Significant Tumor Reduction With Traditional Chinese Medicine in a Patient With Advanced Prostate Cancer: A Case Report

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Abstract
Prostate cancer (PC) is the most common malignancy of the male genitourinary system. For patients with advanced progressive PC, the treatment strategies include second-line endocrine therapy, chemotherapy, and immunotherapy. Such therapeutic techniques are either too expensive or too toxic for some patients, and traditional Chinese medicine (TCM) has become an alternative for its low cost and low toxicity. The application of Shi-pi-san and Gui-zhi-Fu-ling-wan in PC has never been reported. We report their application on a 71-year-old male patient, who was diagnosed with PC and was undergoing endocrine therapy. He originally chose chemotherapy, and experienced acute renal failure, which required hemodialysis during hospitalization. He felt weak and opted for Chinese herbal medicine treatment. After treatment with Shi-pi-san and Gui-zhi-Fu-ling-wan, the patient’s tumor and other symptoms were significantly reduced, and he reported feeling “refreshed.” This case indicates that TCM treatment has unique advantages and is more tolerable than endocrine therapy and chemotherapy. Considering that the patient was undergoing hemodialysis treatment and using low-molecular-weight heparin (LMWH) to prevent blood coagulation while taking TCM, whether LMWH has a synergistic anticancer effect remains to be explored.

Keywords
case report, prostate cancer, Shi-pi-san, Gui-zhi-Fu-ling-wan, traditional Chinese medicine

Case Report
On June 14, 2018, the patient was diagnosed with PC at the age of 69 years (T4N0M0, Glason’s score was 4 + 5 = 9) in another hospital, and he was treated with endocrine therapy for over a year. The pathological diagnosis from the biopsy indicated prostate adenocarcinoma (four on the left side of prostate biopsy), with a Glason’s score of 1130854.

Patients with advanced prostate cancer (PC) often suffer from lower urinary tract obstruction. With the development of the disease, bone metastasis, bone pain, fracture, and other symptoms may occur, impairing the quality of life of patients. Visceral metastasis may also occur, which ultimately reduces patient survival. Presently, for those patients with advanced progressive PC who receive endocrine therapy, the treatment strategies include second-line endocrine therapy, chemotherapy, and immunotherapy. Those therapeutic techniques have their limitations. The second-line endocrine therapy and immunotherapy are expensive and cannot be commonly afforded by all patients, while chemotherapy inevitably has some toxic effects, which can be beyond tolerance thresholds for some patients, especially the elderly. For such patients, traditional Chinese medicine (TCM) could be a viable alternative treatment for cancer. We report a case of PC in a 71-year-old male patient who was given TCM.
of 

$$4 + 5 = 9$$

which was divided into five groups and involved nerve fibers (Figure 1). The immunohistochemical results were as follows: P504S (+), CK (H) (−), p63 (−), AR (+), PSA (weak +), S-100 (nerve fiber +), and (three on the right side of prostate biopsy) prostate adenocarcinoma, a Glason’s score of 

$$4 + 5 = 9$$

divided into five groups.

The patient presented to our hospital on September 16, 2019 with a diagnosis of PC stage IVB (adenocarcinoma, T4N1M1b, bone metastasis), which suggested that continuing the same endocrine therapy would not be effective. The whole abdominal computed tomography (CT) revealed the peripheral invasion of PC with involvement of the left pelvic wall, seminal vesicle, bladder, bilateral lower ureter (maximum diameter: 76 mm × 88 mm), multiple swollen lymph nodes in the pelvic cavity and retroperitoneal (maximum diameter: 25 mm) (Figures 3A, 3C, 4A, and 4C). The magnetic resonance imaging (MRI) of the whole spine revealed diffuse metastatic disease in cervicothoracic lumbosacral vertebrae and bilateral ilium. During treatment the total prostate-specific antigen (PSA) of the patient was >100 ng/mL, and the free PSA was >30 ng/mL.

