LUCA

LUng Cancer-related risk factors and their Impact Assessment

HORIZON-MISS-2021-CANCER-02

LUCIA Workshop – Understanding Lung Cancer

San Sebastian, Sept. 5th, 2023

Prof Dr Julien Guiot

CHU Liège, Belgium

European Commission

Diagnosis and staging of isolated pulmonary nodule & AI

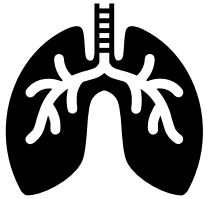
Julien Guiot (MD, PhD)
University Hospital of Liège (CHU Liège)

Some introduction

LUCIA Workshop – Understanding Lung Cancer

LUng Cancer-related risk factors and their Impact Assessment

Lung cancer (LC) is the biggest cancer killer worldwide



- Two large randomized controlled trials have established the efficacy of LC Screening (LCS) using **low-dose computed tomography (LDCT)** in cigarette smokers

- Five-year survival rate in the National Lung Screening Trial (NLST) and the NELSON trial, respectively.

Some introduction

LUCIA Workshop – Understanding Lung Cancer

- US Preventive Services Task Force recommends annual LDCTs for those aged 50 years and older with a 20 pack-year history of smoking
- Evidence also suggests those being screened are not being optimally routed or kept engaged in long term follow-up
- What about never and lighter-smokers ?

NLST and Nelson studies comparison

LUCIA Workshop – Understanding Lung Cancer

LUCA
LUng Cancer-related risk factors and their Impact Assessment

Study	**NLST**	**Nelson**
Country	United States	Belgium, The Netherlands
Control group	Chest scan	No screening
Frequency	0-1-2 years	0-1-3-5 years
Help in smoking cessation	No	Advised at inclusion ± weaning with expert centres
Aim	LC mortality	LC mortality
Age inclusion	55-74 yo	55-75 yo
Smoking min. cons.	30 PY	15 cig/d min 25 years 10 cig/d min 30 years
Maximum weaning time	15 years	15 years
Exclusion criteria	ATCD CP ATCD cancer less than 5 years	ATCD CP less than 5 years ATCD cancer
Number of patients + control group	26723 26733	7915 7907
1st round detection rate	1%	0,9%
Stages I and II proportion	70%	70,8%
Surgery rate	61%	Not specified
Overall mortality reduction	RR 0,97 [0,94-1,01]	M: RR 1,01 [0,92-1 ,11]
Specific mortality reduction	RR 0,92 [0,85-1]	M: RR 0,76 [0,61-0,94] F: RR 0,67 [0,38-1,14]

Key aspects in nodule identification

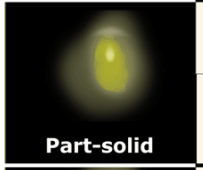
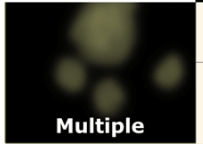
1. Early nodule identification – key objective for patients at risk of lung cancer
2. Radiologist expertise
3. Cinetic artifact
4. Vascular *versus* tissular
5. Longitudinal follow up quantification
6. Determination of the need of biological sampling

Lung nodules

LUCIA Workshop – Understanding Lung Cancer

- Micronodules: <3-4mm
- Lung-Rads for prediction of malignancy
- Fleischner recommendation for follow up
- Volume doubling time

Solid	Size	Follow up		
	< 6 mm (<100mm^3)	Single	Low risk High risk	No routine follow Optional CT at 12 months
		Multiple	Low risk High risk	No routine follow Optional CT at 12 months
	6-8 mm (100-250mm^3)	Single	Low risk High risk	CT at 6-12 mo, then consider CT at 18-24 CT at 6-12 mo, then CT at 18-24
		Multiple	Low risk High risk	CT at 3-6 mo, then consider CT at 18-24 CT at 3-6 mo, then CT at 18-24
	> 8 mm (> 250mm^3)	Single	All	Consider CT at 3 mo, PET/CT or Biopsy
		Multiple	Low risk High risk	CT at 3-6 mo, then consider CT at 18-24 CT at 3-6 mo, then CT at 18-24

