

# Management of Long-Term Sores and Ulcers of Breast Cancer **Survivors With Chinese Herbal Medicines: A Case Report**

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Background: The treatment of long-term sores and ulcers of breast cancer metastatic recurrence is a serious challenge with successful cases rarely being documented. Herein we reported a successful case using the internal vitality supporting method of Chinese herbal medicine (CHM).

Case Summary: A 59-year-old female Chinese patient, 10 years after breast cancer surgery, developed metastatic lesions in the lung. Thereafter she received radiofrequency ablation and adjuvant treatments for 1 year with severe sequelae, a right unhealed sore and ulcer. She became frustrated and depressive. And subsequently sought exclusive treatment under the guidance of a Traditional Chinese Medicine (TCM) physician. The patient's condition was categorized as a Qi (or vitality) deficiency-related sore and ulcer. In the next six months, the patient still follows a traditional Chinese medicine therapeutic regimen based on the internal vitality supporting method of Chinese herbs.

Conclusion: The sore and ulcer from the surgical wound were healed. Up to now, the tumor markers have remained stable. TCM personalized survivorship treatment and psychosocial support can help patients improve their quality of life after acute treatment and in the long-term for cancer survivors.

Keywords: Chinese herbal medicine, sore and ulcer, cancer metastatic recurrence, psychosocial support, post-radiofrequency ablation wound, breast cancer survivors

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# INTRODUCTION

Breast cancer is the most common cancer diagnosed in women worldwide, and it alone accounts for 30% of cancer in women (1). Death rates for female breast cancers were estimated to be 6.9% in 2020 (2).

Surgery represents the only potentially curative therapeutic intervention for breast cancer patients, and postmastectomy locoregional recurrences (LRRs) were found in 5-25% (3). The sites of LRRs were usually confined to the chest wall (68%) and supraclavicular nodes (41%) (3, 4). The lung, bone, and liver were the most common metastatic sites for breast cancer. A total of 60-70% of metastatic breast cancer patients who eventually died were diagnosed with lung metastasis (5). Unique signal transduction pathways were found for breast tumors to metastasize to the lung, and nine genes have been defined as specific for lung-specific metastasis (6-8). Surgery is the first

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line choice of treatment. Other treatments (e.g., cryoablation, intraoperative radiotherapy, high-intensity focused therapy, and ultrasound) are used in the experimental/investigational phase, if applicable (3). Radiofrequency ablation (RFA) is a popularity intervention for its advantages of reduction in tumor mass and intraprocedural pain (9). However, adverse events are common with RFA, such as vascular injury (10), atrio-esophageal fistula (11), and deep esophageal ulcers and abscesses (12-15), which seriously affect patients' quality of life. At present, post-RFA wound management is a serious challenge, as the wound is difficult to heal and has to be kept clean by rising with saline water, which is the main conservative approach for wound management. According to traditional Chinese medicine (TCM) theory, Yang and Qi are the driving forces of biological activities in the human body. Deficiencies in Yang and Qi are common in cancer patients (16). Chinese herbal medicine (CHM) has been utilized as a supplementary treatment (17, 18) for breast cancer patients who received a surgical operation (19-21). We report herein the case of a 59-year-old women who had a surgical operation in the year of 2007. The patient was diagnosed with lung metastasis by CT, for which RFA treatment was then performed. Unfortunately, the cancer recurred and the chest ulcer failed to be controlled following interventional therapy. In the absence of further treatment options, the surgeon decided to offer only palliative treatment. The patient developed anxiety and depressed mood. Without further improvement, the patient turned to CHM for help, and she witnessed a stable improvement in her condition, with the sore and ulcer healed.

# **Ethical Approval**

This case report was a retrospective study; hence it did not belong to the Ethical committee's scope of review, which means that ethical approval was not necessary.

# **Patient Consent**

Written informed consent was obtained from the patient before and after every procedure.

