Changes of serum p53 antibodies and clinical significance of radiotherapy for esophageal squamous cell carcinoma

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AIM: To explore the relationship between serum p53 antibodies (p53-Abs) and clinicopathological characteristics and therapeutic effect in patients with esophageal carcinoma (EC), and to investigate sequential changing regularity of serum p53-Abs after radiotherapy.

METHODS: The serum p53-Ab levels were detected in 46 EC patients and 30 healthy adults by enzyme linked immunosorbent assay (ELISA). The blood samples were collected on the day before radiotherapy and on the administration of an irradiation dose of 20 Gy/10 f/12 d, 40 Gy/20 f/24 d and 60 Gy/30 f/36 d after radiotherapy. The presence of such antibodies and other factors related to a poor prognosis, such as high histological grade and disease stage and lymph node metastasis (< 0.05), but it was not significantly related to sex, age and grade, disease stage and lymph node metastasis (< 0.05). Serum anti-p53 antibodies (p53-Ab) assay was performed part of the research; Tian Y and Zhang ZY did the ELISA assays.

CONCLUSION: Detection of serum p53-Abs is helpful to the diagnosis of esophageal carcinoma. Monitoring for sequential change of serum p53-Abs before and after radiotherapy in patients with esophageal carcinoma is also useful to evaluate the response to the treatment and prognosis of the patients.

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Key words: Esophageal carcinoma; Radiotherapy; Serum p53 antibodies; Enzyme linked immunosorbent assay

INTRODUCTION

Esophageal carcinoma (EC) is one of the most common malignant diseases in China. The prognosis of this disease is unfavorable in spite of advances in therapies. Mutations of the p53 gene are common gene alterations in most malignant tumors, including EC. Mutant p53 protein is accumulated in cells because of its longer half-life compared with wild-type protein. Therefore, p53 overexpression can be detected by immunohistochesomal staining for p53. The anti-p53 antibody (p53-Ab) assay is based on the initial results of Crawford et al. who detected p53-Abs in the sera of patients with breast carcinomas. Because mutation in the p53 gene and the consequent overexpression of p53 are associated with tumor tissues, both wild type and mutant p53 may act as targets of tumor specific humoral and cellular immune responses. The presence of p53-Abs in the sera of patients has been noted in various types of carcinomas. Non-carcinoma patients do not exhibit such antibodies. Close correlations were observed between the presence of such antibodies and other factors related to a poor prognosis, such as high histological grade and...
the absence of hormone receptors\(^{(10)}\). The presence of serum p53-Abs was reported to be an independent prognostic factor for breast carcinoma\(^{(11)}\). Studies have revealed that overexpression of p53 protein closely related to induction of drug resistance in cancer patients and it can be used as a predictor for chemosensitivity of tumor. Specific p53-Ab was found in the sera of cancer patients with p53 protein overexpression. Furthermore, the presence of serum p53-Ab is closely correlated with p53 protein overexpression\(^{(10,11)}\). Thus, serum p53-Ab could theoretically be useful in predicting radiosensitivity in cancer patients. However, the clinical relevance of p53-Ab and radiotherapy for EC has not been fully studied. In the present study, the serum p53-Ab level was detected in 46 EC patients and 30 healthy adults as control by enzyme linked immunosorbent assay (ELISA). We explored the relationship between serum p53-Ab and clinicopathological characteristics and therapeutic effect in EC patients, and investigated the sequential changing regularity of serum p53-Ab after radiotherapy.

