



## Research paper

Correspondence analysis between traditional Chinese medicine (TCM) syndrome differentiation and histopathology in colorectal cancer<sup>☆</sup>

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## ABSTRACT

**Introduction:** Defining Traditional Chinese medicine (TCM) syndrome is considered the key therapeutical principle of TCM. The present study was to explore the correlation between TCM syndrome differentiation and histopathology in colorectal cancer (CRC).

**Methods:** A total of 180 patients were differentiated into 5 TCM syndrome types, including accumulated damp-heat type (ADH), deficiency of both qi and blood type (DBQB), deficiency of liver and kidney yin type (DLKY), deficiency of spleen and kidney yang type (DSKY) and qi stagnation due to spleen deficiency type (QSSD). They were also differentiated into pathologic types, including adenocarcinoma, mucous carcinoma, signet ring cell carcinoma and anaplastic carcinoma. Moreover, the expression of protein 53 (P53), cluster of differentiation 44 (CD44), non-metastasis 23 (nm23), proliferating cell nuclear antigen (PCNA) and B-cell lymphoma-2 (Bcl-2) was detected by immunohistochemistry in 61 patients. Finally, the correspondence analysis between TCM syndrome differentiation and histopathology or pathological molecular markers was conducted.

**Results:** Chi-square test of independence showed that TCM syndrome types correlated with pathological types ( $\chi^2 = 33.456$ ,  $P = 0.001$ ), while not with molecular markers ( $\chi^2 = 7.344$ ,  $P = 0.834$ ). Correspondence analysis showed that the distances between adenocarcinoma and QSSD or DLKY were the shortest among the distances of adenocarcinoma with other TCM syndrome types. Moreover, distances between mucinous carcinoma and ADH, signet ring cell carcinoma and ADH, anaplastic carcinoma and DBQB were the shortest among all the types.

**Conclusion:** TCM syndrome differentiation is strongly correlated with histopathology of colorectal cancer. TCM syndrome differentiation may be used as a supplement in the diagnosis of CRC.

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## 1. Introduction

The development of colorectal cancer (CRC) is thought to be due to uncontrolled cell growth in the rectum, colon, or appendix. It ranks the first in incidence among malignancies and the second in cancer-related deaths in Europe for both genders [1,2]. There are

446,000 new cases of CRC occurring annually in Europe which means that it is a major health issue [3]. The five-year survival rate for CRC is less than 60% in Europe [4]. In addition, more than 90% of CRC s have metastasized or advanced by the time they are diagnosed [5]. Furthermore, the treatments for CRC are always accompanied by side effects including fecal incontinence, sexual dysfunction and bowel dysfunction [6]. Therefore, exploring new tactics for the treatment of CRC is necessary.

Traditional Chinese medicine (TCM) with its holistic emphasis and the connection of man with the social and natural environment has been used to treat CRC over the last 6000 years with some degree of success [7]. Nowadays, TCM is commonly used for

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alleviating the side-effects of surgery and standard treatment such as chemotherapy or radiotherapy, and for improving patient quality of life [8]. TCM has benefits in its own right, which has been reported to induce rectal cancer cell apoptosis [9], prevent tumor metastasis [10], and directly alleviate patients' symptoms such as bleeding, diarrhea, pain, nausea and vomiting [11–13]. TCM may also have direct anti-cancer effects, as described previously [14]. Moreover TCM therapy which could provide a theoretical and practical approach for treating CRC is characterized by treatment based on “syndrome differentiation”. Since individual tumors exhibit different pathologic features, specific therapy for CRC based on their pathologic features, this is the ultimate goal of treatment.

The traditional Chinese medicine (TCM) is the essence of Chinese culture. Syndrome differentiation is a key principle in TCM [15]. As described previously, clinical treatment of a patient is based on the successful differentiation of a specific syndrome [16]. TCM syndrome differentiation has been widely used in diagnosis of diseases including infection, inflammation and autoimmune disorders [15]. Moreover, it bears a close relationship with pathological characteristics in diseases, such as IgA nephropathy [17], non-small cell lung cancer [18] and chronic gastritis [19]. Furthermore, TCM syndrome differentiation and treatment can improve the prognosis of CRC in elderly patients [20]. Yin deficiency and qi deficiency syndrome are considered to be the factors for poor prognosis of CRC [21]. However, study focusing on the relationship between TCM syndrome typing and pathological typing in CRC is rare.

In this studies, primary research was carried out on the correlation of TCM syndrome type and pathological characterization of patients with CRC. Patients were differentiated into 5 syndromes. Meanwhile, they were also differentiated into 4 kinds of CRC according to pathological characterization. Moreover, some of the patients were also diagnosed by the pathological molecular markers, including protein 53 (P53), cluster of differentiation 44 (CD44), non-metastasis 23 (nm23), proliferating cell nuclear antigen (PCNA) and B-cell lymphoma-2 (Bcl-2). Finally, the correspondence analyses between TCM syndrome types and pathological types or pathological molecular markers were conducted. This research reveals the feasibility of TCM syndrome differentiation in diagnosis of CRC.

