Predictive value of p53 expression in the risk of malignant gastrointestinal stromal tumors: Evidence from 19 studies

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Received July 17, 2011; Accepted September 16, 2011

DOI: 10.3892/etm.2011.369

Abstract. The current published data on p53 expression and its predictive value in the risk of malignant gastrointestinal stromal tumors (GIST) has are inconclusive. To derive a more precise estimation of the correlation between p53 and the biological behavior of GIST, a meta-analysis was performed. Studies were identified by searching PubMed and Embase. Inclusion criteria were GIST patients, and the evaluation of p53 expression and risk of malignancy. The odds ratio (OR) for a positive rate of p53 in the benign group vs. that in the malignant group and the ORs for the positive rate of p53 in the National Institutes of Health (NIH) very low risk + low risk group (VL+L) vs. the NIH intermediate risk + high risk (I+H) group were calculated with a 95% confidence interval (CI) for each study as an estimation of the predictive value of p53. A total of 19 studies including 1163 patients were involved in this meta-analysis. The overall OR for the positive rate of p53 in the malignant group vs. the benign group revealed that significantly elevated risks of positive p53 in the malignant group were achieved (OR 0.14, 95% CI: 0.06-0.31, P<0.00001, $P_{heterogeneity}$=0.86). Moreover, significantly elevated risks of correlation between p53 expression and the NIH I+H group were achieved in the comparison of the NIH VL+L group vs. the NIH I+H group (OR, 0.25; 95% CI, 0.17-0.38; P<0.00001, $P_{heterogeneity}$=0.04). The results indicate that p53 expression correlates with poor prognosis in GIST and has a close relationship within the NIH I+H group.

Introduction

Although gastrointestinal stromal tumors (GIST) are rare, they are the most common primary mesenchymal tumor of the gastrointestinal tract (1). GIST expresses the tyrosine kinase receptor, KIT, which is the protein product of the KIT proto-oncogene. GIST is generally characterized by gain-of-function mutations of KIT (2). Moreover, recent studies have described mutations of PDGFRA in certain populations of GIST (3,4). However, 12% of GIST cases do not have mutations of either KIT or PDGFRA. The mechanism of GIST genesis is not yet fully understood. As for the biological behavior, GIST was classified into two groups based upon the clinical outcome by long-term follow-up. Tumors that developed recurrence or metastasis were judged as malignant, including those which caused patient mortality. Tumors with peripheral invasive growth microscopically were also diagnosed as malignant. The other cases without the above evidence of malignancy were classified as benign. GIST has a wide spectrum of biological behavior ranging from benign to malignant. Due to its specific biological behavior, there is not a standard definition of benign and malignant GIST once the patient is diagnosed at an early stage. According to the consensus approach at the National Institutes of Health (NIH) in 2001, the use of risk assessment in predicting GIST behavior has been recommended, in preference to trying to draw a sharp line between benign and malignant lesions. They categorized GIST into 4 groups: very low risk, low risk, intermediate risk and high risk (Table I) (5). Although this system is useful in predicting GIST behavior, it is only based on the experience of a wide range of experts on GIST.

To explore other prognostic factors in GIST, a number of studies have completed research concerning cell-cycle regulatory proteins. p53, one of the cell-cycle regulatory proteins, has been implicated in the pathogenesis and tumor progression of various types of tumors. As in other neoplasms, it was assumed that the overexpression of p53 protein in GIST may be essential for tumorigenesis and therefore significant in predicting patient prognosis, particularly as it is known that when the genome is damaged, p53 suppresses the cell growth cycle by activating the transcription of genes that cause arrest in the G1 phase. This regulatory function may be lost in most neoplasms that have p53 overexpression and GIST is no exception. A number of studies have been designed to test the relationship between p53 and GIST behavior, with conflicting results partially due to the relatively small sample size in each of the published studies. Therefore, we performed a meta-analysis of the published studies to derive a more precise estimation of the association.

