

## Original Article

# Clinical report on 5 cases of advanced malignancies with blood stasis and toxin treated by collateral disease theory

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**Abstract:** Background: “Collateral disease theory”, as an important theory of traditional Chinese medicine, is often used in the clinical treatment of tumors, showing a remarkable effect, especially in advanced malignancies with blood stasis and toxin. Methods: In this study, we analyzed 5 cases of advanced malignancies, and discussed the efficacy of collateral disease theory in advanced malignancies with blood stasis and toxin. The 5 cases were suffered from right lung squamous cell carcinoma, left lung squamous cell carcinoma, stage IV endometrial carcinoma, right submandibular lymphatic follicular lymphoma and right lower lung cancer, respectively. Combining with the pathogenesis of collateral disease in traditional Chinese medicine dialectically and taking insect medicine as an example, traditional Chinese medicine was prescribed. Furthermore, the application effect of “collateral disease theory” in malignancy with blood stasis and toxin was explored. Results: After treated with traditional Chinese medicine, the tumor lesions in the 5 cases were reduced to varying degrees. Conclusion: The treatment based on “collateral disease theory” is effective for advanced malignancy with blood stasis and toxin, but this finding needs to be verified by prospective studies.

**Keywords:** Collateral disease theory, collateral veins, malignancy, stagnation of blood stasis and toxin, insect-like drug

## Introduction

Cancer statistics in 2018 showed that there were 18.1 million new cases of malignancies and 9.6 million deaths worldwide [1]. Cancer is generally the biggest negative health factor for people in all countries in the 21st century. At present, western medicine treatment schemes for tumors include surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapy. Traditional Chinese medicine has a long history in treating tumors. The term “tumors” was recorded in the Oracle Bone Inscriptions excavated from Yin Ruins. “Cancer” was firstly defined in traditional Chinese medicine by Yang Shiyong’s “Renzhai Zhi Zhi Jian Yi Fang” back in the Song Dynasty: “Cancer is a rock-like disease with a hidden poison root” [2]. Studies have shown that malignant tumors are formed by the accumulation of visible excesses such as phlegm turbidity and blood stasis in the col-

laterals, so the theory of tumor collaterals disease was put forward [3-6].

“Collateral disease theory” is one of the vital pathogenesis theories in traditional Chinese medicine. After repeated clinical practice by doctors of past dynasties, its theoretical system has been gradually improved. The collateral disease theory explains the pathogenesis of tumor as deficiency of vital qi, poor local qi and blood movement, water retention in local areas, slow blood circulation in collaterals, even qi stagnation and blood retention, phlegm-dampness condensation, obstruction of collaterals, subtle distribution, and accumulated pathological “cancer poison”, which spreads all over the body with the circulation of collaterals and eventually leads to death [7-9]. Insect-like drugs are nourishing and have the effects of promoting blood circulation, removing blood stasis, dredging collaterals, attacking poison, dispers-

ing stagnation, removing the wind as well as detoxicating and tonifying [10-14]. We have used a comprehensive scheme of traditional Chinese and western medicine to treat malignancies for a long time. In clinical work, by evaluating the results of western medicine imaging, we found that many patients with cancer had their tumor focus reduced to different degrees in the process of using traditional Chinese medicine alone, and we believe the actual effect of traditional Chinese medicine greatly exceeds the mainstream understanding. Here, we are reporting 5 typical cases with complete personal data and continuous treatment of traditional Chinese medicine alone to show the efficacy of traditional Chinese medicine based on the Response Evaluation Criteria in Solid Tumors (RECIST) standard.

### Case analysis

#### *Case 1: "Collateral disease" treatment for lower right lung cancer*

Long, male, 69 years old, was first diagnosed on June 17, 2014. At the diagnosis, his chest CT results revealed mass-like high-density shadow with a range of 3.7\*6.4 cm in right lower lung, double emphysema with multiple large bubbles in both upper lungs, a small amount of effusion in the left chest cavity, bilateral pleural thickening and enlarged mediastinal lymph nodes. For the right lower lung cancer, the holistic concept should be applied to give symptomatic treatment considering syndromes of differentiation. When collateral vessels are narrow and damaged by pathogenic factors, its pathogenesis is characterized by easy stagnation and blood stasis, as well as easy entry and accumulation but difficult circulation. The main pathogenesis of lung cancer is "deficiency of vital qi, mutual accumulation of poison and blood stasis" [15]. Deficiency of vital qi is the internal factor of the occurrence and development of lung cancer, and the mutual accumulation of poison and blood stasis leads to the formation of lumps and poisonous flesh in the lungs. Stagnation of qi, phlegm and blood stasis blocking blood collaterals are the specific pathogenic factors leading to the gradual aggravation of lung cancer. "Deficiency", "poison" and "blood stasis" are always involved throughout the occurrence and develop-

