Clinical question: When is IHC required for subtyping of NSCLC and what is the optimal IHC panel?

Guideline contents > When is IHC required for subtyping of NSCLC and what is the optimal IHC panel?

Information on authorship and revision

Last modified: 9 May 2018 00:02:07

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Cite this page


Contents

- 1 Systematic Review Evidence
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

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Systematic Review Evidence

For patients with advanced stage disease, accurate subclassification of different subtypes of NSCLC is needed to help determine optimal treatment. In small biopsy and cytology specimens of non-small cell lung carcinoma (NSCLC), however, it is not always possible to distinguish squamous cell carcinoma from adenocarcinoma or other subtypes of NSCLC using morphological features alone. In these cases, immunohistochemical stains can be used to help distinguish those tumours likely to be adenocarcinomas from those more likely to represent squamous cell carcinomas. Review of the literature shows that various IHC markers can be used to assist in distinction of squamous cell carcinoma from adenocarcinoma subtypes of NSCLC, although the number of IHC markers used and which specific combinations of IHC markers is quite variable, and most of the studies were at risk of bias. In addition, many of the studies that assessed reliability of IHC subtyping did not provide information regarding how morphologically undifferentiated the tumours were or if subtyping could be inferred from morphology alone.

Evidence summary and recommendations

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<tr>
<th>Evidence summary</th>
<th>Level</th>
<th>References</th>
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<tr>
<td>IHC is useful in subtyping NSCLC using a small panel of IHC markers.</td>
<td>III-2</td>
<td>[4], [5], [6], [7], [8], [9], [10], [11]</td>
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<th>Evidence-based recommendation</th>
<th>Grade</th>
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<tr>
<td>★ A small panel of IHC markers should be used to subtype morphologically undifferentiated NSCLC in small biopsy and cytology samples, with 2 markers usually sufficient (1 adenocarcinoma marker and 1 squamous marker).</td>
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Practice point

IHC to assist in subtyping NSCLC is only required when there is no morphological evidence of glandular or squamous differentiation. The optimal panel of IHC markers is not clear from the literature with many studies using a different range of markers (eg TTF-1, Napsin A, CK5, CK5/6, p40, p63, CK7, surfactant protein A, as well as histochemical markers for mucin such as PAS.) The WHO Classification of Tumours of the Lung (Travis WD et al 2015) recommends using only one squamous marker (ie p40, p63 or CK5/6) and one adenocarcinoma marker (TTF-1 or a histochemical stain for mucin) so as to preserve tissue for molecular testing in the setting of a small biopsy showing a non-small cell carcinoma lacking definite squamous or glandular morphology.
Practice point

It is advisable to limit the number of IHC markers used to 2 so as to preserve tissue for molecular testing if required (1 adenocarcinoma marker such as TTF1, and 1 squamous marker such as p40).

Practice point

In some instances, IHC may also be needed to help determine if the tumour is of lung origin or a metastasis. Clinicopathological correlation and multidisciplinary team meeting discussion can often assist in excluding the possibility of a metastasis to the lung in the setting of a solitary lung lesion, and can help avoid unnecessary use of IHC markers and thereby preserve tissue for molecular testing. IHC markers are not useful in distinguishing primary from metastatic disease in the case of a squamous cell carcinoma in the lung.

References


Back to top

Appendices

- View recommendation components
- View pending evidence
- View body of evidence
- View all comments
- View literature search

Back to top