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ABSTRACT

Objectives: Early detection of lung cancer is pivotal for an optimal prognosis. CT screening is currently implemented in USA. To decrease the amount of CT scans, the application of a blood-based biomarker as part of screening criteria is desirable.

Materials and methods: The EarlyCDT® Lung test was performed in a high-risk cohort composed 246 patients referred from their GP on suspicion of lung cancer. Blood samples were taken at first visit and patients underwent diagnostic workup on suspicion of lung cancer resulting in either a malignant diagnosis or ruled out cancer. Sensitivity and specificity of the EarlyCDT® Lung were calculated in the cohort and subgroups based on age, smoking history, sex and lung cancer stage.

Results: Overall sensitivity in the cohort was 33 % for lung cancer and 31 % for primary lung cancer and lung metastases combined. Sensitivity in age groups was 11 % (60 years or below), 31 % (61−75 years) and 55 % (>75 years). In patients with at least 10 tobacco pack years, sensitivity was 33 % while the sensitivity in patients with at least 50 tobacco pack years was 44 %. The assay sensitivity in stage I-II lung cancer patients was 21 %, while this was 40 % in stage III-IV lung cancer patients.

In a subgroup of patients that met current CT screening criteria (age 55–80 years and minimum 30 tobacco pack years) the sensitivity was 37 %.

Conclusion: The rationale of screening for lung cancer is to find patients in an early and resectable stage. However, the EarlyCDT® Lung test performed best in elderly, late stage lung cancer patients with a heavy smoking history. Based on these results, the current study finds insufficient sensitivity of the EarlyCDT® Lung test to be used as part of inclusion criteria in a low-dose CT program for detection of lung cancer.

1. Introduction

Lung cancer is the leading cause of cancer-related death world-wide and epidemiologic trends estimate a further increase in lung cancer deaths over the next decades [1]. The stage of disease assigned at diagnosis is crucial for patient survival [2] hence significant efforts are made to diagnose lung cancer as early as possible.

Several trials have addressed the application of a low-dose computed tomography (CT) screening program in a high-risk population to diagnose lung cancer at a resectable stage [3–5], the largest being the National Lung Screening Trial (NLST) [6] in USA and the Nelson trial [7] in the Netherlands and Belgium. The NLST reported a 20 % reduction in mortality, and consequently, annual low-dose CT screening has been implemented in USA for patients aged 55–80 years, who are current smokers or have quit smoking within the last 15 years and have a tobacco smoking history of at least 30 pack years [8].

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Despite the positive results of CT screening, issues still remain. In the Nelson trial, only lung cancer-specific mortality was reduced, while all-cause mortality was not significantly different [7]. The false positive rate (i.e. benign nodules) is very high in CT screenings thus causing 40 % of patients in the NLST to have a chest CT showing changes suspected of being lung cancer [6]. Moreover, during the screening program of the Nelson trial, 94 % of new solid nodules turned out to be benign [9] Furthermore, if current U.S. screening criteria were applied, only 9–39 % of patients diagnosed with lung cancer would have been eligible for screening in countries such as Spain and China [10,11]. Finally, over-diagnosis and false-negative CT scans are also potential risks in low-dose CT screening programs [12]. Hence, a comprehensive nodule management program with an integrated malignancy risk tool is wanted [13].

Blood-based biomarkers to detect lung cancer are therefore an appealing alternative. Currently, various molecular candidates such as autoantibodies, complement fragments, microRNAs, DNA methylation and circulating tumor DNA are examined as potential lung cancer specific biomarkers [14]. In this context, a commercially available assay (EarlyCDT® Lung) measuring seven tumor-related autoantibodies (TAA) has been developed for the detection of lung cancer [15]. A meta-analysis performed mostly on case-control studies, found this particular assay to have a pooled sensitivity of 47 % and specificity of 90 % for lung cancer [16]. It has been suggested that such assay could be instrumental for both monitoring high-risk patients, for follow up of patients who have received intended curative treatment, for detection of recurrence and as a screening tool [17].