# **CASE PRESENTATION**

# **Chief Complaints**

The patient was a 59-year-old woman diagnosed with right breast cancer who underwent a right mastectomy in 2007. The patient complained of persistent chest pain and ulcers for 1 year, and she had low quality of life.

# **History of Present Illness**

The patient was sent to Guoyitang TCM Clinic, Beijing University of Chinese medicine on 29 June 2017. She reported having developed an ulcer on the right side of her chest 1 year prior, after receiving RFA treatment in Guangdong hospital. The patient reported coughing with a lot of white sputum. She reported that she had persistent pain on the right side of her chest and there was secretion at the scar, and she had poor

**Abbreviations:** TCM, Traditional Chinese medicine; LRRs, Locoregional recurrences; RFA, Radiofrequency ablation; CT, Computed tomography; CHM, Chinese herbal medicine.

mental status. We observed that her tongue was pale-white-with tenderness and the tongue coating was white with exfoliative tongue fur. The patient's pulse was deep.

# **History of Past Illness and Family History**

In October 2007, the patient had an invasive ductal carcinoma that was diagnosed by puncture. Grade II was confirmed in the right breast tissue and lymph node via microscopy, with metastases involving the axillary lymph node (7) 4/7 and lymph node (9) 5/9 depicted in the surgical pathology report. Immunohistochemical analyses revealed the following: ER (+ + +), PR (+ + +), C-erbB-2 (-), VEGF (++), P53 (+ + +), and Ki-67 (+ + +). Having received postoperative radiotherapy, the patient continued taking toremifene as a means of endocrine therapy for 5 years.

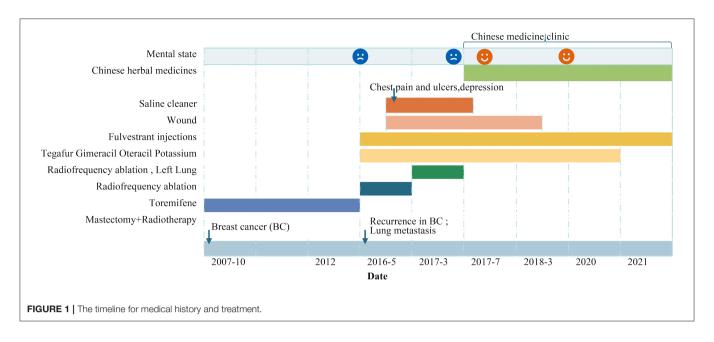
In May 2016, a CT scan demonstrated a recurrence of right breast cancer and aroused suspicions of lung metastasis, after which ultrasound and CT-guided right recurrent breast lesions and radiofrequency ablation of the lung metastases were conducted. Following radiofrequency ablation of the lesions within the lung and right chest wall, the wound did not heal completely, and a chest wall sinus was formed. Next, the patient started taking tegafur gimeracil oteracil potassium capsules (20 mg per day) until January 2020. And is currently being administered fulvestrant injections.

In March 2017, the patient received a secondary radiofrequency ablation for the metastasized lesion in her left lung. Unfortunately, the patient complained of persistent chest pain and ulcers; a chest CT revealed a mass measuring 12 mm at its thickest point, suggesting the presence of recurrence and that the lesion was inoperable. The wound was covered with dressing, and the surgeon recommended the patient use a saline cleaner for the wound  $1\sim2$  times daily. However, in the patient's perspective, she said there has been almost no improvement. She felt that the condition gradually worsened. This clearly devastated the patient and seriously affected her quality of life.

Regarding her psychosomatic symptoms, the patient had suffered chronically from dysthymia after cancer diagnosis. Depressive symptoms increased with cancer diagnosis and multiple RFA therapy regimes. And her psychiatric profile became worse when the wound was still unhealed after 1 year. The timeline for medical history and treatment is shown in **Figure 1**.

