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p53 Antibodies as a Diagnostic Marker for Cancer: Results from a Meta-Analysis

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Editorial Note

P53 is an unequivocal tumor suppressor altered in most sporadic human cancers. The loss of p53 initiates progression of malignancies and it is characterized by more malignant factors, such as an increase of the risk of cancer cells to become more invasive and potentially metastatic, genomic instability and poor cellular differentiation. Many studies have evaluated the clinical stability of serum p53 antibodies (s-p53-Abs). There is a high correlation between the s-p3-Abs and the frequency of p53 gene alteration in tumors [1-6]. The correlation between s-p53-Abs and p53 mutations is significant in many types of cancers. It is interesting to note that in cancers without p53-mut, such as testicular carcinoma [7,8], melanoma [9,10] and hepatoma [11], the lack of p53-mut was followed by a lack of s-p53-Abs. Overall 20%-40% of p53-mut patients had s-p53-Abs in sera. Therefore, p53 and its accumulation, it is not a rule of thumb meaning the generation of s-p53-Abs [12-15] and there must be other factors involved in forming autoantibodies for p53.

Many studies have evaluated the clinical utility of s-p53-Abs. Several cancers'studies have shown that s-p53-Abs correlated with higher tumor grades, whereas other studies observed quite the opposite correlation [16]. Since such weighty matter has not reached a consensus yet, we sought to take this opportunity to conduct a meta-analysis of all the randomized-to-control clinical data to answer such an important question. Our analysis consisted of randomized clinical trials looking at the prognostic value of serum p53-Abs in patients with solid tumors (Table 1). We included a total of 346 patients from 8 clinical studies and showed that s-p53-Abs significantly correlated with a worse survival (p<0.0001; HR: 1.57 [1.28, 1.93]) (Figure 1). Therefore having such antibodies could be indicative of the presence of p53-mut, and its consequent accumulation, ultimately leads to the production of p53 antigen on the cancer cells. Such antigens would be recognized by the immune system, producing antibodies against p53. Such antibodies could be interesting in the investigation of therapeutic or diagnostic purposes. This is the first meta-analysis proving the diagnostic utility of p53-Abs for cancer patients, predicting a worse outcome.

Our study has some limitations. First of all the retrospective nature of the study is intrinsically susceptible to biases. Moreover, the patients were affected from different tumors and received different regiments of treatment (Herceptin, radiotherapy, chemotherapy, nonsteroidal anti-inflammatory drug celecoxib) and the stages that the disease has reached in patients, ultimately could had affected the results' analysis.

The s-p53-value could be used in future to determine patients benefitting from a specific treatment. In our analysis patients were looked independently of treatment and tumor because of the relatively lower number of randomized studies at our disposal. As medicine unfolds more knowledge, a larger number of patients could help to evaluate the impact

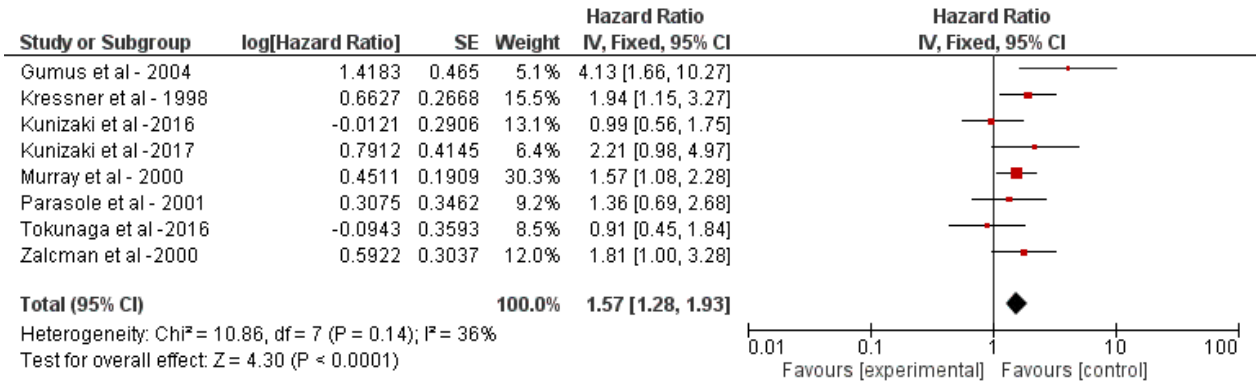

Figure 1. SEM Fractography of the failed bracket (a) 250x, (b) 1000x.