The patient was treated with zoledronic acid 4 mg IV QD once due to the diffuse bone metastasis of the whole body. After the use of zoledronic acid, the patient’s urine output decreased progressively—with a 24-h urine output of 50 mL for more than 48 consecutive hours. And the serum creatinine increased progressively, up to 498.8 μmol/L, cystatin C 1.65 mg/L, urea nitrogen 14.38 mmol/L, and uric acid 556.3 μmol/L. Color Doppler ultrasound of the urinary system showed: hypoechoic mass from the bladder to the prostate area, mild hydrops in both kidneys, cysts in the right kidney, widening of the inner diameter of the bilateral ureters, and residual urine of 108 mL in the bladder. Renal failure was sudden and may be related to the use of zoledronic acid. Color Doppler ultrasound showed that the upper track was obstructed. The urologist recommended a nephrostomy, although the patient and family members rejected the suggestion. Then, a catheter was placed, and the flow of catheter remained at 20 mL. So, hemodialysis was started after urgent consultation with a nephrologist. After three hemodialysis sessions in a week, the patient’s creatinine level decreased compared to that in the prior hemodialysis. He was discharged on September 30, 2019, and dialysis treatment was to be completed in the outpatient department until his creatinine level returned to normal. In addition, the LMWH sodium (Qi-zheng) was used for prophylactic anticoagulation at a dose of 3,500 IU or 5000 IU for each dialysis. After 2 weeks of dialysis, the patient’s creatinine was in the normal range for two consecutive times, 89.7 and 97.2 μmol/L, respectively, thus, we conclude the catheter was successfully removed. Upon catheter removal, 500 mL of urine and blood was discharged, the urine volume gradually recovered, and the patient was provided normal drinking water. During this period, the patient did not receive any anti-tumor therapy, including chemotherapy, immune, or endocrine therapy. Patient received outpatient dialysis treatment only.

On November 16, 2019, the patient requested oral TCM for anti-cancer treatment in the outpatient service. The patient’s condition is as follows: the patient was feeling cold in the daytime average temperature of 26°C even with a thick jacket, experiencing spontaneous sweating, without thirst, excessive saliva, fatigue, poor appetite, loose or watery stools, edema of both lower extremities, occasional prickles in the lower abdomen pain, and his pulse indicated a slippery-like sinking lever, and his tongue was slightly red with a thick and white coating. According to the patient’s symptoms, tongue coating, and pulse, the patient’s symptoms belongs to mixed-type syndromes, including Yang-qi deficiency syndrome and Phlegm–Stasis syndrome (Deng et al., 2020). Based on the physical findings and TCM theory, the adjusted Shi-pi-san and Gui-zhi-Fu-ling-wan were prescribed for the patient. Table 1 displays the component of Shi-pi-san and

![Figure 1. The Patient’s Prostate Puncture Biopsies](image-url)
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Gui-zhi-Fu-ling-wan for specific medications. These recipes were prepared by our hospital pharmacy. All herbal medicines were produced in China.

After taking the above Chinese herbal medicines, the patient visited our hospital on December 7, 2019 for re-examination and removal of the internal jugular vein catheter for hemodialysis. The Doppler ultrasound of his internal jugular vein displayed the right internal jugular vein embedded with a catheter and peripheral thrombosis (about $1.73 \text{ cm} \times 0.47 \text{ cm}$) (Figure 2). He was admitted to the hospital for anticoagulation treatment.

Meanwhile, the patient reported feeling “refreshed” in contrast to feeling “uncomfortable” prior to TCM intake. Re-examination of the whole abdominal CT indicated peripheral invasion with involvement of the left pelvic wall, seminal vesicle gland, bladder, and bilateral lower ureters, and decreased mass (maximum diameter: $60 \text{ mm} \times 43 \text{ mm}$) (Figure 3). The pelvic cavity and retroperitoneal multiple enlarged lymph nodes were decreased (maximum diameter: approximately $11 \text{ mm}$) (Figure 4). According to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, the efficacy of the herbal medicines in the patients was evaluated as PR (37.2% reduction). Due to the limitation of laboratory conditions, PSA cannot be diluted. The indicators of PSA both before and after treatment are: total PSA $> 100 \text{ ng/ml}$, free PSA $> 30 \text{ ng/ml}$, so that, the difference of PSA before and after treatment cannot be compared as the evaluation of curative effect.