# **Diagnostic Assessment and Treatment**

According to TCM syndrome differentiation, the patient was diagnosed with Yang (spleen and kidney) deficiency and Qi deficiency. Professor Dr. Zhang's (Doctor of CHM) main treatment goal was to relieve the patient's pain. She used the internal vitality supporting method (22) to strengthen the patient's anti-pathogenic ability. A treatment course lasted for 7 days. The composition formula is displayed in the **Supplementary Table.** First, the patient was instructed to take the herbal decoction once a day for 7 days. At the second visit, the patient appeared cheerful and lively. The improvement elicited during the treatment was highly significant (**Figure 2**).



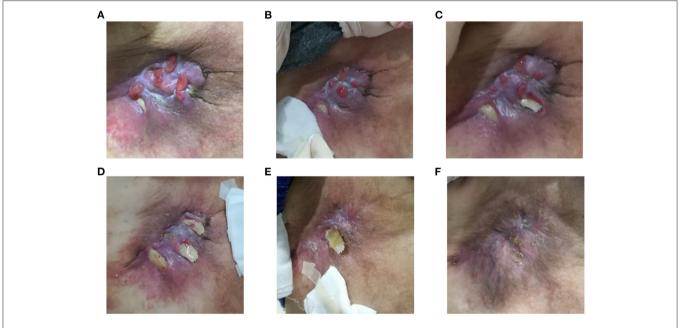


FIGURE 2 | Sore and ulcers. (A) Severe sore at the first visit (with eight ulcers on right chest). (B-E) By the second and fifth visits, the sore and ulcers were significantly improved. (F) At the sixth visit, the ulcers had already healed.

Currently, the patient continues to take Chinese herbs after completing five treatment courses. Over the last 6 months, the wound has healed and the overall situation has remained stable with a slight cough. "I was very surprised at my change because I could hang out easily at home with my family with a comfortable mind", the patient said.

# **Outcome and Follow-Up**

In March 2018, the CT report pointed out that the lesion in the right chest wall with its thickest part measuring 9 mm,

was smaller in size than previously reported (12 mm) in June 2017. The tumor marker test was sustained within the normal range (Table 1).

# **DISCUSSION**

There are three stages in the wound healing process: inflammation, proliferation, and remodeling, which depend on the host's ability to repair tissue (23). It was proposed that

TABLE 1 | Tumor marker test.

with CHM with CHM   CA15-3 14.17 13.11 0.00~25.00 U   CA125 7.12 6.97 0.00~35.00 U   CEA 1.42 2.02 0.00~5.00 ng					
CA125 7.12 6.97 0.00~35.00 U CEA 1.42 2.02 0.00~5.00 ng	Test item			Reference	Units
CEA 1.42 2.02 0.00~5.00 ng	CA15-3	14.17	13.11	0.00~25.00	U/ml
	CA125	7.12	6.97	0.00~35.00	U/ml
CA19-9 - 21.43 0.00~35.00 U	CEA	1.42	2.02	0.00~5.00	ng/ml
	CA19-9	-	21.43	0.00~35.00	U/ml

CA15-3, carbohydrate antigen 153; CA125, carbohydrate antigen 153; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 199.

there was an aspect of surgical tumor resection that triggered the outgrowth of otherwise-dormant metastases, leading to the synchronous pattern of relapse during the postoperative period. In general, 10~41% of breast cancer patients experience recurrences, and 10% develop overt metastases relatively soon after tumor eradication (3, 24). There is compelling evidence of an increased risk of anxiety, depression, and suicide, and neurocognitive and sexual dysfunctions in breast cancer survivors compared with women with no prior cancer (25). Clinically relevant symptoms of stress and depression are common shortly after diagnosis and metastatic recurrence, because women feel uncertainty about the future and their cancer may be perceived as life-threatening. The patient mentioned in this case report who suffered from long-term sores and ulcers of breast cancer metastatic recurrence had low quality of life. From the surgeons' perspective, ulcers of breast cancer metastatic recurrence are local inflammation, and they only recommend washing the ulcer with normal saline, but in this case, the ulcer failed to heal for 1 year. This case was complex and difficult to treat. Seeking the help of a doctor was spiritually necessary for the patient. So when the surgeon was helpless or the treatment plan was not ideal, this led to despair in the patient.