**MATERIALS AND METHODS**

**Clinical data**

A total of 46 consecutive patients with primary EC were enrolled in this study. They consisted of 38 males (82.6%) and 8 females (17.4%), with a mean age of 56.4 years (range, 46-70 years), who were treated at Gansu Provincial Tumor Hospital between April 2005 and June 2007. The patients’ eligibility for this study was as follows: (1) Primary lesion was squamous carcinoma in histology. There was no previous malignant disease or clinical evidence of a second primary tumor elsewhere; (2) Karnofsky performance status ≥ 70, white blood cell and hemoglobin levels within the normal range; and (3) Having not received radiotherapy, chemotherapy and operation. Tumor, nodes and metastasis (TNM) classification was established on the basis of pathologic examinations of biopsied specimens. Lymph node status in the patients was determined by computed tomography (CT). According to the UICC (2002) classification, 10 patients were in stage I, 17 in stage II, 14 in stage III and 5 in stage IV. Twenty-eight patients had no signs of lymph node metastasis, and the other 18 patients had metastasis of mediastinal and/or supraclavicular lymph nodes. Thirty-two had primary lesions < 6 cm and 14 were ≥ 6 cm in size. Five tumors were located in the upper thorax, 21 in the middle thorax and 20 in the lower thorax. To compare the reliability of seronegative testing, a total of 30 healthy volunteers, 19 males and 11 females, with a mean age of 36 years (range, 21-62 years) from our hospital staff and medical students served as controls. Informed consent was obtained from all patients. The blood samples were collected on the day before radiotherapy and on the administration of an irradiation dose of 20 Gy/10 f/12 d, 40 Gy/20 f/24 d and 60 Gy/30 f/36 after radiotherapy, and stored at -80°C until Assay.

**Radiotherapy**

Radiation source was a 6MV linear accelerator. The design of the radiation fields was based on the diagnosis by CT and barium examination. For all patients, a three-field approach was administered: one anterior and two posterior oblique portals. The width of the fields was adjusted to cover gross tumors with 3-4 cm extended margins so as to include subclinical lesions. The length of the field covered clinical tumors with a 3-5 cm extended margin at both ends of the lesion. All patients received conventional fractions, 2.0 Gy per fraction, five fractions per week. The total dose given to the tumor was 60-70 Gy/6-7 W.

**Assay of serum anti-p53 antibodies**

Anti-p53 antibodies in sera of patients was detected using a commercially available sandwich enzyme-linked immunosorbent assay kit (Immunotech, France). The assay was done according to the manufacturer’s instructions, with the following specifications: patient serum was added for 60 min at 37°C to microtiter wells coated with recombinant wild type human p53 protein to detect specific anti-p53 antibodies or with a control protein to detect nonspecific interactions. After washing, goat antihuman immunoglobulin G (IgG) antibody conjugated with peroxidase was added and stayed for 60 min at 37°C. Next, the substrate 3,3',5,5'-tetramethyl benzidine (TMB) was added for 10 min. The enzymatic process was halted by adding 2N hydrogen chloride. Light absorption was measured at 450 nm using a photospectrometer. Because human serum may give rise to variable background signals, an internal control was used to measure the nonspecific background of each sample. This background reflects nonspecific interactions of serum components either with the plastic or with the components used in the ELISA. In the assay, the nonspecific background corresponds to the absorbance measured on wells coated with control protein. The presence of anti-p53 antibodies in a sample is determined by different parameters, i.e., for the specific signal of the sample, index = specific signal of the positive control (low); for p53 net absorbance of the sample, ratio of net absorbance = control protein net absorbance of the sample. An index of 1.1 and a ratio of net absorbance of 1.6 were determined to be positive for the presence of anti-p53 antibodies.

**Clinical evaluation of radiation response**

At the end of RT, all patients received esophageal barium examination and the clinical radiation response was evaluated according to standard X-ray diagnosis of EC after radiotherapy\(^{(12)}\). A complete response (CR) was defined as the disappearance of the mass shadow, no narrowing observed in the esophageal lumen, and none or slight rigidity of the esophageal wall without residual ulceration. Partial response (PR) was > 50% reduction in tumor bulk, but < 100% resolution of the disease and a residual shallow ulcer with a diameter < 1.5 cm, despite the disappearance of the mass shadow. No response (NR) was defined as no improvement in the X-ray findings, with a deep and large residual ulcer or complete...
Table 1  Sequential change of positive rate of serum p53-Abs in EC patients before and after radiotherapy

