Research Article

TP53 Mutations and Survival in Osteosarcoma Patients: A Meta-Analysis of Published Data

Zhe Chen, Jiayi Guo, Kun Zhang, and Yanxing Guo

Luoyang Orthopedic Hospital of Henan Province, Luoyang 471000, China

Correspondence should be addressed to Yanxing Guo; guoyxing01@163.com

Received 12 January 2016; Accepted 5 April 2016

Academic Editor: Lance A. Liotta

Copyright © 2016 Zhe Chen et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Several research groups have examined the association between TP53 mutations and prognosis in human osteosarcoma. However, the results were controversial. The purpose of this study was to evaluate the prognostic value of TP53 mutations in osteosarcoma patients. A meta-analysis was conducted with all eligible studies which quantitatively evaluated the relationship between TP53 mutations and clinical outcome of osteosarcoma patients. Eight studies with a total of 210 patients with osteosarcoma were included in this meta-analysis. The risk ratio (RR) with a 95% confidence interval (95% CI) was calculated to assess the effect of TP53 mutations on 2-year overall survival. The quantitative synthesis of 8 published studies showed that TP53 mutations were associated with 2-year overall survival in osteosarcoma patients. These data suggested that TP53 mutations had an unfavorable impact on 2-year overall survival when compared to the counterparts with wild type (WT) TP53 (RR: 1.79; 95% CI: 1.12 to 2.84; \( P = 0.01 \); \( I^2 = 0 \% \)). There was no between-study heterogeneity. TP53 mutations are an effective prognostic marker for survival of patients with osteosarcoma. However, further large-scale prospective trials should be performed to clarify the prognostic value of TP53 mutations on 3- or 5-year survival in osteosarcoma patients.

1. Introduction

Osteosarcoma is the most common malignancy that occurred in bone. In the past few decades, although neoadjuvant chemotherapy and surgery have made remarkable progress to reduce tumor burden, therapeutic effectiveness of conventional therapies for metastatic osteosarcoma has remained unchanged, with a low five-year survival rate of less than 20% [1, 2]. Despite the rapid development of genetics and cell biology of osteosarcoma, further improvement in survival has not been achieved owing to the lack of effective indicators that are helpful for predicting individual clinical outcome.

Tumor protein p53 (TP53), also known as p53, BCC7, LFS1, or TRP53, is located on chromosome 17p13.1 and plays an important role in tumorigenesis [3, 4]. TP53 mutations were found in most of the human tumor tissues and were the most common genetic alterations [5–8]. Mutations in p53, tumor suppressor gene, have been proved to play a vital role in cell proliferation and in the pathogenesis of osteosarcoma [9–11]. Previous studies have shown that mutations in this gene were associated with poor prognosis in human osteosarcoma [12, 13]. In a recent study, whole-genome sequencing of tumors from 32 osteosarcoma patients showed that cancerspecific TP53 rearrangements were found in more than 50% of patients [14]. However, the clinical significance of TP53 mutations in osteosarcoma is controversial. In some reports, TP53 alterations are associated with poor response to chemotherapy and decreased survival in human osteosarcoma [9, 15–20], whereas other data showed no correlation with chemotherapy response or clinical outcomes of patients with osteosarcoma [20–22]. Therefore, it would be valuable to conduct a quantitative synthesis using rigorous methods. In this study, we conducted an updated meta-analysis of all available studies to identify whether TP53 mutations were involved in the process of cancer as a prognostic marker in patients with osteosarcoma.

2. Materials and Methods

2.1. Selection Criteria and Search Strategy. We identified all available studies that reported the association of TP53 mutations with efficacy survival in osteosarcoma. The electronic
Table 1: Main characteristics of eligible studies.

<table>
<thead>
<tr>
<th>Author (yrs)</th>
<th>Cases</th>
<th>Age (mean yrs)</th>
<th>HG I/II (III/IV)</th>
<th>Metastatic disease</th>
<th>Treatment</th>
<th>PCR exons</th>
<th>Deaths in 2 years, N (%)</th>
<th>Chemotherapy response (criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokoyama et al. (1998) [23]</td>
<td>17</td>
<td>15</td>
<td>(8/7)</td>
<td>2</td>
<td>NC + surgery</td>
<td>4–8</td>
<td>1 (6)</td>
<td>6/14 (S-K)</td>
</tr>
<tr>
<td>Radig et al. (1998) [24]</td>
<td>18</td>
<td>34</td>
<td>10/8</td>
<td>0</td>
<td>Surgery</td>
<td>4–8</td>
<td>2 (17)</td>
<td>NR</td>
</tr>
<tr>
<td>Goto et al. (1998) [12]</td>
<td>32</td>
<td>16</td>
<td>(23/9)</td>
<td>8</td>
<td>NC + surgery</td>
<td>MS</td>
<td>14 (44)</td>
<td>3/31 (N90)</td>
</tr>
<tr>
<td>Tsukiyama et al. (2000) [13]</td>
<td>27</td>
<td>15</td>
<td>NR</td>
<td>2</td>
<td>NC + surgery</td>
<td>5–9</td>
<td>11 (41)</td>
<td>NR</td>
</tr>
<tr>
<td>Patiño-García et al. (2003) [26]</td>
<td>41</td>
<td>14</td>
<td>NR</td>
<td>8</td>
<td>NR</td>
<td>5–8</td>
<td>7 (18)</td>
<td>22/41 (N90)</td>
</tr>
<tr>
<td>Goto et al. (1998) [12]</td>
<td>32</td>
<td>16</td>
<td>(23/9)</td>
<td>8</td>
<td>NC + surgery</td>
<td>MS</td>
<td>14 (44)</td>
<td>3/31 (N90)</td>
</tr>
<tr>
<td>Richter et al. (2013) [28]</td>
<td>17</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
<td>Surgery</td>
<td>5–9</td>
<td>5 (31)</td>
<td>3/17 (Huvos)</td>
</tr>
</tbody>
</table>