The holistic concept is an essential philosophy of TCM. The mind and body together are a dynamic battlefield, in which all the organs and mind are interconnected and bound to each other, and should be considered and treated as a whole, rather than an isolated pathology. In TCM theory, individual health is formed by Yin-Yang; an imbalance between Yin and Yang in the body can render an individual more prone to certain disease (26). This theoretical advantage simplifies the complexity. TCM uses different methodologies to diagnose mental and body disorders. The four diagnostic methods (inspection, listening/smelling, inquiry, and palpation) are the means to obtain patient information. This information is then analyzed using diagnostic models, such as yin/yang, interior/exterior, excess/deficiency, and hot/cold to differentiate the pattern and form a diagnosis. Zhang suggested that the patient's long-term sore and ulcer were due to Qi deficiency; the psychiatric symptoms of the long-term sore and ulcer resulted in emotional upset and stagnation of Qi. These were associated with the impairment of spleen and kidney (Spleen-Yang and Kidney-Yang). Yang-deficiency (e.g., spleen, kidney) may not only be related to hypothalamic-pituitaryadrenal (HPA) axis and hypothalamic-pituitary-thyroid (HPT) axis dysfunction, but also to functional disorders of the cyclic nucleotide and immune systems (27). These factors are involved in depression. The patient's mind and body were affected by the sore and ulcer. Zhang's main treatment goal was to relieve the patient's pain, which could improve the patient's quality of life.

After the malignant lesions had been removed by surgical excision, there was a persistent poor growth of granulation tissue, following delayed wound healing. The patient exhibited middle-staged boils and sores, and the pus was not completely discharged after breaking the ulceration. The patient had a compromised immune function; thus a tonic was used for reinforcing the primordial Qi in order to treat suppurative infection in this situation. This method was named the internal vitality supporting method according to the theory of TCM (22). This therapeutic regimen aimed at strengthening the host's antipathogenic ability and removing pathogenic factors via herbs to achieve the goal of canceling the tumefaction and shrinking its base to avoid ulceration.

The ulcer was effectively healed by Chinese herbs via boosting the primordial Qi, conditioning the internal vitality of key viscera to circulate Qi, activating the energy supply, and dispersing the inflammatory blockage. HuangQi (Radix astragali seu Hedysari), DangShen (Radix codonopsis pilosulae), Baizhu (Rhizoma Atractylodis Macrocephalae), Danggui (Radix Angelicae Sinensis), Baizhi (Radix Angelicae Dahuricae), etc., have been documented to modulate the immune response. These were used in inhibiting cancer cell proliferation, arresting the cell cycle, inducing apoptosis, inhibiting epithelial-mesenchymal transition, regulating immune function (28), and exerting antioxidative and anti-inflammatory effects (29) in cells and animal studies. Compared to local treatment therapies for chronic inflammatory skin disease, this herb intervention altered the gut microbiome, taking advantage of the gut-skin axis to control different skin conditions (30). As these herbs encompass a group of substances that produce a therapeutic effect, multiple pathways and receptors were targeted, plenty of compounds were involved, which acted synergistically to improve cancer-related symptoms, enhance vital energy, and boost immunity. What is more, herbs used in traditional medicine can be significantly effective in reducing depression, depressive symptoms, and improving patients' performance via regulating the HPA axis (31). So as the patient witnessed her wound healing, she became more optimistic.

This case was the first description of management of a longterm sore and ulcer of breast cancer metastatic recurrence with the internal vitality supporting method of Chinese herbal medicine. The patient was effectively cured due to cross-disorder and interdisciplinary collaboration. The holistic concept of TCM provided a novel therapeutic strategy for mind-body medicine.

