Prognostic Significance of p53 Alterations in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis

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ABSTRACT

There is great controversy as to whether alteration of the p53 gene adversely affects survival of non-small cell lung cancer patients. The aim of this study was to qualitatively review the association between p53 alterations and patient outcome by reviewing published papers. Forty-three articles were used. Survival difference was combined by use of the DerSimonian-Laird method. p53 alteration was either detected as overexpression by the protein studies or as mutation by the DNA studies. The incidence of p53 alteration in DNA studies (381 of 1031; 37%) was lower than that in protein studies (1725 of 3579; 48%; \( P < 0.0001 \), \( \chi^2 \) test). The incidence of p53 overexpression and mutation in adenocarcinoma (36 and 34%) was significantly lower than that in squamous cell carcinoma (54 and 52%; \( P < 0.0001 \)). Combined survival differences at 5 years (survival in patients with alteration minus that in patients without alteration) by protein and DNA studies were \(-9.1\%\) (\( P = 0.0091 \)) and \(-22.0\%\) (\( P = 0.0026 \)), respectively. The negative prognostic effect of p53 alteration was highly significant in patients with adenocarcinoma \([-21.8\%\] at 5 years (\( P = 0.000039 \)) by protein studies and \(-48.0\%\) (\( P = 0.000031 \)) by DNA studies \]) but not in patients with squamous cell carcinoma \([-15.6\%\) (\( P = 0.4241 \)) by protein studies and 2.0\% (\( P = 0.8864 \)) by DNA studies \]. In the light of these results, p53 alteration was a significant marker of poor prognosis in patients with pulmonary adenocarcinoma. Whether p53 alteration also provides information that can alter treatment decisions should be asked in clinical trials.

INTRODUCTION

In many types of human cancers, including NSCLC, \(^1\) the p53 tumor suppressor gene is completely inactivated when one copy of the gene is mutated and the remaining allele is subsequently deleted (1). p53 protein is thought to act as a negative regulator of cellular proliferation or as an inducer of apoptosis through the transactivation of genes, including p21, BAX, and GADD45 (1). Missense mutation of the p53 gene usually but not always prolongs the half-life of the protein from minutes to hours and results in nuclear accumulation of the p53 protein, which can be detected by IHC (1).

Lung cancer has been the leading cause of cancer death in North America, and it also became so in Japan in 1998. Lung cancer is divided into two morphological types, SCLC and NSCLC. About 30% of NSCLC patients have localized disease, and successful surgical management with long-term disease control is generally restricted to this group of early-stage patients (2). Using existing prognostic tools, however, it is often difficult to predict either which surgically managed patients are at risk for an early disease relapse or which rare advanced stage patients may experience a favorable survival (2). Therefore, the search for the genetic lesions, identified by recent advances in molecular biology of human cancers to predict the prognosis of patients, are considered to be of great importance in making clinical decisions regarding the optimum treatment regimen.

The p53 gene is most extensively studied in this context because its genetic alteration is common and usually present as a qualitative alteration, i.e., point mutations. In addition, the fact that immunohistochemical detection of nuclear accumulation of p53 protein is usually indicative of missense mutation further facilitated many researches into this field of study. As a result, there have been >60 studies published dealing with the prognostic impact of p53 alterations on prognosis of NSCLC. However, there is a great controversy as to whether p53 adversely affects survival of NSCLC patients. Several authors published extensive reviews on this issue (3, 4). However, no conclusion emerges in that respect, unless quantitative evaluation is introduced.

In the present study, in an attempt to review those papers quantitatively, we used meta-analysis to gain insights as to whether p53 could be useful in the management of NSCLC patients.

MATERIALS AND METHODS

Articles Reviewed. This meta-analysis was limited to studies dealing with the prognostic implication of p53 alterations (overexpression by protein studies or mutation by DNA

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Received 5/9/00; revised 7/18/00; accepted 7/19/00.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

\(^1\) Supported in part by the Aichi Cancer Research Foundation, the Bristol-Meyers Squibb Biomedical Research Grant Program, and the Mitsui Life Social Welfare Foundation.