| Groups       | n | - | + | %  | \( \chi^2 \) | \( p \) |
|--------------|---|---|---|----|-------------|-------|
| Before RT    | 46 | 28 | 18 | 39.1 | 0.000 | 1.000* |
| 20 Gy        | 46 | 28 | 18 | 39.1 | 0.187 | 0.666* |
| 40 Gy        | 46 | 30 | 16 | 34.8 | 4.696 | 0.030* |
| 60 Gy        | 46 | 39 | 7  | 15.2 | 6.646 | 0.010* |

*Before RT vs 20 Gy; †Before RT vs 40 Gy; ‡40 Gy vs 60 Gy; §Before RT vs 60 Gy.

Table 2  Relationship between positive rate of serum p53-Abs and clinical pathophysiological characteristics in EC patients

| Variables              | n  | - | + | %  | \( \chi^2 \) | \( p \) |
|------------------------|----|---|---|----|-------------|-------|
| Age (yr) < 50          | 16 | 10 | 6 | 37.5 | 0.270 | 0.870 |
| Age (yr) ≥ 50          | 30 | 18 | 12 | 40.0 | 0.110 | 0.918 |
| Sex Male               | 38 | 23 | 15 | 39.5 | 0.690 | 0.414 |
| Sex Female             | 8  | 5  | 3  | 37.5 | 0.003 | 0.959 |
| TNM stage I + II       | 27 | 21 | 6 | 22.2 | 6.090 | 0.014 |
| TNM stage III + N      | 19 | 8  | 11 | 57.9 | 0.103 | 0.797 |
| Histological grade I   | 15 | 13 | 2 | 13.3 | 10.430 | 0.002 |
| Histological grade II  | 17 | 11 | 6 | 35.3 | 5.450 | 0.020 |
| Histological grade III | 14 | 4  | 10 | 71.4 | 6.000 | 0.015 |
| Lymph node metastasis | n  | - | + | %  | \( \chi^2 \) | \( p \) |
| Positive               | 18 | 7  | 11 | 61.1 | 2.740 | 0.102 |
| Negative               | 28 | 21 | 7 | 25.0 | 0.000 | 0.997 |
| Size of tumor < 6 cm   | 32 | 22 | 10 | 31.3 | 0.002 | 0.953 |
| Size of tumor ≥ 6 cm   | 14 | 6 | 8 | 57.1 | 0.280 | 0.597 |
| Site of the tumor Upper thorax | 5 | 3 | 2 | 40.0 | 0.000 | 0.997 |
| Middle thorax          | 21 | 13 | 8 | 38.1 | 0.000 | 0.997 |
| Lower thorax           | 20 | 12 | 8 | 40.0 | 0.000 | 0.997 |

TNM: Tumor, nodes and metastasis.

obstruction of the esophageal lumen, regardless of the residual state of the mass shadow.

**Statistical analysis**

The Statistical Package for Social Sciences, version 10.0 was used for statistical analysis. Serum p53-Abs levels were expressed as means ± SD. Student’s t test, Pearson Chi-square and logistic analysis were used to determine the significance of difference between the two groups. A \( p \) value < 0.05 was considered significant.

**RESULTS**

**Comparison of index and ratio of serum p53-Abs**

The index and ratio of serum p53-Abs for EC patients were 1.5847 ± 0.5133 and 3.0293 ± 0.7013, and those for healthy controls were 0.2418 ± 0.1438 and 1.0361 ± 0.2175, the former was higher than the latter (\( p < 0.0001 \)).

**Comparison of positive rate of serum p53-Abs**

The positive rate of serum p53-Ab was 39.1% (18 of 46) for EC patients and 0% (0 of 30) for healthy controls, with a significant difference (\( p < 0.0001 \)). The sensitivity, specificity, accurate rate, positive predictive value and negative predictive value of p53-Ab detection in EC were 39.1%, 100%, 63.2%, 100% and 52%, respectively.

