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Original Article

The feasibility of oral mucosa TCT tests for lung cancer screening

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Abstract: Objectives: To evaluate the feasibility of oral mucosa TCT tests for early detection of lung cancer. Materials and Methods: From July 2013 to January 2014, eighty four chronic and heavy smokers with lung nodule after low-dose or plain chest computed tomography (CT) were given oral mucosa Thinprep cytological tests (TCT) and contrast-enhanced thoracic CT. Those suspected to suffer from lung tumors after contrast-enhanced thoracic CTs were undergone bronchoscopes and/or surgical resections to acquire pathological diagnosis. Oral mucosa was collected using Thinprep and AutoCyte Prep technology. Statistical analyses were performed by SPSS 11.0 software. Results: According to TCT outcomes, thirty cases (30/84, 35.7%) were identified with abnormal TCT results in oral mucosa and allocated to TCT (+) group, and 27 of them were identified with atypical hyperplasia and three with low grade lesions. The residual 54 cases with normal TCT results were allocated to TCT (-) group. In TCT (+) group, 22 cases (22/30, 73.3%) were diagnosed with cancer by contrast-enhanced thoracic CT, which was significantly higher than that in TCT (-) group (1/54, 1.9%), P = 0.001. According to bronchoscopes and/or surgical resections, 18 cases were diagnosed with lung cancer and all of them were in the TCT (+) group. The sensitivity, specificity, positive and negative predictive values of TCT on screening lung cancer were 100%, 81.8%, 60% and 100% respectively. Conclusion: As a preliminary tool of screening lung cancer on chronic smokers with a high risk of developing lung cancer, the oral mucosa TCT has a high sensitivity as well as a good specificity, and the test can be easily conducted.

Keywords: Oral mucosal, TCT, lung cancer, screening

Introduction

Lung cancer has the highest incidence rate and is one of the leading causes of cancer related deaths all over the world. Because half of patients were diagnosed with advanced stage, so the prognosis of lung cancer was poor and the 5-years survival rate in lung cancer was less than 15% [1]. Smoking, environmental factors, history of chronic lung diseases and genetic factors are the prominent risk factors of developing lung cancer, and the linkage between smoking and lung cancer is well established. The data showed that about 90% of patients with lung cancer had a smoking history and about 10% of smokers developed lung cancer. The occurrence of lung cancer, which is influenced by genetic susceptibility, has been positively correlated with smoking quantity. Existing literature shows that the incidence of lung cancer in heavy smokers is the highest. Therefore, in clinical screening, the smoking quantity is usually considered as an index for the high risk population [2-4].

Here we conducted a study and evaluated the feasibility of oral mucosa TCT test for early detection of lung cancer. The results showed that the sensitivity, specificity, positive and negative predictive values of TCT on screening lung cancer were 100%, 81.8%, 60% and 100% respectively.

Materials and methods

Research object and methods

From July 2013 to January 2014, eighty four chronic smokers who went through low-dose or plain CT examination in Cancer Hospital of

Table 1. The effect of smoking quantity (cigarettes per day) and oral mucosa TCT abnormalities

Smoking quantity (per year)	TCT result		X^2	*P*
	Normal	Abnormal		
< 1000	38 (74.5)	13 (25.5)		
≥ 1000	15 (51.7)	14 (48.3)	4.293	0.038

Chinese Academy of Medical Sciences and suspected to have lung cancer were enrolled in our study. They were all males with an average age of 58.6 years and smoked in average 25 cigarettes per day (the average annual smoking amount was 947 cigarettes). Both oral mucosa Thinprep cytological test (TCT) and contrast-enhanced thoracic CT were conducted to all of them. Those suspected to have lung tumors after contrast-enhanced thoracic CT were undergone bronchoscopes and/or surgical resections to acquire pathological diagnosis.