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Key words: gastrointestinal stromal tumors, p53 protein, predictive value, meta-analysis

Table I. National Institutes of Health system of risk grading for gastrointestinal stromal tumors.

	Tumor size (cm)	Mitotic count
Very low risk	<2	≤5/50 HPF
Low risk	2-5	≤5/50 HPF
Intermediate risk	≤5	>5 to ≤10 HPF
	>5 to ≤10	≤5/50 HPF
High risk	>5	>5/50 HPF
	>10	Any mitotic rate
	Any size	>10/50 HPF

Materials and methods

Publication search. Two electronic databases (PubMed and Embase) were searched (last search was updated on 1 June 2010, using the search terms: 'gastrointestinal stromal tumor' and 'p53'). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Only published studies with full-text articles were included. When more than one of the same patient populations was included in a number of publications, only the most recent or complete study was used in this meta-analysis.

Inclusion criteria. The inclusion criteria were as follows: a) evaluation of the p53 expression in GIST and biological behavior; b) benign (non-aggressive)-malignant (aggressive) study or NIH risk study; and c) sufficient published data for estimating an odds ratio (OR) with a 95% confidence interval (CI).

Data extraction. Information was carefully extracted from all eligible studies by two of the authors (Z.L. and C.P.), according to the inclusion criteria listed above. The following data were collected from each study: first author's surname, publication date, category method, total number of benign cases and malignant cases, number of positive p53 patients in the benign group and the malignant group, total number of patients in the NIH very low risk group, low risk group, intermediate risk group and high risk group, and number of patients with positive p53 in each NIH risk group, respectively. Data were extracted separately according to the category for subgroup analyses. We did not define a minimum number of patients required to include a study in our meta-analysis.

Statistical analysis. ORs with 95% CI were used to assess the predictive value of p53 expression in the risk of malignant GIST, according to the method of Woolf. Heterogeneity assumption was calculated by the χ^2-based Q-test. A P-value >0.10 for the Q-test indicates a lack of heterogeneity among studies, so the OR estimate of each study was calculated by the fixed-effects model (the Mantel-Haenszel method). Otherwise, the random-effects model (the DerSimonian and Laird method) was used. The significance of the pooled OR was determined by the Z-test and a value of P>0.05 was considered to be statistically significant. Sensitivity analyses were carried out to investigate whether modification of the inclusion criteria of this meta-analysis affected the final results. An estimate of potential publication bias was carried out by the funnel plot, in which the OR of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the t-test, suggested by Egger (P<0.05 was considered representative of statistically significant publication bias). All the statistical tests were performed with Review Manager Version 4.2 (The Cochrane Collaboration, Oxford, England) and STATA version 9.2 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics. A total of 19 publications met the inclusion criteria (6-24). The studies by Chou *et al*, Padilla *et al*, Romeo *et al* and Kwon *et al* were excluded due to insufficient information to calculate an OR (25-28), and the study by Sakurai *et al* was also excluded since they used telomerase activity as the criteria for measuring the malignant risk of GIST (29). Similarly, the studies by Wang *et al* and Tsai *et al* were excluded as the subsequent articles contained the same patient population (30,31). The study by Wong *et al* was excluded since they focused on proving that the mitotic count remained the best predictor of GIST (32). Hence, a total of 19 groups including 1163 patients were used in the pooled analyses. Table II lists the studies identified and their main characteristics. Of the 19 groups, sample sizes ranged from 11 to 343. Almost all of the patients with GIST were confirmed by histology and immunohistochemistry. No significant differences were found in the age distributions and gender differences among all the studies.