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\(^3\) The abbreviations used are: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CI, confidence interval; IHC, immunohistochemistry.
studies) in patients with NSCLC who underwent surgical resec-
tion of tumors, published in English in the periodical literature. We
excluded papers dealing with patients treated with modal-
ities other than surgery and papers that did not examine resected
specimens but cell lines because of possible artifacts caused by
in vitro selection. As a presentation of prognostic impact, the
paper had to show 3-year- and/or 5-year survival rates (not in
the form of a hazard ratio) for each group of patients with or
without p53 alteration.

The search for the articles was primarily performed using the
PubMed database4 in April 1999. The bibliographies of any
papers thus identified were also hand searched. Sixty-five arti-
cles for p53 were initially found. Thirteen of these articles were
excluded because they did not show 3-year survival rates, or the
observation periods were <3 years. Four articles were excluded
because data that overlapped from the same study group were
published. In these cases, only one article that dealt with more
patients or that was more recent was included. Two papers dealt
with patients treated by modalities other than surgery. One paper
concerned only the type of p53 mutation (missense or null), and
the other paper analyzed cell lines. Thus, 22 papers were ex-
cluded (Table 1), and the remaining 43 papers were included in
our analysis.

**Statistical Method.** To obtain a summary statistic for
3-year and 5-year survival rate differences, a random effect
model described by DerSimonian and Laird (5) was applied. The
method required proportions of subjects who had experienced a
given end point (i.e., survival rates) and denominators of the propor-
tion (i.e., number of subjects for follow-up). Three-year and
5-year survival rates were read on the published survival curves
when the rates were not provided in the text or tables of the
collected articles. The subjects censored before 3 or 5 years
were subtracted from the denominators, giving a conservative
confidence interval for the summary statistic. The censored
cases were counted by tick marks on survival curves when
provided. A \( \chi^2 \) test for homogeneity was performed, as de-
scribed by DerSimonian and Laird (5). Publication bias was
examined by a method described by Begg and Mazumdar (6).
All reported \( P \)s were two-sided; those <0.05 were considered
statistically significant.

### RESULTS

**Incidence of p53 Alteration and Factors Affecting It.**

Table 2 summarizes studies that examined the effect of p53
overexpression on survival. Incidence ranged from 17.5 to
76.8%, and the overall incidence was 48.2% (1725 of 3579).
Eleven studies used DO7, 10 studies used PAb1801, and 3
studies used CM1 as a primary antibody, but the incidence of
p53 overexpression appeared to be independent of antibodies
used (45% for DO7, 49% for PAb1801, and 47% for CM1).
Neither did the incidence of p53 overexpression seem to be
dependent on the cutoff value used. Table 3 shows similar
information in studies that detected p53 mutation as DNA
sequence change. Eight of 11 studies examined only exons 5–8.
The incidence ranged from 25.8 to 50.7% with a mean of 37% (381 of 1031); this was statistically lower that by protein studies
shown above \( (P < 0.0001) \). Tables 4 and 5 summarize studies
used for meta-analysis by histological types. In adenocarci-
noma, the incidences of p53 overexpression and mutation were
36 and 34%, respectively, which were significantly lower than
those of squamous cell carcinoma (54 and 52%, respectively).

**Survival Impact of p53 Alterations.** Although missense
mutation of the p53 gene usually results in nuclear accumulation

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of the p53 protein, p53 overexpression is not always equivalent to p53 mutation. Concordance between the two assays in lung cancer is reported to be 60–70% (7). Therefore, in the present meta-analysis, we decided to analyze protein overexpression studies and DNA studies separately. We calculated 3-year and 5-year survival differences, i.e., the survival rates of patients with p53 alterations minus those of patients without p53 alterations, and combined them by the DerSimonian-Laird method (Fig. 1). This method required the difference of survival rate and number of patients “at risk” at a given time point. However, not all studies showed censored cases on the Kaplan-Meier curve. For example, only 12 of 28 authors listed in Table 1 showed censored cases or number of patients at risk. When tick marks to indicate censored cases on the Kaplan-Meier curve were not shown, we assumed that there was no censored case because of the following observation. The combined survival difference did not differ significantly between the one assuming that there were no patients lost to follow-up and the one obtained assuming that 30% of cases were censored (e.g., −11.411% versus −10.889% for a 3-year survival difference in protein studies).

