Post-print of the Integrative Chinese-Western Medicine Diagnosis and Treatment Guidelines for Secondary Malignant Bone Tumors

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Abstract

Bone metastases are diseases caused by hematogenous metastasis of primary malignant tumors originating outside bone tissue to bone tissue, with bone damage and pain as the main manifestations. Bone metastases can cause skeletal-related events such as pain, pathological fractures, spinal cord compression, and hypercalcemia, which severely affect the quality of life of patients with advanced malignant tumors. Standardized, comprehensive, and integrated Chinese and Western medicine diagnosis and treatment for bone metastases is of great significance for the clinical management of bone metastases and their complications. This guideline was developed under the leadership of the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College, in collaboration with experts in relevant fields from 24 medical institutions nationwide, including Dongzhimen Hospital of Beijing University of Chinese Medicine, China-Japan Friendship Hospital, and Guang' anmen Hospital of the China Academy of Chinese Medical Sciences. The guideline development was based on the current status of integrated Chinese and Western medicine diagnosis and treatment practices for bone metastases both domestically and internationally, systematically reviewed relevant literature evidence, and reached consensus through multiple rounds of expert deliberation. This guideline systematically organizes the definition, etiology, diagnosis, and treatment strategies for bone metastases, aiming to provide an evidence-based basis for clinical diagnosis and the formulation of integrated Chinese and Western medicine treatment plans for this disease, thereby standardizing clinical practice.

Full Text

Guidelines for Diagnosis and Treatment of Secondary Malignant Bone Tumors with Integrated Traditional Chinese and Western Medicine

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Abstract: Secondary malignant bone tumors are diseases characterized by bone damage and pain caused by hematogenous metastasis of malignant tumors originating outside bone tissue. These tumors can induce skeletal-related events (SREs) such as pain, pathological fractures, spinal cord compression, and hypercalcemia, which severely impact quality of life in patients with advanced malignancies. Formal, comprehensive, and integrated traditional Chinese and Western medicine diagnosis and treatment of secondary malignant bone tumors is therefore of great clinical significance for managing the disease and its complications. This guideline was jointly formulated by the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College, in collaboration with experts from 24 medical institutions nationwide, including Dongzhimen Hospital of Beijing University of Chinese Medicine, China-Japan Friendship Hospital, and Guang' anmen Hospital of the China Academy of Chinese Medical Sciences. Based on current domestic and international practices in integrated traditional Chinese and Western medicine for secondary malignant bone tumors, the guideline systematically reviewed relevant literature evidence and reached consensus through multiple rounds of expert consultation. This guideline systematically outlines the definition, etiology, diagnosis, and treatment strategies for secondary malignant bone tumors, aiming to provide evidence-based guidance for clinical diagnosis and the formulation of integrated treatment plans to standardize clinical practice.

Keywords: Neoplasms, second primary; Bone neoplasms; Integrated Traditional Chinese Medicine & Western Medicine; Diagnosis; Guidebook

Introduction

Global cancer incidence continues to rise annually. According to 2022 global cancer statistics, there were 19.96 million new cancer cases and 9.74 million cancer deaths worldwide, posing a serious threat to human health [1]. Bone metastasis is a common complication of cancer, with bone tissue being the most frequently involved organ and the third most common site of distant metastasis. Malignant tumors such as prostate, breast, and lung cancers have particularly high rates of bone metastasis [2]. Secondary malignant bone tumors can cause skeletal-related events (SREs) including pain, pathological fractures, spinal cord compression, and hypercalcemia, which severely affect quality of life in patients with advanced malignancies [3]. Modern medical treatment centered on bisphosphonates and denosumab has limited efficacy and is accompanied by numerous adverse reactions. Other treatment modalities are primarily symptomatic—opioids for pain, surgery for fractures—each with significant limitations. Multiple studies have demonstrated that integrated traditional Chinese and Western medicine plays an important role in the diagnosis and treatment of secondary malignant bone tumors, making formal, comprehensive integrated management clinically significant for treating the disease and its complications [4-6].