Meta-analysis results. The overall OR for the positive rate of p53 in the malignant group vs. the benign group revealed that significantly elevated risks of positive p53 in the malignant group were achieved (OR, 0.14; 95% CI, 0.06-0.31; P<0.00001, $P_{heterogeneity}$=0.86) (Fig. 1). Moreover, significantly elevated risks of correlation between p53 expression and the NIH intermediate risk + high risk (I+H) group were achieved in the comparison of the NIH very low risk + low risk (VL+L) group vs. the NIH I+H group (OR, 0.25; 95% CI, 0.17-0.38; P<0.00001; $P_{heterogeneity}$=0.04) (Fig. 2). The only heterogeneity existed in a comparison of those 14 combined studies of the NIH VL+L group vs. the NIH I+H group (P<0.10). In this analysis, although the p53-positive rate in the study of Yang *et al* (18) did not follow the tendency of other studies, the corresponding pooled OR was not materially altered with or without including both of them. No other single study affected the pooled OR qualitatively as indicated by sensitivity analyses (data not shown).

Publication bias. Begg's funnel plot was performed to assess the publication bias of the literature. The shapes of the funnel plots did not reveal any evidence of marked asymmetry (Figs. 3 and 4).

Table II. Main characteristics of all studies included in the meta-analysis.

Author/(Refs.)	Category	B/M or NIH (VL+ L/I+H)	Age distribution	Gender (male/female)	Size
Feakins (6)	NIH	48/57	No report	No report	105
Gumurdulu *et al* (7)	NIH	3/22	62.3±11.18	16/9	25
Hu *et al* (8)	NIH	14/35	59.2±12.1	25/24	49
Lopes *et al* (9)	NIH	60/283	59 (22-92)	255/258	343
Nakamura *et al* (10)	NIH	22/58	63.4 (20-93)	39/41	80
Neves *et al* (11)	NIH	8/32	56 (22-84)	21/19	40
Pauser *et al* (12)	NIH	35/65	62 (24-90)	45/59	100
Ryu *et al* (13)	NIH	42/83	58 (28-83)	71/54	125
Yang *et al* (14)	NIH	13/8	48 (36-84)	11/10	21
Takeyama *et al* (15)	NIH	18/9	63.0±13.1	16/16	27
Al-Bozom (16)	NIH	5/10	57 (29-79)	7/8	15
Sabah *et al* (17)	NIH	2/21	59 (19-93)	11/12	23
Aoyagi *et al* (18)	NIH	5/6	61.0±9.7	8/3	11
Yalcinkaya *et al* (19)	NIH	5/36	52.8±14.0	25/16	41
Chang *et al* (20)	B/M	11/13	48 (23-95)	15/9	24
Meara (*et al* 21)	B/M	6/8	58 (17-84)	7/7	14
Wang *et al* (22)	B/M	38/35	No report	42/31	73
Ozdamar *et al* (23)	B/M	9/13	48.8±12.9	11/11	22
Panizo-Santos *et al* (24)	B/M	10/15	52.6 (30-80)	18/14	25

B/M, benign/malignant; NIH (VL+ L/I+H), very low + low/intermediate + high.