ment of lung cancer. In the early stage of onset, patients suffer from deficiency of vital qi, deficiency of liver and kidney, and lack of biochemical sources of qi and blood, which makes collaterals unable to nourish viscera normally. On the basis of strengthening body resistance, invigorating spleen and tonifying kidney, the insect medicine can supplement qi and blood and improve the body's disease resistance [16-18]. The patient obtained reexamination after taking the medicine for one month. On July 29, 2014, the chest CT reexamination denoted that no change in the right lower lung mass but reduced right pleural effusion, also, the left pleural effusion was easily absorbed, and the compressed lung was dilated again. Until then, the patient only took the medicine for a short time, so the healthy qi was still in recovering, but the symptoms were obviously improved. Besides strengthening the body resistance, we also adjusted traditional Chinese medicine to use more anti-toxic and anti-tuberculosis drugs for symptom relief through promoting qi circulation, eliminating phlegm, dissipating stagnation and detoxify, and eliminating blood stasis and dredge collaterals, thereby restoring the physiological function of collaterals and removing the wind. The second reexamination was conducted after 5 months on December 31, 2014. The chest CT results showed that the right lower lung mass was reduced, and the oral symptoms were alleviated, which proved that "collateral disease theory" was effective in treating lower right lung cancer, and the above treatment should be continued. On March 23, 2015, chest CT results on the third reexamination showed that the right lower lung mass was larger than that on December 31, 2014. This may be due to patient' healthy qi loss during the illness period, coupled with long-term medication, disease progression, liver and kidney deficiency, and lack of blood and biochemical sources, which makes the collaterals unable to nourish viscera normally. The occurrence of tumors is mostly due to deficiency of vital qi and gathering of evil qi in collaterals, which leads to stagnation and obstruction of qi, phlegm and blood circulation, as well as internal accumulation of evil and toxin, resulting in long-term disease. According to the therapeutic principle of "strengthening the body, cutting it", "resolving the knot" and "removing the guest", adding insect medicine

to the basic formula for strengthening the body resistance and eliminating pathogenic factors can often reach the disease site and relieve the disease. It is necessary to adjust the dosage the insect medicine to attack poison and disperse knot. On June 3, 2015, the patient underwent the 4th chest CT reexamination. Compared with that on March 23, 2015, the range of right lower lung mass was reduced. So, we continued to adjust the dosage of insect medicine. On December 14, 2015, the patient underwent the 5th chest CT reexamination. Compared with that on June 3, 2014, the range of right lower lung mass was reduced, without obvious remaining changes, indicating obviously improved disease condition. Therefore, we continued the application of traditional Chinese medicine for strengthening the body resistance, dispelling pathogenic factors, promoting qi circulation, eliminating phlegm, resolving stagnation and detoxicating, removing blood stasis and dredging collaterals. After that, the patient underwent chest CT reexamination on June 7, 2016, December 12, 2016 and June 21, 2017, respectively. Compared with before, there was no obvious change in the right lower lung mass (**Figure 1**). This showed that patient' condition was stable. Also, their pain was obviously reduced, and the overall symptoms are improved. The patient was instructed to take Chinese medicine and check regularly [19].

Stagnation of blood stasis and toxin in advanced lung cancer should be explained from the perspective of collateral disease theory. The occurrence of tumor is due to deficiency of vital qi, unsmooth local qi and blood, stagnation of water in local areas, slow blood circulation, even stagnation of qi and blood, phlegm-dampness condensation, obstruction of collaterals, subtle distribution, and accumulated pathological "cancer toxin", which followed the collaterals and spread all over the body, eventually leading to death. Luo Shi believes that evils live in the Yang collaterals for a long time, but local accumulation can cause long-term diseases. Due to the deficiency of vital qi and exuberant pathogenic factors, phlegm and blood stasis became poisonous. The body has dysfunction of viscera and abnormal movement of qi and blood, and various physiological and pathological products can't be discharged in time and stagnate in the body, leading to the exuberance of pathogenic factors, corruption of body and formation of cancer poison. Insect

drugs can be used reasonably according to the condition of patients.

