goal of improving treatment outcomes. This technology combines plasma analysis for cell-free DNA and methylation patterns with artificial intelligence to detect malignancies and predict tumor origin sites. The purpose of this systemic literature review is to assess the rising potential of MCED for screening and early detection of lung cancer compared to LDCT. This review utilizes searches of PubMed and ClinicalKey. A total of 14 articles published over the last 20 years were included for analysis. Results indicate that MCED has a higher specificity than LDCT resulting in less false positives, however, the sensitivity of MCED for detecting lung cancer is not consistently high enough to replace LDCT. At this time, LDCT remains the gold standard for screening and early detection of lung cancer and should continue to be utilized in clinical practice. This study focused exclusively on lung cancer, but MCED has the capability to detect more than 50 types of cancer, many without a current screening. Further research should be conducted to explore the role of MCED as an adjunct to traditional cancer screenings.

Introduction

Lung cancer remains the leading cause of cancer-related death worldwide (Krist et al., 2021). Despite recent advancements in screening and treatment, only 15% of patients with lung cancer are still alive 5 years after their diagnosis (de Koning et al., 2020). The United States Preventative Services Task Force (USPSTF) currently provides a grade B recommendation for lung cancer screening in individuals ages 50-80 who have a 20 pack-year history or greater and are currently smoking or have quit within the past 15 years (Krist et al., 2021). The implementation of screening with low-dose CT (LDCT) has been shown to be effective in reducing lung cancer related mortality.

In recent years, multi-cancer early detection (MCED) tests have emerged as a promising screening tool for cancer. This technology works by combining plasma analysis for DNA methylation patterns with artificial intelligence to detect malignancies and predict tumor location (Brito-Rocha et al., 2023). MCED aims to detect early-stage malignancies with high sensitivity and specificity to improve cancer outcomes.

The goal of this study is to assess the capabilities of MCED as a screening tool for lung cancer compared to LDCT regarding sensitivity, specificity, and impact on cancer outcomes.

Statement of the Problem

LDCT is not without adverse effects. Radiation exposure, false positives leading to unnecessary work ups, and overdiagnosis are all concerns for subjecting high-risk individuals to yearly screenings and barriers to patient compliance. While LDCT is the gold standard for screening high risk patients for lung cancer, MCED could potentially offer an easier and less invasive screening option.

Research Question

Among adults who meet the USPSTF guidelines for lung cancer screening, how does multi-cancer early detection testing compare to low dose CT for detecting cancer and improving outcomes?

Literature Review

Sensitivity and Positive Predictive Value

•Shao et al. determined the sensitivity of MCED for lung cancer across all stages was 74.8% (95% CI: 70.3%-78.7%). Sensitivity increased by cancer stage with 21.9% sensitivity for stage I cancers, up to 95.2% sensitivity for stage IV cancers.

•Liu et al. determined the positive predictive value of MCED to be 51%.

•Tang et al. explored the sensitivity of MCED across different races and ethnicities and found no appreciable difference in the sensitivity by race.

•In trial to assess the sensitivity and positive predictive value of LDCT, Horweg et al. determined the sensitivity to be 84.6% (95% CI: 79.6%-89.2%) and the PPV to be 40.4% (95% CI: 98.5%-98.8%)

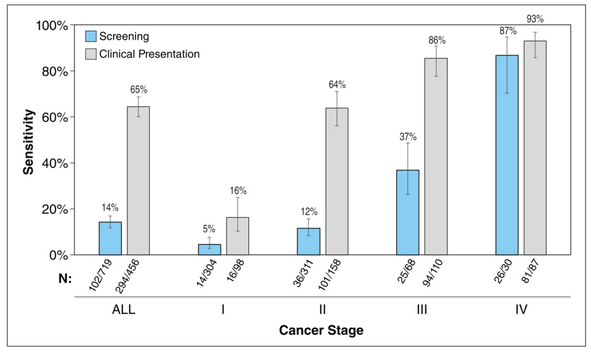
Specificity and False Positive Rates

•In the CCGA study conducted by Klein et al., the specificity of MCED determined to be 99.5% (95% CI: 99.0%-99.8%) indicating a false positive rate of 0.5%.