Multiple guidelines for secondary malignant bone tumors have been developed and updated internationally as clinical evidence accumulates. These include systematic guidelines such as the *ESMO Clinical Practice Guidelines: Bone Health in Cancer (Version 2022)* [7] and the *Spanish Society of Medical Oncology (SEOM) Clinical Guidelines for Bone Metastases in Solid Tumors (2016)* [8]; consensus documents focusing on specific symptoms like the *Expert Consensus on Refractory Cancer Pain* (CRPC, 2017 edition, Interpretation III: Bone Metastasis Pain) [9]; and guidelines addressing specific primary cancers such as the *NCCN Guidelines Insights: Prostate Cancer (Version 1.2021)* [10]. However, these guidelines primarily recommend standardized Western treatment protocols, with limited content on traditional Chinese medicine (TCM) evidence and interventions, and lack comprehensiveness. Therefore, this guideline, led by the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College and developed in collaboration with experts from 24 medical institutions nationwide—including Dongzhimen Hospital of Beijing University of Chinese Medicine, China-Japan Friendship Hospital, and Guang' anmen Hospital of the China Academy of Chinese Medical Sciences—was formulated based on current domestic and international practices in integrated traditional Chinese and Western medicine for secondary malignant bone tumors, through systematic literature review and extensive expert discussion. This guideline summarizes the definition, etiology, diagnosis, and treatment methods to provide decision-making support for clinical diagnosis and integrated treatment planning.

1.1 Basis and Principles for Development

This guideline was developed following the procedures and methods outlined in the *WHO Handbook for Guideline Development (2nd Edition)* [11], under the guidance of the Group Standard Management Measures of the China Association of Chinese Medicine, and in accordance with the rules specified in GB/T 1.1 –2020 *Standardization Work Guidelines Part 1: Structure and Drafting of Standardization Documents* [12] and the *Guiding Principles for Developing/Revising Clinical Diagnosis and Treatment Guidelines in China (2022 Edition)* [13].

1.2 Initiating and Supporting Organizations

This guideline was issued by the China Association of Chinese Medicine on June 14, 2023, with the standard number T/CACM 1523-2023. The China Association of Chinese Medicine is responsible for implementation, with the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College taking the lead, and support from 24 medical institutions nationwide including Dongzhimen Hospital of Beijing University of Chinese Medicine, China-Japan Friendship Hospital, and Guang' anmen Hospital of the China Academy of Chinese Medical Sciences.

1.3 Working Groups and Conflict of Interest

The guideline development was completed jointly by the Guideline Expert Group, Guideline Working Group, and Guideline Secretariat, covering experts in TCM internal medicine, integrated oncology, and oncology. All participants signed a unified conflict of interest statement declaring no direct or indirect financial or non-financial conflicts with the guideline content.

1.4 Scope and Target Population

This guideline applies to tertiary hospitals, secondary hospitals, and community or primary healthcare institutions, and is intended for reference by TCM, integrated TCM-Western medicine, and Western medicine physicians nationwide. The target population consists of patients with non-primary bone malignancies that have metastasized to bone via hematogenous spread, resulting in bone destruction and pain as the main clinical features.

1.5 Identification of Clinical Questions

The project team organized multiple discussions regarding the guideline content and scope, ultimately determining that the guideline would address patients with secondary malignant bone tumors and focus on integrated traditional Chinese and Western medicine diagnosis and treatment. Based on this, the drafting group initially formulated clinical questions through literature review and clinical discussion, which were finalized using expert questionnaires.

Primary outcome measures included: (1) severity of bone metastasis pain (assessed by scoring scales); (2) changes in bone lesions (confirmed by X-ray and bone scan). Secondary outcome measures included: (1) clinical effectiveness (bone pain symptoms, emotional symptoms, sleep symptoms, etc.); (2) quality of life (e.g., quality of life scales); (3) dosage and adverse reactions of Western analgesics; and (4) study types: guidelines, consensus statements, systematic reviews/Meta-analyses, RCTs, and empirical summaries. Exclusion criteria were: (1) RCTs with modified Jadad score $ $3; (2) animal experiments; (3) duplicate publications; (4) studies with erroneous or incomplete data; and (5) studies with incomplete prescriptions or dosages that could not be merged by treatment principle.

