DYNAMIC MONITORING AND CLINICAL SIGNIFICANCE OF TAP, D-DIMER, HCY, CEA, AND NSE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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ABSTRACT

Objective: To investigate the dynamic monitoring and clinical significance of tumour abnormal protein (TAP), D-dimer (D-D), homocysteine (HCY), carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) in patients with non-small cell lung cancer (NSCLC) during treatment.

Materials and methods: From April 2015 to April 2017, a total of 285 patients with NSCLC in our hospital were enrolled as an observation group, including 96 early NSCLC patients and 189 advanced NSCLC patients as well as 132 cases in the surgery group and 153 cases in the postoperative chemotherapy group. Another 292 healthy people were selected as the control group. TAP detection system was used to measure the area of agglomerates. Serum D-D was detected by immunoturbidimetry. HCY was detected by chemiluminescence. Serum NSE and CEA were detected by enzyme-linked immunosorbent assay (ELISA). The levels of TAP, D-D, HCY, CEA and NSE in the preoperative and postoperative chemotherapy groups were studied.

Results: TAP, D-D, HCY, CEA and NSE in the early NSCLC group was obviously higher than in the control group and lower than in the advanced NSCLC group, which was statistically significant (P<0.01). TAP in postoperative chemotherapy group (> 1 cycle) was significantly lower than that before chemotherapy (P < 0.01). The levels of TAP, CEA and NSE in the postoperative chemotherapy group (> 2 cycles) were significantly lower than those before chemotherapy, which was statistically significant (P < 0.01). TAP, CEA and NSE in the surgery group were significantly lower than those before surgery (P < 0.05).

Conclusion: The changes in TAP, D-D, HCY, CEA and NSE closely related to the occurrence and development of NSCLC have a reference value for the evaluation of prognosis.

Keywords: Lung cancer; Tumour abnormal protein, TAP; D-dimer, D-D; Homocysteine, HCY; Carcinoembryonic antigen, CEA; Neuron-specific enolase, NSE; Dynamic monitoring; Clinical significance.

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Introduction

Lung cancer is the leading cause of cancer in males in China, and non-small cell lung cancer (NSCLC) accounts for approximately 80% of these cases, making it the main pathological type of lung cancer. Most NSCLCs are diagnosed as advanced cancers and have low rates of early diagnosis. As a result, the early diagnosis of lung cancer has become an urgent task. The treatment of lung cancer is based on surgical treatment, the only method that can cure lung cancer, and supplemented by radiotherapy and chemotherapy, which are the main methods for the treatment of NSCLC. At present, many serum tumour markers have been found to be closely related to lung cancer and have been reported to have prognostic value11. Tumour abnormal protein (TAP), the product of oncogene and tumour suppress or gene mutations, can maximise the amplification of tumour signals and overcome the defects of conventional tumour markers, thus greatly improving the sensitivity of tumour detection2. The D-dimer (D-D), derived from the lytic tissue-dissolved cross-linked fibrin clot, mainly reflects
the function of fibrinolysis. It is a sensitive, but not specific, marker of acute thrombosis, and an increase in its level represents the formation of a blood clot in the circulatory system\(^3\). Homocysteine (HCY), a sulphur-containing amino acid, is an important product of cysteine and methionine, which may be related to the occurrence of atherosclerosis and other cardiovascular diseases\(^4\). Carcinoembryonic antigen (CEA) is a broad-spectrum tumour marker that can be used for the observation of curative effects and prognosis of a variety of cancer treatments\(^5\). Neuron-specific enolase (NSE), lactate dehydrogenase, blood routine, gender, weight loss, disease stage and other factors have been studied and proven to be able to predict the efficacy and survival time of lung cancer patients. NSE, one of the sensitive markers for the diagnosis of lung cancer, is widely present in neuroendocrine cells and neuronal glycolytic enzymes\(^6\). The purpose of this study was to investigate the dynamic monitoring and clinical significance of TAP, D-D, HCY, CEA and NSE in patients with NSCLC.

**Materials and methods**

**General data**

A group of NSCLC patients (N =285) were enrolled from April 2015 to April 2016 in our hospital in the age range of 40 to 82 years. As the control group, 292 healthy people were enrolled in the age range of 38 to 80 years.

**Inclusion criteria:**
- NSCLC patients diagnosed by pathology or cytology;
- normal hepatonephric function and blood routine and
- complete clinical data.

**Exclusion criteria**\(^7\):
- immunodeficiencies;
- patients with a history of surgery within 1 month;
- recent cardiovascular disease;
- liver and kidney dysfunction;
- recent history of anticoagulant use
- diabetes, rheumatism or another chronic disease.

