POSTERDISCUSSION

BIOMARKERS FOR TREATMENT OF ADVANCED DISEASE AND EARLY DETECTION OF LUNG CANCER

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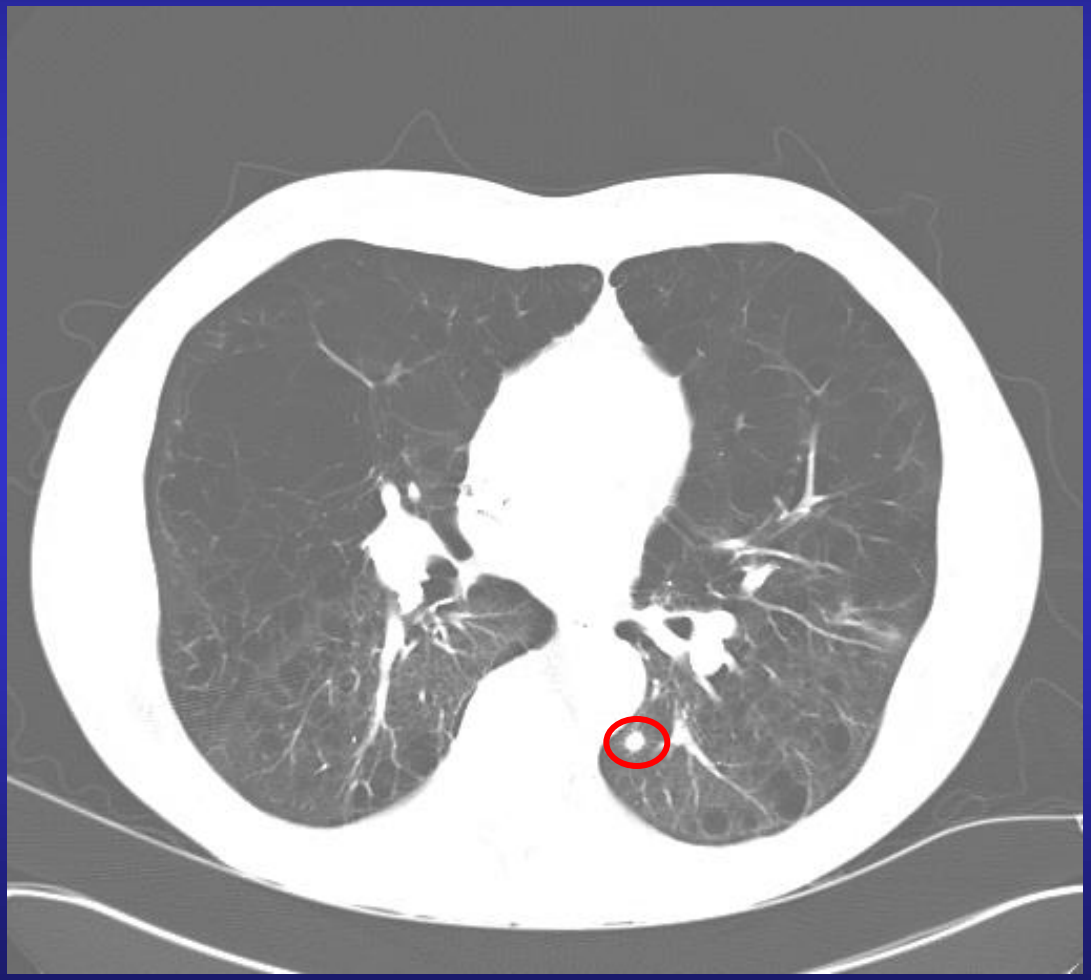
Asymptomatic CT Detected Lung Nodule



False positives in UKLS; NLST NELSON

In the UKLS, we defined false positives as those requiring further diagnostic investigation more immediately than a repeat annual screen, but who subsequently did not have lung cancer.

- **The UKLS False positive rate was 3.6%** and the interval imaging rate was 23.2%.

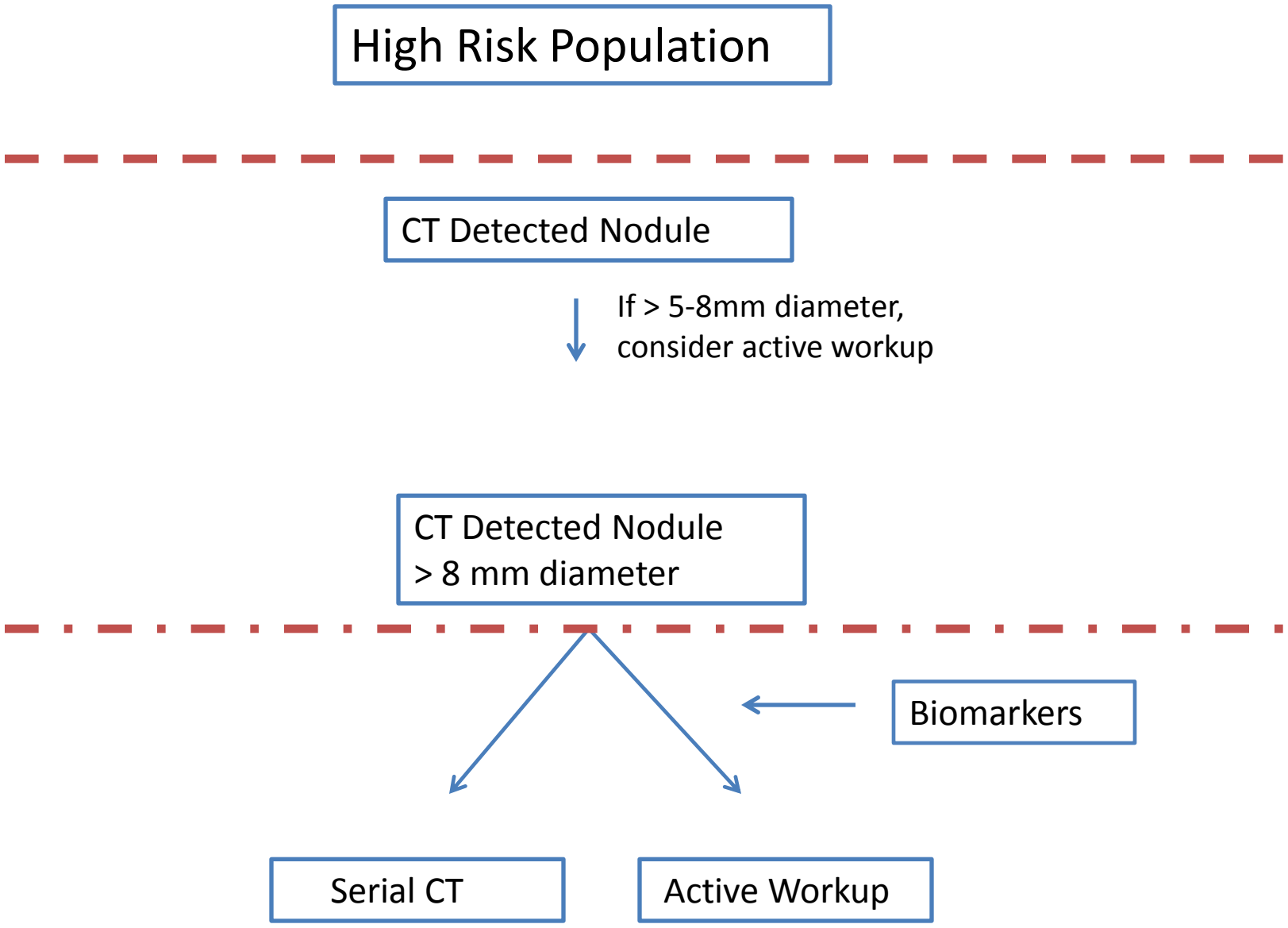
- In NLST, a CT was regarded as positive if it showed any non-calcified nodule at least 4mm in diameter (i).
- The overall false positive rate for the CT screening arm in NLST was 23.3%.

- In the NELSON trial lung nodules with a volume >500 mm^3 or those with a volume-doubling time <400 days, were regarded as positive tests.
- **3.6% of all NELSON participants** (273 out of 7,582) had a false–positive screening result (ii).

