INTERNATIONAL SYMPOSIUM ON LUNG CANCER AND BRONCHOSCOPY

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WHO INTERNATIONAL CLASSIFICATION OF TUMOURS, HİSTOLOGICAL TYPING OF LUNG AND PLEURAL TUMOURS.

Third edition was published in 1999. The aim of this series of publications by the WHO is to facilitate the world-wide adoption of a uniform nomenclature. The third edition represent an advance over its predecessors in a number of respects, although there are some continuing limitations. The major classification of malignant epithelial tumours is into:

- squamous cell carcinoma and its variants
- small cell carcinoma and its variants
- adenocarcinoma and its variants
- large cell carcinoma and its variants, including large cell neuroendocrine carcinoma
- adenosquamous carcinoma
- pleomorphic, sarcomatoid and giant cell carcinoma
- typical carcinoid
- atypical carcinoid

The spectrum of neuroendocrine tumours is addressed at some length. The question is addressed as to whether all neuroendocrine tumours should be grouped together? If this were to be done, small cell carcinoma, large cell carcinoma with neuroendocrine differentiation, typical carcinoid and atypical carcinoid would be grouped together. Such a conceptual grouping would have some merit since they share certain morphological, ultrastructural, immunohistochemical and molecular characteristics, and the differentiation between these entities can pose problems for the histopathologist. Although the actual classification did not adopt this grouping, the dividing lines between neuroendocrine tumours has been more precisely defined. Typical carcinoids must have fewer than 2 mitoses per 2 mm^2, while atypical carcinoids have between 2 and 10 mitoses per 2 mm^2. Both large cell carcinoma with neuroendocrine differentiation and small cell carcinoma have more than 2 mm^2, typical having counts well in excess of this threshold: the distinction between the two is morphological.

Heterogeneity: almost 50% of lung carcinomas exhibit more than one of the major histological types. The third edition sets minimum requirement of 10% of each component for adenosquamous carcinoma. Similarly, there is a minimum requirement for 10% of a carcinoma to show pleomorphic features for it to be classified under this heading. The choice of 10% is arbitrary, but should help to increase the reproducibility of the classification of tumours.

Because of the heterogeneity of lung carcinomas, there is a particular problem of sampling error with small biopsies. For example, one study comparing the classification of lung carcinomas on bronchial biopsy with that of subsequent thoractomy specimens, found kappa coefficients of 0.77 for adenocarcinoma, 0.74 for squamous carcinoma, 0.60 for small cell carcinoma and 0.49 for large cell carcinoma. Clinicians should be aware of the limitations of the histological diagnosis on bronchial biopsy. Fortunately, classification as non-small cell or small cell carcinoma is often sufficient for treatment.

Immunohistochemistry is a very useful ancillary investigation in classifying lung tumours. However, the WHO Classification puts relatively little emphasis on this, in part because the technique is not available world-wide.

PRACTICAL DIFFICULTIES IN INTERPRETING BIOPSIES

Having considered some theoretical aspects, I would like to give some examples of the difficulties in the interpretation of bronchoscopic biopsies:

Crushed small cell carcinoma vs lymphocytic infiltrate: immunohistochemistry is extremely useful. Small cell carcinomas are typically positive for cytokeratins and for CD56, while lymphocytes are positive for lymphocyte common antigen. It would, however, be foolhardy to render a definite diagnosis on a completely crushed specimen.

Squamous dysplasia overlying small cell carcinoma: there is the potential for misdiagnosing squamous cell carcinoma on a superficial biopsy in a patient who has an obvious tumour at bronchoscopy.

Small cell variant of squamous cell carcinoma: Positivity for CD56 would favour small cell carcinoma. Cytokeratin 14 is potentially useful for identifying variants of squamous cell carcinoma.

Typical carcinoid vs atypical carcinoid: The size of many biopsies may preclude an accurate mitotic count; a larger biopsy using a rigid bronchoscope may be necessary.

Carcinoid vs small cell carcinoma: With a small crushed specimen, this differential may be difficult.

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Small cell carcinoma vs large cell neuroendocrine carcinoma: The term intermediate cell type has been dropped. However, it needs to be realised that small cell nuclei can be relatively large and may show some nucleoli. Immunohistochemistry will not help.

Carcinoma vs epithelioid haemangioendothelioma: The latter is variably positive for vascular markers (CD31, CD34 and factor VIII related antigen) but may also be positive for cytokeratins.

Inflammatory pseudotumour vs spindle cell carcinoma: We have seen an example in a 29-year-old lifelong non-smoker who remains well after several years without treatment. The inflammatory pseudotumour showed some positivity for cytokeratins; this has been reported previously in inflammatory pseudotumours at other anatomical sites, particularly the bladder, but not to our knowledge in the lung.

Carcinoma vs DIP: We have also seen a case that was diagnosed by multiple experts as desquamative interstitial pneumonitis, but as post mortem was found to be a well-differentiated adenocarcinoma; cytokeratin positivity would have been helpful in this case.

CARCINOMA OF LUNG-IS IT A PRIMARY OR IS IT A METASTASIS?

The most important source of information is the clinician: has the patient any history of a previous tumour or any symptoms that might suggest an extra-pulmonary tumour.The most useful markers are: Thyroid transcription factor -1 (TTF-1), which is expressed mainly by lung and thyroid, and tumours thereof. (If TTF-1 positive, negativity for thyroglobulin excludes a thyroid primary) Specific cytokeratins 7 and 20.

Squamous carcinoma: not usually a problem. This is fortunate, because immunohistochemistry has very little to contribute to the diagnostic process for squamous cell carcinomas.

Small cell carcinoma: not usually a problem with lung biopsies. If metastatic disease in the skin is biopsied, there is a need to differentiate from Merkel cell tumour.

	TTF-1	cytokeratin 20
small cell carcinoma of lung	90% positive	2% positive
extra-pulmonary small cell carcinoma	36% positive	4% positive
Merkel tumour	negative	92% positive

If a small cell carcinoma is negative for TTF-1, it is less likely to be of pulmonary origin, but positivity for TTF-1 does not demonstrate that it is on pulmonary origin.

Adenocarcinoma: the major problem. Use of TTF-1 and cytokeratins 7 and 20.

	TTF-1
pulmonary adenocarcinoma	75%
non-pulmonary adenocarcinoma (excluding thyroid)	1%

Positivity for TTF-1 proves beyond reasonable doubt that an adenocarcinoma is a primary of lung. Negativity for TTF-1 does not prove that an adenocarcinoma is metastatic from and extra-pulmonary site. Clinicians need to understand the significance of a pathologist saying "not a proven lung primary". The probability that a TTF-1 negative tumour is metastatic to the lung is a function of the prior probability of it being metastatic.

If an adenocarcinoma is negative for TTF-1, cytokeratins 7 and 20 may be helpful. These tow cytokeratins are most powerful when used in combination. Thus CK7-/CK20+ does not occur in primary lung adenocarcinoma but is typical of colorectal adenocarcinoma. The converse is true of CK7+/CK20-. The other combinations (CK7+/CK20+ and CK7-/CK20-) are uninformative in deciding between these two primary sites. If the patient's previous history or the morphology of the tumour suggests a differential a lung primary and a metastasis from kidney, the combination CK7+/CK20- would favour lung, while CK7-/CK20- would favour kidney, modifying the prior probabilities, without giving a categorical answer.

Adenocarcinoma vs mesothelioma is a huge subject in its own right and I cannot address it here.