However, the confidence intervals were likely to be estimated smaller than were actually the case, and this might result in relative overweighing of reports that had more censored cases.

There is a tendency that papers with positive results are more likely to be published. Therefore, publication bias was examined by a method described by Begg and Mazumdar (6) for the studies in Tables 2–5, but no publication bias was detected; all of the zs were <1.96 (not shown).

A χ² test for homogeneity as described by DerSimonian and Laird (5) revealed that in all cases except for cases in combining data with adenocarcinoma, each study was very heterogeneous (see legends to Figs. 1 and 2). Combined 3- and 5-year survival differences were −11.4% (95% CI, −18.6 to −4.1; P = 0.0021) and −9.1% (95% CI, −16.0 to −2.3; P = 0.0091) for protein studies, respectively. For DNA studies, they were −18.7% (95% CI, −28.3 to −9.0; P = 0.0001) and −22.0% (95% CI, −36.3 to −7.7; P = 0.0026), respectively (Fig. 1). It seemed that the effect of p53 alterations detected as p53 mutation was stronger than those detected as protein overexpression.

Because we and others claimed that the prognostic impact of

### Table 2: Studies that examined p53 protein expression included in the present meta-analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>Stage</th>
<th>Method</th>
<th>Antibody</th>
<th>Cutoff</th>
<th>Multi*</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaren et al. (48)</td>
<td>1992</td>
<td>NS</td>
<td>IHC</td>
<td>4 Abs⁶</td>
<td>ND⁷</td>
<td>107 102 51.2</td>
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<td>Quinlan et al. (49)</td>
<td>1992</td>
<td>I–II</td>
<td>IHC</td>
<td>PAB1801</td>
<td>NS</td>
<td>49 65 43.0</td>
</tr>
<tr>
<td>Brambilla et al. (50)</td>
<td>1993</td>
<td>I–IV</td>
<td>IHC</td>
<td>3 Abs⁴</td>
<td>ND</td>
<td>26 21 55.3</td>
</tr>
<tr>
<td>Morke et al. (51)</td>
<td>1993</td>
<td>I–III</td>
<td>FCM</td>
<td>PAB1801</td>
<td>Index⁵</td>
<td>86 26 76.8</td>
</tr>
<tr>
<td>Carbone et al. (52)</td>
<td>1994</td>
<td>I–III</td>
<td>IHC</td>
<td>BP5-12</td>
<td>NS</td>
<td>25 14 64.1</td>
</tr>
<tr>
<td>Ebina et al. (53)</td>
<td>1994</td>
<td>I–IV</td>
<td>IHC</td>
<td>DO7</td>
<td>10</td>
<td>11 52 17.5</td>
</tr>
<tr>
<td>Volin and Mattern (54)</td>
<td>1994</td>
<td>I–IV</td>
<td>IHC</td>
<td>PAB1801</td>
<td>NS</td>
<td>107 102 51.2</td>
</tr>
<tr>
<td>Fujino et al. (55)</td>
<td>1995</td>
<td>Curative</td>
<td>IHC</td>
<td>DO7</td>
<td>5</td>
<td>36 27 57.1</td>
</tr>
<tr>
<td>Lee et al. (56)</td>
<td>1995</td>
<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>50</td>
<td>49 107 31.4</td>
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<tr>
<td>Mitsudomi et al. (7)</td>
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<td>I–III</td>
<td>IHC</td>
<td>DO1</td>
<td>10</td>
<td>67 57 54.0</td>
</tr>
<tr>
<td>Tormosen et al. (57)</td>
<td>1995</td>
<td>I–III</td>
<td>IHC</td>
<td>CM1</td>
<td>1</td>
<td>39 36 52.0</td>
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<tr>
<td>Dalquen et al. (58)</td>
<td>1996</td>
<td>N0</td>
<td>IHC</td>
<td>CM1</td>
<td>1</td>
<td>46 67 40.7</td>
</tr>
<tr>
<td>Dalquen et al. (58)</td>
<td>1996</td>
<td>N1–2</td>
<td>IHC</td>
<td>CM1</td>
<td>1</td>
<td>56 46 54.9</td>
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<td>Nishio et al. (8)</td>
<td>1996</td>
<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>10</td>
<td>95 113 45.7</td>
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<tr>
<td>Ohsaki et al. (59)</td>
<td>1996</td>
<td>I–IV</td>
<td>IHC</td>
<td>DO7</td>
<td>20</td>
<td>44 55 44.4</td>
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<tr>
<td>Pappot et al. (60)</td>
<td>1996</td>
<td>I</td>
<td>ELISA</td>
<td>PAB1801</td>
<td>Median</td>
<td>65 65 50.0</td>
</tr>
<tr>
<td>Xu et al. (61)</td>