## 2. Materials and methods

### 2.1. Patients

The study took place in Shu Guang hospital affiliated to Shanghai University of traditional Chinese medicine between March 2005 and January 2009. A total of 180 patients (approved by the ethical committee of Shanghai TCM-integrated Hospital, Shanghai University of TCM) with confirmed CRC were enrolled in this study. The average age was  $62 \pm 12$  years (range, 31–85 years). These patients included 98 males (54.4%) and 82 females (45.6%). Of these, 107 cases (59.4%) had a diagnosis of colon cancer and 73(40.6%) had a rectal cancer diagnosis.

The sample size was calculated to provide 80% power with the chi-square value of 4.2 after testing the correlation between the TCM syndrome types and pathological types using chi-square test of independence, with a two-sided 5% significance allowing for an anticipated dropout rate of 10%.

### 2.2. Inclusion and exclusion criteria

Patients were included if they were cytologically or pathologically diagnosed with CRC [22]. In addition, patients diagnoses had to be confirmed by a TCM physician to ensure that patients exhibited one of the five TCM syndromes (showed in TCM

syndrome differentiation) [23]. Patients were excluded for the following reasons: (1) Patients did not conform to the inclusion criteria. (2) Patients were treated with immunosuppressants or had serious diseases such as; heart, liver, kidney disease or conditions associated with the blood system. (3) Patients who were pregnant or had an infection were also excluded from our research. (4) Patients who stopped the treatment before the end of the treatment period or who did not comply with the doctors in terms of failing to provide the required data were not included in this study.

### 2.3. TCM syndrome differentiation

The TCM syndrome differentiation for each patient was conducted by two expert TCM physicians in our hospital. The process for TCM syndrome diagnosis was performed independently by each TCM physician and both of them were blind to the type of cancer that each patient had. Any discrepancies of TCM syndrome differentiation between them were resolved by subsequent discussion.

According to routine diagnosis and treatment method of traditional Chinese medicine for disease in Shanghai (Shanghai shi zhong yi bing zheng zhen liao chang gui) [23], the syndrome types were identified as follows: (1) Accumulated damp-heat type (ADH): symptoms include paroxysmal abdominal pain, tenesmus, passing stool with pus and blood, burning pain in anus, or fever, chest distress, bitter taste, deep-colored urine, red tongue with yellow and greasy coating, slippery pulse of arteries and veins. (2) Deficiency of both qi and blood type (DBQB): symptoms include dull abdominal pain, loose stool, shortness of breath and weak, pale complexion, or rectocele drop, pink tongue with white coating, deep and thready pulse. (3) Deficiency of liver and kidney yin type (DLKY): symptoms include dizziness, soreness of loins and tinnitus, low-grade fever and night sweating, dysphoria with feverish sensation in chest bitter taste and dry throat, constipation, red tongue with little or no coating, thread pulse. (4) Deficiency of spleen and kidney yang type (DSKY): symptoms include fear of cold and cold limbs, loose stool, frequent defecating or even diarrhea at dawn, continuous abdominal pain, soreness and weakness of waist and knees, pale complexion, short of breath and weakness, plump tongue with white, thin or greasy coating, thread, soft and weak pulse. (5) Qi stagnation due to spleen deficiency type (QSSD): symptoms include abdominal distension and anorexia, borborygmus and scurrying abdominal pain, loose stool or blood stool, languid, sallow complexion, pink tongue with white, thin or greasy coating, soft pulse. TCM syndrome could not be diagnosed by tongue inspection only and be confirmed when two or more than two symptoms occurred in this patient. If more than two syndrome symptoms occurred in one patient, the syndrome which got more symptoms was regarded as the main syndrome.

### 2.4. The pathologic type differentiation

According to standards for diagnosis and treatment of CRC (2010) [22], pathologic types were identified as follows: (1) Adenocarcinoma, whose tissue was papillary or glandular. (2) Mucous carcinoma, which contained quantity of mucous in cancer tissue. (3) Signet ring cell carcinoma: the cytoplasm was full of mucus. Nuclear was rounded or oval and tilted to the side of cell. The cancer cell was presented as a signet ring. (4) Anaplastic carcinoma: cancers were diffusely infiltrated and did not represent as glands. The cancer cells were small and irregularly or round shaped. It was obvious to see the heteromorphism of nucleus. If the cancer belonged to more than one pathologic type, the type with the highest proportion was regarded as the main type. Moreover, if the types had the same proportion, the cancer was identified as the

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