### Discussion

According to statistics from the American Cancer Society, PC is the most common cancer in men, with a total of 3,650,030 in 2019 (Miller et al., 2019). Patients with advanced PC often experience poor urination. Our patient had similar symptoms of difficulty in urination for 1 year, which was serious but not life-threatening in the long term. This was consistent with an autopsy report, which reported that > 33% of men aged 70 to 79 years who died of other causes had PC prior to their death (Jahn et al., 2015). Therefore, we focused on alleviating the patient’s symptoms and controlling the disease progression. Since the patient could neither tolerate the side effects of chemotherapy nor afford the heavy economic burden of second-line endocrine therapy, TCM treatment was a worthy choice for him. The application of Shi-pi-san and Gui-zhi-Fu-ling-wan in PC has never been reported. In this case, the efficacy of Shi-pi-san and Gui-zhi-Fu-ling-wan in clinical practice has been confirmed by the significant tumor reduction, thus, this is unique case report.

The efficacy of Shi-pi-san and Gui-zhi-Fu-ling-wan in our patient can be explained in two aspects: the TCM theory and anti-cancer mechanism. According to the theory of TCM, the patient’s symptoms—feels cold, experience spontaneous sweating, mental fatigue, lack thirst, poor appetite—are manifestations of Yang-qi deficiency. And excessive saliva, loose or watery stools, and edema of both lower extremities are the manifestations of internal dampness caused by Yang-qi deficiency. Reddish tongue, thick white coating, and deep pulse are also signs of Yang-qi deficiency and internal dampness. Therefore, Shi-pi-san is used to warm Yang, activate Qi, and drain Yin water, which is the correspondence between the prescription and the syndrome. In the TCM treatment, we used Dried Ginger and Monkshood to warm the Yang. We used Poria cocos, Fried Atractylodes macrocephala, Papaya, Costus, and Pericarpium Arecae to activate Qi.

### Table 1. The Components of the Adjusted Shi-pi-san and Gui-zhi-Fu-ling-wan.

| Medicinal plants                              | Weight (g) | Dosage form          |
|----------------------------------------------|------------|----------------------|
| Poria cocos (Fu-ling)                        | 15         | Decoction pieces     |
| Fried Atractylodes macrocephala (Chao-bai-zhu)| 10         | Decoction pieces     |
| Papaya (Mu-gua)                               | 10         | Decoction pieces     |
| Radix Glycyrrhizae Preparata (Zhi-gan-cao)    | 5          | Decoction pieces     |
| Costus (Mu-xiang)                             | 5          | Decoction pieces     |
| Pericarpium Arecae (Da-fu-pi)                 | 15         | Decoction pieces     |
| Monkshood granule (Fu-zi-ke-li)               | 9          | Granule              |
| Cinnamon twig (Gui-zhi)                       | 5          | Decoction pieces     |
| Dried Ginger (Gan-jiang)                      | 5          | Decoction pieces     |
| Radix Paeoniae Rubra (Chi-shao)               | 15         | Decoction pieces     |
| Cortex Moutan (Mu-dan-pi)                     | 10         | Decoction pieces     |
| Peach kernel (Tao-ren)                        | 10         | Decoction pieces     |
| Wine-treated Radix et Rhizoma Rhei granule    | 3          | Granule              |

Note. Decoction in water, one dose per day. For the first time, add 500 ml of water and boil 250 ml of the medicine. For the second time, add 500 ml of water to make 200 ml of the medicine. Take it warm after breakfast and dinner.
Figure 2. The Color Doppler Ultrasound Displaying the Right Internal Jugular Vein Embedded With a Catheter, and Formation of Peripheral Thrombosis