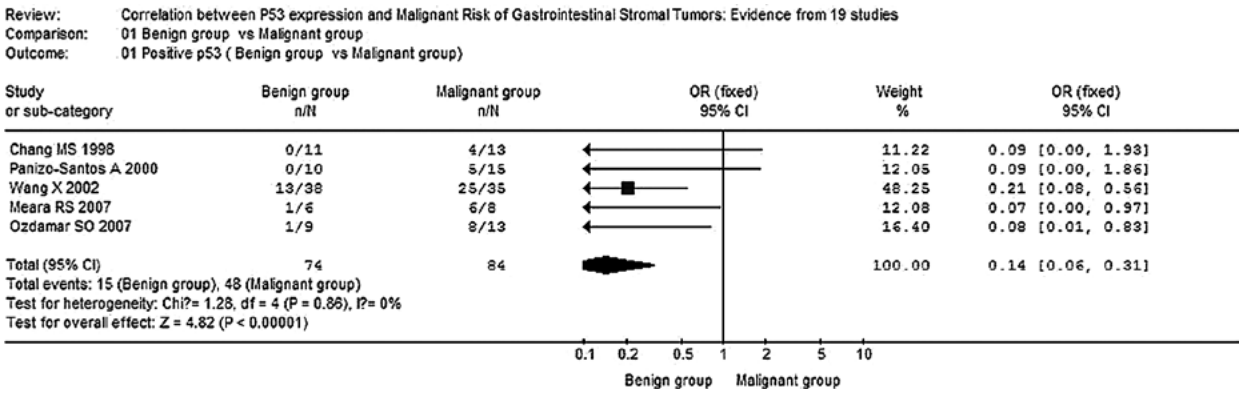

Figure 1. Meta-analysis on positive P53 (benign vs. malignant group).

Discussion

To date, scientists have been looking for various criteria to determine the biological behavior of GIST and only two classification methods have been widely applied and admitted. The most direct way is by classifying the GIST patients into two groups (a malignant group and a benign group), based on clinical outcome by follow-up, to satisfy the criteria as follows: i) Malignant definition: peripheral invasive growth, lymph node metastasis, metastasis to another organ, recurrence or mortality; ii) other cases without evidence of malignancy are classified as benign. This malignant-benign system is used to achieve the guaranteed result of the biological behavior of GIST by long-term follow-up. Therefore, it is difficult to predict the malignant behavior of GIST before any standard system is established. On the other hand, a number of studies have suggested that tumor stage at presentation, tumor size and mitotic activity are significant clinicopathological markers. Accordingly, the NIH system, based on tumor size and mitotic activity, has been established to predict GIST behavior by using risk assessment (very low risk, low risk, intermediate risk, and high risk), rather than attempting to draw a sharp line between benign and malignant lesions. Moreover, the NIH system as a prognostic tool is supported by the guaranteed evidence from certain follow-up studies (24).

Activating mutations of the genes, c-kit and PDGFRα, characterize the tumor entity GIST. The mutation status is important for prognosis and a predictive factor for the response to therapy with the tyrosine kinase receptor inhibitor, imatinib (33).

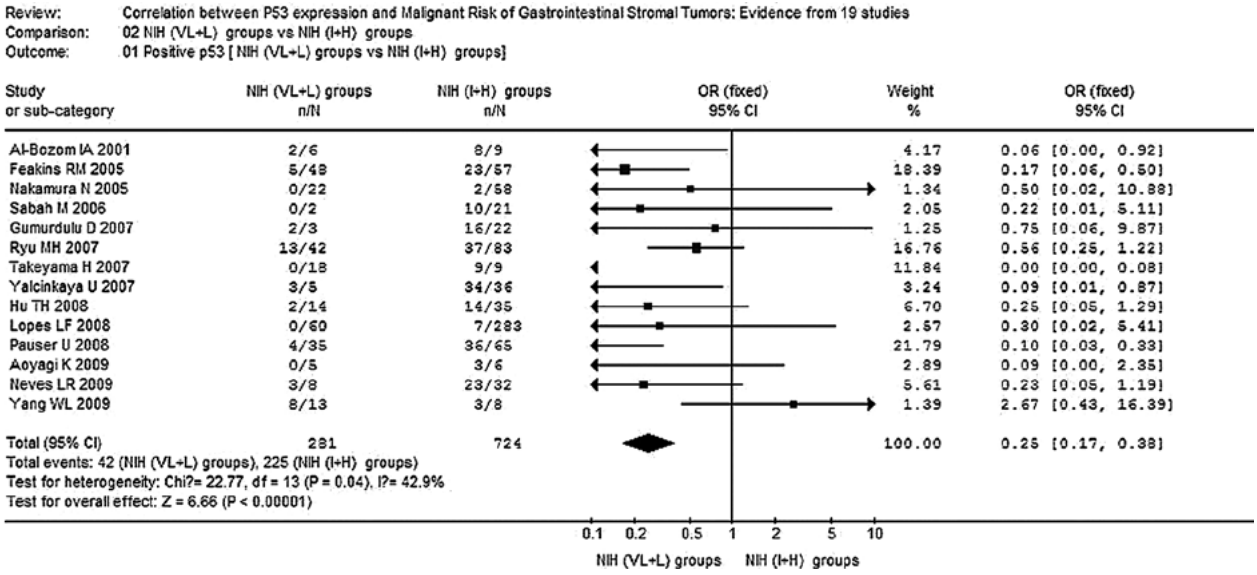

Figure 2. Meta-analysis on positive P53 [NIH (VL+L) vs. NIH (I+H) group].

