

SPAN Lung Pathology Interest Group

Background

The subtyping of Non-small cell carcinomas (NSCLC) on small biopsy samples and cytology specimens can be challenging. A proportion of cases will lack the diagnostic features, as defined in the WHO classification of lung tumours, required for definitive diagnosis of squamous cell or adenocarcinoma. The recommended approach was to report such cases as NSCLC, not further or otherwise specified (NSCLC, NOS). A diagnosis of large cell carcinoma should NOT be given in these circumstances.

Reported figures vary but contemporary data from pathology departments in Scotland have consistently shown a NSCLC, NOS rate of around 20 - 40% for the range of samples on which a lung cancer diagnosis may be made. The actual figures will vary between centres and on the sample type; rates are generally lower for biopsy samples when compared to cytology preparations. These data also suggest that, where the NOS rate is at this level, the *accuracy* of squamous cell and adenocarcinoma classification on small diagnostic samples is quite high (>80%), when compared to a subsequent surgical resection specimen 'gold standard' diagnosis. In Scotland, of course, around 90% of lung cancer tissue diagnoses are made only on small biopsy / cytology samples with no subsequent surgical resection.

Recent work has demonstrated differential efficacy of number of so-called targeted or biological agents used to treat advanced NSCLC, according to tumour cell type. Some data also shows differential response by tumour histology, for the more traditional cytotoxic agents. It is highly likely that in the near future, oncologists will be tailoring drug therapy in NSCLC according to cell type. This will be driven by a number of circumstances where use of the drug will be stipulated by licence, contraindicated due to risk of side effects or recognised better efficacy. This means that there will be a need for as specific a diagnosis as possible on all sorts of small biopsy and cytology samples showing evidence of lung cancer. It is likely that pathologists will feel 'pressure' to report fewer cases as 'NSCLC, NOS' and to be more specific ie adeno or squamous cell carcinoma for example. In some cases the oncologist might need to know the tumour is (likely to be) adenocarcinoma or 'not squamous'.

In practice

In those cases which are specifically classifiable as adenocarcinoma or squamous cell carcinoma on the H&E, no change is required.

For those cases where the features do not allow a more specific classification than NSCLC, NOS, immunohistochemistry can be used to predict the likely tumour histology. The following is based on work done in Aberdeen, using bronchial biopsy samples reported as NSCLC, NOS, from patients who subsequently had their tumours resected. In this way the accuracy of the IHC prediction on the pre-operative material can be measured.

A mucin stain (combined Alcian Blue –PAS without nuclear counterstain) and IHC for TTF1 (Dako 1:50) were used as putative markers for adenocarcinoma.

A number of putative markers for squamous cell carcinoma were tested. IHC for p63 (Novocastra 1:50) gave the best PPV/NPV/specificity & sensitivity. IHC for CK5/6 (Zymed 1:200) was almost as good. HMW CK (34betaE12) and S100A7 were inferior in these tests.

When published, details of the study will be provided on this site.

In practice, we are now using AB/PAS, TTF1, p63 (and although not strictly necessary, CK5/6) on all our NSCLC, NOS biopsies to help predict likely tumour histology.

Any AB/PAS positive cells are taken as predicting an adenocarcinoma.
Any TTF1 positivity is taken as predicting adenocarcinoma.

A p63 or CK5/6 predictive of squamous histology was defined as moderate to strong staining of more than 10% of cells. In most cases staining is moderate / strong with most cells positive. Lesser levels of staining are NOT predictive.

At these defined levels IHC & mucin staining levels, 80% of NSCLC, NOS cases have 'predictive' IHC results. The accuracy of prediction is around 83%. Most squamous carcinomas are identified; some adenocarcinomas fail to express mucin or TTF1 in small biopsies; some true large cell carcinomas have specific cell type IHC results. None of these markers are absolutely type-specific, thus:

Positive cases are reported as NSCLC, probably adeno or squamous cell carcinoma, as appropriate.

Of the 20% or so which DO NOT show predictive IHC, what we have called 'null' IHC, about half these cases are still adenocarcinoma on resection, occasional cases are squamous and around a third are true large cell carcinomas, with 'null' IHC.

Some illustrative images will be posted to assist interpretation. There is no reason why this should not be applied to any biopsy sample. Cytology cell blocks are being tested. The IHC will work but we are checking to make sure the same thresholds can be used. This is extremely important since fixation in cell block preparation may differ and thresholds are an important part of maintaining predictive accuracy. Validation work on this topic is also being carried out in other centres in Scotland.

We will try to answer any questions regarding this proposal.

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Keith Kerr

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