p53 in Non—Small-Cell Lung Cancer

The recent report by Mitsudomi et al. (1) provides evidence that mutations of the p53 (also known as TP53) tumor suppressor gene detected by the polymerase chain reaction—single-strand conformation polymorphism assay are associated with a poorer prognosis in advanced non—small-cell lung cancer. Unfortunately, data regarding the level of p53 protein expression were not provided. Mutations of the p53 gene frequently result in the stabilization of the mutant protein (2). Thus, p53 immunostaining has been claimed as a marker of malignant disease in diagnostic cytology (3). We, therefore, studied the prognostic significance of p53 protein expression in non—small-cell lung cancer, using immunohistochemistry (alkaline phosphatase—antialkaline phosphatase method) with the monoclonal antibody (MAb) p1801, which recognizes the wild-type and mutant gene product.

The analysis of frozen primary tumor sections revealed that nuclear p53 staining was present in 33 (45.2%) of 73 patients with completely (R0) resected non—small-cell lung cancer (International Union Against Cancer classification). Comparison with clinico—pathologic parameters demonstrated that such staining was more frequently detected in younger patients (<50 years, P = .014; \( \chi^2 \)-test), whereas no association was found with the sex, tumor differentiation, tumor histology, or TNM stage of patients. p53 expression was also independent from new prognostic risk factors, such as the presence of micrometastatic tumor cells in bone marrow or regional lymph nodes (4,5), the expression of Lewis-Y blood group precursor antigens (6), or the ploidy status of the tumor (7). Following a median observation time of 780 days, nuclear p53 staining was associated with an increased rate of disease-free survival in subsets of male patients (P = .023) and in patients with early-stage disease (stage I-II; P = .004; Fig. 1, A), but such an association was not found in patients with advanced-stage disease (stage IIIa-IV, P = .465; Fig. 1, B).

Taken together, our data suggest that p53 immunostaining with MAb p1801 does not predict for a poor clinical outcome, as recently claimed by Quinlan et al. (8) but is rather correlated to a reduced relapse rate in early-stage non—small-cell lung cancer. Thus, the reliability of p53 immunostaining for the indirect assessment of mutations in the p53 gene remains questionable, and prognostic evaluations should be therefore based on molecular analysis at the genomic level. It remains to be evaluated whether the favorable prognostic influence observed in our study is
caused by overexpression or by the accumulation of normal, wild-type protein, which might provide an explanation for the unexpected missing prognostic influence of p53 mutations in early-stage lung cancer (1). In this context, it is noteworthy that p53 overexpression correlates with an increased survival in patients with squamous cell carcinoma of the tongue base (9), another type of tumor induced by tobacco smoke. Thus, overexpression of wild-type p53 protein might reflect a specific cellular response to certain carcinogens. This response could lead to the blocking of cells in G0/G1 phase, which facilitates repair of damaged DNA and prevents cells from the accumulation of oncogenic mutations.

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References

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Response
We appreciate the comments and information expressed by Dr. Passlick and his colleagues in reference to our report.

It is controversial how p53 gene alterations affect the clinical outcome of surgically treated patients with lung cancer. Table 1 summarizes the recent reports dealing with this issue (1-7). They all analyzed a relatively limited number of patients, therefore some of the results may be only a reflection of chance. Some investigators examined protein expression by immunohistochemistry and some examined specimens at the DNA level. In general, the positive immunostaining corresponds to the presence of mutation, but this is not always true (8). Since intronic mutations and nonsense mutations, both resulting in truncated protein (and therefore negative immunostaining (8)), are relatively common in p53 mutations found in lung cancer (3), some disagreement may be attributable to this issue. There may also be a publication bias; a positive result is more easily accepted for publication. In some studies, criteria of inclusion of patients are not clearly stated and only a particular subset of the patients may have been analyzed.

Table 1. Summary of reports dealing with effect of p53 gene abnormality on survival of the patients with non-small-cell lung cancer

<table>
<thead>
<tr>
<th>Investigator (ref. No.)</th>
<th>Year of study</th>
<th>No. of patients</th>
<th>Method</th>
<th>Stage</th>
<th>Survival</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinlan et al. (7)</td>
<td>1992</td>
<td>114</td>
<td>IHC</td>
<td>I, II</td>
<td>p53+&lt;p53-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>McLaren et al. (2)</td>
<td>1992</td>
<td>125</td>
<td>IHC</td>
<td></td>
<td>NS</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Mitsudomi et al. (3)</td>
<td>1992</td>
<td>66‡</td>
<td>SSCP</td>
<td>I-IV</td>
<td>NS</td>
<td>.057</td>
</tr>
<tr>
<td>Horio et al. (4)</td>
<td>1993</td>
<td>71</td>
<td>SSCP</td>
<td>I-IIa</td>
<td>p53+&lt;p53-</td>
<td>.014</td>
</tr>
<tr>
<td>Brambilla et al. (5)</td>
<td>1993</td>
<td>95</td>
<td>IHC</td>
<td>I-IV</td>
<td>NS</td>
<td>.305</td>
</tr>
<tr>
<td>Carbone et al. (6)</td>
<td>1993</td>
<td>74</td>
<td>IHC</td>
<td>I-IV</td>
<td>p53+&lt;p53-</td>
<td>.96</td>
</tr>
<tr>
<td>Mitsudomi et al. (7)</td>
<td>1993</td>
<td>120</td>
<td>SSCP</td>
<td>I-IV</td>
<td>p53+&lt;p53-</td>
<td>.01</td>
</tr>
<tr>
<td>Passlick and Izbicki‡</td>
<td>1994</td>
<td>64</td>
<td>IHC</td>
<td>I-IV</td>
<td>NS</td>
<td>.465</td>
</tr>
</tbody>
</table>

*IHC = immunohistochemistry; SSCP = single-strand conformation polymorphism; p53+ = survival of the patients with p53 abnormality; p53- = survival of the patients without p53 gene abnormality; NS = no significant difference.

‡Stage not mentioned, data not analyzed by stage.
§Cell lines established from non-small-cell lung cancer were analyzed.
†Present correspondence.

References