Molecular characterization of early stage lung adenocarcinoma

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Preventing Overdiagnosis
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Room 130 : 11 am
Disclosure

• I serve on the External Advisory Board of Veracyte and Oncimmune
• I am a paid consultant by Natera Inc.
Overdiagnosis, a problem in lung cancer?

- The debate is around efficacy of screening for lung cancer.
- Overdiagnosis bias is the possibility of detecting an indolent lung cancer that would not have been found or that would not have affected the patient’s natural lifespan if the patient were not screened.
- Overdiagnosis may account for up to 18.5% of screening detected lung cancers (Patz JAMA 2014).
- In the COSMOS trial, slow-growing or indolent cancers comprised approximately 25% of incident cases, many of which may have been overdiagnosed (Veronesi Ann IM 2013).
Overdiagnosis

A)

- Incidence
- Time
- Pre-screening era
- Screening era
- Screening completely implemented since a few years
- Overdiagnosis
- No overdiagnosis

B)

- Cumulative incidence
- Age
- Age at which screening begins
- Age at which screening is not done anymore
- No screening
- Period of life with regular screening
- Overdiagnosis
- No overdiagnosis

Chiolero et al. SMJ 2015
Indolent Lung Cancers and Overdiagnosis

Adenocarcinoma
In situ

Minimally Invasive Adenocarcinoma

Adenocarcinoma

Lee AJR 2014, Weichert COPM 2014
Histological features changes with progression

NI

AIS

MIA
Invasion focus
<5mm Diam

ADC

Lee, et al. AJR, 2014
Emmy’s nodule
Baseline
Solid volume 1.869 mL
Nonsolid vol 2.474 mL
Total volume 4.343 mL

Baseline + 28 Months
Solid volume 3.022 mL = 61% growth
Nonsolid vol 2.143 mL = 13% regression
Total volume 5.165 mL = 18% growth

Courtesy of Ron Walker and Kim Sandler
Should Emmy take the risk of over-diagnosis / over-treatment?
A 3 pronged approach

- Structural Imaging
- Cellular & Molecular analysis
- Circulating biomarkers

Early lung ADC - Predicting behavior
Structural Imaging- Radiomics

I) CT imaging

II) Feature extraction

Tumour intensity

Tumour shape

Tumour texture

Wavelet

III) Analysis

Radiomic feature

Clinical data

Prediction accuracy

Aerts and Gillies, Nature 2014
Computer-Aided Nodule Assessment and Risk Yield (Canary)

294 ADCs from NLST Patterns compared to 3 established examplars

Maldonado JTO, 2013
Maldonado AJRCCM 2015
Intra-Heterogeneity of Lung Cancer
Emmy’s Adenocarcinoma

Acinar   Papillary   Lepidic
Inter- and Intra-Heterogeneity of Lung Cancer

Marusyk Nat rev Cancer 2012
Spatial Heterogeneity in Lung Cancer

E C de Bruin et al. Science 2014
Temporal Heterogeneity in Lung Cancer

E C de Bruin et al. Science 2014
Tumors with high neoantigen burden responds better to ICI in advanced lung cancer

Rivzi et al. Science 2015
Clonal neoantigens and sensitivity to immune checkpoint blockade

A high neoantigen burden is associated with significantly longer overall survival in early LUAD. Neoantigen burden is related to response to PD-1 blockade.

McGranahan et al. Science 2016
MDM2 FISH predicts outcome in early ADC

**Table A**

<table>
<thead>
<tr>
<th></th>
<th>tot #</th>
<th>no Gain</th>
<th>Aneuploid</th>
<th>Amplified MDM2</th>
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<tbody>
<tr>
<td>AIS</td>
<td>22</td>
<td>20</td>
<td>2</td>
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<tr>
<td>MIA</td>
<td>30</td>
<td>28</td>
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<td>ADC</td>
<td>52</td>
<td>46</td>
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</table>

**Figure C**

Log rank $p < 0.001$

**Massion/Powell/Borczuk Lab**
Molecular and Cellular Characterization of Early Adenocarcinoma of the Lung

IMAPCT: This project addresses the molecular basis of Overdiagnosis in lung cancer and management of early lung ADC

Funding
NCI U01 CA196405

Publications
Maldonado AJRCCM 2015
Diggins Methods. 2015
Diehn, Nature Med 2014

Shared Resources
Genomic Sciences
Quantitative Sciences
Flow/Mass Cytometry core
Innovative Translational Research
Overall survival of lung cancer by prevalence, interval, and screening in the NLST

Schabath et al. (2016) PLOS ONE
Conclusions

• Overdiagnosis is a real problem in screening detected lung cancers
• Structural imaging and molecular strategies may distinguish between different tumor behaviors.
• Neoantigens are source of T cell activation and its burden may predict response to ICI
• Cytogenetic MDM2 marker predicts behavior of early ADC.
• Mass cytometry will allow a functional proteomic analysis of early ADC as the single cell level hoping to understand differences in signaling behavior and eventually new therapeutic strategies.
Acknowledgments