Subsolid	Size	Follow up
 Groundglass	< 6 mm	No FU indicated
	≥ 6 mm	CT at 6-12 months to confirm persistence, then CT at 3 and 5 years
 Part-solid	< 6 mm	No FU indicated
	≥ 6 mm	CT at 3-6 months to confirm persistence, then annual CT for 5 years
 Multiple	< 6 mm	CT at 3-6 months. If stable CT at 2 and 4 years
	≥ 6 mm	CT at 3-6 months. Subsequent management based on most suspicious nodule

Clinical research tools for malignancy definition

LUCIA Workshop – Understanding Lung Cancer

LUng Cancer-related risk factors and their Impact Assessment

Chen et al. (2018) [7]	- 750 extracted features, among which 76 relevant features were selected - 4-feature signature - Aim: nodule characterization	33 benign CT 42 malignant CT	Benign vs. malignant Accuracy 84% Sensitivity 92.85% Specificity 72.73%
De Koning et al. (2020) [9]	- 15,792 patients, divided into a screening group (T0–T1 year–T2 years–T3 years) and a no-screening group - Follow-up of 10 years - Aim: nodule characterization through volume and VTD	15,792 patients	Benign vs. malignant: impact on mortality At 10 years, cancer mortality = 2.5 deaths/100,000 persons/years (screening group) vs. 3.3 deaths/100,000 (no-screening group) Cumulative ratio 0.76 (p = 0.01)
Ma et al. (2016) [10]	- 583 extracted features - Random forest classifier - Aim: nodule characterization	36 benign CT 94 malignant CT	Benign vs. malignant Accuracy 82.7% Sensitivity 80% Specificity 85.5%
Hawkins et al. (2016) [11]	- 219 extracted features, among which 23 showed concordance correlation > 0.95 - Aim: nodule characterization	328 benign CT 170 malignant CT	Benign vs. malignant Accuracy 80%
Huang et al. (2018) [12]	- 1108 extracted features - Aim: nodule characterization	Training cohort 70 benign CT 70 malignant CT Validation cohort 26 benign CT 20 malignant CT	Benign vs. malignant Accuracy 91% Sensitivity 95% Specificity 88%
Uthoff et al. (2020) [13]	- Extracted features from nodule and perinodular parenchyma tissue - Aim: nodule characterization	Training cohort 289 benign CT 74 malignant CT Validation cohort 50 benign CT 50 malignant CT	Benign vs. malignant Accuracy 98% Sensitivity 100% Specificity 96%
Mao et al. (2019) [14]	- 385 extracted features - Comparison of radiomic model versus model of ACR Lung-RADS - Aim: nodule characterization	Training cohort 156 benign CT 40 malignant CT Validation cohort 75 benign CT 23 malignant CT	Benign vs. malignant Accuracy 89.8% Sensitivity 81% Specificity 92.2%
Maldonado et al. (2021) [18]	- 8-feature signature - Aim: to validate the BRODERS classifier (benign versus aggressive nodule evaluation using radiomic stratification) as a HRCT-based classifier for indeterminate pulmonary nodules	Validation cohort 91 malignant CT 79 benign CT	Benign vs. malignant AUC 0.90 Sensitivity 92.3% Specificity 62%
Mehta et al. (2021) [22]	- 1018 nodule CTs, malignancy rating from 1 to 5 according to volume - Fully supervised and semi-supervised classifiers - Aim: to reach an hybrid algorithm to estimate nodule malignancy by combining imagery and biomarkers/volumetric radiomic features	1018 CTs Malignancy rating from 1 to 5	Benign vs. malignant AUC 0.87 on fully supervised 3D CNN + random forest model (images, biomarkers and volumetric features) AUC 0.93 on semi-supervised random forest (biomarkers only)
Digumarthy et al. (2019) [24]	- 92 extracted features - 2 significant features at baseline - 52 significant features at follow-up - Aim: nodule characterization according to temporal changes	31 benign CT 77 malignant CT	Benign vs. malignant according to temporal changes AUC 0.741
Lee et al. (2014) [16]	- Clinical, thin-section CT and texture features - Aim: prediction of transient vs. persistent pattern of nodule	Transient PSNs 39 benign CT Persistent PSNs 17 benign CT 30 malignant CT	Prediction of persistent part-solid nodules AUC 0.93 if texture analysis was combined to clinical and CT features
Autrusseau et al. (2021) [17]	- >1000 extracted features - Aim: to compare quantitative and qualitative concordance of pulmonary nodule risk assessment by radiomic software between full-dose (FD) chest CT and ultra-low-dose (ULD) chest CT	99 lung nodules - FD chest CT imaging - ULD chest CT imaging	Concordance between FD and ULD chest CT in radiomic-guided nodule risk assessment ICC of 0.82, displaying a good agreement in malignancy similarity index between ULD and FD chest CT

