Lung Cancer Update on Pathology

Zhaolin Xu, MD, FRCPC, FCAP

Professor, Dept of Pathology, Dalhousie University
Pulmonary Pathologist and Cytopathologist, QEII HSC
Senior Scientist, Beatrice Hunter Cancer Research Institute
DISCLOSURE

Grants/research support: Pfizer, Roche, Boehringer Ingelheim, Eli Lilly, Merck Canada

Speaker’s bureau/honoraria: Pfizer, Roche, Boehringer Ingelheim, AstraZeneca, Merck Canada, Novartis, Bristol-Myers Squibb
Objectives:

• To review the changes in the 2015 WHO lung carcinoma classification
• To describe molecular profiling in lung cancer
• To introduce lung cancer immunotherapy with its implication in pathology
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Preinvasive lesions

• For adenocarcinoma
  – Atypical adenomatous hyperplasia
  – Adenocarcinoma in situ

• For squamous cell carcinoma
  – Squamous cell carcinoma in situ

• For neuroendocrine tumors
  – Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
Minimally invasive/Lepidic
Micropapillary adenocarcinoma
Enteric adenocarcinoma

- It resembles colorectal adenocarcinoma
- The enteric pattern > 50%
- IHC may be identical to or different from colorectal adenocarcinoma (CK7, CK20, CDX2, TTF-1)
- Clinical correlation
Enteric adenocarcinoma
# WHO Lung Squamous Cell Carcinoma

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# WHO Lung Squamous Cell Carcinoma

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<td>Sq Ca Papillary Clear cell Small cell Basaloid</td>
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## WHO Lung Squamous Cell Carcinoma

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Squamous Cell Carcinoma
## WHO Large Cell Carcinoma

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<td>Basaloid</td>
<td>Lymphoepithelioma-like</td>
<td>Rhabdoid</td>
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## WHO Large Cell Carcinoma

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<td>Rhabdoid</td>
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Neuroendocrine tumors

- Typical carcinoid
- Atypical carcinoid
- Large cell neuroendocrine carcinoma
- Small cell carcinoma
Other/Unclassified

• Lymphoepithelioma-like carcinoma
• NUT carcinoma
  – An aggressive tumor with NUT (nuclear protein in testis) gene rearrangement t(15;19), t(15;9)
  – Sheets and nests of monomorphous small to intermediate cells
  – Abrupt foci of keratinization
  – Positive for NUT antibody, CK, P63/P40, CD34
  – May also positive for neuroendocrine markers, TTF-1
NUT carcinoma
## Five-year relative survival (%)

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<td>63</td>
<td>67</td>
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<td>Lung and bronchus</td>
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<td>13</td>
<td>15</td>
<td>18</td>
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<td>Breast (female)</td>
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<td>79</td>
<td>88</td>
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<td>Prostate</td>
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<td>75</td>
<td>97</td>
<td>99</td>
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<td>Colon &amp; rectum</td>
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<td>58</td>
<td>62</td>
<td>66</td>
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<td>Stomach</td>
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<td>18</td>
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<td>87</td>
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<td>Non-Hodgkin lymphoma</td>
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<td>52</td>
<td>59</td>
<td>70</td>
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<td>Ovary</td>
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<td>38</td>
<td>44</td>
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<td>Urinary bladder</td>
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<td>Mesothelioma</td>
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<td>10</td>
<td>13</td>
<td>20</td>
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<td>Livre</td>
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<td>9</td>
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<td>Kidney</td>
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<td>55</td>
<td>63</td>
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<td>Uterus</td>
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<td>82</td>
<td>84</td>
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<td>Cervix</td>
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<td>67</td>
<td>73</td>
<td>69</td>
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Source: Surveillance, Epidemiology, and End Results (SEER)1975-2012, National Cancer Institute.
Lung cancer survival rates

Median survival 8 months, 1 year survival 30%

Schiller JH et al. NEJM Jan. 2002

Blue – cases  Red -5 year survival

A – Localized
B – Regional node metastasis or directly beyond primary site
C – Distant metastasis
D – Unknown stage
E – Overall

Cases 5 y survival %

A
B
C
D
E

0 10 20 30 40 50 60 70 80 90 100
%
What do we learn from the history?