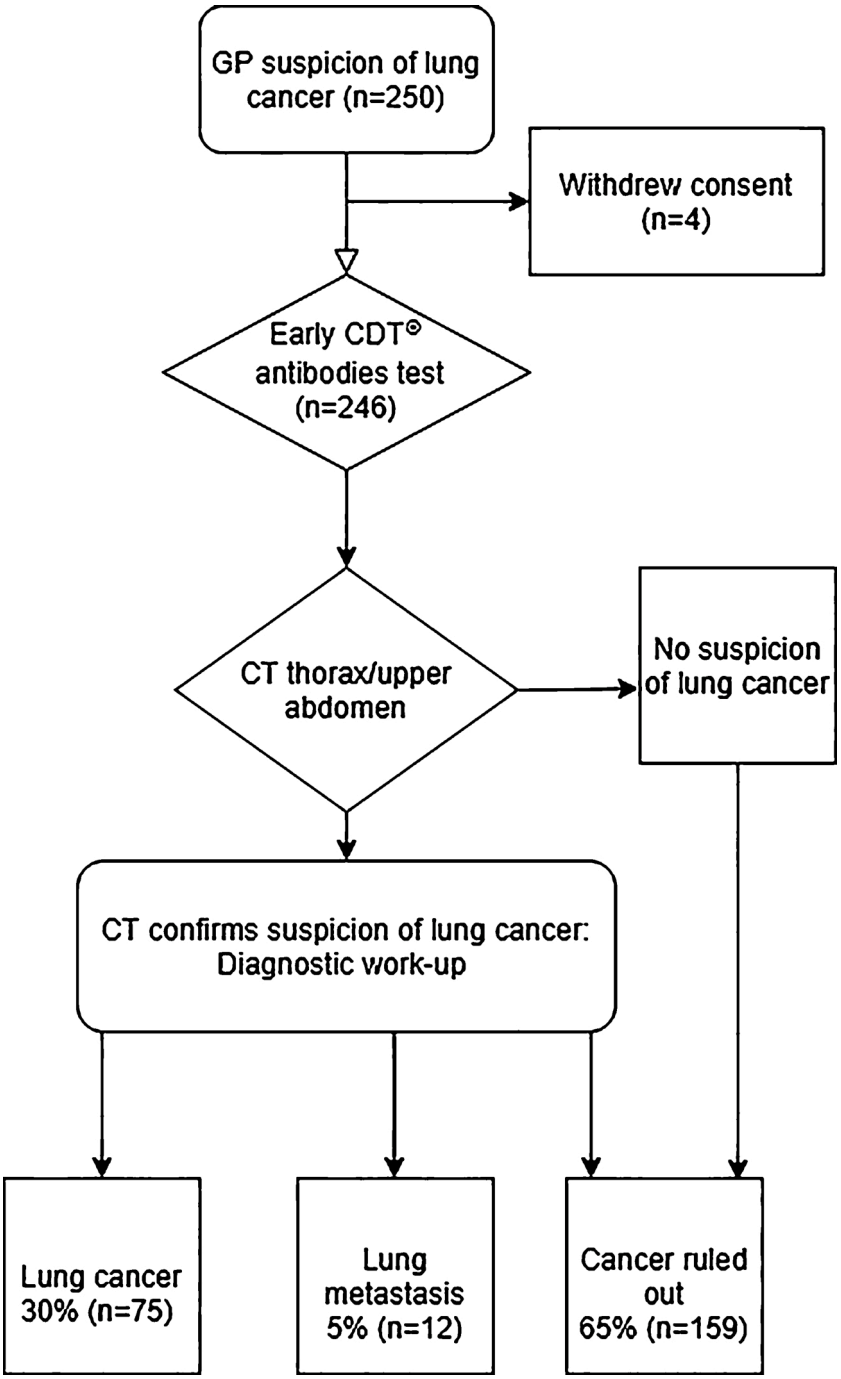

Fig. 1. Flowchart of inclusion and diagnostic work-up of participants.

The purpose of this prospective observational study was to evaluate the performance of the seven-panel TAA assay (EarlyCDT® Lung) in a cohort of patients referred from their general practitioner (GP) on suspicion of lung cancer. The primary aim was to evaluate the ability of the assay to detect cancer in the total cohort. Secondary aims included detection of lung cancer in stage I-II vs stage III-IV, detection of specific histological types of lung cancer and detection of lung cancer in subgroups of age and smoking history, including patients currently eligible for low dose CT screening in USA [8].

2. Materials and methods

2.1. Patient inclusion

In total, 250 patients referred from their GP on suspicion of lung cancer, were included in the study at the Department of Medicine, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark from February 2019 to January 2020. On the first visit blood samples were taken and serum was cryopreserved at −80 °C until analysis of TAA. All patients underwent diagnostic workup as recommended in current international guidelines, resulting in a diagnosis of lung cancer, lung metastasis or ruling out cancer (Fig. 1) [18].