We obtained approval for this study from the Ethics Committee of the hospital. The patients signed informed consent. The patients with NSCLC (N = 285) were divided into a group of 96 cases of early NSCLC and a group of 189 cases of advanced NSCLC as well as a group of 132 cases receiving simple surgery and a group of 153 cases receiving postoperative chemotherapy. There was no statistically significant difference between the observation group and the control group in terms of age, gender and other general data (P > 0.05).

**Methods**

- VSCs were collected from patients with NSCLC, and serum and plasma were separated after anticoagulation. The TAP detection system, including TAP coagulation aids and TAP detection comprehensive diagnostic instruments from Zhejiang Ruisheng Medical Technology Co., Ltd., was used to measure the area of agglomerates. The serum D-D was detected by immunonephelometry using the BE Compact XR Coagulation apparatus, according to the instructions, and the original imported reagents were used. The chemiluminescence method was used for the detection of HCY by Centaur CP from Siemens, and the original imported reagents were used. Serum NSE and CEA were detected by enzyme-linked immunosorbent assay (ELISA) using the DR 8808 immunoassay analyser, according to the instructions.

- NSCLC postoperative chemotherapy group: A 21-day cycle of platinum-based combination chemotherapy was adopted for two cycles of chemotherapy. The relevant indicator levels were detected. The efficacy was observed before chemotherapy and after the end of the first and the second cycle of chemotherapy using the methods referenced in step 1.

- Surgery group: The relevant indicator levels were detected before operation. Six weeks after surgery they were detected using the methods referenced in step 1.

The patients underwent radical resection of lung cancer under general anaesthesia by lateral and lateral recumbency. Take the fifth intercostal thoracotomy, the incision is about 25–30 cm, remove the lesions of the lobe, lymph node dissection after entering the thoracic cavity.

**Results judgment criteria**

**Negatives:** TAP normal (no obvious aggregates): agglomerate area < 121 μm\(^2\); positives: TAP abnormalities (large aggregates): agglomerate area ≥ 225 μm\(^2\); TAP abnormalities (smaller aggregates): 121 μm\(^2\) ≤ aggregate area < 225 μm\(^2\).

Normal values: D-D < 0.2 mg/mL; HCY 5–15
μmol/L; NSE < 16.3 ng/mL; CEA 0–5 ng/mL. The NSCLC postoperative chemotherapy group was divided into progression (PD), stable or unchanged (SD), partial remission (PR) and complete remission (CR) according to RECIST criteria; among them, SD + PR + CR was the effective chemotherapy group, and PD was the ineffective chemotherapy group.

Statistical methods
SPSS 20.0 software package was used for statistical analysis, in which the general measurement data was expressed as mean ± standard deviation (X ± s). The means of two groups were compared by t-test or rank sum test. P < 0.05 was considered statistically significant, and P < 0.01 was considered statistically significant.

Results

Differences in TAP, D-D, HCY, CEA and NSE between control and early NSCLC groups
The levels of TAP, HCY, CEA and NSE in the early NSCLC group were significantly higher than those in the control group (P < 0.01), but there was no significant difference in the D-D level between the two groups (P > 0.05) (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TAP (μm²)</th>
<th>D-D (mg/mL)</th>
<th>HCY (μmol/L)</th>
<th>CEA (ng/mL)</th>
<th>NSE (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early NSCLC group</td>
<td>96</td>
<td>143.11±36.88</td>
<td>0.42±0.31</td>
<td>10.11±3.67</td>
<td>13.99±7.54</td>
<td>13.91±3.88</td>
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<tr>
<td>Control group</td>
<td>292</td>
<td>108.88±29.11</td>
<td>0.36±0.28</td>
<td>8.46±3.23</td>
<td>8.78±4.11</td>
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</tr>
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<td>t/u value</td>
<td></td>
<td>15.062</td>
<td>1.631*</td>
<td>4.194</td>
<td>6.507*</td>
<td>12.08</td>
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<tr>
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<td>&gt;0.05</td>
<td>&lt;0.01</td>
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<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 1: Comparison of TAP, D-D, HCY, CEA and NSE between the control group and the early NSCLC group.
*for u value

Differences in TAP, D-D, HCY, CEA and NSE between the early NSCLC group and the advanced NSCLC group
The levels of TAP, HCY, CEA and NSE in the advanced NSCLC group were significantly higher than those in the early NSCLC group, which was statistically significant (P < 0.01) (Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TAP (μm²)</th>
<th>D-D (mg/mL)</th>
<th>HCY (μmol/L)</th>
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<td>13.99±7.54</td>
<td>13.91±3.88</td>
</tr>
<tr>
<td>Advanced NSCLC group</td>
<td>189</td>
<td>163.12±37.11</td>
<td>3.78±1.81</td>
<td>19.33±6.08</td>
<td>43.21±13.89</td>
<td>42.45±13.56</td>
</tr>
<tr>
<td>t/u value</td>
<td></td>
<td>4.111</td>
<td>6.000*</td>
<td>-15.909</td>
<td>25.698</td>
<td>-26.852</td>
</tr>
<tr>
<td>P value</td>
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<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 2: Comparison of TAP, D-D, HCY, CEA and NSE between early NSCLC group and advanced NSCLC group.
*for u value