1.6 Literature Search, Screening, and Synthesis

1.6.1 Search Strategy For the finalized clinical questions included in the guideline, a systematic search was conducted using a combination of subject headings and free-text terms following the PICOS principle. The search covered CNKI, WanFang, VIP, CBM, PubMed, The Cochrane Library, and Embase databases to collect literature related to the guideline questions, primarily including guidelines, consensus statements, systematic reviews/Meta-analyses, and randomized controlled trials (RCTs). High-quality relevant literature was supplemented for questions without search results to form consensus recommendations. The search timeframe was from database inception to April 10, 2025.

1.6.2 Evidence Screening and Data Extraction 1.6.2.1 Methods: Based on the predetermined inclusion and exclusion criteria established by the guideline working group, two researchers independently conducted literature screening and documented the complete literature exclusion process. Discrepancies were resolved by a third researcher. The process was as follows: (1) In the initial screening phase, literature was excluded based on retrieved information (title, abstract, etc.); full texts were obtained for questionable or potentially eligible literature. (2) In the full-text screening phase, potentially eligible literature from the initial screening was carefully read and analyzed according to the predetermined inclusion and exclusion criteria to determine final eligibility. (3) For included literature, basic information was collected and quality assessment was performed.

1.6.2.2 Inclusion and Exclusion Criteria: Inclusion criteria were: (1) Study subjects: patients with pathologically confirmed malignant tumors and bone metastasis; (2) Interventions: control group receiving conventional Western medicine or placebo, experimental group receiving additional TCM interventions; (3) Outcome measures: at least one primary or secondary outcome measure. Primary outcomes: (1) severity of bone metastasis pain (by scoring); (2) bone lesion changes (by X-ray and bone scan). Secondary outcomes: (1) clinical effectiveness (bone pain, emotional, sleep symptoms); (2) quality of life; (3) dosage and adverse reactions of Western analgesics; (4) study types: guidelines,

consensus statements, systematic reviews/Meta-analyses, RCTs, and empirical summaries. Exclusion criteria: (1) RCTs with modified Jadad score $ $3; (2) animal experiments; (3) duplicate publications; (4) studies with erroneous or incomplete data; (5) studies with incomplete prescriptions or dosages that could not be merged by treatment principle.

1.6.3 Evidence Synthesis Systematic reviews or Meta-analyses with AMSTAR score >8 and publication date $ $2 years were directly included. Those with AMSTAR score < 8 or publication date > 2 years were updated. RCTs with modified Jadad score > 3 were used for systematic review or Meta-analysis as required. RevMan 5.3 software was used for Meta-analysis. For dichotomous variables, relative risk (RR) was used as the effect measure; for continuous variables, $ 50^{2}> 50 $0.1), a random-effects model was used.

1.7 Evidence Grading and Recommendation Formulation

Evidence bodies were graded according to the TCM clinical evidence grading standards and TCM literature evidence grading standards (see appendix). Recommendations and consensus suggestions were established using the nominal group technique and Delphi method. The process was as follows: preliminary recommendations were drafted and surveyed among 27 integrated medicine experts from tertiary hospitals across 20 provinces. For evidence-based items, experts independently completed the *Consensus Recommendation Voting Form* using GRADE grid voting to determine final recommendations. For items without evidence support, experts completed the *Consensus Suggestion Voting Form*, with final suggestions determined by majority vote (>50% approval).

1.8 Guideline Drafting and External Review

The working group drafted the initial guideline manuscript based on the RIGHT framework [14], which was revised and finalized after internal and external expert review and public comment.

1.9 Guideline Dissemination and Implementation

After approval, the guideline will be publicly released on platforms such as CNKI and promoted internationally. The working group will conduct online training sessions to facilitate understanding and application among clinicians and researchers. The guideline will be piloted in 24 domestic hospitals to collect feedback from patients and physicians. Additionally, a database for integrated Chinese and Western medicine management of secondary malignant bone tumors will be established under the National Cancer Center' s big data platform to collect advanced resources and facilitate exchange.