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<td>I–II</td>
<td>IHC</td>
<td>DO1</td>
<td>5</td>
<td>54 65 45.4</td>
</tr>
<tr>
<td>Apolinaro et al. (62)</td>
<td>1997</td>
<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>≥0</td>
<td>56 60 48.3</td>
</tr>
<tr>
<td>Apolinaro et al. (62)</td>
<td>1997</td>
<td>I–III</td>
<td>IHC</td>
<td>PAB1801</td>
<td>&gt;0</td>
<td>57 56 50.4</td>
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<td>Esposito et al. (63)</td>
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<td>NS</td>
<td>IHC</td>
<td>DO7</td>
<td>1</td>
<td>22 39 36.1</td>
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<tr>
<td>Fontanini et al. (64)</td>
<td>1997</td>
<td>I–II</td>
<td>IHC</td>
<td>PAB1801</td>
<td>20</td>
<td>32 41 43.8</td>
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<tr>
<td>Ohno et al. (65)</td>
<td>1997</td>
<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>5</td>
<td>27 40 40.3</td>
</tr>
<tr>
<td>Quantum et al. (66)</td>
<td>1997</td>
<td>I–IV</td>
<td>IHC</td>
<td>PAB1801</td>
<td>1</td>
<td>46 43 51.7</td>
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<tr>
<td>Vega et al. (23)</td>
<td>1997</td>
<td>I–IV</td>
<td>IHC</td>
<td>PAB1801</td>
<td>10</td>
<td>32 30 51.6</td>
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<tr>
<td>Kwiatkowski et al. (67)</td>
<td>1998</td>
<td>I</td>
<td>IHC</td>
<td>PAB1801</td>
<td>h</td>
<td>108 134 44.6</td>
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<tr>
<td>Levesque et al. (68)</td>
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<td>I–IV</td>
<td>ELISA</td>
<td>CM1</td>
<td>Median</td>
<td>43 43 50.0</td>
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<tr>
<td>D’Amico et al. (69)</td>
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<td>IHC</td>
<td>PAB1801</td>
<td>NS</td>
<td>176 232 43.1</td>
</tr>
<tr>
<td>Fu et al. (70)</td>
<td>1999</td>
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<td>IHC</td>
<td>DO7</td>
<td>≥0</td>
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<td>Gerards et al. (71)</td>
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<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>15</td>
<td>50 53 48.5</td>
</tr>
<tr>
<td>Tomizawa et al. (72)</td>
<td>1999</td>
<td>I</td>
<td>IHC</td>
<td>DO7</td>
<td>10</td>
<td>41 62 39.8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1725 1854 48.2</td>
</tr>
</tbody>
</table>

* Multivariate analysis.
* PAB1801, PAB240, PAB421, CM1, and C19. Abs, antibodies.
* ND, not done; NS, not shown; FCM, flow cytometry.
* PAB421, PAB1801, and CM1.
* Fluorescence-control/control >1.
* Combined with RB.
* Analyzed disease-free survival.
* Weak versus moderate.
p53 alterations is stronger in patients with adenocarcinoma than in those with squamous cell carcinomas (7, 8), we asked whether histological types have influence on the effect of p53 alteration on prognosis of patients (Fig. 2). In patients with adenocarcinoma, combined 3-year and 5-year survival differences were 21.8% (95% CI, 29.4 to 14.1; \( P = 0.000000024 \)) and 21.8% (95% CI, 31.0 to 12.5; \( P = 0.0000039 \)) for protein studies; and 41.0% (95% CI, 57.2 to 24.7; \( P = 0.00000079 \)) and 48.0% (95% CI, 70.6 to 25.4; \( P = 0.000031 \)) for DNA studies, respectively. On the other hand, survival impact of p53 alteration was not significant in patients with squamous cell carcinoma. Combined 3-year and 5-year survival differences were 10.0% (95% CI, 44.0 to 24.0; \( P = 0.5652 \)) and 15.6% (95% CI, 53.9 to 22.7; \( P = 0.4241 \)) for protein studies and 19.9% (95% CI, −54.6 to 14.8; \( P = 0.2609 \)) and 2.0% (95% CI, −25.4 to 29.4; \( P = 0.8864 \)) for DNA studies, respectively. This observation might be relevant to the fact that cases with adenocarcinoma were statistically homogeneous, whereas cases with squamous cell carcinoma were heterogeneous.