### *Case 2: "Collateral vein" treatment for left lung squamous cell carcinoma*

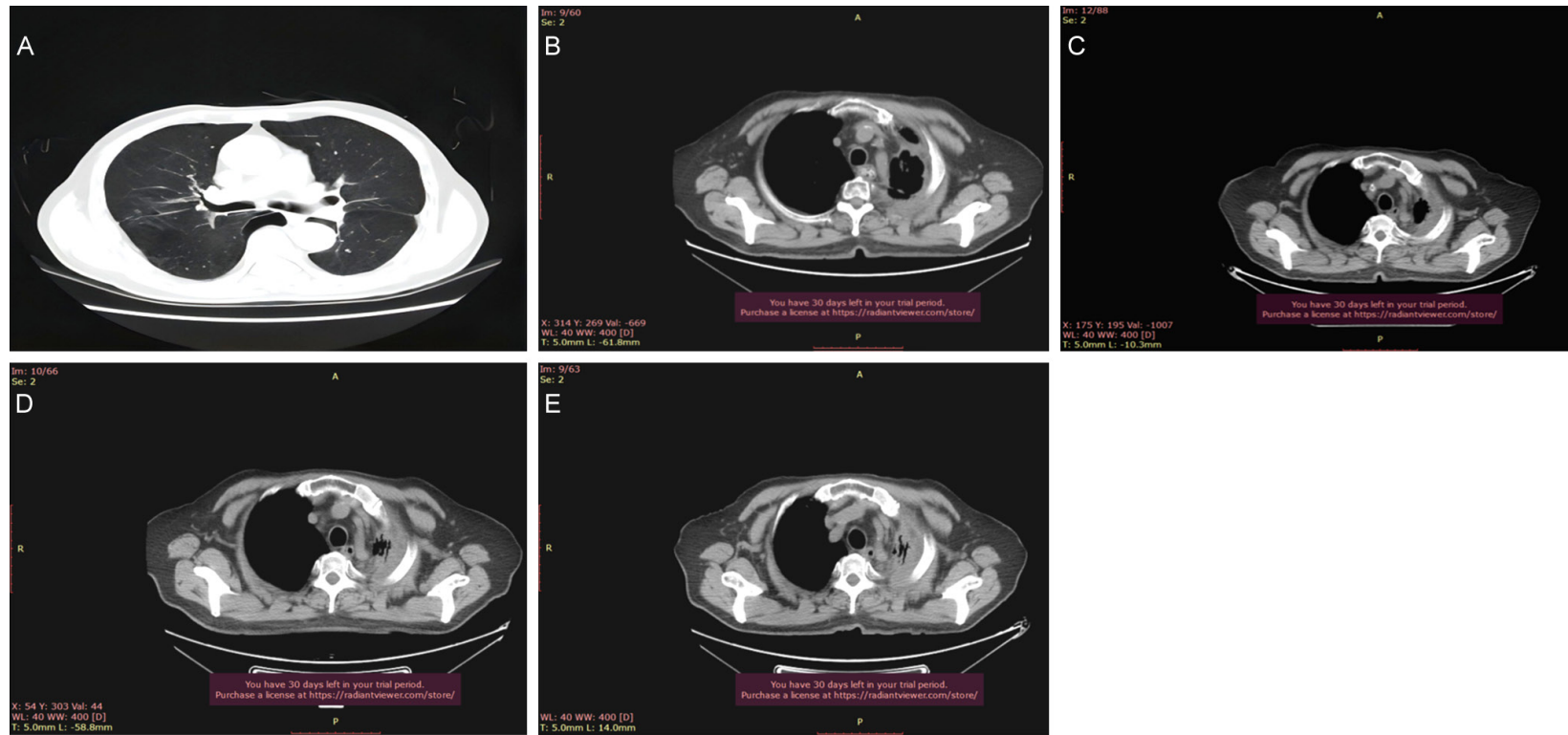
Zeng, male, 70 years old, was diagnosed with squamous cell carcinoma of the left lung by biopsy in the Second Affiliated Hospital of Chongqing Medical University in December 2016, with mediastinal lymph node metastasis and inoperable left pleural effusion. To control the tumor progress, the patient underwent palliative chemotherapy for 6 cycles combined with radiotherapy from February 2017 to July 2017. After the above treatment, residual lesions could still be seen on CT. In November 2017, he went to our hospital for traditional Chinese medicine treatment. Thereafter, annually regular CT showed that the size of the lump and the general symptoms were obviously improved, and the pain was within the tolerance range [20].