2.1 Normative References

The following documents are indispensable for the application of this guideline. For dated references, only the cited version applies; for undated references, the latest version (including all amendments) applies: - *Clinical Terminology of Traditional Chinese Medicine Part 1: Diseases* (GB/T 16751.1–2023) [15] - *Clinical Terminology of Traditional Chinese Medicine Part 2: Patterns* (GB/T 16751.2–2021) [16] - *Clinical Terminology of Traditional Chinese Medicine Part 3: Treatment Methods* (GB/T 16751.3–2023) [17] - *Pharmacopoeia of the People' s Republic of China* (2020 Edition) [18] - *National Essential Medicines List* (2018 Edition) [19] - *International Classification of Diseases 11th Revision (ICD-11) Chinese Version* (2018 Edition) [20]

2.2 Terms and Definitions

Secondary malignant bone tumor: A disease caused by hematogenous metastasis of malignant tumors originating outside bone tissue, resulting in bone damage and pain as the main manifestations.

2.3 Epidemiological Characteristics

Secondary malignant bone tumors result from metastasis of primary tumor cells to bone and are a common complication of cancer [21]. Bone tissue is the most frequently involved organ and the third most common site of distant metastasis. Studies show bone metastasis occurs in 70% of breast cancer and 90% of prostate cancer cases [22], with nearly all malignant tumors capable of metastasizing to bone. Secondary malignant bone tumors can cause SREs including pain, pathological fractures, spinal cord compression, and hypercalcemia [7], with pain being the predominant manifestation that severely impacts patients' quality of life and survival. Clinical efficacy of medication alone for secondary malignant bone tumors is limited, with poor prognosis. Multiple studies demonstrate that integrated traditional Chinese and Western medicine plays an important role in treatment, making comprehensive integrated management clinically significant [4-6].

2.4 Etiology and Pathogenesis

2.4.1 Western Medicine Etiology and Pathogenesis Secondary malignant bone tumors occur when malignant tumor cells metastasize from the primary site via lymphatic or hematogenous routes. Breast, lung, kidney, and prostate cancers are common primary tumors that metastasize to bone [23]. Bone metastasis is attributed to the hematological characteristics of the bone microenvironment and tumor cell homing tendencies. The process involves four steps: tumor cell colonization on bone surfaces, dormancy, reactivation, and proliferation [24]. Metastatic cancer cells erode blood vessels, enter the venous system, and ultimately colonize the bone marrow cavity, where they stimulate

angiogenesis. Once established, tumor cells activate osteoclasts, leading to bone resorption [23].

2.4.2 Traditional Chinese Medicine Etiology and Pathogenesis In TCM, the core pathogenesis of secondary malignant bone tumors involves kidney essence deficiency, malnourishment of collaterals, and intermingled phlegm and blood stasis obstructing the collaterals. The primary cause is chronic disease damaging the kidney, leading to kidney essence depletion and bone marrow malnourishment. Additionally, chronic illness causes collateral stasis, resulting in retention of cancer toxins. Although the disease originates in the kidney, it is closely related to dysfunction of multiple viscera. The pathological characteristics manifest as deficiency as the root and excess as the branch, with mixed deficiency-excess patterns, typically showing systemic weakness with local pathogen accumulation.

Pain from secondary malignant bone tumors can be summarized by two mechanisms: "pain due to obstruction"and "pain due to malnourishment."Pain due to obstruction" occurs when external pathogens invade, causing struggle between pathogenic and healthy qi, leading to abnormal qi and blood flow in viscera and meridians, resulting in qi stagnation, blood stasis, and phlegm coagulation that obstruct collaterals and cause pain. "Pain due to malnourishment" results from long-term tumor invasion gradually consuming healthy qi, leading to insufficient qi and blood production that fails to nourish viscera and meridians, causing dysfunction and pain.

3.1 Western Medicine Diagnosis

Recommendation: During diagnosis, fully utilize modern Western examination techniques for precise localization and characterization while integrating TCM' s holistic concept and pattern differentiation for comprehensive assessment.

3.1.1 Diagnostic Criteria Diagnosis of secondary malignant bone tumors typically requires meeting one of two conditions: (1) Symptomatic patients: clinical symptoms such as bone pain, pathological fracture, or nerve compression plus one imaging modality showing clear metastatic signs support the diagnosis. (2) Asymptomatic patients: at least two imaging examinations showing metastatic changes are required. Imaging should demonstrate typical metastatic manifestations and differentiate from other conditions such as infection, osteoporotic fractures, or primary bone tumors. Pathological biopsy is indicated when diagnosis is uncertain.