**DISCUSSION**

There has been considerable controversy as to whether p53 mutation or p53 overexpression is a poor prognostic indicator in patients with NSCLC who underwent potentially curative resection (9). This has been pointed out in several reviews published to date, but the lack of quantitative evaluation failed to give further insights (3, 4). We showed, by an extensive quantitative

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### Table 3

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Stage</th>
<th>Method</th>
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<th>Positive</th>
<th>Negative</th>
<th>%</th>
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<tr>
<td>Horio et al.</td>
<td>1993</td>
<td>I–III</td>
<td>SSCP</td>
<td>X5–8</td>
<td>Yes</td>
<td>35</td>
<td>36</td>
<td>49.3</td>
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<td>1993</td>
<td>I–IV</td>
<td>SSCP</td>
<td>X5–8</td>
<td>Yes</td>
<td>51</td>
<td>69</td>
<td>42.5</td>
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<tr>
<td>Carbone et al.</td>
<td>1994</td>
<td>I–III</td>
<td>SSCP</td>
<td>X4–8</td>
<td>No</td>
<td>38</td>
<td>37</td>
<td>50.7</td>
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<td>Kashii et al.</td>
<td>1995</td>
<td>I–IV</td>
<td>SSCP</td>
<td>X5–9</td>
<td>No</td>
<td>31</td>
<td>78</td>
<td>28.4</td>
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<tr>
<td>Mitsudomi et al.</td>
<td>1995</td>
<td>I–III</td>
<td>SSCP</td>
<td>X5–8</td>
<td>ND</td>
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<td>82</td>
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<td>I–III</td>
<td>SSCP</td>
<td>Codon 101–300</td>
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<td>I–IV</td>
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<td>ND</td>
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<td>Ohno et al.</td>
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<td>SSCP, seq</td>
<td>X5–8</td>
<td>No</td>
<td>21</td>
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<td>SSCP, seq</td>
<td>X5–8</td>
<td>No</td>
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<td>Huang et al.</td>
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<td>SSCP, seq</td>
<td>X5–8</td>
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<td>SSCP, seq</td>
<td>X5–8</td>
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* Multivariate analysis.

### Table 4

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<th>Author</th>
<th>Year</th>
<th>Stage</th>
<th>Method</th>
<th>Antibody/exons</th>
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<th>Multi*</th>
<th>Positive</th>
<th>Negative</th>
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<tr>
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<td>1992</td>
<td>NS</td>
<td>IHC</td>
<td>4 Abs</td>
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<td>ND</td>
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<td>Harpole et al.</td>
<td>1995</td>
<td>I</td>
<td>IHC</td>
<td>PAb1801</td>
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<td>Yes</td>
<td>49</td>
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<td>I–III</td>
<td>IHC</td>
<td>DO1</td>
<td>10</td>
<td>No</td>
<td>37</td>
<td>33</td>
<td>52.9</td>
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<td>Kawasaki et al.</td>
<td>1996</td>
<td>T &lt; 2 cm</td>
<td>IHC</td>
<td>RSP53</td>
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<td>53</td>
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<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>10</td>
<td>No</td>
<td>37</td>
<td>63</td>
<td>37.0</td>
</tr>
<tr>
<td>Ishida et al.</td>
<td>1997</td>
<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>20</td>
<td>Yes</td>
<td>45</td>
<td>69</td>
<td>39.5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>242</td>
<td>422</td>
<td>36.4</td>
</tr>
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</table>

* Multivariate analysis.