The pathogenesis of lung cancer is "deficiency of vital qi, mutual accumulation of toxic and blood stasis". The lung, liver, spleen and kidney should be the first responsibility in syndromes of differentiation. On the basis of strengthening the body resistance, the treatment strategy should promote qi circulation and eliminate phlegm, dissipate stagnation, detoxify blood stasis and dredge collaterals throughout the whole treatment process. When there was lymph node metastasis, drugs such as Paoshan-jia tablets and litchi seeds should be added to soften and resolve hard mass in addition to basic treatment. This case did not suffer from yin deficiency. If the patient suffers from yin deficiency, turtle shell and tortoise shell can be added to nourish yin and soften hard mass [21]. During the periodic review of the patient, drugs were added or subtracted according to the changes of the conditions. Because most insect drugs are toxic, we should pay attention to avoid the occurrence of drug toxicity events during medication.

### *Case 3: "Collateral disease" treatment for right lung squamous cell carcinoma with mediastinal lymph node metastasis*

Su, a 66-year-old female, was diagnosed with squamous cell carcinoma of the right lung by pathological biopsy in April 2020, and PET/CT

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**Figure 1.** Tumor volume changes during treatment for Long. A. Image on June 17, 2014; B. Image on July 29, 2014; C. Image on December 31, 2014; D. Image on December 14, 2015; E. Image on June 7, 2016.

was performed on April 29, 2020 (**Figure 2A**). The density shadow of the massive soft tissue in the right hilar mass and the abnormal increase of FDG metabolism met the manifestations of central lung cancer. One lymph node in the aortopulmonary window was enlarged and, FDG was increased, considering metastasis. The final diagnosis was right lung squamous cell carcinoma with mediastinal lymph node metastasis. From May 2020 to October 2020, after the completion of radiotherapy and chemotherapy combined with immunotherapy, CT was again performed in a standardized way. In April 2021, there were signs of enlargement and recurrence of lesions. Pulmonary CT showed enlargement lesions, increased peripheral obstructive inflammation, thickened pleura near the right upper lung and potential metastasis (**Figure 2B**). In traditional Chinese medicine, we should treat lung cancer based on “collateral disease theory”. The main pathogenesis is deficiency of vital qi and obstruction of local qi and blood. It is necessary to strengthen vital qi, dissipate stagnation, eliminate blood stasis and dredge collaterals. Long-term accumulation of cancer needed proper use of anti-toxin and anti-insect drugs to slow down the symptoms and restore the physiological function of collaterals. In view of the therapeutic principle of “cutting off the stubborn”, “dispersing the knot” and “removing the guest”, insect drugs were added to the basic formula of strengthening the body resistance and eliminating pathogenic factors, so as to attack the accumulation, soften the hard mass, disperse the knot, combat poison with poison and relieve the disease. Centipede, earthworm and other drugs were used to enhance patient immunity, improve hypercoagulability, relieve symptoms and accumulation, and play an anti-tumor role. In the process of treating advanced lung cancer with traditional Chinese medicine, the insect medicine, such as donkey-hide gelatin, tortoise shell and Cordyceps sinensis, were used to replenish qi and blood and improve the body’s disease resistance. After taking the traditional Chinese medicine, lung CT in July 2021 and October 2021 showed that the lesions in the upper lobe of the right lung were reduced, and the solid components were reduced (**Figure 2C**). No obvious abnormality was found in routine blood examination, and the patient expressed an improvement in general symptoms. It

shows that “collateral disease theory” is effective in treating advanced lung cancer with lymph node metastasis. Patients are required to take medicine on time and check regularly [22].