**Comparison of before and after radiotherapy sequential change**

The level and positive rate of serum p53-Abs had significant differences between before radiotherapy, after administration of an irradiation dose of 40 Gy/20 f/24 d and after administration of an irradiation dose of 60 Gy/30 f/36 d (Table 1).

**Relationship between positive rate of serum p53-Abs and clinical pathophysiological characteristics**

The positive rate of serum p53-Abs in EC was related to histological grade, disease stage and lymph node metastasis, but it was not significantly related to sex, age and to the size and site of tumor (Table 2).

**Logistic analysis**

Logistic analysis showed that the positive rate of serum p53-Abs in EC had positive correlation with disease stage, negative correlation with histological grade and independence with sex, age and with the size and site of tumor (Table 3).

**Clinical response to RT and serum p53-Abs**

At the end of RT, CR was achieved in 21 patients, RR in 18 and NR in 7. In patients with CR plus PR, 61.1% (11/39) were positive for serum p53-Abs, but 100% (7/7) of patients with NR were positive for serum p53-Abs. The positive rate of serum p53-Abs in EC patients with effect was significantly lower than those without effect after radiotherapy (\( p < 0.0001 \)).

**DISCUSSION**

p53 protein plays a crucial role in the regulation of the cell cycle and has been implicated in cell differentiation, apoptosis, DNA synthesis, and repair\([13,14]\). This nuclear protein, because of its critical function in triggering cell death via apoptosis in cells affected by irreparable genomic damage, has been designated as the “guardian of the genome” by Lane\([15]\).

Mutations in the p53 tumor suppressor gene are
among the most common genetic alterations in human malignancies. In ovarian carcinoma, alterations in this tumor suppressor gene occur in approximately 50% of cases. The commonly termed overexpression of p53 corresponds to a cellular accumulation of a biologically inactive protein stabilized either by a decreased rate of degradation of mutated gene product or by complex formation with certain proteins, such as viral oncoproteins or heat-shock protein 70. In normal cells, p53 protein, through its short half-life, is present at such low levels that it is undetectable by conventional immunohistochemical methods. However, the results obtained in a number of studies on the prognostic impact of overexpression of p53 protein in ovarian carcinoma tissue were controversial. Whereas some investigators reported impaired clinical outcome in patients with p53 overexpressing tumors, others failed to demonstrate a relation between the course of the disease and p53 expression.

Recently, circulating p53-Ab has been detected in the serum or plasma of patients with various carcinomas. Detection is made by a simple and rapid ELISA procedure. The positive rate for p53-Ab was reported to be 24% for lung cancer, 19% for pancreatic cancer and 25% for colorectal cancer. The frequency of positive p53-Ab in patients with EC ranges from 25% to 53% in the literature. Our study detected p53-Ab in 18 (39.1%) of the 46 patients with EC, while it was not detected in any of the 30 healthy subjects. This positive rate for p53-Ab in esophageal cancer patients is thus similar to that in the published literatures. The index and ratio of serum p53-Abs for patients with EC before radiotherapy were obviously higher than those for healthy controls (P < 0.05). This suggests that the detection of serum p53-Ab in patients with EC is helpful to its diagnosis. We also found that the positive rate of serum p53-Abs in EC was related to the histological grade, disease stage and lymph node metastasis (P < 0.05), but it was not significantly related to sex, age and the size and site of tumor (P > 0.05). The lower the histological grade and clinical stage, the higher the level and positive rate of serum p53-Abs in EC, indicating that the positive serum p53-Abs is a poor characteristic and identifying marker of unfavorable prognosis for patients with EC.