•Croswell et al. conducted a study to explore the false positive rate of LDCT from the NLST study, finding a 31% chance of receiving a false positive over two consecutive yearly screenings.

•Pinksy et al. conducted a subsequent study to explore the relationship between lung cancer risk and false positive screenings. They showed that the lowest risk individuals (based on pack years) had a 12.9% false positive rate, and the highest risk individuals had a 25.9% false positive rate.

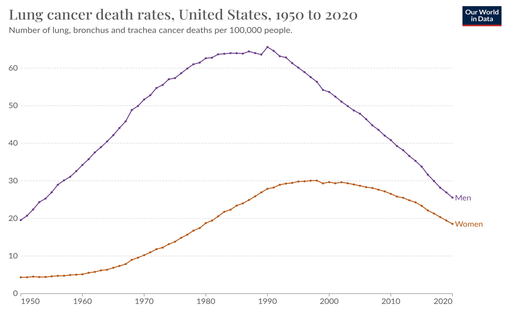
•The National Lung Screening Trial (NLST) is the largest study to date on lung cancer screening. It was determined that 96.4% of positive screens were false positives. The criteria defining a positive screening have since changed to become stricter which has reduced the false positive rate.



(Shao et al., 2020)

Impact on Lung Cancer Outcomes

- A study done by Chen et al. determined the prognostic significance of MCED. Results show that cancers detected by MCED have a higher mortality than those which go undetected.
- Because MCED is so new, no long-term studies are available to determine its impact on cancer outcomes. However, Hubbel et al. modelled mortality benefits using previously published sensitivity data. This study estimates a 26% reductive in mortality by screening with MCED.
- The NLST trial was conducted over 10 years and estimates a >20% reduction in lung cancer mortality among those who are screening with LDCT compared to those who are not.



Discussion

- The sensitivity of LDCT for lung cancer detection is 84.6% (Horeweg et al., 2014). The sensitivity of MCED was determined to be 69% for detecting all cancers. However, the sensitivity of MCED increased with cancer stage ranging from 21.9% in stage I to 90.7% for stage IV (Shao et al., 2023).
- The specificity of MCED was determined to be 99.5% indicating a false positive rate of only 0.5% (Klein et al., 2021). Conversely, Croswell et al. determined the false positive rate of LDCT in detecting lung cancer was 31% (Croswell et al., n.d.).
- Liu et al. determined the positive predictive value (PPV) of MCED to be 51%. Comparatively, LDCT was found to have a variable PPV based on variations in the criteria defining a positive screen. Horweg et al. determined the PPV of LDCT to be 40.4% whereas the NLST found a PPV of only 3.8% (“Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening,” 2011).
- Chen et al. discovered that MCED testing may have prognostic significance in that cancers detected through MCED tended to be more aggressive and less survivable than those not detected. This was used to justify that, although MCED does not have universally high sensitivity for lung cancer across all stages, the tests show promise in detecting the most aggressive cancers (Chen et al., 2021).
- A model created by Hubbell et al. estimates an absolute reduction in cancer related deaths of 74-104 per 100,000 person years in those screened with MCED compared to patients who are diagnosed through regular care. The NLST study, found a 20% reduction in lung cancer related deaths in individuals screened with LDCT. This translates to an absolute reduction of lung cancer deaths of 62 deaths per 100,000 person years.

Applicability to Clinical Practice

At this time, LDCT continues to be the gold standard for lung cancer screening and has been shown to reduce mortality by 20% in high-risk individuals who undergo yearly screening (“Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening,” 2011). Though MCED does not currently outperform LDCT in the detection of lung cancer, it can detect almost 80% of stage II and later lung cancers with a minimal risk for false positives (Shao, et al., 2023). For this reason, MCED may still have a place in cancer screening. This is especially true with consideration of additional benefits of MCED which were not explored in this study. These include enhanced accessibility, reduced cost compared to multiple traditional screening methods, and screening for multiple cancers (including those without current screening methods). MCED testing is a promising technology with the potential to improve cancer outcomes through early detection and clinicians should consider utilizing this technology as an adjunct to traditional lung cancer screening.

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