OVERDIAGNOSIS OF LUNG CANCER

Appropriate Treatment for Lung Cancer

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NOTHING TO DISCLOSE
OVERDIAGNOSIS IN LUNG CANCER SCREENING

- Detection of disease, that in the absence of screening, would have never been diagnosed.
- Screening seeks to detect occult disease in asymptomatic individuals.
- Concern – results in unnecessary treatment, morbidity, follow-up, cost and anxiety for patients with disease that otherwise would not have been detected.
OVERDIAGNOSIS IN LUNG CANCER SCREENING

- Pathologic features may explain favorable outcome for the minority of lung cancers
- ADC - lepidic growth (AIS, MIA, LPA)
- Histologic grade
- Invasive characteristics: visceral pleural invasion, STAS, vascular invasion
- Molecular characteristics (EGFR/ALK mut)
2015 WHO CLASSIFICATION OF LUNG ADENOCARCINOMA

- Comprehensive histologic subtyping – 5% increments
- Solid ADC – mucin + or TTF-1 + (from large cell ca)
### STAGE I ADENOCARCINOMA (N=514)

**RECURRENCE-FREE SURVIVAL (RFS) BY IASLC HISTOLOGIC TYPE**

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>5 Year RFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS (1)</td>
<td>100</td>
</tr>
<tr>
<td>MIA (8)</td>
<td>100</td>
</tr>
<tr>
<td>Lepidic NM (29)</td>
<td>90</td>
</tr>
<tr>
<td>Papillary (143)</td>
<td>83</td>
</tr>
<tr>
<td>Acinar (232)</td>
<td>85</td>
</tr>
<tr>
<td>Inv Mucinous Ad (13)</td>
<td>76</td>
</tr>
<tr>
<td>Solid (67)</td>
<td>71</td>
</tr>
<tr>
<td>Micropapillary (12)</td>
<td>64</td>
</tr>
<tr>
<td>Colloid (9)</td>
<td>71</td>
</tr>
</tbody>
</table>

*Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011*
573 resected lung Adenoca
Predominant histologic pattern was prognostic for overall, recurrence free and disease specific survival
MV analysis: Independent MIP/SOL vs LEP/AC/PAP: HR 1.6 (CI:1.1-2.3) p=0.01
For patient group that received adjuvant chemotherapy, solid predominant AD was a significant predictor for OS.
IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION

- PREINVASIVE LESIONS
  - ATYPICAL ADENOMATOUS HYPERPLASIA
  - ADENOCARCINOMA IN SITU (≤3 cm, formerly BAC pattern) †
    - non-mucinous
    - mucinous
- MINIMALLY INVASIVE ADENOCARCINOMA (≤3 cm, a lepidic predominant tumor with ≤5mm invasion)

- INVASIVE ADENOCARCINOMA
  † Size should be specified. AIS and MIA should be completely sampled histologically

ADENOCARCINOMA IN SITU
NONMUCINOUS
ADENOCARCINOMA IN SITU NONMUCINOUS
MINIMALLY INVASIVE ADENOCARCINOMA NONMUCINOUS
MINIMALLY INVASIVE ADENOCARCINOMA
NONMUCINOUS
LEPIDIC PREDOMINANT
Patients distribution by lepidic pattern and their recurrence-free probability (RFP)

- **Lepidic pattern (patient, %)**
  - AIS: n=2 (0.2%)
  - Lepidic: n=103 (10%)
  - Others: n=907 (87%)

1038 Stage I Adca

- MIA: n=34 (3%)

- **RFP by lepidic pattern**

Clinicopathologic characteristics of four recurrent cases in lepidic predominant ADC

<table>
<thead>
<tr>
<th>Case</th>
<th>surgical procedure</th>
<th>type of rec.</th>
<th>duration until rec.</th>
<th>staple margin</th>
<th>stage</th>
<th>Ly</th>
<th>V</th>
<th>PL</th>
<th>micro-papillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lobectomy</td>
<td>distant (bone)</td>
<td>1.4 yrs</td>
<td>NA</td>
<td>IA</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>wedge resection</td>
<td>local rec. (lung)</td>
<td>1.1 yrs</td>
<td>2 mm</td>
<td>IA</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>wedge resection</td>
<td>distant (chest wall)</td>
<td>3.3 yrs</td>
<td>5 mm</td>
<td>IA</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>lobectomy</td>
<td>local rec. (lung)</td>
<td>3.8 yrs</td>
<td>NA</td>
<td>IA</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Lepidic predominant ADC with no recurrence (n=99)
- lymphatic invasion: 6% (n=6)
- vascular invasion: 4% (n=4)
- micropapillary pattern: 2% (average)