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4058 Meta-Analysis of p53 Alteration in Patients with NSCLC

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review of published reports, that p53 alteration was more prevalent in squamous cell carcinoma of the lung than in adenocarcinoma, and that p53 was a significant marker in patients with poor prognosis who have adenocarcinoma but not in patients with squamous cell carcinoma.

The ideal study of prognostic factor should have statistical power consideration, avoidance of patient population bias, or methodological validation with optimized cutoff points (10, 11). In light of these criteria, none of the 65 studies were definitive, resulting in the accumulation of many pilot studies. It is also true that it is very difficult to perform a definitive study. Therefore, we attempted to compile published data by use of meta-analysis. Because meta-analysis was originally developed to combine published randomized control trials (12), there are several problems in applying this methodology to combining studies for prognosis. Meta-analysis has no power to adjust methodological validation with optimized cutoff points (10, 11).

Table 5  Studies included for meta-analysis of patients with squamous cell carcinoma. All studies in Table 5 are subset analyses by histological types, and thus they are also in Table 2.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Stage</th>
<th>Method</th>
<th>Antibody/exons</th>
<th>Cutoff</th>
<th>Multi*</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaren et al. (48)</td>
<td>1992</td>
<td>I–IV</td>
<td>IHC</td>
<td>4 Abs</td>
<td>10</td>
<td>ND#</td>
<td>43 32</td>
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<tr>
<td>Mitsudomi et al. (7)</td>
<td>1995</td>
<td>I–III</td>
<td>IHC</td>
<td>DO1</td>
<td>10</td>
<td>No</td>
<td>23 22</td>
</tr>
<tr>
<td>Tormanen et al. (57)</td>
<td>1995</td>
<td>I–III</td>
<td>IHC</td>
<td>CM1</td>
<td>1</td>
<td>Yes</td>
<td>25 22</td>
</tr>
<tr>
<td>Nishio et al. (8)</td>
<td>1996</td>
<td>I–III</td>
<td>IHC</td>
<td>DO7</td>
<td>10</td>
<td>No</td>
<td>46 42</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>137 118</td>
</tr>
</tbody>
</table>

DNA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Stage</th>
<th>Method</th>
<th>Antibody/exons</th>
<th>Cutoff</th>
<th>Multi*</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitsudomi et al. (74)</td>
<td>1993</td>
<td>I–IV</td>
<td>SSCP</td>
<td>X5–8</td>
<td>ND</td>
<td>29</td>
<td>29 18</td>
</tr>
<tr>
<td>Mitsudomi et al. (7)</td>
<td>1995</td>
<td>I–III</td>
<td>SSCP</td>
<td>X5–8</td>
<td>ND</td>
<td>29</td>
<td>29 18</td>
</tr>
<tr>
<td>Fukuyama et al. (81)</td>
<td>1997</td>
<td>I–IV</td>
<td>SSCP</td>
<td>X5–8</td>
<td>Yes</td>
<td>26</td>
<td>26 31</td>
</tr>
<tr>
<td>Vega et al. (23)</td>
<td>1997</td>
<td>I–IV</td>
<td>SSCP, seq</td>
<td>X5–8</td>
<td>Yes</td>
<td>12</td>
<td>12 28</td>
</tr>
<tr>
<td>Huang et al. (22)</td>
<td>1998</td>
<td>I–III</td>
<td>SSCP, seq</td>
<td>X5–8</td>
<td>No</td>
<td>22</td>
<td>22 27</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>118 122</td>
</tr>
</tbody>
</table>

| Total             | 255 240 | 51.5 |

*\* Multivariate analysis.

\# ND, not done; seq, sequencing.

were outside exons 5–9. p53 IHC fails to detect 20–30% of mutations, especially in the form of nonsense, splice, or null mutations (15). In the recent report by Ahrendt et al. (16), it was reported that sensitivity of dideoxynucleotide direct sequencing and GeneChip assay for p53 mutation detection is 76 and 81%, respectively. In this context, none of the assays are infallible at detection of p53 alteration, and it is possible that these factors also affect the survival impact of p53 alterations.