At the end of RT, CR was achieved in 21 patients, RR in 18 and NR in 7. In patients with CR plus PR, 61.1% (11/18) were positive for serum p53-Abs, but 100% (7/7) of patients with NR were positive for serum p53-Abs. The positive rate of serum p53-Abs in EC patients with effect was significantly lower than those without effect after radiotherapy. This suggests that serum p53-Ab overexpression can be one of the reference indicators for predicting radiosensitivity in patients EC. Future studies will be required to reveal and confirm the correlation between radiosensitivity and serum p53-Abs.

We also found that the serum p53-Abs level was useful for the monitoring of treatment. In the present study, the level and positive rate of serum p53-Abs had significant differences between before radiotherapy, after administration of an irradiation dose of 40 Gy/20 f/24 d and after administration of an irradiation dose of 60 Gy/30 f/36 d. It was reported that the presence of p53-Ab correlates closely with p53 overexpression and/or mutation. This suggests that the p53 immune response in the patients can be attributed to accumulation of mutant p53 in the nucleus of tumor cells. The p53 protein was decreased and the tumor cell was destroyed through effective radiotherapy, the source of mutation of the p53 gene was eliminated, and then the immune response was weakened. Thus, monitoring of sequential change of serum p53-Abs before and after radiotherapy in patients with EC is helpful to evaluating the response to treatment and prognosis. A larger series of studies will be required to reveal and confirm the correlation between radiosensitivity and serum p53-Abs.

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COMMENTS

Background

Mutations of the p53 gene are common gene alterations in most malignant tumors, including esophageal carcinoma. Mutant p53 protein is accumulated in the cell because of its longer half-life compared with wild-type protein. p53 protein plays a crucial role in the regulation of the cell cycle and has been implicated in cell differentiation, apoptosis, DNA synthesis and repairment. In addition, it has been shown that patients with various types of neoplasias have p53 antibodies in their sera. ELISA was used to detect anti-p53 antibodies in the sera. The authors explored the relationship between serum p53-Abs and clinicopathological characteristics and therapeutic effect in patients with esophageal carcinoma, and investigated the sequential changing regularity of serum p53-Abs after radiotherapy.

Research frontiers

Studies have revealed that overexpression of p53 protein is closely related to induction of drug resistance in cancer patients and it can be used as a predictor for chemosensitivity to tumor treatment. Specific p53-Ab was found in the sera of cancer patients with p53 protein overexpression. Furthermore, the presence of serum p53-Ab is closely correlated with p53 protein overexpression. Thus, serum p53-Ab could theoretically be useful in predicting radiosensitivity in cancer patients. However, the clinical relevance of p53-Ab and radiotherapy for esophageal carcinoma has not been fully studied.

Innovations and breakthroughs

From the results of this study, the following conclusions can be drawn that the positive rate of serum p53-Abs in esophageal carcinoma is related to histological grade, disease stage and lymph node metastasis, but it is not significantly related to sex, age and the size and site of tumor. The level and positive rate of serum p53-Abs had significant differences between before radiotherapy, after administration of an irradiation dose of 40 Gy/20 f/24 d and after administration of an irradiation dose of 60 Gy/30 f/36 d. The positive rate of serum p53-Abs in esophageal carcinoma patients with effect is significantly lower than those without effect after radiotherapy.

Applications

Detection of serum p53-Abs is helpful to diagnosis of esophageal carcinoma. Monitoring of sequential change of serum p53-Abs before and after radiotherapy in patients with esophageal carcinoma is also useful in evaluating the response to the treatment and prognosis of the patients.

Peer review

The authors detected the serum p53 antibody level in patients with esophageal
squamous cell carcinoma and its sequential changes before and after radiotherapy. The results showed that changes of serum p53-Abs are helpful to the diagnosis of esophageal carcinoma. Monitoring of sequential change of serum p53-Abs before and after radiotherapy in patients with esophageal carcinoma is helpful to evaluating the response to the treatment and prognosis of the patients. Therefore, this study has values in clinical management of the patients.

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