Prognostic Significance of TP53 Tumor Suppressor Gene Expression and Mutations in Human Osteosarcoma: A Meta-Analysis

Emilios E. Pakos,1 Panayiotis A. Kyzas,1 and John P. A. Ioannidis1,2,3

1Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; 2Biomedical Research Institute, Foundation for Research and Technology-Hellas, Ioannina, Greece; and 3Institute for Clinical Research and Health Policy Studies, Department of Medicine, Tufts-New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts

ABSTRACT

Purpose: Various studies examining the relationship between tumor suppressor protein TP53 overexpression and/or TP53 gene mutations and the response to chemotherapy and clinical outcome in patients with osteosarcoma have yielded inconclusive results. The purpose of the current study was to evaluate the relation of TP53 status with response to chemotherapy and/or clinical outcome in osteosarcoma.

Experimental Design: We conducted a meta-analysis of 16 studies (n = 499 patients) that evaluated the correlation between TP53 status and histologic response to chemotherapy and 2-year survival. Data were synthesized in summary receiver operating characteristic curves and with summary likelihood ratios (LRs) and risk ratios.

Results: The quantitative synthesis showed that TP53 status is not a prognostic factor for the response to chemotherapy. The positive LR was 1.21 (95% confidence interval, 0.86–1.71), and the negative LR was 0.91 (95% confidence interval, 0.77–1.07). There was no significant between-study heterogeneity. TP53-positive status tended to be associated with a worse 2-year survival, but the overall results were not formally statistically significant. The association was formally significant in studies that clearly stated that measurements were blinded to outcomes (risk ratio, 2.05; 95% confidence interval, 1.23–3.44), and in studies using reverse transcription-PCR for evaluating TP53 alterations (risk ratio, 1.76; 95% confidence interval, 1.07–2.91).

Conclusions: TP53 status is not associated with the histologic response to chemotherapy in patients with osteosarcoma, whereas TP53 gene alterations may be associated with decreased survival.

INTRODUCTION

The TP53 gene has been considered to be important for carcinogenesis. This tumor suppressor gene, located at chromosome band 17p13, was initially identified as a regulator of genomic stability (1, 2). Subsequently, the gene was found to have a broader function, acting as “a guardian of DNA” activated after cellular stress, such as DNA damage, aberrant proliferative signals, heat shock, or hypoxia (3). The wild-type TP53 protein regulates genes involved in DNA repair, cell cycle arrest, and programmed cell death, and mutations have been implicated in carcinogenesis (4–6). Mutations of the TP53 gene are frequent in human osteosarcoma cells (7, 8). Several studies have tried to investigate the clinical significance of TP53 gene alterations or TP53 protein overexpression in osteosarcoma (9–24), given the implication of TP53 in apoptosis induced by various cytotoxic chemotherapeutic agents (25). These studies have yielded conflicting results. Many studies failed to show any relationship between TP53 status (either protein expression or the presence of gene alterations) and response to chemotherapy or disease progression (9, 10, 12–14, 17, 18, 22, 24). However other investigations suggested associations with poor response to chemotherapy and decreased survival (15, 16, 19, 21), whereas others were apparently inconclusive (11, 20, 23). Most studies had limited sample size. Thus a quantitative synthesis using rigorous methods would be important to perform.

We accordingly conducted a meta-analysis of all available studies relating TP53 expression and TP53 gene alterations with response to chemotherapy and/or clinical outcome, as defined by 2-year survival, because all studies had at least 2 years of follow-up.

MATERIALS AND METHODS

Identification and Eligibility of Relevant Studies. We considered all studies examining the association of TP53 expression and/or TP53 gene alterations with osteosarcoma outcomes. Sources included MEDLINE and EMBASE (last search update September 2003). The search strategy was based on combinations of “osteosarcoma,” “p53,” “TP53,” “p53 protein,” “p53 mutation,” and “17p13 gene.” References of retrieved articles were also screened. Investigators were contacted and asked to supply additional data when key information relevant to the meta-analysis was missing.