Figure 3. CT Scans Indicating Decreased Tumor Size
and drain the Yin water. At the same time, the patient has occasional prickles pain in the lower abdomen, slippery pulse, and PC is a pelvic mass and pelvic cavity blood stasis. As part of the treatment, Gui-zhi-Fu-ling-wan was chosen. Gui-zhi-Fu-ling-wan was created by Zhongjing Zhang and for “women’s pelvic cavity blood stasis.” Modern basic research has reported that Gui-zhi-Fu-ling-wan can also induce apoptosis of myoma cells. (Lee et al., 2019). Therefore, Gui-zhi-Fu-ling-wan were chosen to eliminate blood stasis in the patient’s pelvic cavity, and wine-treated Radix et Rhizoma rhei can also induce apoptosis of myoma cells. (Lee et al., 2019). Therefore, Gui-zhi-Fu-ling-wan were chosen to eliminate blood stasis in the patient’s pelvic cavity, and wine-treated Radix et Rhizoma rhei was added to enhance the power of promoting blood circulation and removing blood stasis. To summarize, we treat this patient from two aspects of adjusting the overall balance of Yin and Yang, strengthening the body’s immunity and eliminating local pelvic tumor, that is, removing pathogenic factors, so that, we have achieved gratifying curative effects.

With regard to molecular mechanisms, modern pharmacological studies have reported that pachytearic acid, which is extracted from *Poria cocos* induces mitochondrial dysfunction and initiates PC cell apoptosis by inducing the activity of caspase-9/-3 and increasing the ratio of Bax/Bcl-2 protein (Gapter et al., 2005). Research by Son et al. (2017) has reported that *Atractylodes macrocephala* extract can promote the proliferation of lymphocytes and simultaneously release a large amount of tumor necrosis factor (TNF)-alpha and interleukin (IL)-6. Among them, TNF-alpha can activate death receptors on the surface of

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**Figure 4. CT Scans Indicating Decreased Size of the Pelvic Cavity and Multiple Retroperitoneal Enlarged Lymph Nodes**
tumor cells, causing tumor destruction (Knutson & Disis, 2005). In the *Papaya* extract, dietary isothiocyanate promotes cell apoptosis by activating the caspase-8 and -9 pathways and phosphorylation of anti-apoptotic protein Bcl-xL, among which the c-Jun N-terminal kinase (JNK) pathway is critical for cell apoptosis mediated by phosphorylation of the anti-apoptotic protein Bcl-xL (Basu & Haldar, 2008). Licorice polysaccharides, which are extracted from *Glycyrrhiza Preparata* can activate CD4+ and CD8+ cells, and CD8+ cells can directly recognize and eliminate cancer cells. Meanwhile, licorice polysaccharides significantly inhibit tumor growth in CT26 tumor-bearing mice. This activation of CD4+ and CD8+ increases the production of cytokines, especially IL-2, IL-6, and IL-7, and reduces TNF-alpha levels (Ayeka et al., 2017). Among them, the cytokines IL-2 and IL-6 are involved in destroying cancer cells by antigen-presenting macrophages in the process of tumor immune monitoring (Haabeth et al., 2011). Previous studies by Ayeka et al. (2016) have also indicated that licorice polysaccharides inhibited the growth of cancer cells and up-regulated IL-7 in vitro. The *Costus* extract can inhibit the proliferation, cloning, and metastatic potential of PC-3 cells, and can cause G(0)/G(1) and G(2)/M cell cycle arrest in PC-3 cells. It induces PC-3 cells apoptosis by producing reactive oxygen species, reducing glutathione, permeabilizing mitochondrial and lysosomal membranes, inducing caspase-9/-3 activity, promoting PARP-1 cleavage, damaging DNA, and increasing the ratio of the Bax/Bcl-2 protein (Elkady, 2019; Kim et al., 2008). *Mongshhood* extract can inhibit tumor cell proliferation, while reducing the lipopolysaccharide (LPS)-induced apoptosis of mouse peritoneal macrophages by reducing nitric oxide (NO) and reactive oxygen species (ROS) production, indicating that it may exert anti-cancer effects through an anti-inflammatory mechanism (Huang et al., 2013). *Dry Ginger* extract, 6-Shogaol inhibits the growth of PC cells by inhibiting STAT3 and nuclear factor kappa B (NF-κB) signaling pathways (Saha et al., 2014). In addition, the use of *Radix Paeoniae Rubra* and *Cortex Moutan* significantly reduced the size of mouse bladder tumors. *Radix Paeoniae Rubra* reduces Gil stage cells and significantly increased sub-0 stage cells, thereby inhibiting tumor cell proliferation (M.-Y. Lin et al., 2016). *Cortex Moutan* can block tumor cells in G1 and S phases and cause the expression of phosphatidylserine outside the cell membrane. It induces the activation of caspase-8 and caspase-3 and the degradation of poly (adenosine diphosphate-ribose) polymerase. *Cortex Moutan* can also inhibit tumor cell invasion (M.-Y. Lin et al., 2013). The study of Cassiim and de Kock (2019) has suggested that *Peach kernel* extract can resist tumor cell proliferation, and the low ATP level caused by amygdalin can cause cell pyknosis or necrosis. Emodin, the *Radix et Rhizoma Rhei* extract can inhibit the viability of PC cells and promote apoptosis (Zheng et al., 2018). However, how these drugs interact still requires further research for confirmation.