SS ranging from 80% to 100% for a specificity of 72% to 96%

Frix et al. j pers. Med. 2021

Clinical research tools for malignancy definition: CAD

CAD (Computer Aided Detection or Diagnosis)
-> combining elements of artificial intelligence with radiological and pathology image processing

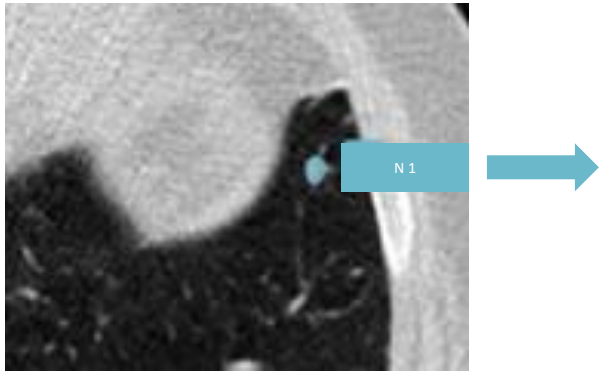
Aiming to assist in the detection and/or diagnosis of diseases by improving the accuracy of scan analysis

Key points:

1. CAD performance is high in detecting any type of pulmonary nodule
2. CAD assists and improves RAD's performance as a second reader

Clinical research tools for malignancy definition: CAD

LUCIA Workshop – Understanding Lung Cancer



Lung - RADS

LUCIA Workshop – Understanding Lung Cancer

LUCA

LUng Cancer-related risk factors and their Impact Assessment

Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Probably Suspicious Findings for which additional diagnostic testing is recommended	4A	**Solid nodule(s):** ≥ 8 to < 15 mm at baseline **OR** growing < 8 mm **OR** new 6 to < 8 mm	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm solid component	5-15%	2%
		Part solid nodule(s): ≥ 6 mm with solid component ≥ 6 mm to < 8 mm **OR** with a new or growing < 4 mm solid component			
		Endobronchial nodule			
Suspicious Findings for which additional diagnostic testing and/or tissue sampling is recommended	4B	**Solid nodule(s)** ≥ 15 mm **OR** new or growing, and ≥ 8 mm	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm solid component. *For new large nodules that develop on an annual repeat screening CT, a 1 month LDCT may be recommended to address potentially infectious or inflammatory conditions*	> 15%	2%
		Part solid nodule(s) with: a solid component ≥ 8 mm **OR** a new or growing ≥ 4 mm solid component			
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)	S	**Modifier - may add on to category 0-4 coding**	As appropriate to the specific finding	n/a	10%
Volumetric measurements	1.5 mm = 1.8 mm^3 4 mm = 33.5 mm^3 6 mm = 113.1 mm^3 8 mm = 268.1 mm^3		10 mm = 523.6 mm^3 15 mm = 1767.1 mm^3 20 mm = 4188.8 mm^3 30 mm = 14137.2 mm^3		

Volume Doubling Time

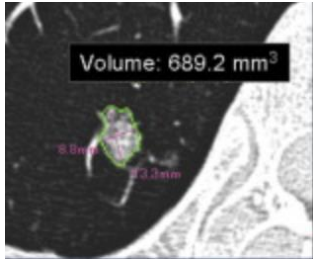
LUCIA Workshop – Understanding Lung Cancer

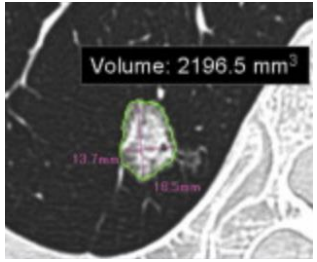
LUCA
LUng Cancer-related risk factors and their Impact Assessment

The **volume doubling time** (**VDT**) is defined as the time required for a growing nodule to double its volume.