2.2. Subgroups

A number of subgroup analyses were performed in the cohort: Subgroup analysis of male vs female; five subgroup-analyses of patients with a tobacco smoking history of 10+, 20+, 30+, 40+ and 50+ pack years; three subgroup analyses based on age 60 years or below, age 61−75 years and age above 75 years. In addition, a subgroup was formed, consisting of patients eligible for low dose CT screening using current screening criteria (lung cancer subjects and controls aged 55–80 years and with a minimum tobacco history of 30 pack years).

Finally, two subgroup analyses were performed on lung cancer stage I-II vs controls and stage III-IV lung cancer subjects vs controls (IASLC 8th edition [19]). The control group was made up of the enrolled patients were cancer was ruled out.

2.3. Autoantibody detection

Serum samples were analyzed for cancer specific autoantibodies using the seven-panel EarlyCDT® Lung Kit (Oncimmune Ltd, Nottingham, Great Britain). The enzyme-linked immunosorbent assay measuring autoantibodies against p53, SOX2, CAGE, NY-ESO-1, GBU4-5, MAGE A4 and HuD was performed according to manufacturer's recommendations at the Department of Clinical Biochemistry, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark.

The Early-CDT® Lung test uses autoantibody-specific cut-off values, and reports the results as "High level", "Moderate level" or "No Significant level" for every autoantibody. In this study, if any of the autoantibody results were "High" or "Moderate" they were regarded as a positive test, while "No significant level" in all autoantibody tests was treated as a negative result.

2.4. Statistics

Patient characteristics are presented as mean and standard deviations (SD). Sensitivity, specificity, positive predictive value and negative predictive value of the different groups are presented with a 95 % confidence interval. All statistical analyses are performed using R statistical software (Fox & Leanage, 2016).

2.5. Ethics

The study was approved by the Regional Committee on Health Research Ethics in Southern Denmark (ID: S-20180052) and the Danish Data Protection Agency (ID: 18/33058). Subjects gave informed consent to participate.

3. Results

3.1. Patients

A total of 250 patients were included in the study, four withdrew consent, leaving 246 participants. Diagnostic work-up resulted in 30 % (75/246) of patients with a diagnosis of lung cancer, 5% (12/246) with lung metastases originating from primary tumors in other organs and 65 % (159/246) where cancer was ruled out. Characteristics on age, sex and smoking status are presented in Table 1. Lung cancer stage and histologic types are shown in Table 2.

3.2. Performance of EarlyCDT® Lung test

Serum samples from the 246 patients were analyzed using the EarlyCDT® Lung test (Table 3). Sensitivity of the assay for detection of lung cancer was 33 % (25/75). Furthermore, the assay detected autoantibodies in two of the 12 metastatic cancers not originating from the lungs, thus yielding a sensitivity of 31 % (27/87) for detection of any lung malignancy, both primary tumors and metastases. Assay specificity for the detection of both lung cancer specifically and for any malignant diagnosis with lung metastases was 88 %.

The assay was tested in subgroups of patients with different tobacco smoking history (Table 3). Sensitivity of the assay in the subgroup of patients with at least 10 tobacco pack years was 33 % while the sensitivity measured in patients with at least 50 tobacco pack years was 44 %.

In subgroups based on age, the assay yielded a sensitivity of 11 % in patients 60 years or below. When tested in subgroups of patients aged 61−75 and >75 years, the sensitivities were 31 % and 55 %, respectively (Table 3).

The assay was tested in a subgroup of patients that met current CT screening criteria [8], aged 55–80 years and with a minimum of 30 pack years (screening group, Table 3). A total of 83 patients met these criteria, of which 35 (42 %) were diagnosed with lung cancer. Consequently, current CT screening criteria would miss 40 out of 75 (53 %) lung cancer cases in the cohort. Sensitivity and specificity of the assay in this subgroup were 37 % and 81 %, respectively.

Out of 75 lung cancers, 28 (37 %) were diagnosed in stage I-II and 47 (63 %) in stage III-IV. The assay sensitivity of the former was 21 %, while this was 40 % in the latter (Table 3). Specificity was 88 % in both groups.

4. Discussion

The present study evaluated the performance of the EarlyCDT® Lung test on detection of lung cancer in a cohort of 246 participants referred from their GP on suspicion of lung cancer. A total of 75 patients turned out to have lung cancer. The overall sensitivity of the assay was 33 % in the cohort and, if tested in subgroups of patients, differed between 11 %–55 % depending on age, tobacco smoking history and early or late stage disease. Overall specificity of the assay was 88 % and differed between 76 %–94 % in subgroups.

The EarlyCDT® Lung test has previously been tested in high-risk

Table 1
Participants characteristics presented as mean (standard deviation) or per cent.