All studies examining the relation of TP53 status to response to chemotherapy and/or clinical outcome (death) were eligible for our meta-analysis. We accepted all studies measuring TP53 status, regardless of the method of detection [immunohistochemistry (IHC) for measuring protein levels and reverse transcription-PCR (RT-PCR) techniques for identifying mutations in exons 4–9 or microsatellite markers for loss of...
heterozygosity or other gene changes]. Whenever reports pertained to overlapping patients, we retained only the largest study to avoid duplication of information.

**Definitions and Standardizations.** For consistency, we use “TP53” for the gene name, “TP53” for the expressed protein, and “TP53 status” for covering both the gene and protein markers. TP53 alterations increase the half-life of TP53 protein, leading to nuclear accumulation of mutant TP53, which can be detected by IHC (21, 26). However TP53 protein accumulation measured by IHC does not necessarily correspond to TP53 mutations detected by RT-PCR (27–29). Thus, the overall analysis considered all studies, regardless of whether protein expression or mutants were being evaluated, but we also performed separate analyses for TP53 protein expression and TP53 gene alterations. In the overall analysis, for studies using both IHC and RT-PCR we used the IHC data but also examined RT-PCR data, and results were similar (data not shown). For studies using IHC, we used prespecified rules to standardize, as much as possible, the definition of a positive test for studies that used different cutoff thresholds. We defined TP53 protein positivity as nuclear cell stain in at least 10% of the tumor cells, a definition followed by most studies. When different definitions were used, we accepted the cutoff closest to the 10% level.

We defined “response to chemotherapy” by the percentage of histologic necrosis of tumor cells in specimens obtained after chemotherapy. A cutoff of 90% necrosis was used to separate responders from nonresponders. Equivalent cutoffs were used for studies using other classifications. Thus, for studies using the Huvos grading system to evaluate histologic necrosis (30), we considered as responders those with grade 3 or 4 response, whereas in Salzer-Kuntschik’s classification (31), we considered as responders those with class 1, 2, or 3 response.

The clinical outcome of interest was mortality. Clinical outcomes were standardized to include 24 months follow-up in all studies to avoid some studies contributing very long-term follow-up data as compared with others. All studies had at least 24 months of follow-up, and censoring was very uncommon before this time point.

**Data Extraction.** Two investigators extracted data from eligible studies independently, discussed discrepancies, and reached consensus for all items. We extracted data on characteristics of studies and patients, measurements, and results. In each report we recorded author names, journal and year of publication, country of origin, years of patient enrollment, number of patients analyzed, stage and grade of osteosarcoma, demographics, chemotherapy and surgery used, timing of TP53 status measurement (before or after chemotherapy), type of measurement, antibodies used for IHC, exons analyzed with RT-PCR, definition of positive test, and blinding of measurements to the study outcomes. Data on the main outcomes were entered in $2 \times 2$ tables showing the histologic response/nonresponse to chemotherapy and the occurrence/nonoccurrence of death within 24 months per TP53 status. We also recorded the number of patients censored alive before 24 months.

**Statistical Analysis.** Data on the diagnostic performance of TP53 status for determining histologic response to chemotherapy were evaluated by constructing a summary receiver operating characteristic (SROC) curve and estimating the combined positive and negative likelihood ratio [LR (LR+, LR−)].

For a diagnostic or predictive test, the sensitivity (true positives) and specificity (1 − false positive) are related with each other; therefore, it is not totally correct to estimate these two quantities independently. To bypass this problem, one may use the SROC method. The SROC curve is estimated by the regression $D = a + bS$, where $D$ is the difference of the logits of the true positive and false positive rate, and $S$ is the sum of these logits (32). Both weighted and unweighted regressions were estimated. The SROC curve shows the trade-off between sensitivity and specificity across the included studies.