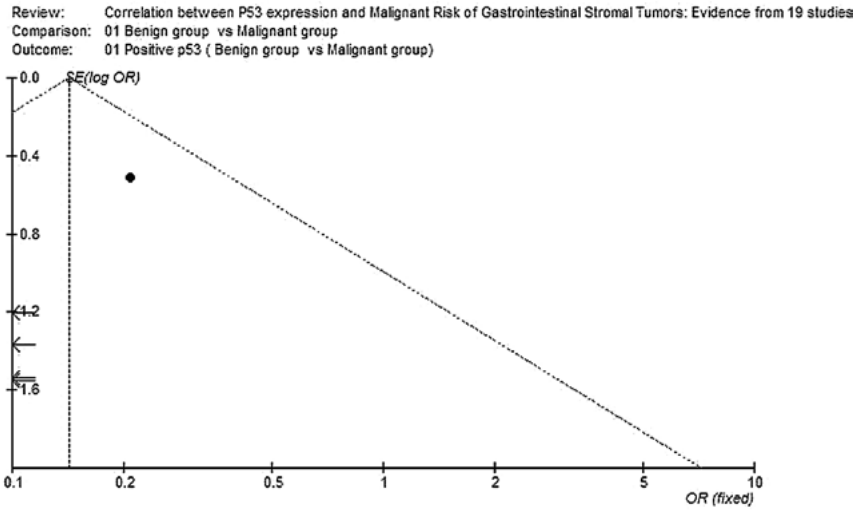

Figure 3. Begg's funnel plot for publication bias test (benign vs. malignant group).

Altered cell cycle regulation may underlie the tumorigenesis and/or the progression of human malignancies. Regarding p53 expression in GIST, certain studies have been carried out, with conflicting results. Cai *et al* evaluated p53 expression in 55 GIST patients and concluded that p53 expression may be associated with the transformation of leiomyoma into leiomyosarcoma, and may be used as a predictive marker for prognosis (35). Hillemanns *et al* found four out of five metastasizing GIST cases to be p53 positive and concluded that positivity may indicate a more aggressive course (34). Chang *et al* studied 31 intestinal tumors divided into two groups, clinically aggressive and clinically benign (20). They found p53 expression in 31% of aggressive cases and 0% of benign cases and concluded that p53 expression, in conjunction with other parameters such as cellularity, MI, tumor size, degree of necrosis and pleomorphism, is important in predicting malignancy. By contrast, Lopes *et al* studied 33 cases of GIST and did not find this correlation between p53 and behavior, although in their study, 8 out of 14 cases with tumor size <5 cm in diameter and 3 out of 19 cases with tumor size >5 cm showed some positivity with p53, which they ignored and considered statistically insignificant (36).

Whether p53 expression is a prognostic or predictive marker in malignant GIST has attracted considerable attention. With a goal to explore the possible association between p53 and the biological behavior of GIST, we performed this meta-analysis of the published studies to derive an overall pooled estimation. Our meta-analysis showed that p53 expression appeared more often in recurred or metastasized GIST (malignant group) than in tumors with disease-free follow-up (benign group). Furthermore, p53 expression was significantly associated with the established prognostic criteria (NIH system), and was consistent with most previous GIST studies (6,11-13,15,16-19). NIH I+H showed more positivity with p53 than NIH VL+L tumors.