Note. Exons: exons of the TP53 gene analyzed by polymerase chain reaction. N: number; yrs: years; HG: histological grades; NC: neoadjuvant chemotherapy; 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.
showed that TP53 mutations were remarkably associated with a higher risk of death within 2 years compared with their counterparts with WT TP53 (Figure 2, RR: 1.79; 95% CI: 1.12 to 2.84; \( P = 0.01 \)). Sensitivity analysis showed that the pooled RR was stable and was not remarkably changed when each study was omitted (Figure 3). These analyses suggested that TP53 mutations in patients with osteosarcoma predicted poor 2-year overall survival, whereas more clinical studies should be conducted taking into account the age, sex, metastasis, histological grades, primary sites, and treatment of osteosarcoma patients.

### 3.4. Publication Bias and Sensitivity Analysis

The publication bias of the literature included in this study was assessed by means of funnel plots. The shape of the funnel plots was symmetrical, demonstrating that no publication bias existed.
in this analysis (Figure 3). In addition, sensitivity analysis was conducted to assess whether individual study affected final summary results. The sensitivity analysis showed that none of the studies remarkably affected the pooled RRs and CIs, and deletion of any one study had no significant effect on the final results (data not shown).

4. Discussion

Osteosarcoma, a malignant tumor in bone, is harmful to the health of children and adolescents, accounting for approximately 5% of tumors in childhood. But so far there have been no effective clinical prognostic markers to determine outcomes of patients and response to chemotherapy. In numerous studies using sequencing, TP53 mutations have been proven to be a powerful prognostic indicator for ER-positive tumors, including breast tumors. The majority of TP53 alterations are missense mutations that occur in exons 5 to 8, highly conserved regions, and principal structural domains of the TP53 protein [11]. In the included studies, silent deletions, missense and nonsense mutations, aberrant methylation, and one single-nucleotide substitution were observed in TP53 genes of patients with osteosarcoma. TP53 mutations may promote tumorigenesis and the identification of TP53 mutations was helpful to assess the clinical features of osteosarcoma (tumor grade, type, aggressiveness, and metastatic potential) [29, 30]. A previous meta-analysis showed that TP53 status is not associated with the histologic response to chemotherapy [21], while another meta-analysis showed that high TP53 expression predicted poor overall survival and disease-free survival in patients with osteosarcoma and Ewing’s sarcoma. The results obtained in these studies were conflicting. As we know, mutations may reduce the stability of proteins and induce truncated protein not detected by immunological histological chemistry. Therefore, the result of the article by Jiang and colleagues [31] is controversial. Although the other meta-analysis published in 2004 showed that TP53 gene alterations were associated with decreased survival [21], due to limitation of sample size, the conclusion was not strong. To examine the prognostic role of TP53 mutations in osteosarcoma patients, we systematically reviewed the published literature and performed a meta-analysis.

The present meta-analysis with a larger sample size showed that TP53 mutations were prognostic predictors for survival of osteosarcoma patients (RR = 1.79; 95% CI: 1.12–2.84; P = 0.01) (Figure 2). Sensitivity analysis suggested that the pooled RR was stable and significance of the pooled RR did not change when a single study was removed (Figure 3). In conclusion, the present meta-analysis indicated that TP53 mutations are a valuable prognostic indicator for poor prognosis in osteosarcoma patients.

However, some limitations do exist in this meta-analysis. Firstly, the sample size of this study was still small and there were only 8 available literatures with 210 osteosarcoma patients. Secondly, publication bias may exist in meta-analyses. Despite our best efforts, there still were some literatures that were not included in this meta-analysis due to the lack of detailed data. Thirdly, other factors in eligible studies may increase between-study heterogeneity. The heterogeneity may be from the individual differences of patients and medical technology. Fourthly, treatments of the patients and some osteosarcoma features (such as tumor type, aggressiveness, and metastatic potential) should be taken into account, which might be related to the survival time of patients with osteosarcoma. Therefore, further studies with larger sample sizes must be performed in the future to evaluate the prognostic significance of TP53 mutations in osteosarcoma.

In conclusion, the results from the present meta-analysis suggested that TP53 mutations are useful predictive biomarkers of 2-year overall survival in osteosarcoma patients, which will provide guidance for the clinical treatment.

Competing Interests

The authors declare that they have no competing interests.

References