Specimens of bilateral buccal mucosa were collected using a cytobrush device which was taken out and put into the specified container with the liquid sent to exam after the brush washed 10 times. Thinprep automatic pelleter was adopted to make smears, and a microscope is used to observe and diagnose by two independently experienced cytologist. TCT results were categorized according to the Bethesda System (TBS 2001) used for reporting buccal mucosa cytology. The cytological results are as following: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of uncertain significance (ASC-US), atypical squamous cells-cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC).

Statistical analysis

Catagoric data was tested by X^2 test and measurement data was tested by T test. $P < 0.05$ indicated statistically significant. SPSS 11.0 statistical software were used to conduct the analysis.

Results

General characteristics

The oral mucosa TCT results for 54 cases with normal results were allocated into TCT (-) group and 30 cases with abnormal readings were allocated into TCT (+) group. In TCT (+) group, we observed 27 cases with atypical hyperplasia and 3 with low-grade lesions. Low-dose CT results revealed that 23 cases with pulmonary nodules were suspected of lung cancer and all these cases were underwent bronchoscopes or/and resections and 18 of them were diagnosed with lung cancer.

The relationship between oral mucosa TCT and smoking quantity

Our results demonstrated that for those persons with smoking ≥ 1000 cigarettes per year, the TCT positive rate was 48.3%. For those smoking less than 1000 per year, the TCT positive rate was 25.5%. The difference between the two groups is significant ($P = 0.038$) (**Table 1**).

The relationship between oral mucosa TCT and positive results of CT

Among the TCT (+) group, 22 cases (22/30, 73.3%) were suspected for lung cancer by contrast-enhanced thoracic CT examinations. But in the TCT (-) group, only one (1/54, 1.9%) suspected for lung cancer by contrast-enhanced thoracic CT examinations. The positive rate of CT in the oral mucosa TCT (+) group was significantly higher than that in the oral mucosa TCT (-) group, and the difference was statistically significant, $P = 0.001$ (**Table 2**).

The relationship between oral mucosal TCT and pathological diagnosis

Through contrast-enhanced thoracic CT, 23 patients were suspected to have abnormal pulmonary nodules and with the possibility of lung cancer. Bronchoscopes or/and surgeries were conducted to them and pathological diagnosis was acquired, the results showed that 18 of them were diagnosed with lung cancer and all of them in the TCT (+) group. This revealed that lung cancer diagnosis rate in the TCT (+) group was 60%, and it was significantly higher than that in TCT (-) group, $P = 0.001$ (**Table 3**).

Evaluation index for lung cancer screening using TCT

The sensitivity, specificity, positive and negative predictive values of TCT for lung cancer were 100%, 81.8%, 60% and 100% respectively.

Table 2. Relationship between oral mucosa TCT results and the positive results of CT

TCT results	Contrast-enhanced CT		X^2	P
	Normal	Abnormal		
Normal	53 (98.1%)	1 (1.9%)		
Abnormal	8 (26.7%)	22 (73.3%)	49.559	0.001

Table 3. Relationship between oral mucosal TCT and pathological diagnosis of lung cancer

TCT results	Pathological diagnosis		X^2	P
	Normal	Cancer		
Normal	54 (100%)	0 (0%)		
Abnormal	12 (40%)	18 (60%)	41.236	0.001

Sensitivity = 18/18 = 100%

Specificity = 54/66 = 81.8%

Positive predictive value = 18/30 = 60%

Negative predictive value = 54/54 = 100%

Discussion

Due to the fact that nearly two thirds of patients with lung cancer were diagnosed with advanced stage, especially in China, the prognosis of them were poor and the 5-years survival rate was less than 15%. But for those patients with early stages have the chance of accepting surgical treatment, the 5-years survival rate may be increased to 80%-90%. Therefore, early diagnosis was the key factor for increasing the cure rate and the survival rate [5-7]. As a tool of screening lung cancer, low-dose CT for early diagnosis of lung cancer was more accurate than the chest x-ray, and decreased the mortality rate by 20% [8]. In China, as a little more expensive tool which has not been covered by the medical insurance plans, the low dose CT is not often used for the lung cancer screening popularly. Apart from that, low dose CT has some limitations in detecting main bronchial lesions in early stages, and bronchoscopes are the most accurate means of early detection for main bronchial lesions. However, due to its invasive property, healthy individuals are reluctant to undergo bronchoscopes.