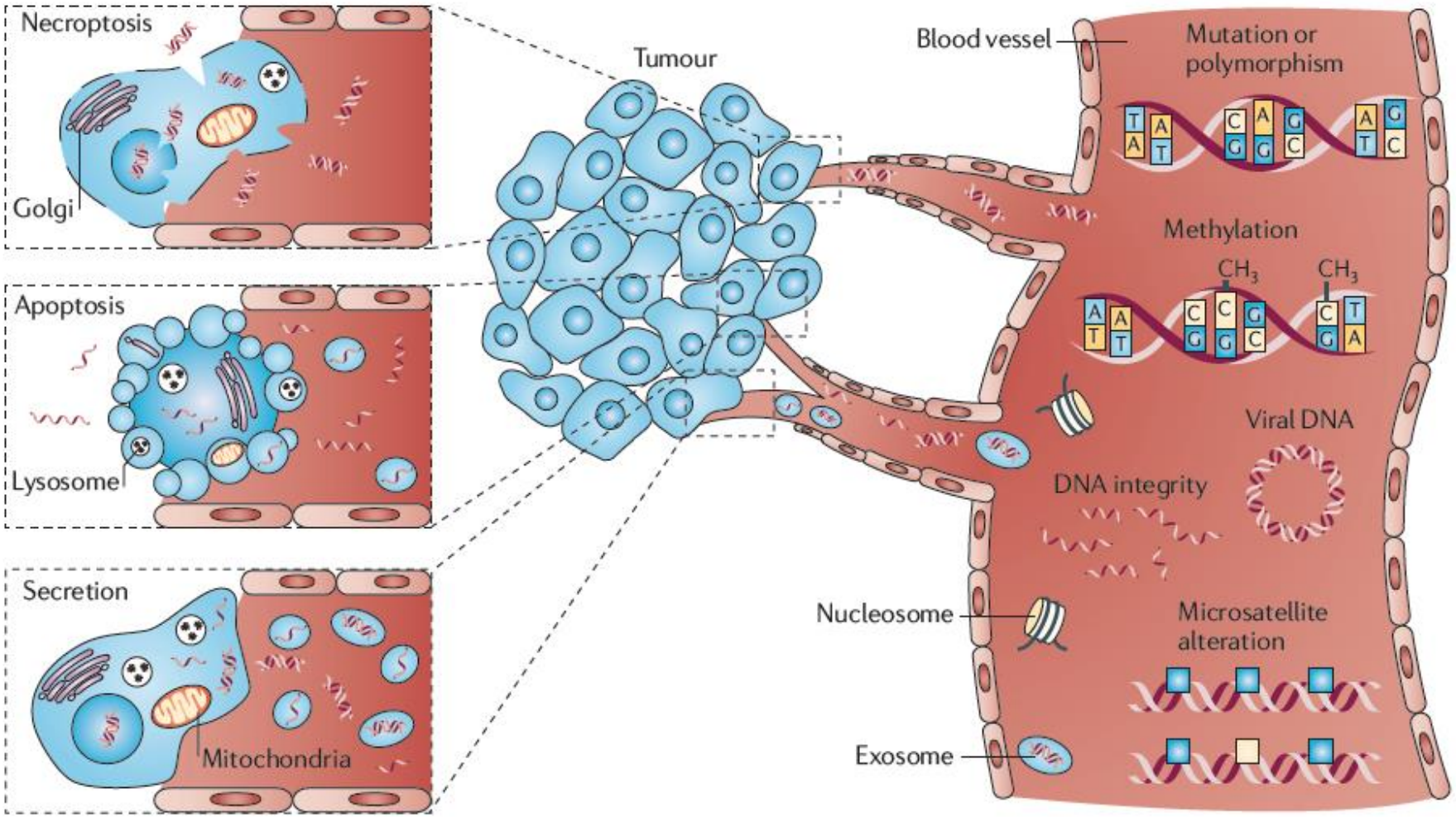
(i) N Engl J Med .2011; 365: 395-409.
(ii) Eur Respir J. 2013; 42: 1659-1667.

Need for Biomarkers for Early Detection of Lung Cancer

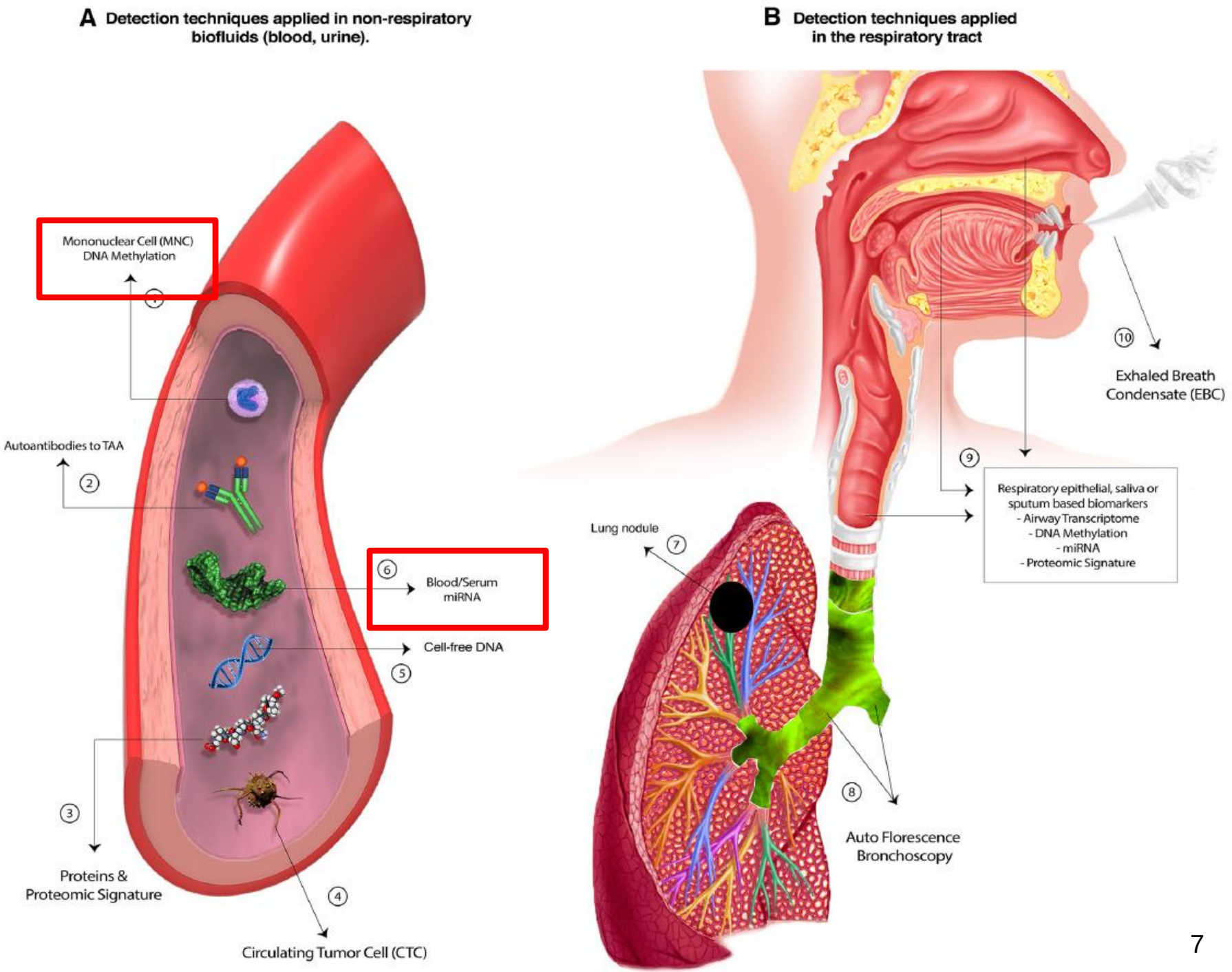
- Risk assessment
- Undetermined CT scan detected nodules (20%)
- “False- positive” nodules (3-5%)


High Risk Population
CT Detected Nodule
If > 5-8mm diameter,
consider active workup
CT Detected Nodule
> 8 mm diameter
Biomarkers
Serial CT
Active Workup

Cell Free NA in blood (Liquid Biopsy)



(Nat Rev Cancer 2011;11:426)


A Detection techniques applied in non-respiratory biofluids (blood, urine).
Mononuclear Cell (MNC)
DNA Methylation
1
Autoantibodies to TAA
2
6
Blood/Serum
miRNA
Cell-free DNA
5
3
Proteins &
Proteomic Signature
4
Circulating Tumor Cell (CTC)
B Detection techniques applied in the respiratory tract
10
Exhaled Breath
Condensate (EBC)
9
Respiratory epithelial, saliva or
sputum based biomarkers
- Airway Transcriptome
- DNA Methylation
- miRNA
- Proteomic Signature
Lung nodule
7
8
Auto Florescence
Bronchoscopy

Novel plasma circulating microRNA signature for early detection of non-small cell lung cancer in liquid biopsy

30PD

Tomasz Powrózek, Paweł Krawczyk, Barbara Kuźnar-Kamińska, Dariusz Kowalski, Kinga Winiarczyk, Marta Olszyna-Serementa, Halina Batura-Gabryel, Janusz Milanowski

Introduction

Significant difference in microRNAs (miRNAs) expression is frequently observed between cancer patients and healthy individuals. Moreover, possibility of miRNAs detection in blood samples (liquid biopsy) make them valuable biomarkers of early stage tumor development, including non-small cell lung cancer (NSCLC).

Matherial and methods

The aim of the study was evaluation of novel circulating miRNAs-448,506,944,3662,4316 and 4478 as biomarkers of early stage NSCLC development. miRNAs expression was analysed in plasma samples of 80 NSCLC patients (45 patients in stage I-IIIA and 35 patients in stage IIIB-IV) and 80 healthy individuals using qRT-PCR method. The diagnostic accuracy of studied biomarkers was assessed using logistic regression model and receiver operating curves (ROC) with area under curve (AUC) analysis.

Results

Significantly higher expression of miRNA-448, 944, 3662 and 4478 was detected in plasma of lung cancer patients compared with healthy individuals ($p<0.0001$). Combined analysis of 4-miRNAs signature demonstrated high diagnostic power for detection of operable stages (I-IIIA) of NSCLC with sensitivity of 84.8% and specificity of 96.6% (AUC=0.930). Moreover, miRNA-944 expression demonstrated diagnostic accuracy for detection of operable squamous cell carcinoma (sensitivity: 85.7% and specificity: 90.3%; AUC=0.982), while miRNA-3662 expression- for operable adenocarcinoma (sensitivity: 82.4%; specificity: 93.5%; AUC=0.926). Expression of miRNAs-506 and 4316 showed no diagnostic value in NSCLC patients.

