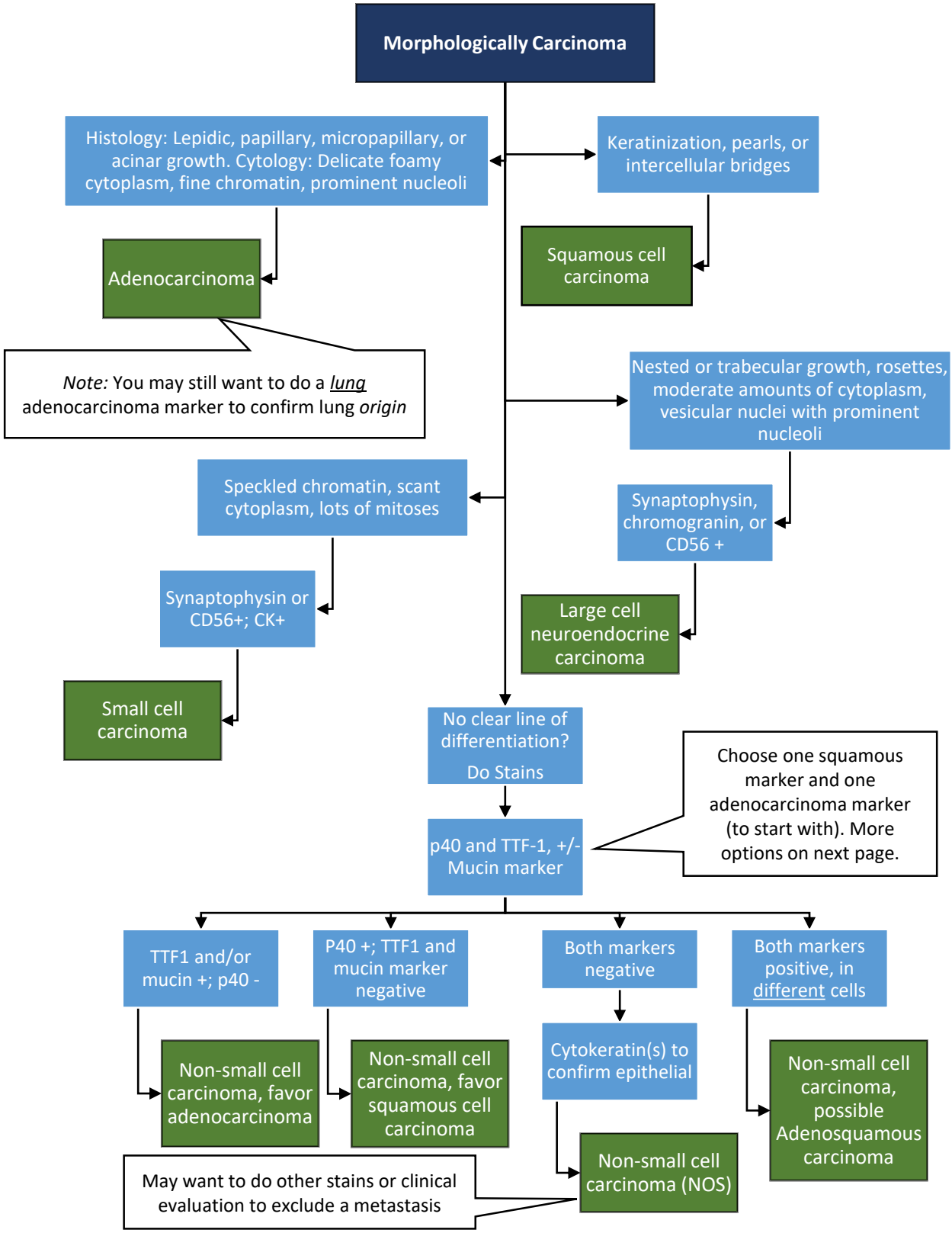
Classification of Lung Carcinomas with Limited Tissue

Prepared by Kurt Schaberg

Diagnostic Algorithm

Try to be as *specific* as you can be, while also *sparing* as much tissue as you can for molecular testing (critical for lung cancer!)



Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015.

Classification Guidelines

Some carcinomas can only be diagnosed on ***resection*** (not on Bx): Adenocarcinoma in situ, Minimally invasive carcinoma, Adenosquamous carcinoma, Large cell carcinoma, Sarcomatous carcinoma

If you can make the diagnosis morphologically → can call Adenocarcinoma or Squamous cell carcinoma

If can't tell *morphologically*, then do stains:
A simple panel of 2 stains (1 squamous and 1 adenocarcinoma) is usually adequate (e.g., p40 and TTF1)
A positive mucin stain (e.g., PAS-D, or mucicarmine) can also identify some adenocarcinomas.
Report as "Non-small cell carcinoma, favor…." (either adenocarcinoma or squamous cell carcinoma)
Do not do neuroendocrine stains unless there are morphologic findings to suggest neuroendocrine differentiation (neuroendocrine differentiation in an SCC or adeno doesn't impact treatment/prognosis).

Immunohistochemical Staining

Adenocarcinoma	Squamous cell carcinoma
TTF1	p40 (most specific)
Napsin A	CK5/6
CK7 (less specific)	p63 (less specific)

Note: Some primary lung adenocarcinomas, including Mucinous adenocarcinoma, Colloid carcinoma, and Enteric adenocarcinoma, can be TTF-1 negative. They can even stain with CK20 and CDX2. These cases require careful clinical correlation to exclude a metastasis from the GI tract.