LRs are also metrics that combine both sensitivity and specificity in their calculation. LR+ is defined as the ratio of sensitivity over $1 − \text{specificity}$, whereas LR− is defined as the ratio of $1 − \text{sensitivity}$ over specificity. When there is absolutely no discriminating ability for a diagnostic or predictive test, both LRs equal 1. The higher the LR+ and the lower the LR−, the better the discriminating ability. Although there is no absolute cutoff, a good diagnostic test may have LR+ above 5 and LR− below 0.2. Between-study heterogeneity was assessed with the Q statistic (33). In the absence of significant heterogeneity, study-specific LR values were combined with fixed effects models (34).

Data on the predictive ability of TP53 overexpression or TP53 gene alterations for death were also combined across studies using risk ratios for 2-year mortality (33). The risk ratio shows the rate of 2-year mortality in the group with TP53 overexpression or TP53 gene alterations divided by the rate of 2-year mortality in the group without TP53 expression or TP53 gene alterations. Between-study heterogeneity in the risk ratios was assessed with the Q statistic (33). In the absence of significant heterogeneity, risk ratios were combined with fixed effects models (34). Random effects estimates were also obtained (data not shown), but they were considered less appropriate because several studies had very small numbers of events, and they would offer no advantage in the absence of between-study heterogeneity (34).

Sensitivity analyses examined the effect of limiting the evaluation to studies using the 10% IHC cutoff and studies that clearly stated that measurements of TP53 status were blinded to outcomes. We also examined using appropriate bias diagnostics whether there was evidence that the results differed in small versus large studies (35) or were changing gradually over time with the publication of more recent studies (36).

Analyses were conducted with SPSS 10.0 (SPSS, Inc., Chicago, IL), Meta-Analyst (Joseph Lau, Boston, MA), and Meta-Test (Joseph Lau, Boston, MA). $P$ values are two-tailed.

**RESULTS**

**Eligible Studies.** We initially identified 23 reports examining the role of TP53 status in patients with osteosarcoma. Of those, five reports were excluded: four due to lack of any informative clinical data (37–40), and one because of overlapping with another study (41). Three reports pertained to the same study (22, 42, 43), and two (42, 43) described outcomes on a subset of patients included in the other study (22). We retained the publication with the larger sample size, but we also used information for 2-year survival from the subset publications because no such data were provided in the publication with the
larger sample size. Two patients from one study (20) were included in another study (11). We accepted both studies, but we excluded these two patients from the first study (20). In all, 16 independent eligible studies, which enrolled a total of 499 patients, were included in the quantitative synthesis. Nine studies (282 patients) had data on histologic response to chemotherapy, and 14 studies (436 patients) had data on 2-year survival.

Ten studies stated that osteosarcoma was of high grade at diagnosis. Ten studies stated that determination of TP53 status was blinded to outcomes (9, 17, 19–21). The incidence of histologic response to chemotherapy ranged from 10% to 59%, and 2-year mortality rates ranged between 6% and 52% across the eligible studies. Both the chemotherapy response rates and 2-year death rates differed significantly across studies ($P < 0.001$ for both). This may be due to differences in the case mix of the study populations (e.g., grade and stage) and/or the therapies used.

**Data Synthesis: Response to Chemotherapy.** TP53 status had no discriminating ability to identify poor versus good responders to chemotherapy. When all studies were considered, the SROC curve passed very close to the diagonal, suggestive of total lack of discriminating performance (Fig. 1). According to the SROC, a sensitivity of 50% corresponded to a specificity of 56%, and a specificity of 50% corresponded to a sensitivity of 57% in the weighted analysis. Unweighted estimates were similar (Fig. 1).

Separate analyses with studies using either IHC or PCR were similar (Table 2). In the main analysis and various sensitivity analyses, $LR^+$ remained in the range of 1.06–1.49, and $LR^-$ remained in the range of 0.89–0.95, values characteristic of very poor discriminating performance (Table 2). There was no significant between-study heterogeneity for either $LR^+$ or $LR^-$ in any of these analyses. There was also no evidence that large studies yielded markedly different results compared with smaller studies or that early studies differed significantly against later publications. No specific study showed large discriminating ability.