### *Case 4: “Collateral disease” treatment for high-grade serous carcinoma of endometrium*

Tan, a 69-year-old female, was diagnosed with stage IV endometrial carcinoma by pathological biopsy in Chongqing Traditional Chinese Medicine Hospital on December 23, 2019, with multiple intra-abdominal metastasis and lung metastasis. She underwent palliative therapy in our hospital on December 30, 2019, and was diagnosed with type II endometrial carcinoma with left pelvic lymph node metastasis by post-operative pathology. On April 22, 2020, the patient came to our hospital for reexamination, and the results of chest, abdomen and pelvic cavity CT found metastatic lesions in lung and abdominal cavity (**Figure 3A**). After that, from April 2020 to August 2020, palliative chemotherapy combined with targeted therapy was performed for 5 cycles, but there were still tumor lesions in December 2020. So, oral Chinese medicine treatment was formulated. Based on the basic theory of traditional Chinese medicine, Su Wen Acupuncture Theory says that “healthy qi exists in the body, and evil can’t be dried up”. In patients with cancer, qi, blood, phlegm and toxin are condensed, forming local solid evil. Also, because of the deficiency of vital qi in the body, which is related to the blood, patients show poor blood circulation, stagnation of collaterals, and pathological state of deficiency and excess. Therefore, with regard to cancer treatment, eliminating evil is the key, and strengthening the body resistance is the fundamental. Based on the “collateral disease theory”, one of the main pathogeneses of tumors is blood stasis. Drugs for promoting blood circulation and removing blood stasis should be used, and those for attacking poison and dispersing insects should be prescribed to relieve the symptoms. Most patients with cancer have metastasis, with pain all over the body. In this case, the patient had abdominal pain. Insect-like drugs for removing the wind and detoxifying can be applied. In the theory of collateral diseases, insects are good at treating wind. They are able to remove the wind, dredge collaterals, detoxify, and relieve pain, exerting



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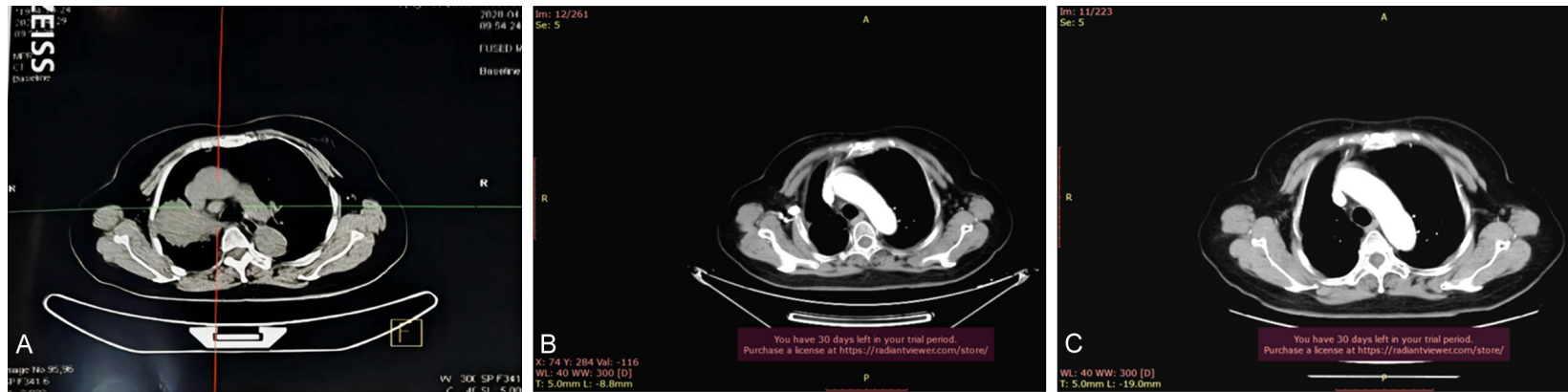


Figure 2. Tumor volume changes during treatment for Su. A. PET/CT image of lungs on April 29, 2020; B. CT image of lungs on April 22, 2021; C. CT image of lungs on October 29, 2021.