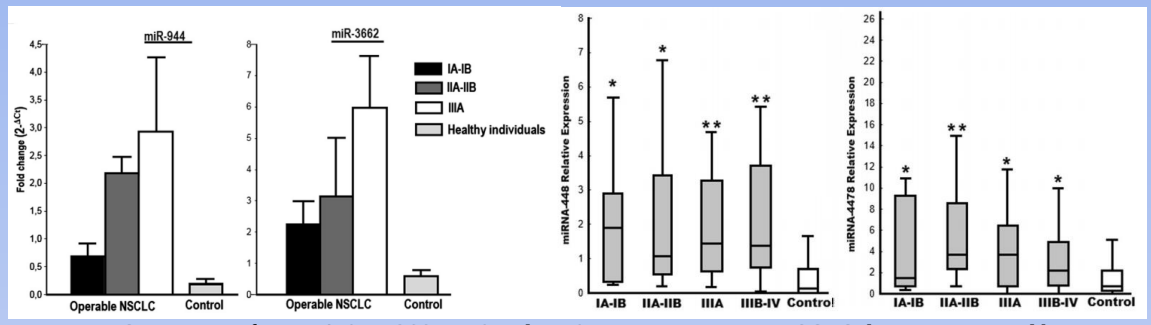


Figure 1. Comparson of miRNA-944, 3662, 448 and 4478 expression among NSCLC disease stages and between NSCLC patients and healthy individuals

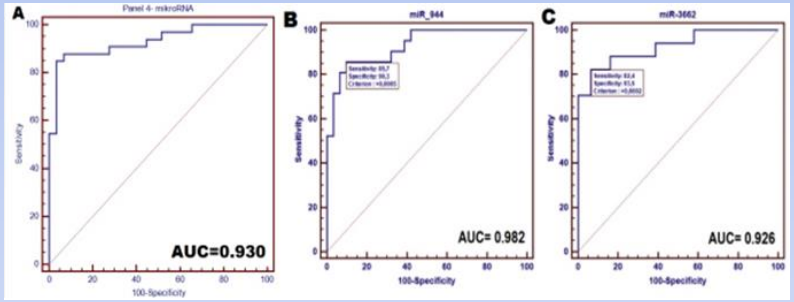


Figure 2. ROC analysis wit AUC:
A – 4 miRNA signature for stage I-IIIA of NSCLC
B- miRNA-944 for detection of squamous cell carcioma operable stages
C- miRNA-3662 for detection of adenocarcinoma operable stages

Conclusions

Novel signature of 4 circulating miRNAs may be considered as valuable diagnostic tool which could improve non-invasive diagnosis of NSCLC or complements CT lung screening. Moreover, miRNA-944 may be considered as marker of early differentiation of squamous cell carcinoma, whereas miRNA-3662 as early adenocarcinoma marker.

Novel plasma circulating microRNA signature for early detection of non-small cell lung cancer in liquid biopsy

Purpose of the study:

- Investigation of novel miRNAs in NSCLC patients as tumor biomarkers using liquid biopsy technique
- miRNAs selected for the study (miRNA-448, 506, 944, 3662, 4316, 4478) were not previosuly investigated as NSCLC biomarkers
- Designation of miRNAs signature with high diagnostic accuracy for detection of NSCLC operable stages (I-IIIA)
- 80 NSCLC patients (45 with stage I-IIIA and 35 with stage IIIB-IV) and 80 healthy individuals without lung disorders were enrolled to the study

miRNAs expression was assessed in plasma samples using qRT-PCR method with taqman probes againts studied molecules

Results:

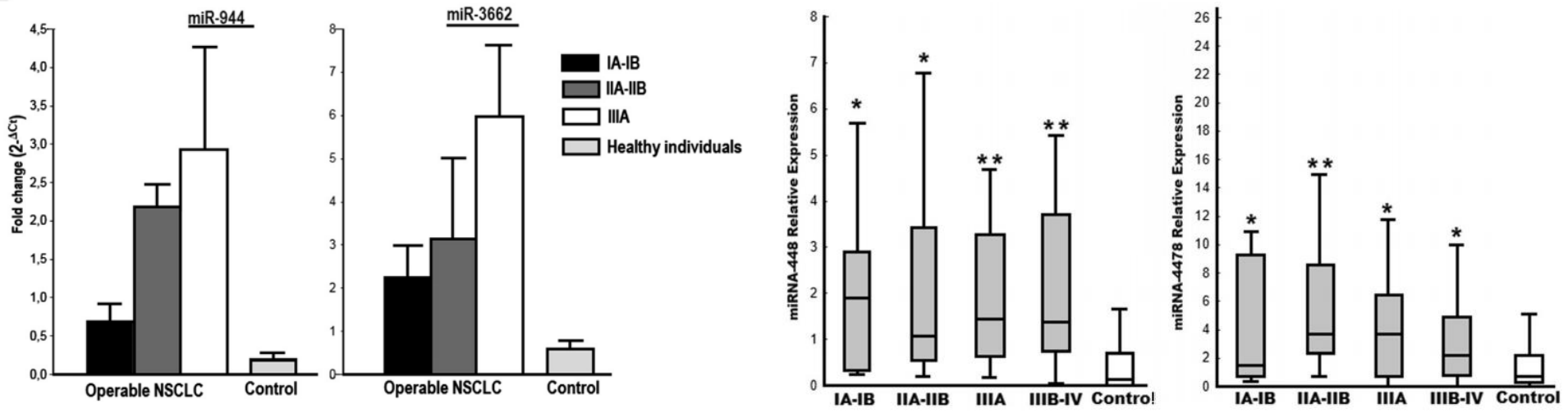
-Significantly higher expression of **miRNA-448, 944, 3662 and 4478** was detected in plasma of lung cancer patients compared with healthy individuals ($p<0.0001$)

- Expression of miRNAs-506 and 4316 showed no diagnostic value in NSCLC patients
- Combined analysis of **4-miRNAs signature** demonstrated high diagnostic power for detection of operable stages (I-IIIA) of NSCLC with sensitivity of 84.8% and specificity of 96.6% (AUC=0.930)
- miRNA-944 expression demonstrated diagnostic accuracy for detection of operable squamous cell carcinoma (sensitivity: 85.7% and specificity: 90.3%; AUC=0.982), while miRNA-3662 expression- for operable adenocarcinoma (sensitivity: 82.4%; specificity: 93.5%; AUC=0.926)

Table 2 Associations of patients' clinicopathological factors with aberrant miRNA-448 and miRNA-4478 expression; high-expression was assessed as miRNAs expression over median expression in whole group, low-expression was assessed as miRNAs expression equal or below median expression in whole group

Factors		Number (%)	miRNA-448			miRNA-4478		
			Low	High	*p*	Low	High	*p*
Median age	≥64	50 (55.5)	24 (48)	26 (52)	0.532	27 (54)	23 (46)	0.209
	<64	40 (44.5)	22 (55)	18 (45)		16 (40)	24 (60)	
Gender	Male	62 (68.9)	35 (56.5)	27 (43.5)	0.173	32 (51.6)	30 (48.4)	0.363
	Female	28 (31.1)	11 (39.3)	17 (60.7)		11 (39.3)	17 (60.7)	
Patomorphological diagnosis of NSCLC	AC	30 (46.2)	16 (53.3)	14 (46.7)	NS	22 (73.3)	8 (26.7)	*0.043*
	SCC	35 (53.8)	20 (57.1)	15 (42.9)		16 (45.7)	19 (54.3)	
LC diagnosis	NSCLC	65 (72.2)	36 (55.4)	29 (44.6)	0.241	38 (58.5)	27 (41.5)	*0.002*
	SCLC	25 (27.8)	10 (40)	15 (60)		5 (20)	20 (80)	
Disease stage of NSCLC	I–IIIA	40 (61.5)	20 (50)	20 (50)	0.313	23 (57.5)	17 (42.5)	NS
	IIIB–IV	25 (38.5)	16 (64)	9 (36)		15 (60)	10 (40)	
Disease stage of SCLC	IIIA–IIIB	10 (40)	4 (40)	6 (60)	NS	4 (40)	6 (60)	0.121
	IV	15 (60)	6 (40)	9 (60)		1 (6.7)	14 (93.3)	
Smoking status of NSCLC patients*	Smoker	55 (84.6)	32 (58.2)	23 (41.8)	0.321	32 (58.2)	23 (41.8)	NS
	Non-smoker	10 (15.4)	4 (40)	6 (60)		6 (60)	4 (40)	
Cigarette consumption in NSCLC patients*	>20 pack-years	45 (69.2)	26 (57.8)	19 (42.2)	0.563	23 (51.1)	22 (48.9)	0.078
	≤20 pack-years	10 (15.4)	6 (60)	4 (40)		9 (90)	1 (10)	
	Non-smokers	10 (15.4)	4 (40)	6 (60)		6 (60)	4 (40)	