Key points:

1. A longer VDT suggests a more benign course, whilst a short VDT is indicative of a more aggressive lesion with higher histological grade
2. A VDT below 400 days represents a high likelihood of malignancy, whereas a VDT above 500 days is overwhelmingly characteristic of a benign nodule

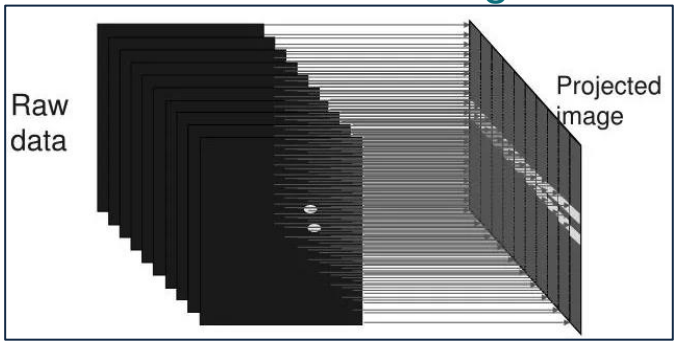




Maximum Intensity Projection

LUCIA Workshop – Understanding Lung Cancer

Maximum Intensity Projection (MIP) consists of projecting the voxel with the highest attenuation value on every view throughout the volume onto a 2D image

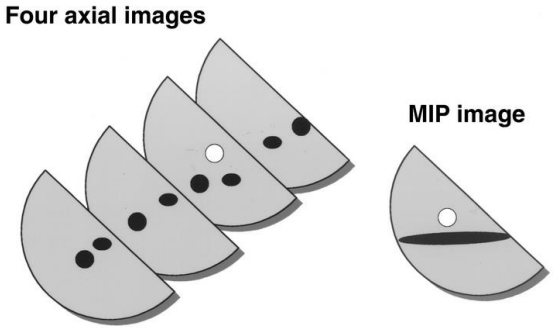


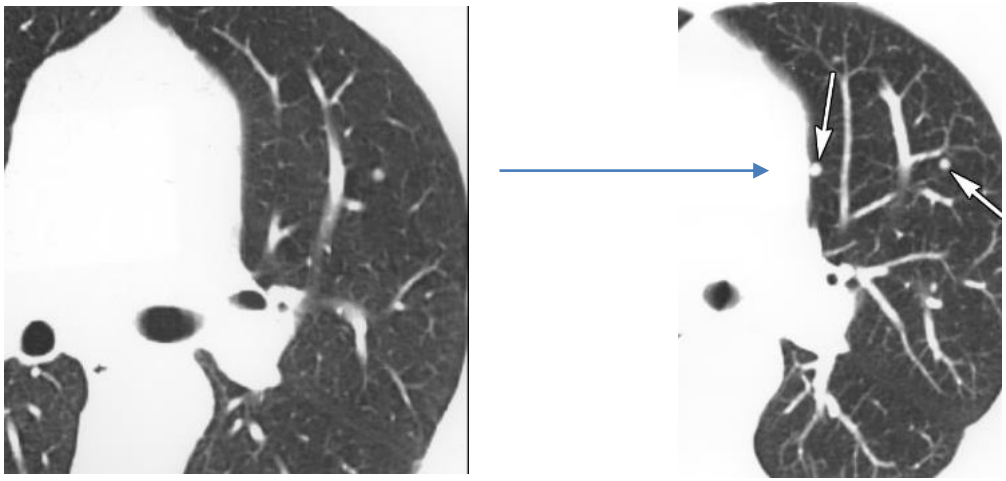
Key points:

1. The primary clinical application of MIP is to **improve the detection of pulmonary nodules** and assess their perfusion
2. MIP also helps characterize the **distribution of small nodules**.
3. Also, MIP sections of variable thickness are excellent for **assessing the size and location of vessels**, including the pulmonary arteries and veins