Recently, increasing real-world data have suggested that TCM has evident benefits in cancer treatment in terms of improving quality of life (Tang et al., 2019) and prolonging survival (Shih et al., 2021). The data include benefits on ovarian cancer (Zhu et al., 2019), advanced liver cancer (Zhao et al., 2021), and PC (P. H. Lin et al., 2019). However, the anti-tumor use of TCM is not simply to pile up anti-tumor drugs, but to use drugs under the guidance of the Chinese medicine theory, and this aspect is rarely reported. Hence, this will be the focus of our future study.

After TCM intake, the patient’s symptoms were evidently alleviated that he felt so “refreshed,” and his being “uncomfortable” was significantly relieved. His primary tumor and lymph node metastasis were also significantly reduced after TCM use. Since the patient underwent hemodialysis, and the low-molecular-weight heparin (LMWH) was used simultaneously with the Chinese herbal medicines, it is worthy to explore the role of LMWH in the treatment. To date, no strong evidence to prove the anticancer effect of LMWH has been found. No significant difference in the survival benefit was observed among PC patients receiving standard treatment with or without LMWH (Klerk et al., 2005). Another study, which used LMWH in patients with advanced cancer (Kakkar, 2004), also revealed no significant difference in the survival benefits of patients in 1, 2, and 3 years after the addition of LMWH daily for 1 year on the basis of standard treatment. Only subgroup analyses suggested that the benefit of LMWH starts to exhibit on patients who survived for > 17 months. Altinbas et al. (2004) have reported that patients with small cell lung cancer treated with LMWH 5000 IU once daily for 18 weeks along with standard chemotherapy had a progression-free survival period of 10 months, which was significantly compared with the control group for 6 months. Although basic research has indicated that anticoagulants, such as unfractionated heparin or LMWH, can promote cancer cell apoptosis (Yekh, 2001), and inhibit tumor cell proliferation (Carmazzi et al., 2011) and tumor angiogenesis (Norby & Östergaard, 2008), they do not affect the growth of locally implanted tumors (Maat & Hilgard, 1981; Milas et al., 1985). In particular, LMWH does not affect tumor cell proliferation (Sciumbata et al., 1996); thus, the inhibitory effect of LMWH on tumor cell proliferation depends on the cell type and the molecular weight of heparin (Carmazzi et al., 2011). To date, the use of anticoagulants, including LMWH, has been more focused on metastasis than on primary tumors (Bobek & Kovafik, 2004). This promotes the hypothesis that TCM plays a vital role cancer
treatment, and LMWH may play a synergistic role. The synergistic anticancer effect of LMWH may not be related to its anticoagulant effect because thrombus of the internal jugular vein catheter still occurred during LMWH use in this patient. Moreover, studies have reported that removing the anticoagulant sequence from heparin could still retain its anticancer activity (Casu et al., 2009; Folkman et al., 1983; Lapierre et al., 1996; Sciumbata et al., 1996). Thus, whether LMWH has a synergistic anticancer effect remains unclear and should be further explored.

In conclusion, the patient’s tumor shrank significantly after using Shi-pi-san, Gui-zhi-Fu-ling-wan and LMWH, which can be explained from the perspective of TCM theory. However, this is only a case. The anticancer effects of Shi-pi-san and Gui-zhi-Fu-ling-wan in PC patients with Yang-qi deficiency syndrome and Phlegm–Stasis syndrome still need to be further confirmed by prospective randomized clinical trials. At the same time, whether it is necessary to use LMWH in combination to play a better anti-tumor effect also needs further pharmacological confirmation.

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