Powrozek T et al. Tumor Biol. 2015



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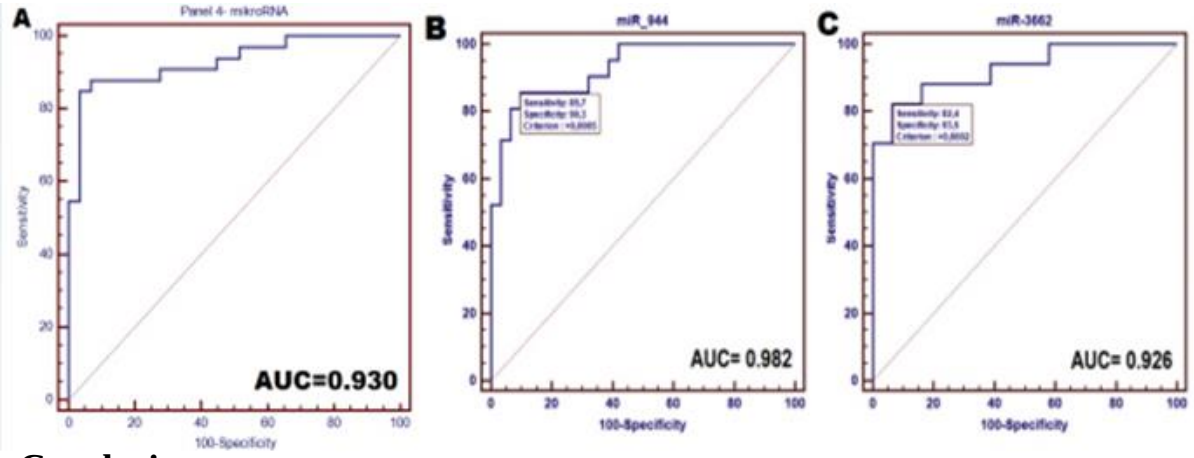

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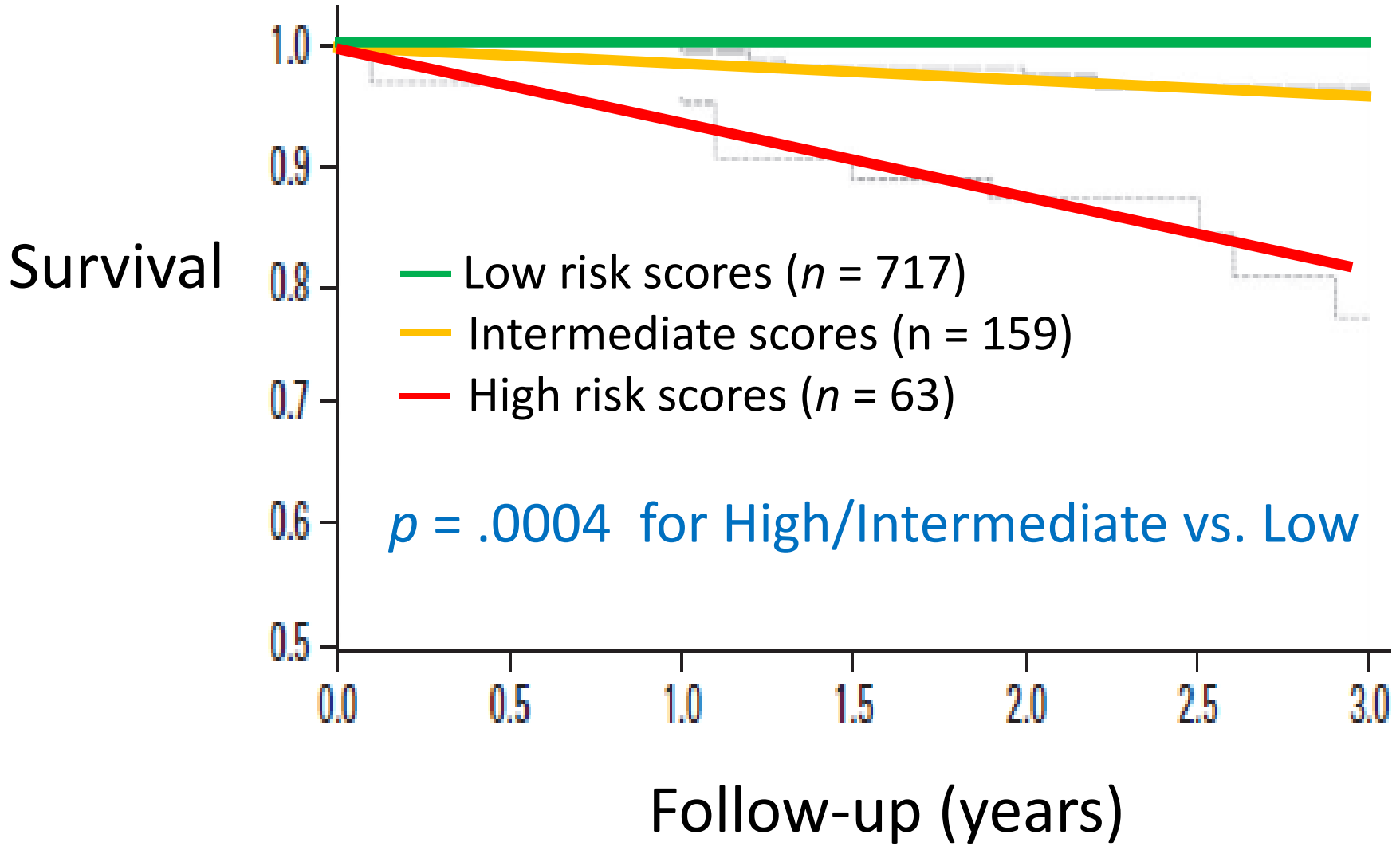
Conclusion

Novel signature of 4 circulating miRNAs may be considered as valuable diagnostic tool which could improve non-invasive diagnosis of NSCLC or complements CT lung screening. Moreover, **miRNA-944** may be considered as marker of early differentiation of **squamous cell** carcinoma, whereas **miRNA-3662 as early adenocarcinoma marker**. The above findings confirms localization of gene encoding miRNA-944 within intron of *p63* gene (its expression is marker of squamous differentiation). Whereas, miRNA-3662 sequence is complementary to mRNA of suppressor genes (*PTAR1*, *SEPT10* and *NPR3*), which disorders are associated with adenocarcinoma differentiation.

COMMENTS

- How and why was these particular miRNA selected?
- The “signature”: what does that mean? A “signature” requires a statistical algorithm!
- The “signature” needs further validation.
- What about the many signatures already out on the market? How do they compare?
- How do they compare to tissue miRNA signatures?
- What is the biology behind the signatures?

miRNA Biomarker Signature: Sozzi et al. 2014 JCO
Multicentric Italian Lung Detection 3-Year Survival



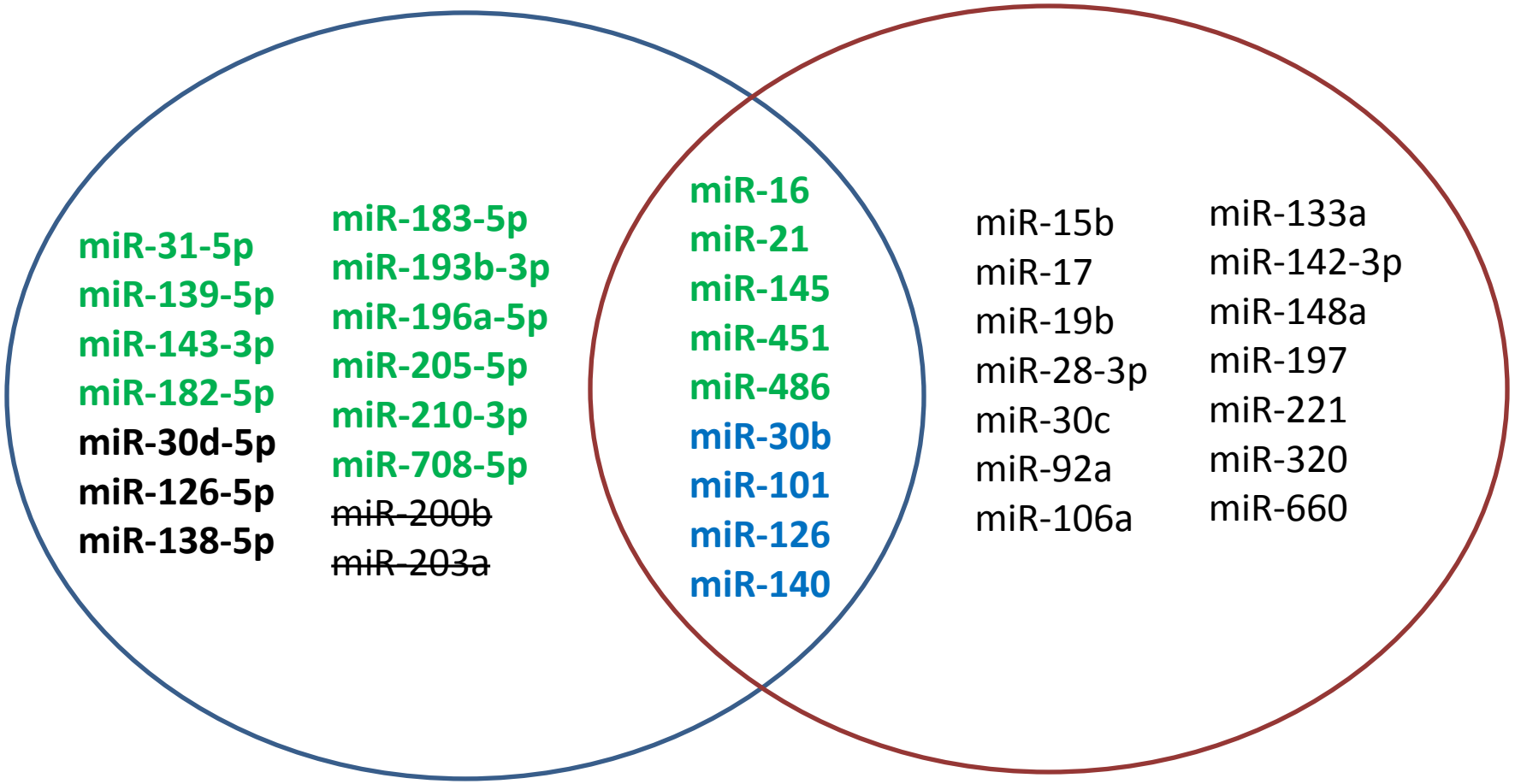
Sozzi et al. signature overlap with tissue miRNAs