Maximum Intensity Projection

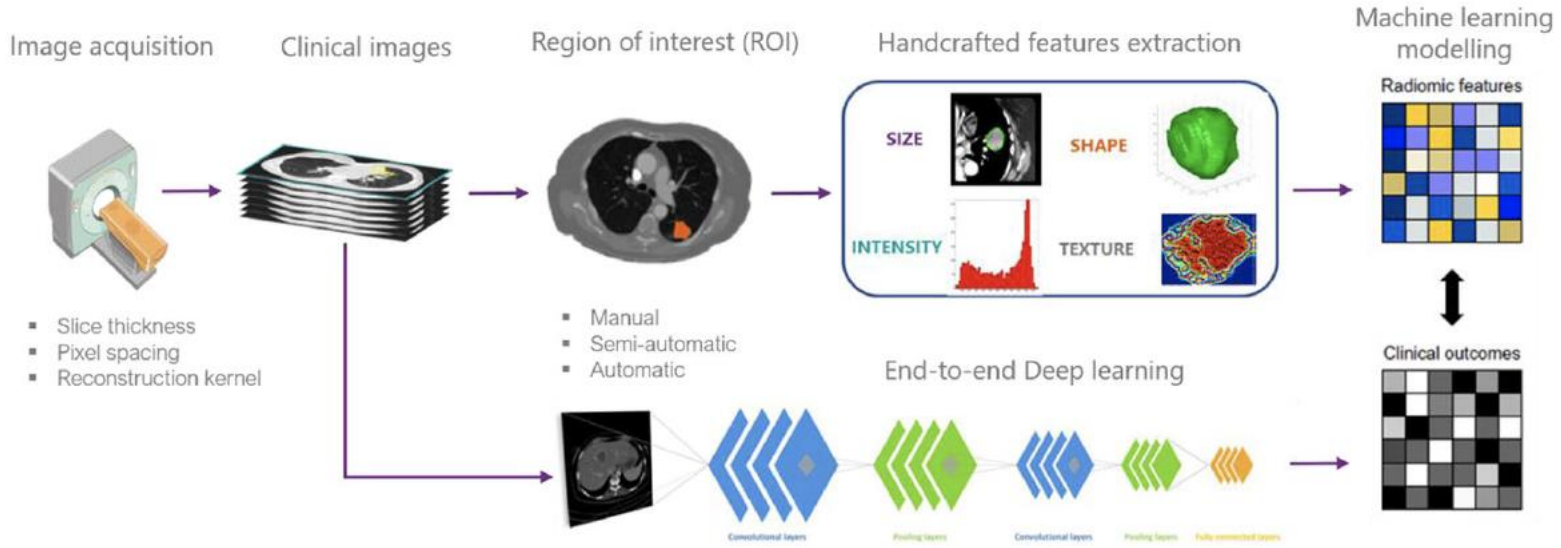
LUCIA Workshop – Understanding Lung Cancer





Nodule qualification

LUCIA Workshop – Understanding Lung Cancer



Guiot et al. Medicinal RR 2021

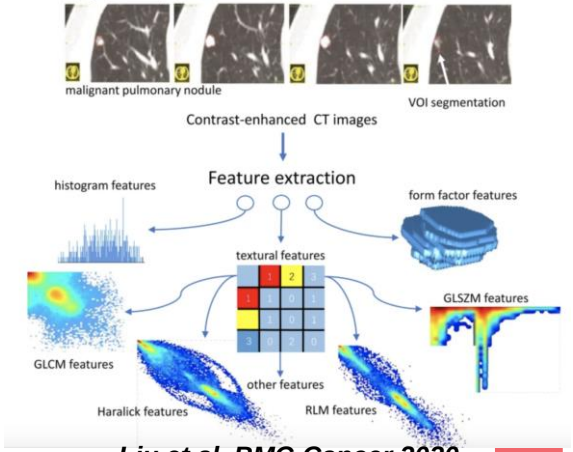
Clinical Research Tools: nodule qualification