Pathological biopsy is the gold standard for diagnosis but is not routinely recommended. Biopsy is indicated when multiple primary tumors coexist

and imaging cannot determine the source of bone destruction, as immunohistochemistry/molecular pathology can identify the primary tumor and guide systemic therapy. When previously controlled tumors develop new bone lesions, biopsy is needed to exclude post-radiation osteonecrosis, benign bone disease, or second primary malignancies to avoid misdiagnosis. For planned targeted/immunotherapy, biopsy tissue is needed for next-generation sequencing (NGS), programmed death-ligand 1 (PD-L1), receptor status, etc., to match precise treatment protocols. For planned aggressive procedures such as en bloc spinal/extremity tumor resection, radiofrequency ablation, or bone cement augmentation, pathological confirmation by biopsy is mandatory to ensure treatment rationality and avoid unnecessary trauma.

3.1.2 Clinical Manifestations Histopathology or cytology confirming malignancy accompanied by SREs—a series of complications from bone metastasis —with typical manifestations including pathological fractures, spinal cord compression, or bone radiation and orthopedic surgery (such as fracture reduction or spinal deformity correction) implemented due to treatment needs [10].

3.1.3 Laboratory Tests Bone biomarkers include bone alkaline phosphatase, microRNA, urinary N-terminal peptide (NTx), and C-terminal peptide (CTx) [25], supplemented by hematological tests such as complete blood count and tumor markers. MicroRNA is a class of non-coding small RNAs detectable during early bone invasion [26]. Serum alkaline phosphatase (ALP) and bone-specific alkaline phosphatase (BLP) can be used for early diagnosis of bone metastasis from breast tumors [27].

3.1.4 Imaging Examinations **3.1.4.1 X-ray:** As an initial imaging modality, X-ray is significant for detecting secondary bone tumors, with core value in early lesion sensitivity and biological information acquisition. However, it is not suitable for patients with metallic implants and has limited scanning range. Sensitivity for secondary malignant bone tumor diagnosis is 30%-50%, specificity 90%-95%. It is important for showing lesion location, extent, and basic features of bone destruction. Lytic lesions appear as moth-eaten changes, while blastic lesions appear as cotton-wool changes. However, bone destruction must reach a certain degree for detection, resulting in low sensitivity; therefore, it is not recommended for early screening [29].

3.1.4.2 CT: CT tomography is superior to X-ray, with sensitivity of 70%-85% and specificity of 80%-90% for secondary malignant bone tumor diagnosis. CT can present bone destruction details at high resolution, including cortical invasion extent and surrounding soft tissue masses, and accurately differentiate osteolytic or osteoblastic lesions. Bone metastases often show trabecular disruption, cortical discontinuity, and adjacent soft tissue masses that enhance to varying degrees on contrast scans. CT is also a key tool for assessing treatment response, precisely measuring tumor size and volume changes. Volume reduction is an important indicator of treatment efficacy. CT can observe morphological

changes from infiltrative/irregular to well-defined/regular patterns and assess changes in bone, soft tissue, and blood supply. However, soft tissue resolution is limited, and it is less sensitive than radionuclide tomography for whole-body metastasis screening.

3.1.4.3 ECT: ECT is the first choice for whole-body bone metastasis screening, with sensitivity of 72%-95% and specificity of 56%-70%, capable of detecting extensive bone metastases 3-6 months earlier than X-ray/CT [30]. It is primarily used for initial screening, assessing metastasis extent and number for staging, and monitoring treatment response by comparing uptake intensity changes. However, bone scans may yield false-negative results for osteolytic metastases and false-positive results during post-treatment repair or in non-metastatic bone diseases, and cannot provide detailed lesion location or distribution.

3.1.4.4 MRI: MRI is suitable for evaluating lesions in the spine, pelvis, and long bones, with sensitivity of 90%-95% and specificity of 85%-95%, making it the most sensitive technique for detecting bone marrow lesions. MRI clearly shows relationships between tumors and surrounding nerves, vessels, and other structures, providing important information for treatment planning. For spinal metastases, MRI accurately determines spinal cord invasion and assesses compression. Functional imaging, particularly diffusion-weighted imaging (DWI), is valuable. However, it is not suitable for patients with metallic implants and has limited scanning range.