23 Highly replicated (3x) tumor tissue miRNAs

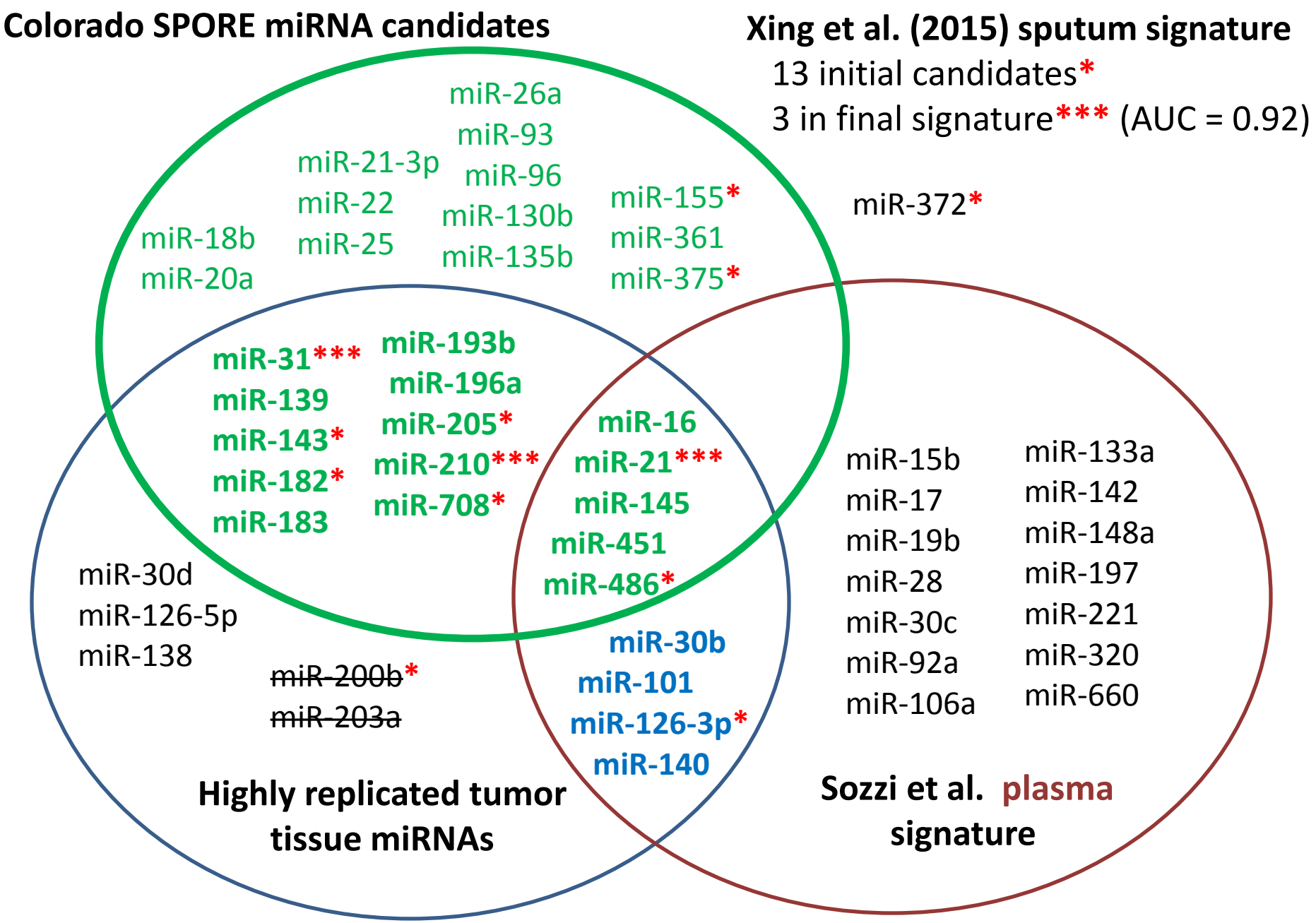
21 replicated by us

15 most informative

Sozzi et al. plasma signature



Overlap with Other Signatures



Vote Counting

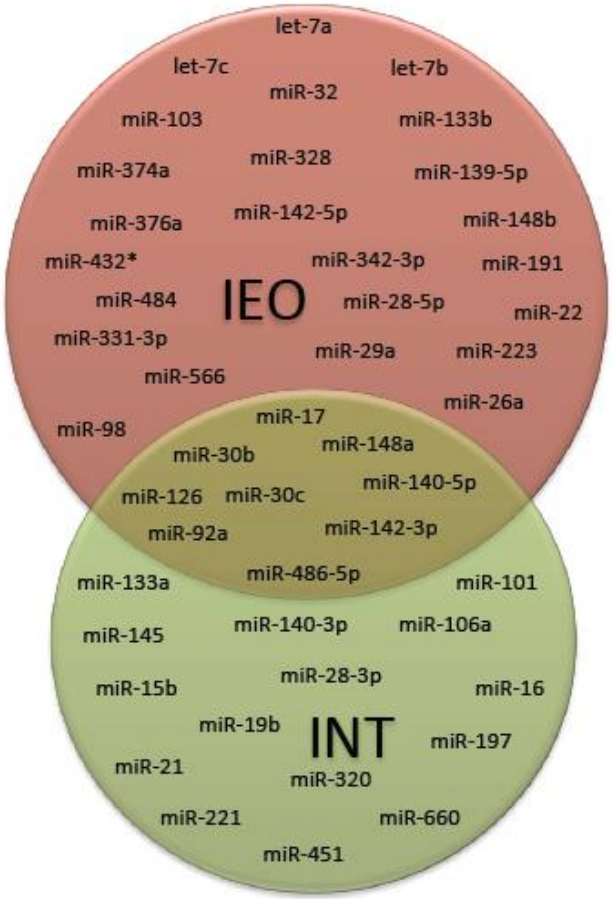
Guan et al. 2012
Meta-analysis
Journal of Experimental & Clinical Cancer Research
- ranked 52/182

Rikke B. et al. 2015

miRNA	Guan et al. 2012 meta-analysis	Statistical Significance Our Study (45 tumor-normal samples)	
	Number of supporting studies	*p*-values (1-tailed)	Fold change
miR-126-3p	10	< .005	-4
miR-210-3p	9	< .005	3
miR-486-5p	8	< .005	-5
miR-21-5p	7	< .005	3
miR-182-5p	6	< .005	3
miR-31-5p	6	< .005	3
miR-451a	6	< .005	-4
miR-205-5p	5	< .005	8
miR-139-5p	5	< .005	-4
miR-200b-3p	5	0.13	1.2
miR-30d-5p	5	< .005	-2
miR-183-5p	4	< .005	3
miR-145-5p	4	< .005	-3
miR-143-3p	4	< .005	-3
miR-203a	3	.095	1.3
miR-196a-5p	3	< .005	11
miR-708-5p	3	< .005	4
miR-126-5p	3	.005	-2
miR-140-3p	3	< .005	-2
miR-138-5p	3	< .005	-2
miR-193b-3p	3	< .005	2
miR-30b-5p	3	< .005	-2
miR-101-3p	3	< .005	-1.4

miRNA	AUC stage I	Serum NSCLC/NC	Lung AC/NL	Lung SCC/NL	High expression in blood cells	Reported in NSCLC	Reported in other cancers
miR-141	0.875	up	up	up	no	no	18663219; 23935962
miR-193b	0.855	up	up	up	NA	no	24778027
miR-200b	0.849	up	up	up	no	no	23272653; 20551052
miR-301	0.841	up	up	NS	NA	20595154	no
let-7g	0.840	up	NS	up	NA	no	24709885
miR-331	0.748	up	NS	up	NA	no	21035526
miR-758	0.747	up	up	NA	NA	no	no
miR-744	0.726	up	up	NA	NA	no	22432036
miR-106a	0.958	up	NS	up	yes	21544802	20234369; 25140035
miR-19a	0.948	up	up	NS	yes	no	no
miR-17	0.918	up	NS	up	yes	no	23056289
miR-19b	0.916	up	NS	up	yes	no	23874370; 24498016
miR-93	0.899	up	NS	up	yes	no	23748853; 24498016
miR-20b	0.875	up	NS	up	yes	20595154	no
miR-106b	0.838	up	up	up	yes	no	20234369; 23874370
miR-215	0.828	up	up	NS	yes	no	22353773; 24993656
miR-25	0.826	up	NS	up	yes	no	24595006; 24651474
miR-200c	0.820	up	up	up	yes	no	22954417; 23272653
miR-93*	0.739	up	up	NA	yes	no	no
miR-24	0.715	up	NS	up	yes	no	23697990

cfmiRNA



	Summary	Serum	Plasma
Sens	0.85	0.87	0.79
Spec	0.84	0.82	0.85
PLR	5.23	4.82	4.84
NLR	0.20	0.18	0.25
DOR	31.77	32.74	19.84
Q value	0.85	0.84	0.77
AUC	0.92	0.91	0.83

