Update on 2021 WHO Classification of Lung Tumors

Anja C. Roden, MD

Department of Laboratory Medicine and Pathology

Presenter:

Anja C. Roden, M.D.
Professor of Laboratory Medicine and Pathology
Division of Anatomic Pathology

Department of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, Minnesota
Disclosure

• No disclosures

Outline

• New entities and terminology in 2021 WHO classification
• Thoracic SMARCA4-deficient undifferentiated tumor
• Bronchiolar adenoma/ciliated muconodular papillary tumor
• Nomenclature in small biopsies
• Spread through airspaces (STAS)
Cancer Deaths in 2021 (US)

**Males**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Deaths</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Lung</td>
<td>69,410</td>
<td>22%</td>
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<tr>
<td>Prostate</td>
<td>34,130</td>
<td>11%</td>
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<td>Colon &amp; rectum</td>
<td>28,520</td>
<td>9%</td>
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<tr>
<td>Pancreas</td>
<td>25,270</td>
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<td>Liver &amp; intrahepatic bile duct</td>
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<td>Leukemia</td>
<td>13,900</td>
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<tr>
<td>Esophagus</td>
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<td>Urinary bladder</td>
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<td>Non-Hodgkin lymphoma</td>
<td>12,170</td>
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<tr>
<td>Brain &amp; other nervous system</td>
<td>10,500</td>
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<tr>
<td><strong>All Sites</strong></td>
<td>319,420</td>
<td>100%</td>
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**Females**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Deaths</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Lung</td>
<td>62,470</td>
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<tr>
<td>Breast</td>
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<td>Colon &amp; rectum</td>
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<td>Uterine corpus</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
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<td>Leukemia</td>
<td>9,760</td>
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<td>Non-Hodgkin lymphoma</td>
<td>8,550</td>
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<tr>
<td>Brain &amp; other nervous system</td>
<td>8,100</td>
<td>3%</td>
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<tr>
<td><strong>All Sites</strong></td>
<td>289,150</td>
<td>100%</td>
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Canada Cancer Registry Database. With permission. Accessed 6/2021

Lung Cancer Incidence (Canada)

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<tr>
<th>Year</th>
<th>AdenoCa</th>
<th>SQCC</th>
<th>Large cell Ca</th>
<th>NSCLC, NOS</th>
<th>SCLC</th>
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Age-standardized rate (per 100,000)
Lung Cancer

- 26% of NSCLC patients alive ≥ 5 years after diagnosis
- 5-yr survival rate for metastatic disease
  - 6% with chemo
  - 15-50% if eligible for targeted therapies or immunotherapies
→ Biomarker testing

Lung Tumors – 2021 WHO

- No major changes
- New entities or terminology:
  - Thoracic SMARCA4-deficient undifferentiated tumor
  - Bronchiolar adenoma/ciliated muconodular papillary tumor
  - Lymphoepithelioma-like carcinoma → Lymphoepithelial carcinoma
  - Enteric adenocarcinoma → enteric-type adenocarcinoma
- 8th edition of AJCC/UICC TNM staging (2017)
Thoracic SMARCA4-Deficient Undifferentiated Tumor

- 66 yo male
- Smoker
- Left suprahilar mass
- Additional masses in right lung, liver, adrenal gland
Differential Diagnosis

- Poorly differentiated non-small cell carcinoma
- Lymphoma
- Malignant melanoma
- Sarcoma

Neg: NUT, desmin, SMA, CD20, CD31, CD45, SALL-4, S100, multiple keratins; INI-1 expression preserved
Thoracic SMARCA4-deficient undifferentiated tumor

- Median age, 39-59 years (range, 27-90)
- Male (9:1) & smoker predominance
- Rapidly progressive tumors
- Mediastinum > pulmonary hilum, pleura with or w/o chest wall
- Often multiple sites and metastatic (77-83%)
- Tumor diameter, median, 13 cm (3.5 – 21 cm)
SMARCA4-UT

- Rhabdoid and/or poorly differentiated morphology
- Variably discohesive
- Focal myxoid stroma or desmoplastic small round cell tumor – features (7%)

SMARCA4-UT

- Loss of BRG1 (& BRM) expression (25% - diffuse severe reduction)
- Preserved INI-1 expression
- Commonly + for SOX2, CD34 and/or SALL4
- +/- Keratin (focal), claudin 4 (rare), TTF-1 (rare), synaptophysin
- Neg: Desmin, NUT, S100, p40
**SMARCA4-UT**\(^5,6\)