**Data Synthesis: Survival at 24 Months.** TP53-positive status tended to be associated with a worse 2-year survival with a 1.30-fold higher risk of death at 2 years ($P = 0.12$) without

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**Table 1** Characteristics of eligible studies

<table>
<thead>
<tr>
<th>Author (y)</th>
<th>No. analyzed</th>
<th>Metastatic disease</th>
<th>Age (y)</th>
<th>TP53 status method</th>
<th>IHC Antibodies</th>
<th>PCR Exons</th>
<th>IHC cutoff</th>
<th>Blinding</th>
<th>Chemotherapy response (criteria)</th>
<th>Deaths in 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gorlick (1999)</td>
<td>53</td>
<td>10</td>
<td>17 (mean)</td>
<td>IHC</td>
<td>1801/DO-7</td>
<td>&gt;0%</td>
<td>Yes</td>
<td>18/53 (Huvos)</td>
<td>16/53</td>
<td></td>
</tr>
<tr>
<td>Serra (1999)</td>
<td>41</td>
<td>NR</td>
<td>&gt;14 (median)</td>
<td>IHC</td>
<td>1801/DO-7</td>
<td>5%</td>
<td>NR</td>
<td>24/41 (N90)</td>
<td>11/41</td>
<td></td>
</tr>
<tr>
<td>Kawaguchi (2002)</td>
<td>23</td>
<td>NR</td>
<td>55 (mean)</td>
<td>IHC/PCR</td>
<td>1801</td>
<td>5–9</td>
<td>10%</td>
<td>NR</td>
<td>NR</td>
<td>12/23</td>
</tr>
<tr>
<td>Jensen (1998)</td>
<td>25</td>
<td>NR</td>
<td>67 (median)</td>
<td>IHC</td>
<td>DO-7</td>
<td>10%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>11/25</td>
</tr>
<tr>
<td>Yokoyama (1998)</td>
<td>17</td>
<td>2</td>
<td>15 (mean)</td>
<td>PCR*</td>
<td>DO-1</td>
<td>4–8</td>
<td>10%</td>
<td>NR</td>
<td>6/14 (S-K)</td>
<td>1/17</td>
</tr>
<tr>
<td>Radig (1998)</td>
<td>18</td>
<td>0</td>
<td>34 (mean)</td>
<td>IHC/PCR*</td>
<td>DO-7</td>
<td>5–9</td>
<td>10%</td>
<td>NR</td>
<td>NR</td>
<td>12/27</td>
</tr>
<tr>
<td>Goto (1998)</td>
<td>27</td>
<td>2</td>
<td>15 (median)</td>
<td>PCR*</td>
<td>DO-7/Rsp53</td>
<td>MS</td>
<td>&gt;0%</td>
<td>NR</td>
<td>3/31† (N90)</td>
<td>14/32</td>
</tr>
<tr>
<td>Kakar (2000)</td>
<td>32</td>
<td>8</td>
<td>16 (mean)</td>
<td>IHC/PCR</td>
<td>DO-7/Rsp53</td>
<td>MS</td>
<td>&gt;0%</td>
<td>NR</td>
<td>5/13 (N90)</td>
<td>NR</td>
</tr>
<tr>
<td>Ueda (1993)</td>
<td>17</td>
<td>0</td>
<td>23 (mean)</td>
<td>IHC</td>
<td>240/1801</td>
<td>10%</td>
<td>NR</td>
<td>7/17 (S-K)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Oozaki (2000)</td>
<td>70</td>
<td>11</td>
<td>16 (mean)</td>
<td>IHC</td>
<td>DO-7</td>
<td>10%</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>17/70</td>
</tr>
<tr>
<td>Oda (2000)</td>
<td>22</td>
<td>0</td>
<td>17 (median)</td>
<td>IHC</td>
<td>NR</td>
<td>10%</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>1/22</td>
</tr>
<tr>
<td>Papai (1997)</td>
<td>21</td>
<td>0</td>
<td>20 (mean)</td>
<td>IHC</td>
<td>DO-7</td>
<td>5%</td>
<td>Yes</td>
<td>4/19 (N90)</td>
<td>8/21</td>
<td></td>
</tr>
<tr>
<td>Patino-Garcia (2003)</td>
<td>41</td>
<td>8</td>
<td>14 (median)</td>
<td>PCR</td>
<td>DO-7</td>
<td>5–8</td>
<td>10%</td>
<td>NR</td>
<td>22/41 (N90)</td>
<td>7/38</td>
</tr>
<tr>
<td>Entz-Werle (2003)</td>
<td>54</td>
<td>6</td>
<td>13 (median)</td>
<td>PCR</td>
<td>MS</td>
<td>NR</td>
<td>30/53 (Huvos)</td>
<td>4/54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junior (2003)</td>
<td>25</td>
<td>1</td>
<td>29 (mean)</td>
<td>IHC</td>
<td>DO-7</td>
<td>5%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6/14</td>
</tr>
</tbody>
</table>