3.1.4.5 PET-CT: PET-CT is commonly used for whole-body cancer screening, with sensitivity of 85%-95% and specificity of 85%-90%. It is particularly useful when the primary tumor is unknown, enabling comprehensive assessment of metabolic activity and cancer spread to identify tumor origin and stage. However, it is costly, cannot easily differentiate benign bone disease, and may yield false-positive results after recombinant human granulocyte colony-stimulating factor (rhG-CSF) administration.

3.1.4.6 Differential Diagnosis: Differentiating secondary malignant bone tumors from benign tumors, primary/second primary tumors, and post-treatment changes relies on combining morphological features, functional imaging, clinical context, and dynamic follow-up. Benign bone tumors often show well-defined margins without soft tissue masses, while secondary malignant tumors typically appear infiltrative with indistinct borders, cortical destruction, soft tissue masses, and high metabolism on PET-CT, often with a history of primary tumor [31]. Differentiating from primary or second primary tumors requires attention to location, age, and characteristic imaging features [32]. Post-treatment changes typically show sclerotic repair, clear margins, volume reduction or stability, and no new lesions; stability over 3-6 months of follow-up can confirm the diagnosis.

3.2 Traditional Chinese Medicine Diagnosis

Diagnostic criteria for secondary malignant bone tumors were formulated with reference to the "cancer disease" diagnostic criteria in the 14th Five-Year Plan textbook *Internal Medicine of Traditional Chinese Medicine* (2021 edition) [33].

4.1 Treatment Goals

For patients with malignant tumors metastasized to bone, integrated Chinese and Western medicine treatment aims to reduce tumor invasion and destruction of healthy bone, effectively alleviate bone metastasis pain, and reduce adverse reactions from Western medications to achieve toxicity reduction and synergistic enhancement. TCM advocates multiple combined modalities to improve symptoms, enhance quality of life, and reduce adverse reactions.

4.2 Integrated Chinese-Western Medicine Treatment Strategy

Integrated Chinese and Western medicine treatment has synergistic effects. TCM can reduce adverse reactions from Western medicine and enhance efficacy. Multiple studies [4-6] show that integrated treatment is more effective than TCM or Western medicine alone in managing complications (bone destruction, bone pain) and can effectively relieve adverse reactions from Western treatments.

4.3 Traditional Chinese Medicine Treatment

4.3.1 Syndrome Differentiation and Treatment 4.3.1.1 Qi Stagnation and Phlegm Obstruction Pattern - Symptoms: Local distending pain at bone metastasis sites with palpable masses (unchanged skin color, varying sizes); heavy limbs; chest and rib-side fullness, breast distension in women; limited limb movement; poor appetite; sticky mouth sensation; or cough with thick, white sputum; loose stools; pale dark tongue with white greasy coating; wiry slippery pulse. - **Treatment Principle:** Regulate qi, relieve depression, transform phlegm, and disperse nodules. - **Formula:** Recommended: Haiyu Yuhu Decoction [34] (Evidence level: Class 3; Recommendation strength: Grade III) (*Waike Zhengzong*): Zaoxiu, Banzhilian, Haizao, Kunbu, Huangyaozi, Danshen, Qingpi, Chenpi, Sheng Banxia (decoct first), Beimu, Lianqiao, Chuanxiong, Danggui.

4.3.1.2 Qi Stagnation and Blood Stasis Pattern - Symptoms: Stabbing pain at bone metastasis sites with fixed location, aggravated by pressure, chest and rib-side fullness, irritability or depression, frequent sighing; collateral blood stasis (purple lips, gums, nails, skin ecchymosis, or abdominal varices), subcutaneous petechiae; dry mouth with bitter taste; rough skin, numb limbs, irritability and forgetfulness, local sensory abnormalities; purple dark tongue or with petechiae, thin white coating, engorged sublingual veins; choppy or deep wiry pulse. - **Treatment Principle:** Move qi, activate blood, transform stasis,