- Surgical treatment is effective but has limitations
- Majority of the lung cancer cases with no surgical indications at the time of diagnosis
- Chemotherapy / radiation is palliative
- Solutions
  - Prevention
  - Early detection
  - New modalities
Relevant mutations in Non-small cell lung carcinoma

Sequist et al. 2011
Mutations in cancer types

Adenocarcinoma  n=438

- EGFR 10%
- KRAS 36%
- BRAF 1%
- PIK3CA 1%
- ALK 0.2%
- HER2 0%
- No mutation 52%

Squamous cell carcinoma  n=166

- EGFR 0.6%
- KRAS 1.8%
- BRAF 0%
- PIK3CA 2.4%
- ALK 0%
- HER2 0%
- No mutation 95%

QEII HSC data unpublished
EGFR mutations

**Mutations associated with drug resistance**

- T790M (50%)*
  - D770_N771 (ins NPG)
  - D770_N771 (ins SVQ)
  - D770_N771 (ins G), N771T
  - V789L
  - S789I

- D781Y (<1%)

**Exon 19**

- G719C
- G719S
- G719A
- V689M
- N700D
- E709K/Q
- S720P

(5%)

**Exon 20**

- ΔE746-A750
- ΔE746-T751
- ΔE746-A750 (ins RP)
- ΔE746-T751 (ins A/I)
- ΔE746-T751 (ins VA)
- ΔE746-S752 (ins A/V)
- ΔL747-E749 (A750P)
- ΔL747-A750 (ins P)
- ΔL747-T751
- ΔL747-T751 (ins P/S)
- ΔL747-S752
- ΔL747-T752 (E746V)
- ΔL747-T752 (P753S)
- ΔL747-S752 (ins Q)
- ΔL747-P753
- ΔL747-P753 (ins S)
- ΔS752-I759

(45%)

**Exon 21 (activation loop)**

- L858R (40–45%)
  - R859S
  - E799T
  - K746R
  - L851Q
  - G779D

(40–45%)

**Exon 18** (nucleotide-binding loop)

- (5%)
EML4-ALK gene rearrangement

FISH Assay for ALK Rearrangement*

Telomere  2p23 region  Centromere

ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]

*Assay is positive if rearrangements can be detected in ≥15% of cells
FISH = fluorescence in situ hybridization

Horn L, Pao W JCO 2009;27:4232-4235
TKI Targeted therapy

• **EGFR mutations**
  – TKIs – gefitinib, erlotinib, afatinib, AZD9291, CO-1686
  – ORR 68%, DCR 86%, median PFS 12 m, OS 23.3 m
  – ↑PFS, quality of life, safety profile, convenience
  – EGFR exon 19 deletion in which afatinib vs chemotherapy median survival 31.7 : 20.7 m p<0.0001

• **ALK gene rearrangement**
  – ALK TKI – crizotinib, ceritinib, alectinib
  – In 1\(^{\text{st}}\) line setting vs chemotherapy: ORR 74% vs 45%, PFS 10.9 vs 7.0 m, but no OS benefit
  – Phase 3 in 2\(^{\text{nd}}\) line setting vs chemotherapy: ORR 65% vs 20%, PFS 7.7 vs 3.0 m but no OS benefit
Atlantic Molecular Profiling Network

- Role of central lab (Atlantic Canada Molecular Oncology Centre)
- Started lung cancer molecular tests since Sept. 2012
- Multiplexed genotyping
- Tests including EGFR, KRAS, BRAF, PIK3CA, Her2 and ALK
- Volume of molecular tests
  - About 2400 cases in total (2012-2015)
  - QE II 50%, all other centers 50%
  - >90% are for adenocarcinoma
- Reflexive testing
## Case distribution

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<td>311</td>
<td>492</td>
<td>361</td>
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<td>400</td>
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<td>564</td>
<td>422</td>
<td>1423</td>
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<td>96</td>
<td>721</td>
<td>892</td>
<td>742</td>
<td>2451</td>
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Consideration for lung cancer molecular profiling

- Testing all bronchogenic adenocarcinoma cases
- Testing squamous cell carcinoma if a non-smoker, young age, family history
- Neuroendocrine carcinoma almost always negative
- Multiplexed genotyping approach
- Next generation sequencing
- Reflexive testing
- Consent issue
- Sample requirement
- Turn around time (2-3 w)
Specimen requirement