Prior studies revealed that the lung epithelial tissues exposed to tobacco often suffers from chromosome deletion and the methylation in promoter region in their tumor suppressor genes [4, 9, 10]. In smokers, both oral and lung tissues are exposed to the same carcinogens and suffer from the same kind of molecular and cellular modifications. Using polymerase chain reaction (PCR), Bhutani and his associates compared tumor suppressor genes p16 in oral mucosa and bronchial mucosa of 125 cases of healthy long-term smokers. In bronchial tissue, the methylation rate in p16, FHIT, and two simultaneous promoters were found to be 23%, 17% and 35% respectively. Methylation rate in p16, FHIT, and two simultaneous promoters were 19%, 15% and 31% respectively in oral tissue. The research demonstrated that modifications of anti-oncogenes and promoters in the bronchial tissue had a significant correlation to that in oral tissue ($P < 0.0001$) [3]. Lung tissue changes caused by smoking can be evaluated by examinations of these changes in oral cavity mucous epithelium. The tumor suppressor genes in oral mucosa and pulmonary epithelium of chronic smokers likely undergo similar biological changes. This fact lays the foundation for the feasibility of using oral mucosa as a lung cancer screening method.

Our study attempted to evaluate the feasibility of using the oral mucosa TCT as a viable screening method for early detection of lung cancer in heavy smokers. We evaluated the correlation between the abnormal oral mucosa TCT and pathological changes detected through other cytological and pathological screening methods. This study, through the comparison of oral mucosa TCT, low dose CT screening, and final pathology results demonstrated that in heavy smokers (more than 1000 cigarettes per year) showed that the proportion of abnormal TCT was 48.3%. In the cases with TCT (+) results, 73.3% of them were suspected of lung cancer according to the contrast-enhanced thoracic CT examinations, and 60% of them were confirmed as lung cancer by pathology. The sensitivity, specificity, positive predictive and negative predictive values of oral mucosa TCT screening on lung cancer were 100%, 81.8%, 60% and 100% respectively.

The early screening of lung cancer can offer huge social economic benefits. Data shows that the rate of smoking cessation in the patients receiving CT screening is higher than that of the patients receiving simple consultancy, and the success rate is comparable with the

intervention of drugs [11]. If CT screening is undergone once each year, the total cost for lung screening is $2500 for the whole life, but it can lead to huge savings of health care expenditures relating to lung cancer. As a result, American Cancer Society recommended a low dose CT screening to be taken for the individuals with heavy smoking history once year [12-14]. China has a massive cigarette consumption rate and the smoking rate in adult men is 52.9%, (over 300 million). This rate is higher in rural areas as well as that in economically underdeveloped regions [15, 16]. The cost of low-dose CT screening is relatively high for many regions, and is not incorporated into medicare payment plans. Therefore, general application of low-dose CT screening is problematic in China. For all these reasons, TCT detection in oral mucosa can be considered as a proper screening test in China.

Although this study had many limitations and was an observational study with a small sample, it opened the door for further research associated with the application of oral mucosal TCT screening for early lung cancer detection. A large sample study is desirable in order to further confirm the feasibility of oral mucosal TCT detection in the preliminary screening of lung cancer. We believe oral mucosa TCT has the potential to become a reliable method for early detection of lung cancer in high-risk population.

Conclusion

TCT detection in oral mucosa is a simple, cost-effective and non-invasive method for early detection of lung cancer. Our study showed that oral mucosa TCT screening for lung cancer had a higher sensitivity and satisfactory specificity. Therefore, smokers and especially heavy smokers should be routinely submitted to the oral mucosa TCT. For those tested positive in oral mucosa TCT screening, low dose CT and bronchoscopes will be recommended.

Disclosure of conflict of interest

None.

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