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Study Reference	Patients	Methods	Prognostic value of s-p53-Abs	Type of Study	Treatment
Gumus et al., 2004	76 patients with transitional urinary bladder cell carcinoma.	S-p53-Abs ELISA. Antibodies for p53-wt 184 CRC patients	There was an association between the presence of s-p53-Abs and tumor p53 gene overexpression (p=0.001).	Prospective	14 patients with superficial tumours underwent only TUR, 34 underwent TUR with intravesical treatment (Mitomycin C or Bacillus Calmette-Guerin). Patients with invasive bladder cancer underwent profound TUR and chemotherapy (MVAc, n=11), radiotherapy (n=9) and Mainiz pouch II operations as urinary diversion after radical cystectomy (n=8).
Kressner et al., 1998	184 CRC patients. Dukes' stage: A (n= 31); B (n= 84); C (n= 41); D (n=28)	S-p53-Abs ELISA. Antibodies for p53-wt 184 CRC patients	p53-Abs correlated with shorter survival (p=0.02).	Retrospective	They underwent colorectal resection
Kunizaki et al., 2016	170 CRC patients	S-p53Ab, CEA ELISA. Antibody for p53-wt	Positivity for s-p53Ab in CRC did not correlate with overall survival. Kaplan-Meier analysis revealed significant differences between patients with elevated s-p53Ab and CEA and those with elevated levels of either one or neither of these factors (p< 0.001).	Retrospective	They underwent colorectal resection
Kunizaki et al., 2017	208 GC patients	S-p53Ab Detected with anti-p53 detection kit MESACUP anti-p53 Test Antibody for p53-wt	Did not observe any significant correlation between S-p53Ab in GC and overall survival (hazard ratio(HR)=2.052; 95% confidence interval(CI)= 0.891–4.726; p= 0.091). Conversely, Cox regression analysis revealed that a high level of CA19-9 was an independent prognostic factor for GC (hazard ratio(HR)=3.864; 95% confidence interval(CI)= 1.248–11.959; p= 0.019).	Retrospective	They underwent elective surgery with regional lymph node dissection
Murray et al., 2000	231 SCLC patients	S-p53-Abs ELISA. Antibodies for p53-wt	High levels of p53-Abs correlated with worse survival compared to patients with lower levels of the antibodies (p=0.02).	Retrospective	They received a treatment regime including platinum, or any combination as opposed to single agent treatment
Parasole et al., 2001	80 HCC patients	S-p53-Abs ELISA. Antibodies for p53-wt	Anti-p53 was not useful as a prognostic factor.	Retrospective	21 patients received percutaneous ethanol injection, and 15 were treated with surgical resection; 10 patients underwent radiofrequency interstitial tumor ablation. Only 4 patients received systemic chemotherapy, whereas 8 received TACE; in 5 cases, 2 types of locoregional treatment were combined.
Tokunaga et al., 2017	244 CRC patients	CEA, CA19-9, S-P53Ab Antibody for p53-wt	S-P53Ab had no power to predict the prognosis (p =0.786). Combined CEA and CA19-9 positivity was an exclusive independent prognostic factor (p=0.034).	Retrospective	They underwent chemotherapy or surgical resection.
Zalcman et al., 2000	97 SCLC patients	S-p53-Abs ELISA. Antibodies for p53-wt	Patients with limited-stage SCLC and p53-Ab had a median survival time of 10 months, whereas limited-stage SCLC patients without p53-Ab had a 17-month median survival time (p=0.014).	Prospective	SCLC patients received identical standard therapeutic regimens in the 4 centres: 6 courses of chemotherapy (CT) including cisplatin, etoposide, doxorubicin and cyclophosphamide

Table 1. Main characteristics of included studies.