Adenocarcinoma Subtypes/Patterns

Use for non-mucinous adenocarcinomas. If an adenocarcinoma subtype/architectural pattern is identified on biopsy, it should be reported. Report in 5% increments and classify based on predominant pattern.

Subtype	Characteristics
Lepidic	Growing along the surface of alveolar walls (like AIS), non-invasive
Acinar	Round to oval glands with a central lumen space surrounded by tumor cells
Papillary	Glands growing along central fibrovascular cores
Micropapillary	Cells growing in papillary tufts forming florets that lack fibrovascular cores (poorer prognosis)
Solid	Polygonal tumor cells growing in sheets (poorer prognosis)

If exclusively lepidic on biopsy report as "Adenocarcinoma, lepidic pattern" (or something similar). On resection, this could represent Adenocarcinoma in situ (AIS), Minimally invasive adenocarcinoma, or simply a lepidic component of an invasive adenocarcinoma. Radiographic correlation is required pre-operatively.

Criteria for invasion: 1)histologic subtype other than lepidic (e.g., acinar), 2)desmoplastic stroma associate with tumor, 3)vascular or pleural invasion, or 4)Spread through air spaces (STAS)

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Lung Neuroendocrine Tumors

Note: Lung neuroendocrine neoplasms are graded based on mitoses and necrosis. Ki67 may be helpful to confirm your morphologic impression, but is not currently used for grading (unlike in the GI tract).

	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell carcinoma
Smoking association	No	Maybe	Yes	Yes
Mitoses/2mm^2	0-1	2-10	>10 (median 70!)	>10 (median 80!)
Necrosis	No	Focal, if any	Yes	Yes, extensive
Neuroendocrine morphology	Yes	Yes	Yes	Yes
Ki-67 Proliferation index	Up to 5%	Up to 20%	40-80%	Almost 100%
TTF1 expression	Usually not	Usually not	~50%	Usually, Yes (85%)
Combined with non-small cell component (e.g., squam)	No	No	Sometimes	Sometimes

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Criteria for Diagnosis:

Typical Carcinoid: A tumor with "carcinoid morphology" (organoid or trabecular growth, uniform polygonal cells, finely granular "salt and pepper" chromatin, inconspicuous nucleoli, abundant eosinophilic cytoplasm) and <2 mitoses per 2 mm^2, lacking necrosis, and >0.5cm (if less than 0.5 cm, it is designated as a "tumorlet").

Atypical Carcinoid: A tumor with "carcinoid morphology" and 2-10 mitoses per 2 mm^2 and/or necrosis (often punctate).

Large Cell Neuroendocrine Carcinoma: A tumor with:
1) "Neuroendocrine morphology" (organoid nesting, palisading, rosettes, trabeculae)
2) High mitotic rate: >10 mitoses per 2 mm^2 (median 70)
3) Necrosis (often large zones)
4) Cytological features of non-small cell carcinoma: large cell size, vesicular, coarse, or fine chromatin, frequent nucleoli, and abundant cytoplasm (low N:C ratio)

Small Cell Carcinoma: A tumor with:
1) Small cell size (usually smaller than 3 resting lymphocytes)
2) Scant cytoplasm
3) Finely granular chromatin (no nucleoli)
4) High mitotic rate: >10 mitoses per 2 mm^2 (median 80)
5) Frequent necrosis (often large zones)

Lung Cancer Molecular *(basic)*

Major Genetic Changes

~70% of lung cancers are inoperable
→ Dx and all testing done on core Bx or FNA

Must test **Adenocarcinoma** for: EGFR, ALK, ROS1 in all cases (molecular/FISH/IHC); PD-L1 (IHC)
Consider testing for: BRAF, KRAS, HER2, RET,
(Can consider some of these tests in non-adenocarcinomas if mixed histology or small biopsy)

Alteration	Small cell carcinoma (%)	Adenocarcinoma (%)	Squamous cell carcinoma (%)
Mutation			
EGFR Caucasian	<1	10-20	<1
EGFR Asian	<5	35-45	<5
KRAS Caucasian	<1	15-35	<5
KRAS Asian	<1	5-10	<5
BRAF	0	<5	0
PIK3CA	<5	<5	5-15
RB	>90	5-15	5-15
P53	>90	30-40	50-80
Amplification			
EGFR	<1	5-10	10
FGFR1	<1	<5	15-25
MYC	20-30	5-10	5-10
Gene Rearrangement			
ALK	0	5	<1
ROS1	0	1-2	0
NTRK1	0	<1	0

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Driver mutations are essential for tumor survival ("oncogene addiction"), so targeting them results in cancer cell death.

EGFR mutations→ can treat with receptor tyrosine kinase inhibitors: **E**rlotinib, gefitinib, afatinib, etc.
→ Eventually develop acquired resistance (usu. < 1 yr); Most commonly T790M mutation
KRAS mutations→ resistant to EGFR-targeted therapy (and no current specific treatments)
AL**K** and ROS1 rearrangement→ respond to **c**rizotinib

Associations

Adenocarcinomas:
EGFR and ALK→ usually never smokers, Asian, non-mucinous, peripheral location
KRAS→ usually smokers, mucinous, non-Asians, perihilar location (like small cell and SCC)
ALK rearrangements→ usu. Young, never smokers, associated with cribriform morphology