- *SMARCA4* (BRG1) - member of SWI/SNF (BAF) chromatin-remodeling complex
  - Tumor suppressor
  - Regulates transcription
  - Promotes cell differentiation
- Biallelic inactivation of *SMARCA4*
- No germline *SMARCA4* mutation
- *TP53* mutation (69% of cases)

**SMARCA4-UT**\(^6\)

- Median survival, 4-7 months; local complications
- Limited response to chemotherapy & surgery
SMARCA4-UT - Differential Diagnosis\(^6\)

- NUT carcinoma
- Germ cell tumor
- Neuroendocrine carcinoma
- Lymphoma
- Melanoma
- Sarcomas
- SMACRA4-deficient NSCLC (5% of NSCLC)
- Metastatic SMACRA4-deficient carcinoma (uterus, ovary, stomach, kidney, pancreas)

Bronchial Adenoma / Ciliated Muconodular Papillary Tumor\(^7-10\)

- Benign, no recurrence or metastasis
- Peripheral, peribronchiolar, not associated with proximal bronchi
- CT: solid or ground glass nodules, some with cavitation
- Middle age to elderly, median age, 72 yo, no sex predilection
- Tumor diameter 0.6-2.5 cm
BA / CMPT

- Peribronchiolar
- Papillary and/or flat (glandular) architecture
Bronchial Adenoma / Ciliated Muconodular Papillary Tumor

- Peribronchiolar
- Papillary and/or flat (glandular) architecture
- Bilayered
  - Luminal epithelial cells (mucous cells and ciliated cells or cells resembling type II pneumocytes and club cells)
  - Continuous basal cell layer → p40 and TTF-1 helpful
- No nuclear atypia; rare mitoses
- Potential molecular alterations: *BRAF, EGFR, KRAS, HRAS, ALK, AKT1*
**BA/CMPT**

**Differential Diagnosis**

- Adenocarcinoma (including AIS) – lacks continuum of basal cell layer
- Papilloma (central, endobronchial)
- Peribronchiolar metaplasia
  - Lack of expression of BRAF, ALK
  - Ill-defined borders
  - Often multicentric
  - Background of ILD or small airways disease

**Small Biopsies**

**2021 WHO – Nomenclature**

- Adenocarcinoma
- Squamous cell carcinoma
- Adenocarcinoma with lepidic pattern
- NSCC – favor adenocarcinoma
- NSCC – favor squamous cell carcinoma
- NSCC with spindle and/or giant cell features
- NSCC, NOS
- Small cell carcinoma
- NSCC with neuroendocrine morphology and positive neuroendocrine markers, possible large cell neuroendocrine Ca
• 77-yo female
• 0.8 cm RUL nodule found incidental
• Medically complex history → no surgical candidate

Invasive non-small cell carcinoma, favor adenocarcinoma
77-yo female with clinically recurrent lung carcinoma
NSCC NOS; Squamous cell and adenocarcinoma patterns both present (see comment)

Small Biopsies
Tissue Preservation

- Divide cores $\rightarrow \geq 2$ blocks
- IHC based on morphology
- Dual stains: TTF-1 / p40
  p40 / Napsin
  CK5 / TTF-1
- Neuroendocrine markers only if morphology indicates
- If ordering stains – get unstained (be aware of short shelf-life of unstained slides)
Spread Through Airspace (STAS)\textsuperscript{11,12}

- Tumor cells within airspaces beyond the edge of main tumor
- Present in 15-56% of NSCLC
- Patterns: Micropapillary structures
  - Solid tumor cell nests
  - Discohesive single tumor cells
- Occurs in adenocarcinoma, SQCC, neuroendocrine neoplasms (all subtypes), pleomorphic carcinoma
- Not included in tumor size
Spread Through Airspace (STAS)\textsuperscript{13}

- Reduced recurrence free and overall survival in any stage lung adenocarcinoma
- Associated with aggressive pathologic features, KRAS mutations in stage I-II adenocarcinoma; among other associations
- Limited resection (wedge resection, segmentectomy) – possibly higher risk for recurrence than lobectomy
- If present in sublobar resection → might be indication for subsequent lobectomy

Take Home Message

- Thoracic SMARCA4 deficient undifferentiated tumor
- Bronchiolar adenoma/ciliated muconodular papillary tumor
- Small biopsies – preserve tissue
- Spread through airspace (STAS)
References

References