of our finding of the negative prognostic utility of s-p53-Abs in the field of oncology and treatment response. Our data is in agreement with a significant portion of studies (mostly replying on ELISA method) where the s-p53-Abs predicts worse survival in cancer patients. The importance of a high prevalence of s-p53-Abs and its correlation with p53-mut in cancer merits further investigation to assess other biomarkers that could be useful for predicting likelihood of response to anti-p53 drugs, anti-HER2 and other TRKs.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Funding Sources

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References

1. HTavassoli, M, Brunel N, Maher R and Johnson N W et al. "p53 Antibodies in the Saliva of Patients with Squamous Cell Carcinoma of the Oral Cavity." *Int J Cancer* 78 (1998): 390-391.
2. Lubin, R, Schlichtholz B, Teillaud J L and Garay E et al. "p53 Antibodies in Patients with Various Types of Cancer: Assay, Identification, and Characterization." *Clin Cancer Res 1* (1995): 1463-1469.
3. Davidoff, A M, Iglehart J D and Marks J R. "Immune Response to p53 is Dependent Upon p53/HSP70 Complexes in Breast Cancers." *Proc Natl Acad Sci U S A* 89 (1992): 3439-3442.
4. Angelopoulou, K and Diamandis EP. "Detection of the TP53 Tumour Suppressor Gene Product and p53 Auto-Antibodies in the Ascites of Women with Ovarian Cancer." *Eur J Cancer* 33 (1997): 115-121.
5. Angelopoulou, K, Stratis M and Diamandis E P. "Humoral Immune Response against p53 Protein in Patients with Colorectal Carcinoma." *Int J Cancer* 70 (1997): 46-51.
6. Houbiers, J G, Van der Burg S H, Van de Watering L M and Tollenaar R A et al. "Antibodies against p53 are Associated with Poor Prognosis of Colorectal Cancer." *Br J Cancer* 72 (1995): 637-641.
7. Mattioni, Manlio, Soddu Silvia, Prodosmo Andrea and Visca Paolo et al. "Prognostic Role of Serum p53 Antibodies in Lung Cancer." *BMC Cancer* 15 (2015): 148.
8. Peng, H Q, Hogg D, Malkin D and Bailey D et al. "Mutations of the p53 Gene Do Not Occur in Testis Cancer." *Cancer Res* 53 (1993): 3574-3578.
9. Lübbe, Jann, Reichel Martin, Burg Güner and Kleihues Paul. "Absence of p53 Gene Mutations in Cutaneous Melanoma." *J Invest Dermatol* 102 (1994): 819-821.
10. Luca, M, Lenzi R, Leejackson D and Gutman M et al. "p53 Mutations are Infrequent and do not Correlate with the Metastatic Potential of Human-Melanoma Cells." *Int J Oncol* 3 (1993): 19-22.
11. Puisieux, A, Galvin K, Troalen F and Bressac B et al. "Retinoblastoma and p53 Tumor Suppressor Genes in Human Hepatoma Cell Lines." *FASEB J 7* (1993): 1407-1413.
12. Winter, S F, Sekido Y, Minna J D, McIntire D et al. "Antibodies against Autologous Tumor Cell Proteins in Patients with Small-Cell Lung Cancer: Association with Improved Survival." *J Natl Cancer Inst* 85 (1993): 2012-2018.
13. Cawley, H M, Meltzer S J, De Benedetti V M and Hollstein M C et al. "Anti-p53 Antibodies in Patients with Barrett's Esophagus or Esophageal Carcinoma can Predate Cancer Diagnosis." *Gastroenterology* 115 (1998): 19-27.
14. Hammel, P, Leroy-Viard K, Chaumette M T and Villaudy J et al. "Correlations between p53-Protein Accumulation, Serum Antibodies and Gene Mutation in Colorectal Cancer." *Int J Cancer* 81 (1999): 712-718.
15. Brevern, M C von, Hollstein M C, Cawley H M and De Benedetti V M et al. "Circulating anti-p53 Antibodies in Esophageal Cancer Patients are Found Predominantly in Individuals with p53 Core Domain Mutations in their Tumors." *Cancer Res* 56 (1996): 4917-4921.
16. Sobhani, Navid, D'Angelo Alberto, Wang Xu and Young Ken H et al. "Mutant p53 as an Antigen in Cancer Immunotherapy." *Int J Mol Sci* 21 (2020): 4087.

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