Variable	All participants	Lung cancer patients	Controls
Age (years)	65 (16)	68(16)	64 (17)
Sex (female/male)	118/128	35/40	83/88
Tobacco pack years	27 (38)	37 (29)	22(40)
Current smokers	55/246 (22 %)	22/75 (29 %)	35/171 (20 %)
Former smokers	133/246 (54 %)	46/75 (61 %)	87/171 (51 %)
Never smokers	58/246 (24 %)	7/75 (9 %)	49/171 (29 %)

Table 2
Lung cancer stage and histologic type.

Lung cancer stage	
Stage I	11/75 (15 %)
Stage II	17/75 (23 %)
Stage III	22/75 (29 %)
Stage IV	25/75 (33 %)
Histologic type	
Adenocarcinoma	52/75 (69 %)
Squamous-cell carcinoma	14/75 (19 %)
Small-cell carcinoma	3/75 (4 %)
Other*	6/75 (8 %)

* Other: Primary lung cancers such as carcinoid tumor, low differentiated carcinoma, non-small-cell lung cancer-not otherwise specified.

Table 3
Performance of the EarlyCDT® Lung test in different subgroups of patients.

Total cohort	Sensitivity; n (95 % CI)	Specificity; n (95 % CI)	PPV	NPV
Lung cancer	0.33; 25/75 (0.23–0.45)	0.88; 150/171 (0.82–0.92)	0.54	0.75
Any malignant tumor	0.31; 27/87 (0.22–0.42)	0.88; 140/159 (0.82–0.93)	0.59	0.70
Smoking history subgroups				
Screening group#	0.37; 13/35 (0.21–0.55)	0.81; 39/48 (0.67–0.91)	0.59	0.64
10+ pack years	0.33; 21/63 (0.22–0.46)	0.86; 80/93 (0.77–0.92)	0.62	0.66
20+ pack years	0.33; 18/54 (0.21–0.47)	0.84; 58/69 (0.73–0.92)	0.62	0.62
30+ pack years	0.34; 15/44 (0.20–0.50)	0.81; 43/53 (0.68–0.91)	0.60	0.60
40+ pack years	0.35; 11/31 (0.19–0.55)	0.76; 31/41 (0.60–0.88)	0.52	0.61
50+ pack years	0.44; 8/18 (0.22–0.69)	0.79; 15/19 (0.54–0.94)	0.67	0.60
Age subgroups				
Age ≤ 60	0.11; 2/18 (0.01–0.35)	0.94; 59/63 (0.85–0.98)	0.33	0.79
Age 61–75	0.31; 11/35 (0.17–0.49)	0.87; 69/79 (0.78–0.94)	0.52	0.74
Age >75	0.55; 12/22 (0.32–0.76)	0.76; 22/29 (0.56–0.90)	0.63	0.69
Lung cancer stage subgroups				
Stage I-II lung cancer	0.21; 6/28 (0.08–0.41)	0.88; 150/171 (0.82–0.92)	0.22	0.87
Stage III-IV lung cancer	0.40; 19/47 (0.26–0.56)	0.88; 150/171 (0.82–0.92)	0.47	0.84
Sex				
Male	0.32; 13/40 (0.19–0.49)	0.86; 76/88 (0.77–0.93)	0.52	0.74
Female	0.34; 12/35 (0.19–0.52)	0.89; 74/83 (0.80–0.95)	0.57	0.76

95 % CI: 95 % confidence interval. #: The screening group consisted of participants aged 55–80 years and with at least 30 tobacco pack years. PPV: Positive predictive value. NPV: Negative predictive value.

cohorts or lung cancer patients matched with control subjects on age, sex and smoking status [20–22]. As seen in Table 3, the TAA assay performs best in heavy smokers, patients older than 75 years and late stage disease; sex does not seem to influence outcome. A study from Chapman et al. [20] found a sensitivity of 47 % in a case control study with lung cancer samples from UK, USA, Ukraine and Russia matched with healthy controls. Mean age was 60 years, 36 % of patients were male and 12 % of patients were non-smokers; total pack-years of patients were not disclosed. These results are in contrast with the current prospective study. In our study the yielded sensitivity was 33 %, even though lung cancer patients were slightly older, diagnosed at a later stage and included approximately the same percentage of non-smokers. The difference seen, could be because of the different study setup.

In an audit of physician-ordered TAA in high-risk patients by Jett et al. [21], the sensitivity of the assay was found to be 37 % (13/35). The study setup resembles the current study, although only a positive TAA resulted in immediate diagnostic work-up. Median age was 61 and male/female ratio 36 %/64 %. Smoking history was not revealed. The results do not differ substantially from the current study, probably because of the similar real-life setup and characteristics of participants.