# **DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

# **ETHICS STATEMENT**

Written informed consent was obtained from the relevant individual(s) for the publication of any potentially identifiable images or data included in this article. Written consent and accompanying photos were obtained from the patient and her husband for publication.

# **AUTHOR CONTRIBUTIONS**

YZ drafted the manuscript. BZ treated the patient and provided the case analysis. WZ and YZ provided the critical analysis in preparing this article. TL revised the manuscript. All the authors approved the final version.

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# **REFERENCES**

- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics 2021. CA Cancer J Clin. (2021) 71:7–33. doi: 10.3322/caac.21654
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. (2021) 71:209–49. doi: 10.3322/caac.21660
- Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. Local cancer recurrence: the realities, challenges, and opportunities for new therapies. CA Cancer J Clin. (2018) 68:488–505. doi: 10.3322/caac.21498
- Katz A, Strom EA, Buchholz TA, Thames HD, Smith CD, Jhingran A, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. *J Clin Oncol.* (2000) 18:2817–27. doi: 10.1200/JCO.2000.18.15.2817
- Dan Z, Cao H, He X, Zhang Z, Zou L, Zeng L, et al. A pH-responsive hostguest nanosystem loading succinobucol suppresses lung metastasis of breast cancer. *Theranostics*. (2016) 6:435–45. doi: 10.7150/thno.13896
- Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, et al. Genes that mediate breast cancer metastasis to lung. *Nature*. (2005) 436:518– 24. doi: 10.1038/nature03799
- Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell. (2011) 147:275–92. doi: 10.1016/j.cell.2011.09.024
- 8. Jin L, Han B, Siegel E, Cui Y, Giuliano A, Cui X. Breast cancer lung metastasis: molecular biology and therapeutic implications. *Cancer Biol Therapy.* (2018) 19:858–68. doi: 10.1080/15384047.2018.1456599
- Macchi M, Belfiore MP, Floridi C, Serra N, Belfiore G, Carmignani L, et al. Radiofrequency versus microwave ablation for treatment of the lung tumours: LUMIRA (lung microwave radiofrequency) randomized trial. *Med Oncol.* (2017) 34:96. doi: 10.1007/s12032-017-0946-x
- Kim SY, Le PU, Kosharskyy B, Kaye AD, Shaparin N, Downie SA. Is genicular nerve radiofrequency ablation safe? A literature review and anatomical study. *Pain Phys.* (2016) 19:E697–705. doi: 10.36076/ppj/2019.
- Schuring CA, Mountjoy LJ, Priaulx AB, Schneider RJ, Smith HL, Wall GC, et al. Atrio-esophageal fistula: a case series and literature review. Am J Case Rep. (2017) 18:847–54. doi: 10.12659/AJCR.903966
- Koruth JS, Kuroki K, Kawamura I, Brose R, Viswanathan R, Buck ED, et al. Pulsed field ablation versus radiofrequency ablation: esophageal injury in a novel porcine model. Circ Arrhythm Electrophysiol. (2020) 13:e008303. doi: 10.1161/CIRCEP.119.008303
- McCarty TR, Rustagi T. New indications for endoscopic radiofrequency ablation. Clin Gastroenterol Hepatol. (2018) 16:1007–17. doi: 10.1016/j.cgh.2017.10.023
- Mensah ET, Martin J, Topazian M. Radiofrequency ablation for biliary malignancies. Curr Opin Gastroenterol. (2016) 32:238– 43. doi: 10.1097/MOG.0000000000000258
- Chandrasekhara V, Topazian M. Biliary radiofrequency ablation: burning issues. Gastrointest Endosc. (2018) 88:519–20. doi: 10.1016/j.gie.2018.05.006