The efficacy of NSCLC postoperative chemotherapy group
All 153 NSCLC patients in the postoperative chemotherapy group completed two cycles of chemotherapy without serious side effects or delayed drug use or chemotherapy changes. The efficacy was evaluated by RECIST criteria: 20 SD patients, 62 PR patients, 15 CR patients and 56 PD patients (Table 3).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TAP (μm²)</th>
<th>D-D (mg/mL)</th>
<th>HCY (μmol/L)</th>
<th>CEA (ng/mL)</th>
<th>NSE (ng/mL)</th>
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<tr>
<td>t/u value</td>
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<td>4.111</td>
<td>6.000*</td>
<td>-15.909</td>
<td>25.698</td>
<td>-26.852</td>
</tr>
<tr>
<td>P value</td>
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<td>&lt;0.01</td>
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<td>&lt;0.01</td>
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</table>

Table 3: The curative effect observation of NSCLC postoperative chemotherapy group.

Differences in TAP, D-D, HCY, CEA and NSE between the NSCLC surgery group and the postoperative chemotherapy group
The levels of TAP, CEA and NSE in the two cycles of the effective chemotherapy group were significantly lower than those before chemotherapy, which was statistically significant (P < 0.01). TAP levels after one cycle in the effective chemotherapy group were significantly lower than those before chemotherapy (P < 0.01).

The levels of TAP, CEA and NSE in the postoperative group were lower than those before surgery, which was statistically significant (P < 0.05). Indicators in the ineffective chemotherapy group were different than those before chemotherapy, but this was not statistically significant (P > 0.05) (Table 4).

Discussion
Lung cancer is clinically divided into NSCLC and SCLC. NSCLC accounts for approximately 80% of these cases, including undifferentiated carcinoma, adenocarcinoma, and squamous cell carcinoma. SCLC is not classified in diagnosis and treat-
ment clinically\(^8\). Currently, evaluation of clinical efficacy is mainly based on CT imaging technology, but it is difficult to detect micrometastases, subclinical lesions and negative lesions. Lung cancer has a high demand for imaging equipment and simple and effective detection methods. However, the detection of tumour markers has the characteristics of minimal trauma, accuracy, simplicity and low cost. Diagnosis of tumours by TAP is achieved through glycoproteins with abnormal sugar chain structures and is a highly specific, highly sensitive method.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TAP (μmol/L)</th>
<th>D-D (mg/mL)</th>
<th>HCY (µmol/L)</th>
<th>CEA (ng/mL)</th>
<th>NSE (ng/mL)</th>
</tr>
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<tr>
<td>Effective chemotherapy</td>
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<td></td>
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<tr>
<td>Pre-chemotherapy</td>
<td>97</td>
<td>165.12±37.11</td>
<td>3.78±1.81</td>
<td>19.33±3.78</td>
<td>43.21±13.89</td>
<td>42.45±13.56</td>
</tr>
<tr>
<td>1 cycle</td>
<td>97</td>
<td>133.11±36.88</td>
<td>2.42±0.32</td>
<td>14.13±3.56</td>
<td>23.99±7.23</td>
<td>23.91±5.78</td>
</tr>
<tr>
<td>2 cycles</td>
<td>97</td>
<td>110.34±29.12</td>
<td>1.33±0.27</td>
<td>10.41±3.21</td>
<td>15.78±4.11</td>
<td>18.86±2.16</td>
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<tr>
<td>Ineffective chemotherapy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prechemotherapy</td>
<td>56</td>
<td>161.41±35.56</td>
<td>4.56±1.24</td>
<td>25.67±7.45</td>
<td>57.56±14.61</td>
<td>45.34±14.21</td>
</tr>
<tr>
<td>1 cycle</td>
<td>56</td>
<td>160.13±35.31</td>
<td>2.75±0.31</td>
<td>23.78±9.98</td>
<td>45.56±12.78</td>
<td>42.67±14.52</td>
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<tr>
<td>2 cycles</td>
<td>56</td>
<td>160.25±34.34</td>
<td>3.67±0.45</td>
<td>24.78±7.11</td>
<td>64.78±13.42</td>
<td>47.42±15.21</td>
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<td>Surgery group</td>
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<tr>
<td>Before surgery</td>
<td>132</td>
<td>145.13±34.76</td>
<td>0.78±0.43</td>
<td>11.12±2.61</td>
<td>14.21±6.76</td>
<td>15.56±5.33</td>
</tr>
<tr>
<td>After surgery</td>
<td>132</td>
<td>130.56±33.54</td>
<td>0.63±0.42</td>
<td>10.35±2.65</td>
<td>9.42±1.71</td>
<td>9.76±1.43</td>
</tr>
</tbody>
</table>

Table 4: Comparison of TAP, D-D, HCY, CEA and NSE between the NSCLC surgery group and the postoperative chemotherapy group.