**NOTE.** Antibodies, antibodies used for detection of TP53 protein with IHC. Exons, exons of the TP53 gene analyzed by polymerase chain reaction.

Abbreviations: Huvos, histological response based on the Huvos grading system; NR, not reported; N90, histological response based on >90% tumor cell necrosis; PCR, polymerase chain reaction; S-K, histological response based on Salzer-Kuntschik’s classification; MS, microsatellite primers.

* PCR here represents PCR/single-strand conformational polymorphism.

† Three of 31 with IHC determinations and 2 of 31 with PCR determinations.
significant differences between studies (no statistically significant between-study heterogeneity; Fig. 2). The observed trend did not change considerably when we excluded patients who presented with metastatic disease at diagnosis. The risk ratio was smaller in studies with IHC determinations than in studies with determinations of TP53 gene alterations and reached formal statistical significance only in the latter group (Table 3). The survival difference was somewhat stronger and formally statistically significant in studies that stated that measurements were blinded to outcomes. Larger studies tended to show stronger association of TP53-positive status with 2-year mortality when compared with smaller studies ($P < 0.10$).

**DISCUSSION**

This meta-analysis showed that TP53 status (either TP53 protein overexpression detected with IHC or TP53 gene alterations detected by RT-PCR) in patients with osteosarcoma had no discriminating ability for identifying poor versus good responders to chemotherapy. TP53-positive status showed a modest association with worse 2-year survival, particularly in studies evaluating TP53 gene alterations. This was not clear in studies evaluating TP53 protein overexpression or in the overall analyses.

The potentially discrepant results concerning response to chemotherapy and survival are challenging. The discrepancy may be due to bias because the correlation with survival was modest and not formally significant for the protein-level data. Alternatively, it might offer a hint on the potential mechanism of action of TP53. TP53 may contribute to tumorigenesis as an early event and determine osteosarcoma features such as tumor grade, type, aggressiveness, and metastatic potential without regulating response to chemotherapy (44). Chemotherapy may

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Likelihood ratios for the association between TP53 status and no histologic response to chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>$N$ ($n$)</td>
</tr>
<tr>
<td>All</td>
<td>9 (282)</td>
</tr>
<tr>
<td>IHC only</td>
<td>6 (174)</td>
</tr>
<tr>
<td>PCR only</td>
<td>4 (132)</td>
</tr>
<tr>
<td>Sensitivity analyses*</td>
<td>3 (85)</td>
</tr>
</tbody>
</table>

NOTE: All figures are based on random effects calculations. All $P$ values for between-study heterogeneity were $>0.1$.
Abbreviations: CI, confidence interval; PCR, polymerase chain reaction
* Only one study with 17 subjects used the 10% cutoff; thus, this sensitivity analysis would not be meaningful.
eliminate metastatic cells according to TP53 status, resulting in modulation of overall survival, but the effect on the primary tumor mass may be less prominent. Finally, the methods for determining response to chemotherapy are not very accurate, and this might have affected the ability to detect a modest association.