Recently, the EarlyCDT® Lung test was evaluated in the context of the German Lung Cancer Screening Trial (LUSI) [22]. Sensitivity was found to be as low as 13 %. Control patients were either CT screening participants with a normal CT or benign pulmonary nodules. Inclusion criteria in LUSI were age 50–69 years and long-term smoking (smoking at least 15 cigarettes per day for at least 25 years or smoking at least 10 cigarettes per day for 30 years, including ex-smokers who had stopped smoking not more than 10 years ago). Compared to the current study, patients did not differ considerably in terms of age and smoking history. A possible explanation for the discrepancy in sensitivity is, that participants in LUSI were asymptomatic, and as a result, the majority of lung cancer patients were diagnosed at stage I-II. This is in line with the current study, where the sensitivity in stage I-II was considerably lower than stage III-IV (21 % vs 40 %).

Current screening criteria in USA rely on age and tobacco pack-years [8]. To test the performance of the EarlyCDT® Lung test in a subgroup of participants that would be eligible for low dose CT screening, a subgroup of patients aged 55–80 with a minimum of 30 pack-years was formed. Sensitivity of the EarlyCDT® Lung test did not improve remarkably (37 %) when used in the subgroup. Using current CT screening criteria alone, 47 % of lung cancer cases would be detected in this cohort - where the GP already suspects lung cancer. If screening criteria were supplemented with a positive EarlyCDT® Lung test, the screening would only find 17 % (13/75) of total lung cancer cases. Consequently, the reduction in costs of such a screening program would be considerable, since only 27 % (22/83) of patients currently eligible for CT screening would be included in a screening program with these inclusion criteria.

The primary object of lung cancer screening is to diagnose patients in an early and resectable stage. A recent prospective Scottish trial (ECLS) [23] used a positive EarlyCDT® Lung test as an inclusion criterion for the intervention arm combined with at least 20 tobacco pack-years or an immediate family history of lung cancer. The study managed to find lung cancer in earlier stages (stage I-II 41.1 % in the intervention arm vs 26.8 % in the control), but while the intervention arm received biannual low-dose CT for 2 years, the control arm received standard care (i.e. symptomatic presentation). Thus, the contribution of EarlyCDT® Lung test in a CT screening program remains unclear.

Low-dose CT screening for detection of lung cancer is established in USA, and a range of European countries are currently assessing how best to implement lung cancer screening, with respect to the best fit screening inclusion criteria, participants approach methods and solid nodules management algorithms (23). According to this study, if applying a positive EarlyCDT® Lung test as part of the screening criteria, the screening program would miss a significant number of lung cancer cases. Therefore, its implementation in screening criteria cannot be supported.

4.1. Limitations

The cohort of this study is solely formed on the basis of their GP's suspicion of lung cancer. Thus, lung cancer patients and controls are not matched in risk of lung cancer. Although this is a limitation of the study, it is also a strength, since it may be more applicable in clinical reality. During the diagnostic work-up, indeterminate findings were followed up for at least a year, to minimize subsequent development of lung cancer.

5. Conclusions

In this study we found that the EarlyCDT® Lung test in a high-risk cohort, based on GP suspicion of lung cancer, detected 33 % of total lung cancer cases and only 21 % of stage I-II lung cancer cases. In patients under the age of 60, sensitivity was as low as 11 %. In patients fulfilling the current lung cancer CT screening criteria of age and smoking, the EarlyCDT® Lung test would only detect 17 % of lung cancer cases. Contrary to the rationale of screening, the EarlyCDT® Lung test primarily found late stage lung cancers in elderly, heavy smokers. In conclusion, based on the results from the cohort, this study finds insufficient sensitivity of the EarlyCDT® Lung test to be used as part of rule-in screening criteria in a low dose CT screening program.

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Transparency document

The Transparency document associated with this article can be found in the online version.

CRediT authorship contribution statement

Morten Borg: Formal analysis, Conceptualization, Writing - original draft. **Sara W.C. Wen:** Resources, Writing - review & editing. **Line Nederby:** Resources, Writing - review & editing. **Torben Frøstrup Hansen:** Conceptualization, Resources, Writing - review & editing. **Anders Jakobsen:** Conceptualization, Resources, Writing - review & editing. **Rikke Fredslund Andersen:** Resources, Writing - review & editing. **Ulla Møller Weinreich:** Supervision, Project administration, Writing - review & editing. **Ole Hilberg:** Conceptualization, Project administration, Supervision, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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