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Evaluation of correlation between the expression of p53 as an immunohisto-chemical marker & prognosis of gastric cancer

Nastaran Ranjbari [1], Neda Hojatpanah [2*]

[1]Assistant Professor of Pathology, Department of Pathology, Imam Khomeini Hospital, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[2]MD, Resident of Pathology, Department of Pathology, Imam Khomeini Hospital, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Corresponding author:: Neda Hojatpanah, MD, Resident of Pathology, Department of Pathology, Imam Khomeini hospital, School of Medicine, Ahvaz Jundishapur University
of Medical Sciences, Ahvaz, Iran. Tel: +989106006032, E-mail: hojatpanahn@gmail.com

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Abstract

Background: Gastric cancer is the most common form of gastro intestinal malignancy in certain part of the word and the most common type is Adenocarcinoma. The tumor suppressor gene p53 is a nuclear protein which plays a key role in tumor progression. Therefore in this study, we investigate p53 expression in gastric cancer specimens and possible relationship between this marker and clinical-pathological factors of disease.

Materials and methods: This study included 54 patients with primary Adenocarcinoma of stomach whom under- went gastrectomy at the Ahvazs Emam Khomeini hospital. Tumor specimens examined by immuno-histochemical staining with monoclonal antibody against p53. For evaluate value of p53, A stain was considered positive, when %20 of cancer cells showed a positive nuclear staining.

Result: P53 marker was positive in 40 cases (%74). Stronger expression of p53 was related with higher grade (p=0/035) and lymph node metastasis (p=0/033). No significant differences were seen between value of p53 marker with age, sex, tumor size, depth of invasion and tumor type. Expression of p53 was not correlated with vascular and neural invasion or involvement of margins ($p \geq 0.05$).

Conclusion: In gastric cancer, the expression of p53provides significant information about prognosis and evalua- tion of p53 level could be a useful tool in identification of patients with more aggressive disease.

Keywords: p53, Adenocarcinoma, Immunohistochemical staining

Background

In the last several years, developments in molec- ular genetics have shown that activation of onco- genes and inactivation of tumor-suppressor genes, results in cancer development in various organs (1). It has been shown that the p53 gene is a tu- mour-suppressor gene and its mutations play an important role in the development of human ma- lignancies (2). Mutations of p53 are common and found in various human cancers (3, 4). Although, gastric cancer is the most common form of gastro- intestinal malignancy in certain parts of the world, relatively little is known about the molecular oc- currences leading to its development (1). Im- munohistochemical studies show that antibodies against p53 proteins may be used as screening method for the presence of p53 (5). Therefore, the intent of the present immuno-histochemical study is to determine to what extent histopathological findings are identified in the p53 tissue status of patients with resectable gastric cancer.

Materials and Methods

Patients: This study included 54 patients with primary gastric cancer, all of whom underwent gastrectomy at the Department of Surgery of Emamkhomeini hospital of the Ahvaz jundishapur University of Medical sciences, from 2003-2012.

Immunohistochemical staining: All tumour spec- imens were fixed in 10% formaldehyde and em-
bedded in paraffin. The 4 µm thick sections were cut from the paraffin blocks containing repre- sentative histological features of the tumors. Par- affin was removed from the sections in xylene after hydration the sections were placed in Phos- phate Buffered Saline (PBS) at pH 7.4 and %3H2O2 was applied in order to abolish nonspecific bind- ing of the primary antibody. Then the slides were incubated with the monoclonal antibodyp53- Do7 overnight at 4°C. In the next step, the slides were incubated with rabbit anti-mouse antibody. Weak nuclear counterstaining was performed with he- matoxylin. Incidences of nuclear accumulation of p53 protein were determined for each specimen, also depth of tumour invasion, Grade, microscopic vessles and neural invasion, lymph node status and margins and lauren type. For evaluate value of p53, A stain was considered pos- itive, when %20 of cancer cells showed a positive nuclear staining.