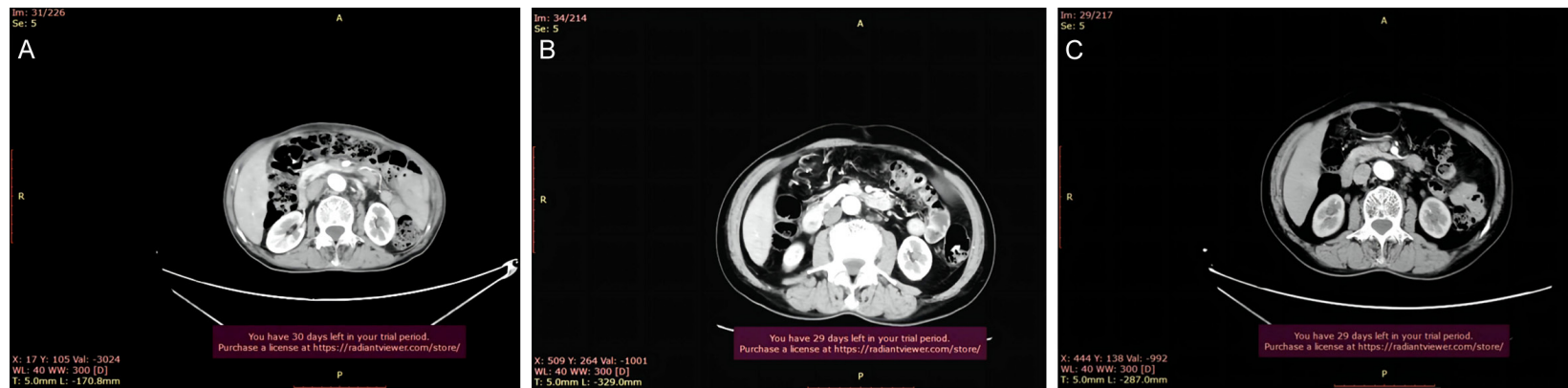


Figure 3. Tumor volume changes during treatment for Tan. A. CT image of abdomen+pelvis on April 22, 2020; B. CT image of abdomen+pelvis after the patient taking Chinese medicine on June 22, 2021; C. Abdominal+pelvic CT image of the patient after taking Chinese medicine on September 24, 2021.

analgesic effect. This patient has abdominal metastasis and a small amount of effusion, so she received Traditional Chinese medicines such as Wuling Powder and Zhuling Decoction, which are used to warm yang, strengthen spleen and kidney and induce diuresis. Then, *Broussonetia papyrifera* seeds were used to tonify the kidney and clear liver, remove blood stasis and induce diuresis. Combined with the change of patient's conditions, drugs for promoting qi circulation and eliminating bloating was used to relieve poor qi movement. Re-examinations on June 22, September 24 and December 28, 2021 (**Figure 3B, 3C**) showed stable tumor focus without obvious changes [23]. The patient stated that the symptoms of the whole body were improved, and the pain was alleviated. The nurses told the patient to review regularly and take the medicine on time.