Another challenging result of this meta-analysis was the stronger observed association of poor survival with the presence of gene alterations rather than with IHC positivity. The correlation between IHC and RT-PCR is not straightforward (45, 46). Not all mutations yield a stable protein, and some result in protein truncation not detected by IHC (27). Furthermore, TP53 protein detected with IHC is not always mutant. Nonmutated wild-type TP53 protein may also accumulate in some cells after exposure to DNA-damaging agents or by binding to other cellular proteins (27). Currently used IHC antibodies cannot discriminate between mutant and wild-type TP53 protein (45). Along the same lines, studies using sequencing for TP53 mutations in breast cancer have shown strong association with survival, whereas those using IHC failed to show this (29). Other investigators have suggested that the combination of IHC and RT-PCR data may provide complementary prognostic information (47). Such inferences should be made cautiously because chance differences cannot also be excluded.

Given these measurement issues and the small sample size of most studies, it is probably not surprising that there is a large body of literature showing that TP53 status correlates with outcomes for various malignancies as well as a considerable body of literature of “negative” studies. The documentation or rebuttal of such associations should preferably be performed with large-scale evidence on many hundreds of patients because single studies of limited sample size, when seen in isolation, may yield spurious results.

Some limitations of this meta-analysis should be discussed. First, publication bias may be a problem in meta-analyses. We tried to identify all relevant data and retrieve additional unpublished information, but some missing data were unavoidable. Typically, publication bias results in seeing stronger associations in smaller studies than in larger studies. However, in our meta-analysis, we reassuringly observed a stronger association of TP53-positive status with 2-year mortality in larger studies. Moreover, the association was clearer in high-quality studies with blinded assessment of outcomes. Second, there was some unavoidable variability in definitions of methods, measure-

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**Table 3** Risk ratio for association between TP53 status and mortality in 24 months

<table>
<thead>
<tr>
<th>Studies</th>
<th>N (n)</th>
<th>Q</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>14 (436)</td>
<td>13.31</td>
<td>1.30 (0.93–1.79)</td>
</tr>
<tr>
<td>Excluding metastases</td>
<td>14 (413)</td>
<td>12.96</td>
<td>1.29 (0.91–1.83)</td>
</tr>
<tr>
<td>IHC only</td>
<td>9 (288)</td>
<td>11.79</td>
<td>1.23 (0.86–1.75)</td>
</tr>
<tr>
<td>PCR only</td>
<td>7 (193)</td>
<td>2.12</td>
<td>1.76 (1.07–2.91)</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific 10% cutoff</td>
<td>4 (127)</td>
<td>1.91</td>
<td>1.37 (0.84–2.25)</td>
</tr>
<tr>
<td>Stated blinding</td>
<td>4 (155)</td>
<td>3.82</td>
<td>2.05 (1.23–3.44)</td>
</tr>
</tbody>
</table>

NOTE. All P values were >0.10 for between-study heterogeneity. Risk ratio was estimated with fixed effects models. Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.
ments, and outcomes in each study, despite our effort to standardize definitions. Third, the sample size of the meta-analysis is still modest. However, given that osteosarcomas are not very common on a population basis, the sample size of this investigation is one of the largest to date among studies targeting this malignancy.

Finally, the estimates that we obtained were unadjusted for other parameters that may be related to osteosarcoma outcomes such as tumor size, histologic type, and chemotherapeutic regimens. However, treatment in the analyzed studies was not determined based on TP53 status. It is unknown whether a detrimental effect of TP53 status on survival may be explained by other tumor determinants such as size, type, and grade. Moreover, the interaction of this marker with other molecular markers such as P-glycoprotein (37, 48) or p21 (49) remains unknown and should be a matter for further investigation. Multivariate models also including other parameters should consider including TP53 status in the future as a predictor of outcome in osteosarcoma.

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