These data indicate the impact of the tumor suppressor gene, p53, on GIST progression. Our results confirmed p53 as

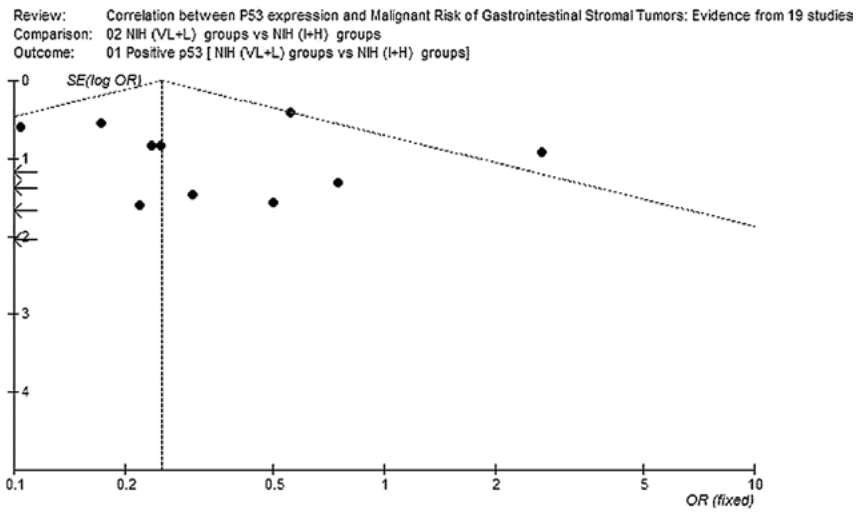

Figure 4. Begg's funnel plot for publication bias test [NIH (VL+L) vs. NIH (I+H) group].

a powerful immunohistochemical marker for predicting the risk of malignancy in GIST and having a close correlation with NIH I+H. However, a small sample size, varied clones of antibodies tested and potential heterogeneity, limit us to conclude more precise results. Lopes *et al* studied p53 expression in 343 GIST patients and found expression only in 2.6% of cases, of which all belonged to the high-risk group for aggressive behavior according to the NIH consensus approach (9). They revealed that p53 expression exists with a lower positive rate but is not a common phenomenon for the specified group. Therefore, mitotic count and tumor size are still the most significant prognostic criteria for the classification of GIST, and in conjunction with p53 expression are important in predicting malignancy, particularly for the NIH I+H group.

Immunohistochemical staining should be positive for wild-type p53 as well as for mutant-type p53, but wild-type p53 is barely detectable by immunohistochemistry. However, most positive cells represent mutant p53 since the half-life of the wild-type p53 protein is very short, and mutant-type p53 is altered in structure with a longer half-life and greater stability. At this point there should be a molecular incidence of p53 mutation driving the progression of GIST to more malignant behavior in theory.

Notably, c-kit and PDGFRA mutations represent the primary genetic alteration found in the majority of cases of GIST. Carcinogenesis and tumor progression are favored by the accumulation of genetic events.

El-Rifai *et al* demonstrated that malignant GIST contains more genetic alterations than tumors of a benign nature (37). We assumed that p53 mutation may be one of the significant incidents in the progression of GIST. p53, a tumor suppressor gene, is mapped on chromosome 17p and has a crucial function in DNA repair and in the regulation of apoptosis. Mutation of p53 leads to disruption of these pathways and results in a selective growth advantage for tumor cells. At present, studies focusing on p53 mutation are still few in number. However, it is necessary to conduct large trials to explore the correlation of the p53 mutation genotype with the biological behavior of GIST. Moreover, p53 mutation may be a molecular incident in the progression of GIST. The p53 gene also requires further investigation with regard to resistance to imatinib and prognosis in metastatic GIST. Molecular p53-targeting agents, such as small-molecule MDM2 antagonists, termed nutlins, and PRIMA-1, which are able to restore the DNA-binding property of a wide range of mutant p53 proteins, may be developed and put into clinical use. Furthermore, the combination of such p53-targeting agents and imatinib may improve outcomes in GIST patients with a p53 mutation.

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