LUCIA Workshop – Understanding Lung Cancer

LUCA

LUng Cancer-related risk factors and their Impact Assessment

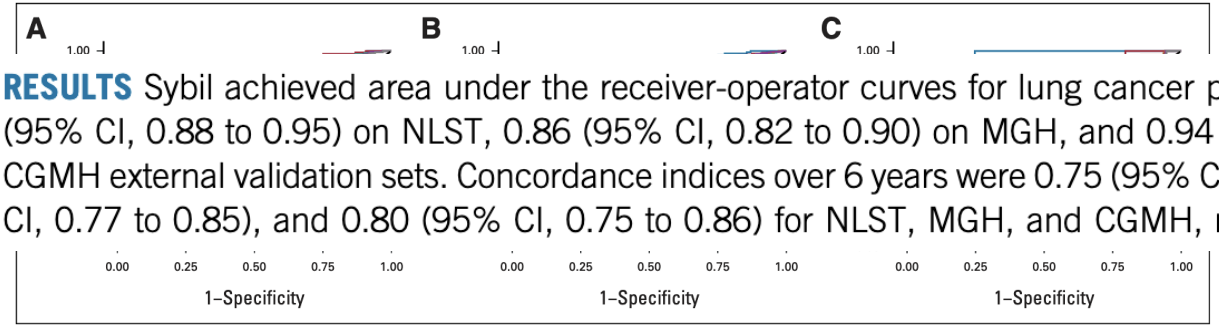
Liu et al. (2016) [36]	- 219 extracted radiomic features, among which 59 robust features were selected - Aim: search for correlation with EGFR mutation status in adenocarcinomas	298 malignant CT	Prediction of mutation status AUC EGFR+ status prediction 0.647, improved to 0.709 when adding a clinical model
Rios Velasquez et al. (2017) [37]	- 26 relevant features selected - Aim: search for correlation with KRAS and EGFR mutation status in adenocarcinomas	Training cohort 353 malignant CT Validation cohort 352 malignant CT	Prediction of mutation status AUC EGFR + versus EGFR− status 0.70 AUC KRAS + versus KRAS− status 0.63 AUC EGFR+ versus KRAS+ status 0.80
Tang et al. (2018) [39]	- Pathology markers studied: CD3 count and %PDL1 - 490 extracted features, among which 12 robust features were selected, then targeted into 4 features to generate 4 clusters (immune-pathology informed model) - Aim: to predict immune modulator status in NSCLC	Training cohort 114 malignant CT Validation cohort 176 malignant CT	Prediction of immune modulator status Favorable outcome in low CT intensity and high heterogeneity with low PDL 1 and high CD3
Wu et al. (2020) [40]	- 18 relevant features selected - Comparison of radiomic models (ground-glass and solid features) with other models (Brock model, clinical semantic and volumetric models) - Aim: to predict invasiveness of lung adenocarcinoma by using ground-glass and solid features from part-solid nodules	Training cohort 229 NSCLC Validation cohort 68 NSCLC	Prediction of invasiveness AUC 0.98 for the model combining ground-glass and solid features Improvement of 0.14 in AUC when adding ground-glass radiomic features to solid features
Coroller et al. (2015) [41]	- 445 extracted features, among which 35 relevant features were selected - Aim: to determine the capability of radiomic analysis to predict distant metastasis	Training cohort 98 malignant CT Validation cohort 84 malignant CT	Prediction of distant metastasis A multivariate radiomic signature (3 features) yielded a high prognostic performance for distant metastasis (CI 0.61)
Coroller et al. (2016) [49]	- 15 relevant radiomic features selected - Aim: to assess if radiomics can predict response after neoadjuvant chemoradiation (NCT) in locally advanced NSCLC	127 malignant CT Training cohort 80% Validation cohort 20%	Prediction of response after NCT AUC for pathologic gross residual disease prediction (7 features) > 0.6 AUC for pathologic complete response (1 feature) 0.63 AUC for poor response 0.63 (spherical disproportionality) or 0.61 (heterogeneous texture)
Kim et al. (2017) [50]	- 37 relevant radiomic features selected - Aim: to determine if radiomic features combined to conventional clinical features improved predictive performance in prediction of PFS in EGFR+ adenocarcinoma	48 malignant CT (NSCLC, EGFR mutant)	Prediction of response to TKI - Addition of radiomics to clinical factors improved predictive performance of response to TKI (concordance index: combined model 0.77, clinical model 0.69; $p < 0.0001$)
Lafata et al. (2019) [52]	- 39 extracted features - Aim: to verify the hypothesis that lung texture, in addition to lung density, is partly responsible for correlation between PFT and CT imaging	64 malignant CT (NSCLC)	Prediction of PFTs - Higher DLCO correlated with dense, heterogeneous pulmonary tissue ($p < 0.002$) - Lower FEV1 correlated with homogeneous, low attenuating pulmonary tissue ($p < 0.03$)



Liu et al. BMC Cancer 2020

Sybil: A Validated Deep Learning Model to Predict Future Lung Cancer Risk From a Single Low-Dose Chest Computed Tomography