(*Wang et al. PLoS One 2012;7:e41561*)

DNA methylation of *SHOX2* and *PTGER4* as a plasma-based tool to differentiate between patients with malignant and benign lung disease

Anne Schlegel, Oliver Hasinger, Selina Esche, Melanie Martini, Thomas König, Gunter Weiss

Introduction

Recently, a DNA methylation panel of the genes *SHOX2* and *PTGER4* has been evaluated in three independent case-control studies comprising a total of 330 plasma specimens from lung cancer (LC) patients and healthy individuals with promising results (AUC = 91 to 95%). Here, we report on evaluation of this marker panel in patients with LC or benign lung disease (BLD).

Method

- Triplex real-time PCR assay detects
- Methylated *SHOX2/PTGER4*
- *ACTB* reference (methylation independent)
- 3.5 ml plasma samples (liquid biopsy)
- DNA extraction and bisulfite conversion with Epi proColon Plasma Quick Kit
- DNA assayed in PCR triplicates
- Aggregated Cts used for ROC curve analysis

Clinical Specimens

- 172 plasma specimens:
- 50 LC, 50 BLD, 72 healthy subjects

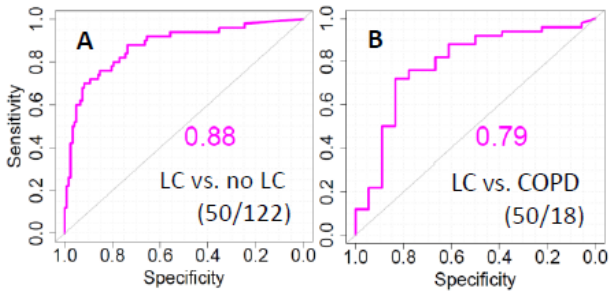
BLD	Asthma	COPD	Pneumonia	other
N = 50	5	18	11	16
Lung Cancer	NSCLC Adeno	NSCLC Squam	Other	SCLS
N = 50	19	25	6	--
	Stage I	Stage II	Stage III	Stage IV
	12	11	16	11

Table 1: Patient characteristics of LC and BLD

Results

The marker panel showed significant discriminatory power to distinguish LC cases from the remaining subjects (AUC = 0.88, Fig. 1A), including BLD patients (AUC = 0.85) and healthy subjects (AUC = 0.89). The results of the clinically most important group of COPD patients (18 cases) were significantly different from the LC group (AUC = 0.79, Fig. 1B).

Figure 1: ROC–Curve–Results from different comparisons



AUC	High specificity cutoff		High sensitivity cutoff	
	Sens.	Spec.	Sens.	Spec.
0.88	60%	95%	94%	56%

Table 2: Performance of marker panel LC vs. no LC

Conclusion

- A high sensitivity cutoff may be used for further risk stratification of patients with findings in LDCT
- A high specificity cutoff has the potential to be used in screening applications and subsequent timely treatment of lung cancer

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Introduction

- Recently evaluated DNA methylation panel of *SHOX2/PTGER4*
  - Three independent case-control studies
  - 330 plasma specimens of lung cancer (LC) vs. healthy individuals
  - Results: AUC = 91 to 95%

Aim

- Evaluate marker panel in patients with LC or benign lung disease (BLD)

Method

- Triplex real-time PCR (SHOX2/PTGER4, ACTB reference)
- 3.5 ml plasma samples (liquid biopsy)
- DNA extraction and bisulfite conversion (Epi proColon Plasma Quick Kit)
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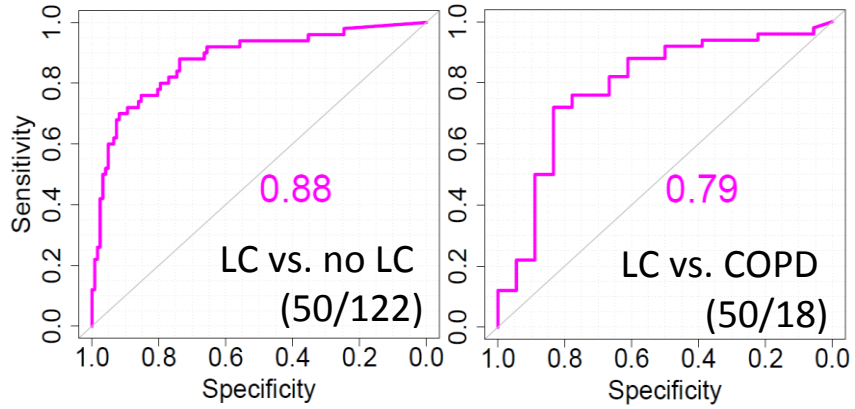
Lung Cancer	NSCLC Adeno	NSCLC Squam	Other	SCLS
N = 50	19	25	6	--
	Stage I	Stage II	Stage III	Stage IV
	12	11	16	11

Results

- Marker panel discriminates in relevant comparisons:
  - LC vs. BLD/healthy: AUC = 0.88
  - LC vs. BLD: AUC = 0.85
  - LC vs. healthy: AUC = 0.89
  - LC vs COPD: AUC = 0.79

Figure 1: ROC–Curves from different comparisons



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Conclusion

- A **high sensitivity** cutoff may be used for further **risk stratification** of patients with findings in LDC
- A **high specificity** cutoff has the potential to be used in **screening** applications and subsequent timely treatment of lung cancer

Tab 2: Performance of marker panel LC vs. no LC

AUC	High specificity cutoff		High sensitivity cutoff	
	Sens.	Spec.	Sens.	Spec.
0.88	60%	95%	94%	56%

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COMMENTS

- What is the correlation to tissue based methylation panel?

- What is “healthy controls”?

Smokers/former smokers/ never-smokers?

Incidence in a High-Risk Cohort

Table 3.

Prevalence and odds for gene promoter methylation and cytologic atypia in proximal sputum samples obtained 3 to 18 and 19 to 72 months prior to cancer diagnosis

Biomarker	Cases (%) *	Controls (%) *	Odds ratio (CI)	Adjusted odds ratio † (CI)
3-18 Months prior to cancer diagnosis				
P16	22 (42)	13 (29)	1.8 (0.9-4.5)	2.2 (0.9-5.2)
PAX5 β	24 (46)	16 (34)	1.7 (0.7-3.7)	1.9 (0.8-4.3)
MGMT	17 (33)	10 (21)	1.8 (0.7-1.9)	1.7 (0.7-4.5)
DAPK	24 (46)	16 (34)	1.7 (0.7-3.7)	1.6 (0.7-3.7)
GATA5	18 (35)	12 (26)	1.5 (0.6-3.7)	1.9 (0.7-5.1)
GATA4	26 (50)	20 (43)	1.4 (0.6-3.0)	1.5 (0.6-3.6)
RASSF1A	7 (14)	3 (6)	2.3 (0.6-9.4)	1.7 (0.4-7.6)
Atypia ‡	19 (37)	10 (21)	2.1 (0.9-5.2)	2.0 (0.8-5.2)
19-72 Months prior to cancer diagnosis				
P16	17 (37)	12 (27)	1.6 (0.7-3.9)	1.8 (0.7-5.0)
PAX5 β	17 (37)	16 (36)	1.1 (0.5-2.5)	1.0 (0.4-2.6)
MGMT	6 (13)	12 (27)	0.4 (0.1-1.2)	0.4 (0.1-1.3)
DAPK	18 (39)	14 (31)	1.4 (0.6-3.4)	1.3 (0.5-3.1)
GATA5	16 (35)	14 (31)	1.2 (0.5-2.8)	1.3 (0.5-3.1)
GATA4	22 (48)	22 (49)	1.0 (0.4-2.2)	1.0 (0.4-2.5)
RASSF1A	5 (11)	3 (7)	1.7 (0.4-7.6)	1.2 (0.3-6.0)
Atypia‡	8 (17)	8 (18)	1.0 (0.3-2.9)	0.9 (0.3-2.9)

Belinsky SA et al. Cancer Research 2006

Differences between primary and metastatic non-small cell lung cancer tumors predictive biomarkers

Zoran Gatalica*, Rebecca Feldman, Ken Russell, Andreas Voss and Sandeep Reddy
Caris Life Sciences, Phoenix, AZ 85040, USA; *zgatalica@carisls.com