Statistical analysis: The kendalls tau-b test was
used for testing differences about tumor size, depth of invasion and Grade. The pearson chi- square test was used for other factors such as lau- ren type, lymph node status. All calculations were performed using the statistical software SPSS ver- sion 15.

Results

In 54 primary gastric carcinomas, we compared common prognostic markers such as age, sex, tu- mour size, Lauren type, depth of invasion, tumor grading, lymph node status, vascular and neural invasion, involvement of surgical margins and p53 expression. The tumors examined in this study were separated into two groups, based upon the percentile of p53-protein-positive cell nuclei. A total of 40 tumours (%74) stained positive for p53; 14 tumors with a p53 protein expression of <20% were treated as negative results.

There was no obvious relation between p53 staining and the age or sex of the patients. No sig-
nificant correlations were found between p53 tis-
sue status and tumor size, lauren type, depth of invasion,
vascular and neural invasion and in-
volvement of surgical margins.

In contrast, there was a significant association between p53 tissue status and the metastatic
spread to lymph nodes. p53 positive tumors were
associated with a higher incidence of metastasis to lymph nodes (%88.5) than were p53 negative
tumors (%11.5; $p<0.05$). Furthermore, differences
were also noted in tumor Grading. Stronger ex- pression of p53 was related with higher grade
($p<0.05$).

Discussion

Recent data have shown that mutations of the p53 gene are common in certain human tumors, including lung and colon tumors (5, 6). In con- trast, the significance of p53 expression in gastric carcinomas remains a point of controversy (7). Therefore in this study, immunohistochemical examination methods were employed to investi- gate p53 expression in resected gastric cancer specimens. In the present study, %74 of the gastric cancers were considered p53 positive (>20% of cancer cells staining positive) that was different between various studies (1-6, 8, 9). One explana- tion for these results can be derived from differ- ences in immunohistochemical techniques em- ployed and p53 antibodies used. The correlation of p53 positive tissue status and age or gender was confirmed in the study of Lee KE et al (13) but in our study and chakavarthi et al was not (1). As chakavarthi et al (1), no correlation was found be- tween positive p53 tissue status and type of tu- mor, in contrast to Lazar D and Lee KE et al (14, 13) that expression of p53was more in intestinal type. The correlation of p53 positive and size of tumor was confirmed in the study of Tzanakis, Shiroko and Lee et al (8, 11, 13) but in our study was not. As Lazar D et al (14), correlation was found between positive p53 tissue status and his- tological grade of tumor differentiation but chakavarthi et al and Muller (1, 9) did not found. Positive expression of p53 correlated with depth of tumor invasion in the study of Seo et al, Shiro- ko et al and Lazar et al (2, 11, 14) but was not con- firmed in our study and chakavarthi et al and Mul- ler (1, 9). In the own collective, lymph node metas- tases were found more frequently among p53 pos-
itive tumors ($p<0.05$). This observation was con- firmed in studies by chakavarthi et al (%88.3) (1), Tzanakis (8), Yonemura et al ($p<0/001$) (10), Shi- roko et al and Pinto-de-Sousa et al (11, 12).In the Muller et al study was not such finding (9). No correlation was found between positive p53 tissue status and vascular and neural invasion and in- volvement of margins in our study, but Pinto-de- Sousa et al and Lazar et al (12, 14) found correla- tion with vascular invasion.

Conclusion

Immunohistochemical analysis of primary gas- tric cancer appears to be a simple method screen- ing the presence of mutant p53 protein. This study was able to demonstrate that p53 immuno-reactivity in gastric cancer is closely associated with Grade of tumor and lymph node metastasis. Therefore, data on the immunhistochemistry of p53 expression in gastric cancer may be clinically useful in obtaining information on the metastatic potential to lymph nodes and additionally in de- termining the treatment of these patients.

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Conflict of Interest

There is no conflict of interest to be declared.

Authors' contributions

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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