Studies\(^9, 10\) have found that TAP examination is more sensitive than current lung cancer detection techniques. There was no relationship between TAP and tumour size, but TAP decreased in end-stage secretory glycoproteins, decreased metabolism of cancer cells or advanced tumours. D-D, a marker for a specific fibrinolytic process, is a fibrin monomer cross-linked by an activating factor and hydrolysed to form a degradation product. Studies have shown\(^11\) that increased D-D levels indicate secondary fibrinolysis in vivo followed by thrombosis.

HCY is an intermediate metabolite inducing damage to endothelial cells through oxidation and stress, which can enhance inflammatory responses and promote proliferation of vascular smooth muscle cells\(^12\) produced by metabolism of methionine. Genetic defects and nutritional deficiencies are all major factors that may cause elevated HCY levels. CEA is a glycoprotein of specific human embryonic antigen determinant, and its content is low in adults. Zhou et al.\(^13\) showed that the sensitivity of CEA is highest in lung adenocarcinoma, between 35% and 70%. NSE, a glycolytic enzyme, is currently recognised as the most sensitive specific marker of SCLC. Its level is closely related to disease outcome, therapeutic response, tumour size, degree of brain damage and prognosis\(^14\), thus, it is the most sensitive biochemical indicator of neuronal damage.

This clinical study showed that the levels of TAP, HCY, CEA and NSE were higher in the early NSCLC group, but the levels of TAP, D-D, HCY, CEA and NSE were significantly higher in the advanced NSCLC group than in the early NSCLC group. The TAP, CEA and NSE levels were significantly lower in the effective chemotherapy group after two cycles compared to pre-chemotherapy. The TAP levels were significantly lower in the effective chemotherapy group after one cycle compared to pre-chemotherapy. TAP, CEA and NSE levels in the postoperative group were lower than those before surgery. There is no strict correspondence between tumour markers and tumours, and one marker is expressed in multiple tumours. It is suggested that a tumour can also produce multiple markers. TAP is a common substance of various tumours and does not depend on the tissue structure and specific location of tumour substances.

Therefore, it can perform combined detection of multiple tumours and improve the accuracy and sensitivity of tumour detection. With the increase of TAP area, the shorter survival time and the severity of the disease all indicate that the sensitivity is high. In this study, the changes in TAP levels between the early and late NSCLC groups or pre-chemotherapy and post-chemotherapy groups correlate as above: the changes in TAP levels are higher than the changes in the D-D, HCY, CEA and NSE levels, suggesting that TAP monitoring is valuable for chemotheraphy of NSCLC. Elevated D-D levels indicate the appearance of secondary fibrinolysis.
nolysis. The function of fibrinolysis is to maintain the permeability of the vascular wall and the fibrinolysis system, which simultaneously repairs the lung tissue of lung cancer patients. As a result, the degradation products increase the D-D levels, which is related to tumour metastasis and prognosis; therefore, the advanced NSCLC group has significantly elevated D-D levels compared to the early NSCLC group. This study indicates that HCY levels are of significance in the early and advanced NSCLC groups. The decrease in plasma folic acid and vitamin B12 levels may be associated with elevated HCY levels. SCLC, a neuroendocrine system tumour, can be characterised as a neuroendocrine cell with a higher degree of malignancy, accounting for 25% to 30% of lung cancers. It usually overexpresses NSE, which is the final enzyme that catalyses the glycerol decomposition stage during glycolysis, and its detection rate is as high as 65% to 100% due to overexpression in SCLC patients. Therefore, changes in NSE levels between early and advanced NSCLC groups and the control group or pre-chemotherapy and post-chemotherapy groups are significantly different, which is consistent with the report of Wu et al. 

CEA is a non-organ-specific tumour-associated antigen and is overexpressed in breast cancer, gastric cancer, colon cancer, rectal cancer, pancreatic cancer and NSCLC, especially in adenocarcinoma. In this study, CEA was significantly different between the early and advanced NSCLC groups and the control group or pre-chemotherapy and post-chemotherapy groups. CEA elevation cannot make a diagnosis of the tumour, but its elevation indicates that the tumour easily relapses, has a short survival period, is unresectable and has a poor prognosis, which is a reliable indicator of tumour size and metastasis.

In summary, the changes in TAP, D-D, HCY, CEA and NSE levels in patients with lung cancer are closely related to the occurrence and development of the disease and have important value for the prognosis.

References