Publication No. 1PD

Abstract

Background: Metastatic non-small cell lung cancer (NSCLC) carries especially poor prognosis. Recently developed targeted therapies and predictive value of their biomarkers, coupled with tumor heterogeneity, dictate thoughtful profiling of tumor samples in order to achieve maximum therapeutic response.
Methods: We analyzed 10,764 profiled samples of NSCLC from over 75,000 cancer cases in our database (Caris Life Sciences, Phoenix, AZ), and categorized them based on available clinical and pathologic information into primary tumors, lymph node and distant organ metastases, in order to detect site-specific actionable targets (biomarkers). Additionally, we identified 154 patients with matched primary and metastatic tumors. Biomarkers were detected using a multiplatform approach consisting of immunohistochemistry (IHC), in-situ-hybridization (ISH) and sequencing methods (Sanger and Next Generation Sequencing).
Results: Numerous biomarkers of targeted biological therapies [e.g. 2.4% ALK and 1.0% ROS1 rearrangement, 2.9% HER2 and 4.0% cMET amplification; EGFR: 49.2% overexpression, 29.5% gene amplification and 12.3% mutations) and immune checkpoints inhibitors (25% PD-L1 expression), as well as chemotherapeutic agents (e.g. BRCA1 and 2, ERCC1, TUBB3, RRM1, TOPO1, TS) were readily detected in both squamous cell and adenocarcinomas. Lymph node metastases of lung adenocarcinomas had significantly higher ALK (8% vs. 1%), EGFR (50% vs. 42% for IHC; 39% vs. 28% for ISH), PD-L1 (36% vs. 25%) and ROS-1 (3% vs. 1%) detection rate than primary tumors. Distant organ metastases also exhibited higher cMET amplification (7% vs. 3%) than primary tumors. Squamous carcinomas (SCC) showed higher ALK expression in lymph node metastases (10%) than in the primary site (1%). Similarly, SCC PD-L1 expression was higher in lymph node metastases (42%) than in primary tumor (33%). Trends observed in unmatched cohort were also confirmed in patient-matched tissues cohort. Both, gains (e.g. PD-L1 expression, cMET amplification, TP53 mutations) and losses (e.g. KRAS mutations) were observed.
Conclusions: Comparison of comprehensive molecular profiling data of NSCLC identified significant and therapeutically important differences between primary and metastatic tumor sites (up to 47% of matched samples for some biomarkers). These findings highlight the importance of extent and timing of the tissue sampling for the purpose of molecular profiling.

Introduction

The treatment and outcome of the patients with NSCLC has dramatically improved in the past decade (1) due to the targeted treatment modalities. Despite it, locally advanced and/or metastatic NSCLC carries especially poor prognosis. Recently developed targeted therapies and predictive value of their biomarkers, coupled with tumor heterogeneity, dictate thoughtful profiling of tumor samples in order to achieve maximum therapeutic response (2, 3). In the present study, we profiled a large case-series of primary and metastatic (lymph node and distant) NSCLC subtypes (including matched cases) in an attempt to explore the differences in molecular profiling between the primary and metastatic NSCLCs.

Methods

The study included >10,000 profiled samples of both primary and metastatic NSCLC (adenocarcinomas and squamous cell carcinomas) from over 75,000 cancer cases in our database (Caris Life Sciences, Phoenix, AZ), and categorized them based on available clinical and pathologic information into primary tumors, lymph node and distant organ metastases, in order to detect site-specific actionable targets (biomarkers). Additionally, we identified 154 patients with matched primary and metastatic tumors. Biomarkers were detected using a multiplatform approach consisting of immunohistochemistry (IHC), in-situ-hybridization (ISH) and sequencing methods (Sanger and Next Generation Sequencing/Truseq/Miseq panel) as described previously (4, 5).

Results

Figure 1. Differences in biomarker expression, amplification and mutation rates between primary and metastatic adenocarcinomas (A) and squamous cell carcinomas (B).

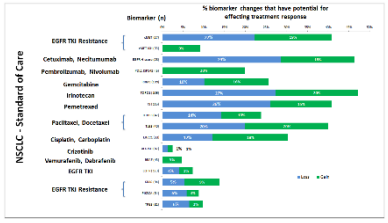

Figure 2. Differences in biomarkers between matched primary and metastatic NSCLC (n=154; 130 ADC, 14 SCC). Figure demonstrates changes in biomarkers predictive of standard of care for NSCLC between matched primary and metastatic (lymph nodes and distant metastasis) specimens. Blue bars indicate loss of expression (biomarker goes from positive to negative) for IHCs, loss of amplification or fusion for ISH, or loss of variant (mutated to variant no longer detected) for mutation. Green bars indicate gain of expression (IHC) gain of amplification (ISH) or a gain of a variant (NGS).

Results, contd.

Illustrative case of NSCLC with *KRAS* and *APC* mutations in both primary and metastatic tumor and discordant EGFR and PD-L1 expressions.

Tissue site	PD-L1 (IHC)	EGFR (IHC)	NGS
Primary NSCLC (18.04.2012)	Negative	Negative	KRAS G12A APC Y1143F
Skin metastasis (10.06.2015)	Positive	Positive	KRAS G12A APC Y1143F
Bone metastasis (iliac bone) (12.04.2015)	Negative	Positive	KRAS G12A APC Y1143F

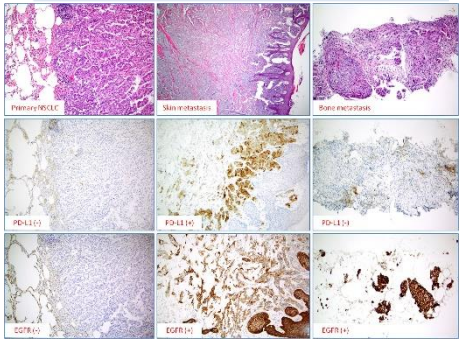

Figure 3. IHC staining images of H&E (top panel), PDL1 (middle panel) and EGFR (lower panel) of primary (left panel) and metastatic lesions (right panels). Primary lung specimen (4/2012) from 52 year-old female with lung adenocarcinoma demonstrates negative EGFR and PDL1 status. Profiling of subsequent metastases (skin/bone; 2015) reveal positive PDL1 status in the skin and positive EGFR status in the skin and bone.

Conclusions

- Comparison of comprehensive molecular profiling data of NSCLC identified significant and therapeutically important differences between primary and metastatic tumor sites.
- Many of these observations were confirmed in matched samples and these biomarker differences effect several standard of care therapy options
- These findings highlight the importance of extent and timing of the tissue sampling for the purpose of molecular profiling.