### *Case 5: "Collateral disease" treatment for lymphofollicular lymphoma*

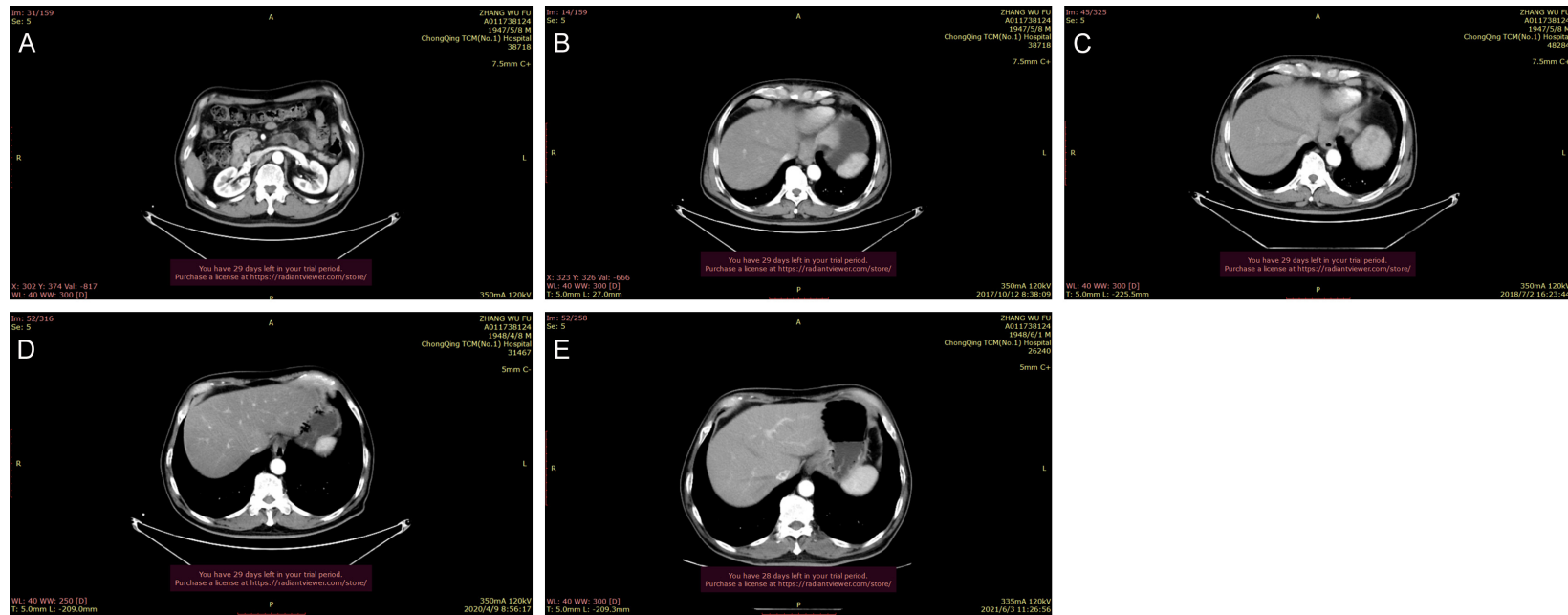
Zhang, a 65-year-old male, was first diagnosed in the First Affiliated People's Hospital of Chongqing Medical University, and was considered to have "mixed tumor of right submandibular gland" by color Doppler ultrasound. Later, he was diagnosed with right submandibular lymphofollicular lymphoma by pathological examination. He underwent surgical resection on February 20, 2013. Afterwards, PET-CT showed that the metabolic activity increased in parathyroid, neck, subclavian fossa, mediastinum, retroperitoneal cavity and groin. On October 12, 2017, the CT reexamination in Chongqing Traditional Chinese Medicine Hospital showed that there were many swollen lymph nodes in the whole body, and recurrence and metastasis were considered (**Figure 4A**). Since then, oral Chinese medicine treatment has been prescribed. The occurrence of tumors is mostly due to deficiency of vital qi and stagnation of evils in collaterals, which leads to long-term stagnation and obstruction of qi, phlegm and blood circulation, as well as internal accumulation of evil and toxin. So insect-like drugs for resolving stagnation and tackling key problems are often used. The patient suffered from multiple lymph node metastasis and severe pain. In view of the cancer poison which spreads all over the body with collaterals, insect drugs such as earthworm, *nidus vespae* and centipede were used to remove the

wind, detoxify and dredge collaterals. At the same time, they also improve immunity and resist tumor. This patient had multiple metastases, including visible digestive tract metastasis. Dialectical treatment was applied. The lesions were mostly in the middle and upper Jiao. *Huoxiang* stalk and *Perilla* stalk, stir-fry hedgehog skin, disperse knot in chicken's gizzard-skin can be used to regulate qi and relieve depression and eliminate blood stasis. Dung beetles can activate qi. *Angelica dahurica*, *bletilla striata* and *crinis carbonisatus*, etc., can relieve swelling and constipation, and stop bleeding. If necessary, Zuojin pill and calcined Wazil, etc. can be combined. Annually regular CT check showed that the tumor focus was shrinking year by year (**Figure 4B-E**). The general symptoms were gradually improving, and the pain was obviously reduced. Patients were told to take medicine on time and have regular check-ups [24].