- **Biopsy specimen**
  - Formalin fixed paraffin embedded tissue
  - Tumor size $\geq 1\text{mm}^2$, tumor cells $\geq 10\%$ for molecular tests
  - Formalin fixation time 8-36 h

- **Cytology specimen (FNA)**
  - Formalin fixative
  - Cell block
  - Enough tumor cells available

- **Tissue processing / cutting**
  - Routine histology preparation
  - Consideration for possible tests
  - Consecutive cutting at once if possible
PD-L1/PD1 in immunotherapy
PD-L1/PD1 in immunotherapy
PD-L1/PD1 in immunotherapy

Tumor cell

PD1

PD-L1

MHC

TCR

T cell
PD-L1/PD1 in immunotherapy

Tumor cell

MHC

T cell

PD1

PD-L1

TCR
PD1/PD-L1 in immunotherapy

- PD1 expressed in cytotoxic T cells
- PD-L1 expressed in tumor cells
- PD1 binding to PD-L1 inactivates cytotoxic T cells
- Blocking PD1/PD-L1 binding resumes T cell’s cytotoxic function
- Either blocking PD1 or PD-L1 is effective in anticancer effect
- PD-L1 tests
  - Two diagnostic platforms
  - Five companion diagnostics
# PD-L1 testing in clinical trials

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<th>Nivolumab</th>
<th>Pembrolizumab</th>
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<td>Tumor cells</td>
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<td>Tumor and immune cells</td>
<td>Tumor and immune cells</td>
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| Detailed cut-off | ≥ 1%  
≥ 5%  
≥ 10% | < 1%  
1-49%  
≥ 50% | TC3 (≥ 50%) or IC3 (≥ 1%)  
TC2/3 (≥ 5%) or IC2/3 (≥ 5%)  
TC1-3 (≥ 1%) or IC1-3 (≥ 1%)  
TC0 (< 1%) and IC0 (< 1%) | TC (≥ 1%)  
TC (≥ 5%)  
TC (≥ 25%)  
IC (≥ 10%) | 25% |
| Health Canada    | NSCLC, Melanoma | NSCLC Melanoma | No | No | No |
| FDA              | NSCLC, Melanoma, Advanced RCC | NSCLC Melanoma | “Breakthrough” for bladder and lung cancer | “Breakthrough” for Merkel cell carcinoma | “Breakthrough” for bladder cancer |
Blueprint proposal

• FDA, AACR, ASCO convened a workshop titled “Complexities in Personalized Medicine: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies” on March 24, 2015
• An industry work group volunteered to develop a blueprint proposal
• The goal: to agree and deliver a package of information/data upon which analytic comparison of the various diagnostic assays may be conducted, potentially paving the way for post-market standardization and/or practice guideline development as appropriate.
• Blueprint Working Group Members:
  – Steven Averbuch, VP, Bristol-Myers Squibb
  – Kenneth Emancipator, Executive Medical Director, Merck Research Laboratories
  – Ian McCaffery, Head, Companion Diagnostic Development, Genentech
  – Abigail McElhinny, VP, Ventana Medical Systems Inc.
  – Dave Stanforth, Director, Companion Diagnostics, Agilent Technologies
  – Jill Walker, Executive Director, Companion Diagnostic Development, AstraZeneca
  – Doug Ward VP & General Manager, Ventana Medical Systems Inc.
Blueprint preliminary results

- Compared 4 assays: Dako 28-8 (BMS), 22C3 (Merck), and Ventana SP263 (AstraZeneca), Ventana SP124 (Roche).
- Approximately 39 tumor biopsy samples from patients with NSCLC were assessed.
- 3 assays (Dako/BMS, Dako/Merck, and Ventana/AstraZeneca) had a high degree of concordance comparing each other.
- The results of this preliminary study should not alter current guidelines as indicated for each therapeutic-diagnostic validated combination pair.
Consideration for PD-L1 testing

• Testing PD-L1 for non-small cell lung cancer cases
• Along with other molecular tests if possible
• Reflexive testing approach
• Using validated companion diagnostics
  – Antibody
  – Assay protocol
  – Assessment
• Turn around time 2-3 d
Prospective cancer diagnosis