Pharoah et al. (17) claimed that three important questions should be asked in interpreting the results of meta-analysis, in their recent meta-analysis on significance of p53 mutations on prognosis in breast cancer: (a) whether all relevant studies were included for the analysis should be asked, but it is difficult to assess. We made every effort to collect papers that were sufficient to estimate survival impact of p53 alterations as of April 1999; (b) whether there is study heterogeneity is also important. It is easy to imagine that differences in study population, in methods to detect p53 alterations, and in measurement of confounding factors and others may result in study heterogeneity. Indeed, heterogeneous effects were observed in several subsets in the present study. In addition, even if DerSimonian-Laird’s random-effect model was applied, null hypothesis on homogeneity was rejected except for the adenocarcinoma subset (see legends to Figs. 1 and 2). However, there were no available methods to separate studies further to obtain homogeneous groups because of lack of information on confounding factors. L’Abbe et al. (12) recommended the use of the DerSimonian-Laird method when the homogeneity assumption is rejected; and (c) publication bias is another source of heterogeneity. But in our cases, no publication bias was detected, according to Begg and Mazumdar (6), suggesting that the obtained summary statistic was not far from the true average value. However, it should be kept in mind that this methodology did not completely exclude biases, because there might have been rejection or even nonsubmission of negative data. In addition, the selection of only papers published in English likely introduces bias.

The present meta-analysis indicated that p53 alteration was
a significant marker of poor prognosis in patients with adenocarcinoma but not in patients with squamous cell carcinoma. This interesting result may be relevant to the following observations. Kawasaki et al. (18) examined nuclear p53 accumulation in small-sized adenocarcinoma of the lung and concluded that nuclear p53 overexpression occurs in the transition from the early to advanced stage of replacement-type adenocarcinoma development. On the contrary, p53 overexpression is present in dysplasias, preneoplastic lesions of squamous cell carcinoma (19, 20). These lines of evidence suggest that p53 alteration may have different roles in adenocarcinoma and in squamous cell carcinoma, i.e., p53 alteration is required for squamous carcinogenesis, whereas it plays a significant role in malignant progression of adenocarcinoma.

Recently, several authors claimed that functionally or topographically different p53 mutations have a different effect on survival of patients with cancer. de Anta et al. (21) showed that p53 null mutation but not missense mutation is a poor prognostic indicator in patients with NSCLC, whereas Huang et al. (22) claimed that p53 mutations occurring in exons 7 and 8 were more predictive of poor prognosis. However, again on this point, there is a controversy. Vega et al. (23) claimed that mutation occurring in exon 5 is predictive of poor prognosis. It has been shown that, depending on the site of mutation or on substituted base, sequence alteration may have different effects on p53 function (24). A rapid p53 functional assay using a yeast system has been developed recently (25). The prognostic effect of the p53 alteration with functional defect detected by this assay would certainly be of interest.

In conclusion, we showed that p53 mutation or overexpression was an indicator of poor prognosis, especially in patients with adenocarcinoma, by meta-analysis. Although standardization and validation of the assay will still remain as a matter of future studies, the next step will be to examine the capability of p53 alterations to predict the optimal treatment regimen for lung cancer patients. If patients with altered p53 really have a poorer prognosis than those without p53 alteration, patients with p53 alteration can be a target for experimental therapeutic approach. Another concern is that it is generally believed that tumors with p53 alterations are more resistant to cancer chemotherapeutic agents than those without p53 mutation, except those that act on microtubules (26). Therefore, patients with lung cancer that retain normal p53 function may benefit from adjuvant chemotherapy. To address these issues, it may be necessary to use such a promising molecular marker as p53 alteration for stratification in the setting of prospective randomized clinical trials for pa-
Patients with lung cancer, especially those for adenocarcinoma. At the same time, an effort to obtain more reliable prognostic indicators by analyzing multiple genes should be made, because it may well be too naive to think that a single gene mutation can predict various aspects of clinical courses of lung cancer patients.

ACKNOWLEDGMENTS

We thank Kazuo Tajima for pertinent comments and Mitsuko Suzuki for secretarial assistance.

REFERENCES


Meta-Analysis of p53 Alteration in Patients with NSCLC


Prognostic Significance of p53 Alterations in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis

T. Mitsudomi, N. Hamajima, M. Ogawa, et al.


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