Peter G. Mikhael, BSc[1,2]; Jeremy Wohlwend, ME[1,2]; Adam Yala, PhD[1,2]; Ludvig Karstens, MSc[1,2]; Justin Xiang, ME[1,2]; Angelo K. Takigami, MD[3,4]; Patrick P. Bourgouin, MD[3,4]; PuiYee Chan, PhD[5]; Sofiane Mrah, MSc[4]; Wael Amayri, BSc[4]; Yu-Hsiang Juan, MD[6,7]; Cheng-Ta Yang, MD[6,8]; Yung-Liang Wan, MD[6,7]; Gigin Lin, MD, PhD[6,7]; Lecia V. Sequist, MD, MPH[3,5]; Florian J. Fintelmann, MD[3,4]; and Regina Barzilay, PhD[1,2]



RESULTS Sybil achieved area under the receiver-operator curves for lung cancer prediction at 1 year of 0.92 (95% CI, 0.88 to 0.95) on NLST, 0.86 (95% CI, 0.82 to 0.90) on MGH, and 0.94 (95% CI, 0.91 to 1.00) on CGMH external validation sets. Concordance indices over 6 years were 0.75 (95% CI, 0.72 to 0.78), 0.81 (95% CI, 0.77 to 0.85), and 0.80 (95% CI, 0.75 to 0.86) for NLST, MGH, and CGMH, respectively.

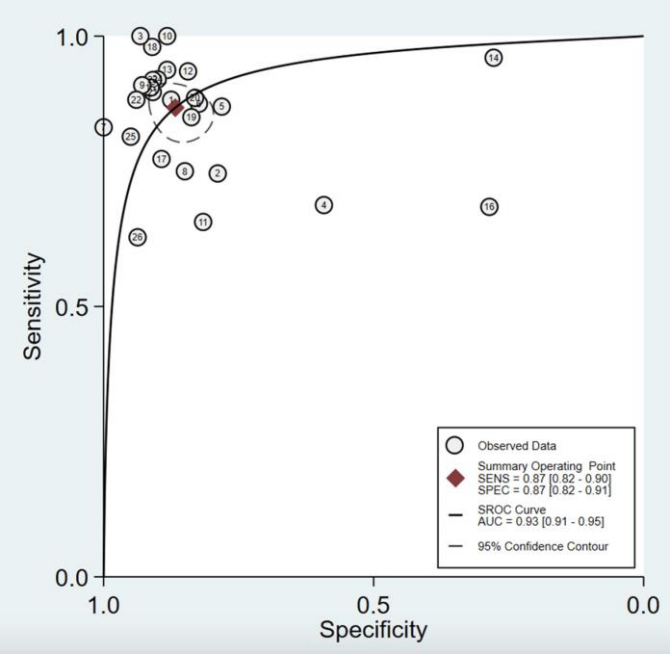
FIG 2. Receiver operating characteristic curves displaying Sybil's ability to predict future lung cancer over 6 years following a single low-dose computed tomography from the (A) NLST, (B) MGH, and (C) CGMH test sets. CIs for each curve can be found in Table 1. AUC, area under the curve; C-index, concordance index; CGMH, Chang Gung Memorial Hospital; MGH, Massachusetts General Hospital; NLST, National Lung Screening Trial.

Sensitivity and specificity of AI-aided diagnosis for lung cancer diagnosis

LUCIA Workshop – Understanding Lung Cancer

LUCA

LUng Cancer-related risk factors and their Impact Assessment



Liu et al. PONE 2023

Take home message

LUCIA Workshop – Understanding Lung Cancer

- Identification is firstly clinician-dependant
- Computer-based automatized tools (CAD) for detection
- Add-on value of MIP reconstruction
- Size-based approach for patient monitoring
- Volume doubling time and algorithm for risk stratification
- Lung-RADS useful but difficult to use in daily practice
- Need for implementation of integrated models including risk-based approach but also imaging-based
- Need for validation of texture-based models including risk of neoplasia but also classifier predicting histology

LUCA

LUng Cancer-related risk factors and their Impact Assessment

HORIZON-MISS-2021-CANCER-02

LUCIA Workshop – Understanding Lung Cancer

San Sebastian, Sept. 5th, 2023

Prof Dr Julien Guiot

CHU Liège, Belgium

European Commission