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# SUPPLEMENTARY MATERIAL

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- Yeh MH, Chao CH, Koo M, Chen CY, Yeh CC, Li TM. Association of traditional Chinese medicine body constitution and moderate-to-severe cancer-related fatigue in cancer patients. Complement Ther Med. (2019) 43:44–8. doi: 10.1016/j.ctim.2019.01.004
- Su CX, Wang LQ, Grant SJ, Liu JP. Chinese herbal medicine for cancer-related fatigue: a systematic review of randomized clinical trials. Complement Ther Med. (2014) 22:567–79. doi: 10.1016/j.ctim.2014.04.007
- Tao W, Luo X, Cui B, Liang D, Wang C, Duan Y, et al. Practice of traditional Chinese medicine for psycho-behavioral intervention improves quality of life in cancer patients: a systematic review and meta-analysis. *Oncotarget.* (2015) 6:39725–39. doi: 10.18632/oncotarget.5388
- Ma TT, Zhang GL, Dai CF, Zhang BR, Cao KX, Wang CG, et al. Scutellaria barbata and Hedyotis diffusa herb pair for breast cancer treatment: potential mechanism based on network pharmacology. J Ethnopharmacol. (2020) 259:112929. doi: 10.1016/j.jep.2020.112929
- Tao WW, Jiang H, Tao XM, Jiang P, Sha LY, Sun XC. Effects of Acupuncture, Tuina, Tai Chi, Qigong, and traditional Chinese medicine fiveelement music therapy on symptom management and quality of life for cancer patients: a meta-analysis. *J Pain Symptom Manage*. (2016) 51:728– 47. doi: 10.1016/j.jpainsymman.2015.11.027
- Tsai YT, Lai JN, Wu CT. The use of Chinese herbal products and its influence on tamoxifen induced endometrial cancer risk among female breast cancer patients: a population-based study. *J Ethnopharmacol.* (2014) 155:1256– 62. doi: 10.1016/j.jep.2014.07.008
- Zuo Y, Huang G. Surgery of Traditional Chinese Medicine, A Practical English-Chinese Library of Traditional Chinese Medicine. House of Shanghai University of TCM (1990). p. 33–5.
- Tejada S, Manayi A, Daglia M, Nabavi SF, Sureda A, Hajheydari Z, et al. Wound healing effects of curcumin: a short review. Curr Pharm Biotechnol. (2016) 17:1002-7. doi: 10.2174/1389201017666160721123109
- Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. (2019) 321:288–300. doi: 10.1001/jama.2018.19323
- Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. J Natl Cancer Inst. (2018) 110:1311–27. doi: 10.1093/jnci/djy177
- Lin SJ, Cheng YY, Chang CH, Lee CH, Huang YC, Su YC. Traditional Chinese medicine diagnosis "Yang-Xu Zheng": significant prognostic predictor for patients with severe sepsis and septic shock. Evid Based Complement Alternat Med. (2013) 2013:759748. doi: 10.1155/2013/7 59748
- Chen HJ, Lin YJ, Wu PC, Hsu WH, Hu WC, Wu TN, et al. Study on Yang-Xu using body constitution questionnaire and blood variables in healthy volunteers. Evid Based Complement Alternat Med. (2016) 2016:9437382. doi: 10.1155/2016/94 37382
- Wei D, Wang L, Chen Y, Yin G, Jiang M, Liu R, et al. Yangyin Fuzheng Decoction enhances anti-tumor efficacy of cisplatin on lung cancer. *J Cancer*. (2018) 9:1568–74. doi: 10.7150/jca.24525

- Kocaadam B, Sanlier N. Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Crit Rev Food Sci Nutr. (2017) 57:2889–95. doi: 10.1080/10408398.2015.1077195
- Salem I, Ramser A, Isham N, Ghannoum MA. The gut microbiome as a major regulator of the gut-skin axis. Front Microbiol. (2018) 9:1459. doi: 10.3389/fmicb.2018.01459
- Noori T, Sureda A, Sobarzo-Sánchez E, Shirooie S. The role of natural products in treatment of depressive disorder. Curr Neuropharmacol. (2022). doi: 10.2174/1570159X20666220103140834

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