References

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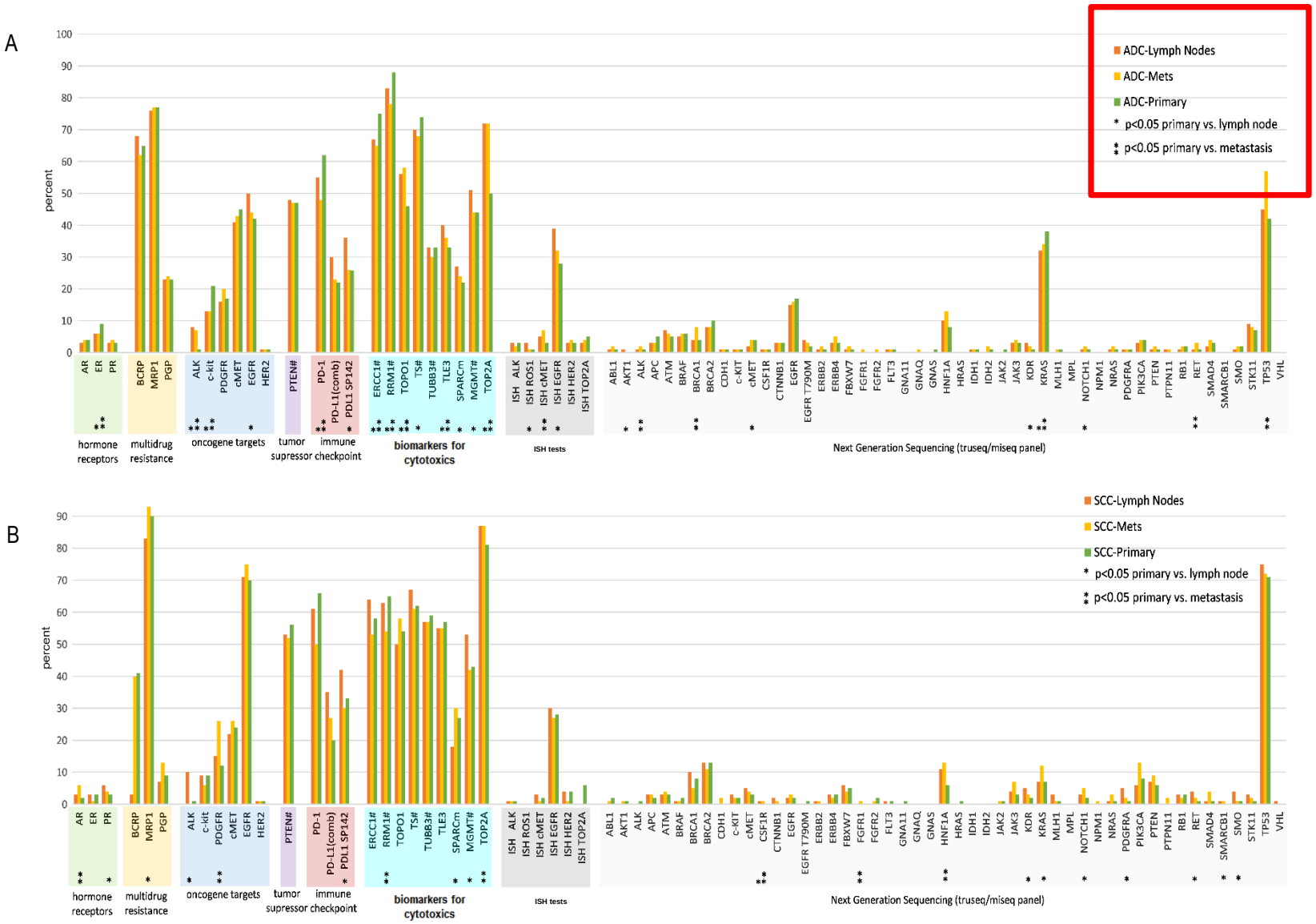
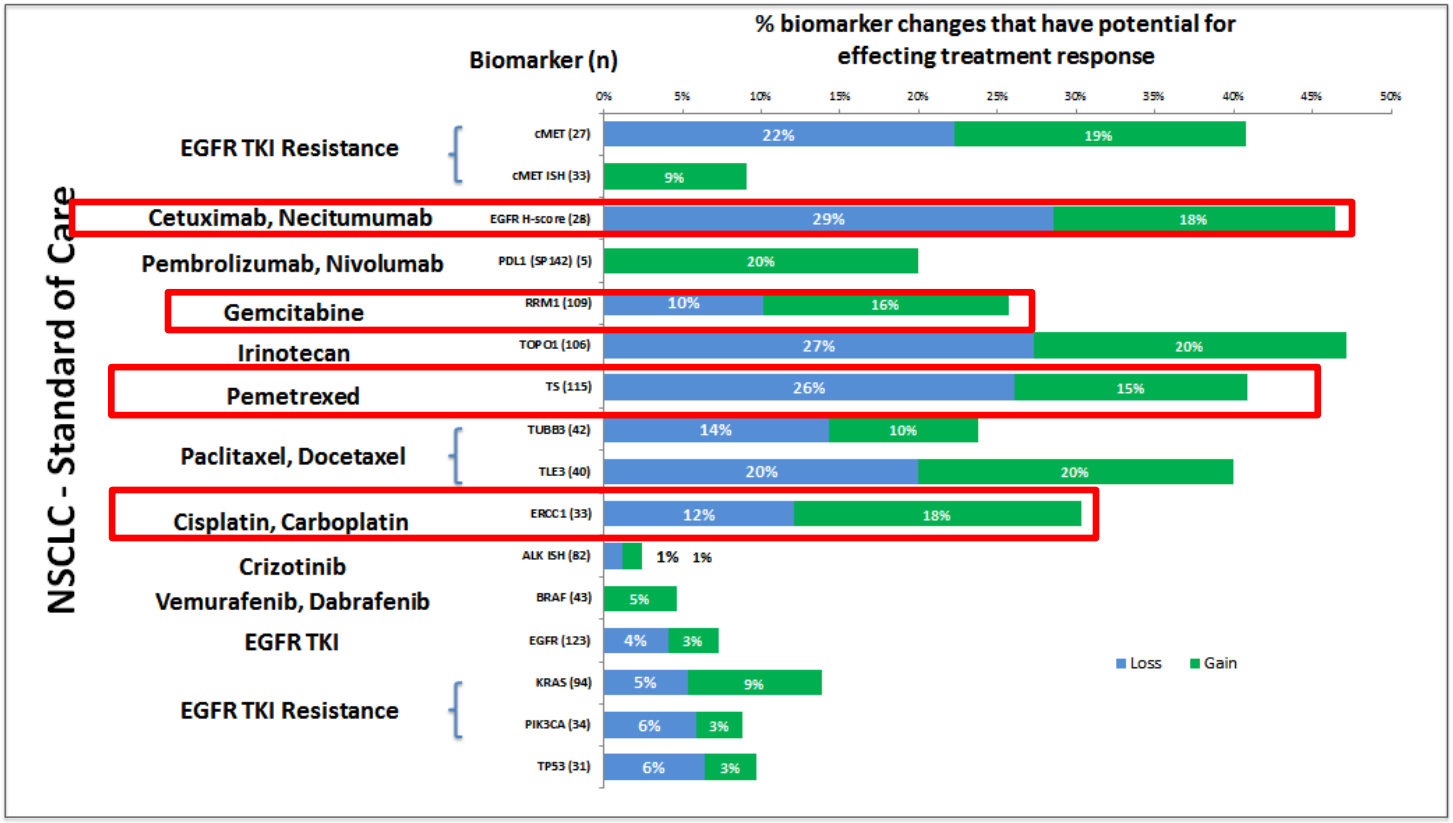


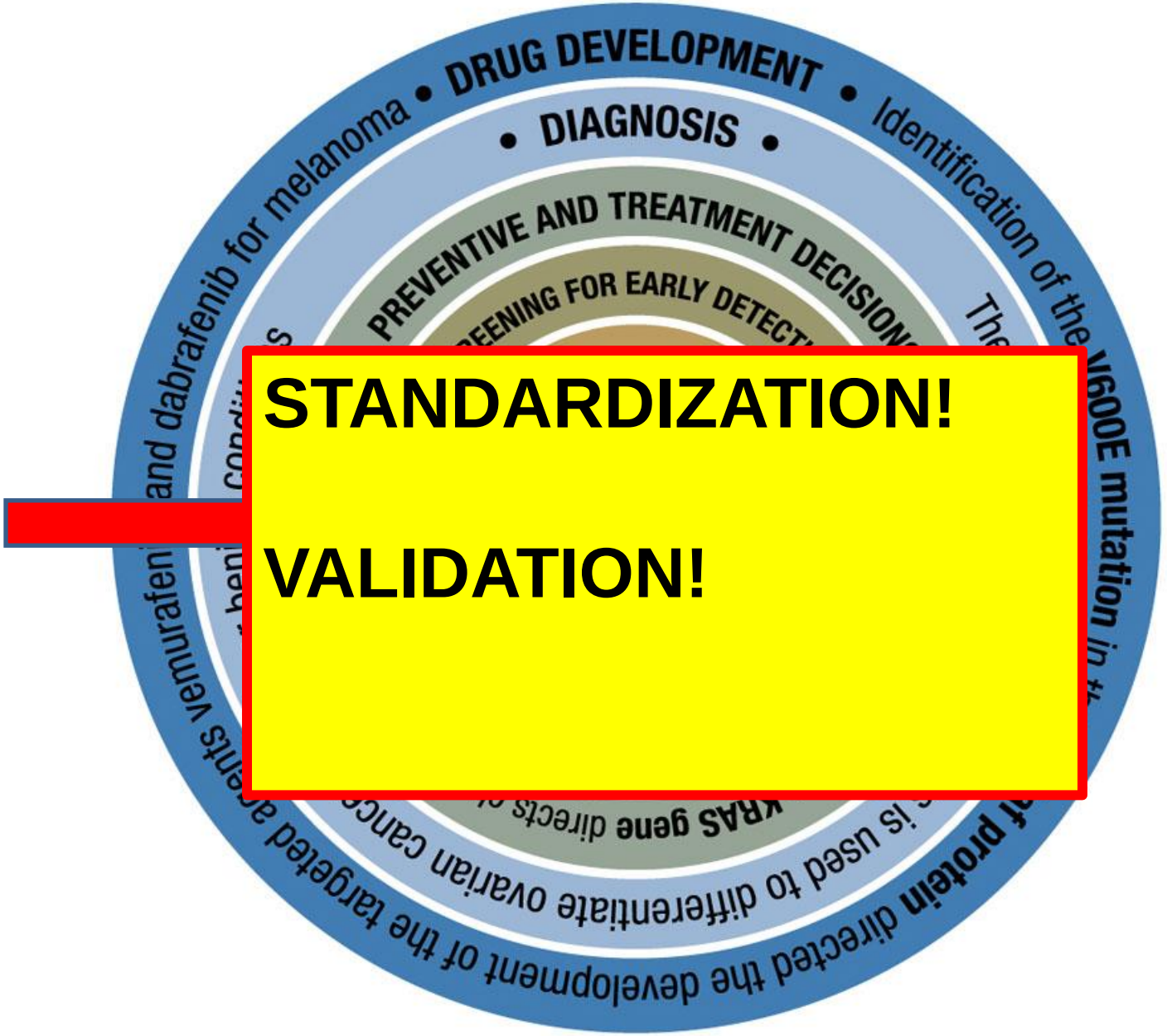
Figure 1. Differences in biomarker expression, amplification and mutation rates between primary and metastatic adenocarcinomas (A) and squamous cell carcinomas (B).

Biomarkers that display significantly different rates of expression, amplification/fusion and mutation in matched primary vs. metastases (lymph node or distant metastasis) in NSCLC (n=154; 130 ADC, 14 SCC)



COMMENTS:

- Interesting study showing disconcordance between primary tumor vs metastasis for therapeutically relevant biomarkers
- Is metastases biopsy relevant surrogate for primary tumor? Too low sensitivity?
- Many of the biomarkers- drug associations are not fully validated (e. g. ERCC1, RRM1, etc)



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