### Discussion

The treatment for tumors in traditional Chinese medicine has a long history. The incidence of tumors is mostly due to congenital or acquired malnutrition, which leads to deficiency of vital qi, decreased ability of defending external pathogens, dysfunction of zang-fu organs, poor circulation of qi and blood in collaterals, local stagnation of qi and blood stasis, accumulation of phlegm and poison over time, which blocks the local collaterals, so that the collaterals can't pass qi and blood and nourish zang-fu organs normally. Poison and evil accumulate in the body, forming cancer poison and tumor lesions over time [25]. Modern research [26] pointed out that the application value of collateral disease theory in tumor prevention and treatment lies in regulating immune function by nourishing and activating collaterals. Tumor angiogenesis was inhibited to treat tumor. Treatments based on collaterals theory were performed to promote blood circulation and remove blood stasis to correct the hypercoagulable state of patients. According to the theory of collateral diseases, Luo Shi believes that pathogenic factors persist in Yang collaterals for a long time, and accumulate into diseases. Due to deficiency of vital qi, exuberant pathogenic factors, turbid phlegm and blood stasis turning into poison, dysfunction of viscera, abnormal operation of qi and blood, various physi-

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**Figure 4.** Tumor volume changes during treatment for Zhang. A. Image of enhanced CT scan of upper abdomen on October 12, 2017; B. CT image of tumor site on October 12, 2017; C. CT image of tumor site on July 2, 2018; D. CT image of tumor site on April 9, 2020; E. CT image of tumor site on June 8, 2021.



ological and pathological products can't be discharged in time and stagnate in the body, leading to the exuberance of pathogenic factors, corruption of body and formation of cancer poison. Following this theory, cancer treatment should be based on strengthening the body resistance, dredging collaterals as well as detoxification to eliminate evil and improve the hypercoagulable state of blood in patients. If the collaterals are unblocked, the evil has no fixed place. Insect drugs are flesh-and-blood sentient beings, which can tonify qi and blood. Most of them are salty and pungent. The pungent taste can be dispersed and act positively for qi. They are salty, scattered, between soft and hard, and can enter the blood. According to the collateral disease theory of "long-term illness entering collaterals", the tumor is a disease with cancer poison deeply hiding in the collaterals. In the late stage, it flows all over the body with the collaterals, and the insect's medicinal properties are good at tackling the difficulties and breaking the accumulation in collaterals, so as to attack the evil. When deficiency is present, patients can also be treated with insect drugs that supplement vital qi, strengthen body resistance and resist evil and replenish vital qi. Modern experimental studies have also confirmed that insect drugs can induce cell apoptosis, inhibit cell proliferation, resist angiogenesis and improve immunity [27].

In modern Chinese medicine, the pathogenesis of collateral diseases of malignancies can also be summarized as the result of the long-term interaction of blood stasis, turbid phlegm, damp toxin and other evils in the collateral channels. Namely, the "collateral diseases" are caused by the intrinsic evil toxin. Pathogenic qi has been living in the Yang collaterals for a long time, but long-term local accumulation can cause disease. Due to the deficiency of vital qi, exuberant pathogenic factors, turbid phlegm and blood stasis turning into poison, dysfunction of zang-fu organs, and abnormal operation of qi and blood, various physiological and pathological products can't be discharged in time and stagnate in the body, leading to the exuberance of pathogenic factors, corruption of body and formation of toxic collateral diseases. The theory has been frequently used for modern tumor diseases. Modern experimental results showed that Chongshengsui powder could inhibit the growth of tumor cells by inhibiting the expression of vascular endothelial growth

factor (VEGF), thus inhibiting the proliferation of vascular endothelial cells and slowing angiogenesis. This research treated gastric cancer by invigorating spleen, dredging collaterals, removing blood stasis and eliminating phlegm. In our report, after treated with traditional Chinese medicine, the 5 cases showed reduced or controlled lesions, as well as relieved general symptoms. All these results showed that "collateral disease theory" is an integral dialectic for treating advanced malignancies without subdividing the anatomical location of tumor lesions. Through the "collateral disease theory", we can analyze that the pathogenesis of malignancies is the cancer toxin and blood stasis. By overall differentiation, it can be clarified which is more important between deficiency and excess. According to different symptoms and constitutions, we can reasonably use the methods of promoting blood circulation to remove blood stasis, regulating qi to relieve depression, clearing away heat and toxic substances, eliminating phlegm and dampness, strengthening body resistance, eliminating evil, and fighting poison with poison.

### Conclusion

The efficacy of treatment based on the "collateral diseases theory" for patients with advanced malignancies with blood stasis and toxin is ideal, effectively reducing or controlling the symptoms. In addition, traditional Chinese medicine has little toxic and side effects during treatment, which can obviously improve the quality of life of patients. But this finding still needs to be verified by prospective studies.

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### Disclosure of conflict of interest

None.

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