LUNG CANCER – PART SOLID NODULES IN NLST

- 19 part solid nodules screen baseline dxd lung ca
- No LN enlargement or mets at resection
- Path: 18 AD (6 BAC, 1 mixed BAC, 1 acinar, 1 mucinous); 1 Squamous cell ca
- Stage: 1A (n=15), 1B (n=3); Multilobar stage IV (T4N0M1) BAC dxd in one pt 25 months after study randomization died 68 months later
- All 18 pts with solitary or dominant part solid nodule underwent surgery and none died of lung ca

Yip, R et al: AJR 2017;208:1011-1021
LUNG CANCER – PART SOLID NODULES IN NLST

- From randomization average time to dx was 18.6 months and average time of followup was 79.2 months
- Median volume doubling time was 476 days (total) and 240 days (solid component)
- No pts with solitary or dominant part solid nodule had LN enlargement or metastases at pathology and none died of lung cancer within followup time of NLST

Yip, R et al: AJR 2017;208:1011-1021
GRADING OF LUNG CANCER

- No established grading system for lung cancer
- Grading system for adenocarcinoma will need to be different from squamous cell carcinoma
- Adenoca
  - Predominant subtypes
  - Two most predominant patterns
  - Highest grade
  - Nuclear features
  - Mitotic count

PROPOSED GRADING SYSTEM FOR SQUAMOUS CELL CARCINOMA

<table>
<thead>
<tr>
<th>Morphologic feature</th>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour budding</td>
<td>1</td>
<td>No budding in 10 HPFs</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&lt;15 budding foci per 10 HPFs</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>≥15 budding foci per 10 HPFs</td>
</tr>
<tr>
<td>Tumour nest size</td>
<td>1</td>
<td>&gt;15 cells (large nest size)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5–15 cells (intermediate nest size)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&lt;5 (or 2–4) cells (small nest size)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Single cell invasion</td>
</tr>
<tr>
<td>Combined score</td>
<td>2–3</td>
<td>Grade 1 (well differentiated)</td>
</tr>
<tr>
<td></td>
<td>4–6</td>
<td>Grade 2 (moderately differentiated)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Grade 3 (poorly differentiated)</td>
</tr>
</tbody>
</table>

HPF: high-power field. Reproduced and modified from [33].

SPREAD THROUGH AIR SPACES (STAS) IN INKED MARGIN OF RESECTION
SPREAD THROUGH AIR SPACES (STAS) IN INKED MARGIN OF RESECTION

Kadota K et al; JTO 2015; 10:806-14
STAS – Cumulative Incidence of Recurrence in Limited Resections

Multivariate analysis, presence of tumor STAS remained independently associated with the risk of recurrence (hazard ratio, 3.08; \( P=0.014 \)).

*Kadota K et al; JTO 2015; 10:806-14*
CLINICAL SIGNIFICANCE OF STAS
GROWING EVIDENCE

- Adenocarcinoma (n=13)
  - Sun PL et al Zhonghua Bing Li Xue Za Zhi 2017;46:303-8; Yi E et al; ANZ J Surg 2018;88:327-31

- Squamous cell carcinoma (n=3)
  - Kadota K et al: AJSP, 2017, 41:1077-86
  - Yanagawa N et al: Lung Cancer 120; 14-21, 2018


- Carcinoid

- Non-angiogenic pattern – co-option of blood vessels
  - Szabo, V J Pathol 2015; 235: 384–396
CLASSIFICATION OF LUNG CANCER NOW REQUIRES GENETIC TESTING

MSK-IMPACT NGD data, 2017 – now includes 468 genes

Courtesy of Marc Ladanyi

Jordan EJ Ca Discovery 7:596-609, 2017
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- ADC - lepidic growth (AIS, MIA, LPA)
- Histologic grade
- Invasive characteristics: STAS, vascular invasion, visceral pleural invasion
- Molecular characteristics (EGFR/ALK mut)
- Goal – less intervention for GGN/PSN detected by screening