and disperse nodules. - **Formula:** Recommended: Taohong Siwu Decoction [35] (Evidence level: 1B; Recommendation strength: Grade II) (*Yizong Jinjian*): Danggui, Baizhi, Taoren, Chishao, Chuanxiong, Zhi Caowu. - **Patent Medicine:** Tianchan Capsules [36-37] (National Drug Approval No. Z20123030) (Evidence level: 1B; Recommendation strength: Grade II) for mild to moderate cancer pain from lung, gastric, and liver cancers with qi stagnation and blood stasis pattern. - **Safety:** Two studies [36-37] reported adverse events. In one study [36], the Tianchan group had 7 cases of nausea/vomiting, 6 of dizziness, 2 of constipation, 1 of mild abdominal pain, and 1 of respiratory depression. The control group reported 18 adverse events including 8 cases of nausea/vomiting, 6 of dizziness, 2 of constipation, and 1 each of mild abdominal pain and respiratory depression. Adverse event rates were 21.7% (control) and 20.2% (treatment), with no statistically significant difference.

4.3.1.3 Qi and Blood Deficiency Pattern - **Symptoms:** Continuous pain at bone metastasis sites, numbness with preference for pressure, aggravated by movement; fatigue, pale lips and nails, pale complexion, shortness of breath, reluctance to speak; emaciation, spontaneous sweating worsened by activity; numb limbs, dizziness, palpitations, insomnia, forgetfulness, poor appetite, loose stools; women may have scanty pale menstruation; pale tender tongue; thin weak pulse. - **Treatment Principle:** Boost qi and nourish blood, support healthy qi and relieve pain. - **Formula:** Recommended: Bazhen Decoction [38] (Evidence level: 1B; Recommendation strength: Grade II) (*Ruizhutang Jingyan Fang*): Danggui, Chuanxiong, Baishao, Shudi, Renshen, Baizhu, Fuling, Zhigancao. - **Safety:** One study [38] reported adverse events: Bazhen Decoction group had 32 cases of thrombocytopenia, 19 of leukopenia, 35 of nausea/vomiting, 30, 28, 15, and 13 cases of other events. Overall adverse event rate was significantly lower than control ($P<0.05$). - **Patent Medicine:** Recommended: Gushukang Capsules [39-41] (National Drug Approval No. Z20060270) (Evidence level: 1A; Recommendation strength: Grade I). - **Safety:** One study [41] reported adverse events: Gushukang group had 1 case each of hip varus and spiral blade cut-out (3.51% total complications); control group had 1 case hip varus, 3 spiral blade cut-outs, 2 secondary femoral neck fractures, and 2 contralateral hip refractures (15.69% total). Complications were significantly lower in the Gushukang group ($P<0.05$).

4.3.1.4 Qi and Yin Deficiency Pattern - **Symptoms:** Fatigue, weakness, shortness of breath, reluctance to speak, palpitations with activity, accompanied by dry throat, mouth dryness, tidal fever, night sweats, scanty urine, dry stools; tender red tongue with teeth marks on edges, dry scanty coating; thin weak or empty rapid pulse. - **Treatment Principle:** Boost qi and nourish yin, support healthy qi and disperse nodules. - **Formula:** Shengmai Dihuang Decoction with modifications (Evidence level: Class 3; Recommendation strength: Grade III) (*Jinjian*): Shashen, Maidong, Wuweizi, Fuling, Danpi, Zexie, Fabanxia, Huangqin.

4.3.1.5 Yin Deficiency with Excessive Heat Pattern - **Symptoms:** Dull

pain at bone metastasis sites with five-center heat, bone steaming tidal heat; red lips and malar flush, irritability, night sweats, insomnia, emaciation, thirst, dry stools, short yellow urine; red tongue with scanty coating; thin rapid pulse. - **Treatment Principle:** Boost qi and nourish yin, clear heat and resolve toxins. - **Formula:** Recommended: Modified Qinggu San [42] (Evidence level: 1B; Recommendation strength: Grade II): Yinchaihu, Huhuanglian, Qinjiao, Biejia, Digupi, Zhimu, Gancao, Taoren, Banzhilian, Mohanlian, Nüzhenzi, Tubiechong, Wugong. - **Safety:** One study [42] reported adverse events: Modified Qinggu San group had 7 cases of constipation, 4 nausea, 1 vomiting, 4 dizziness, 5 somnolence, 2 urinary difficulty, 2 pruritus; control group had 16 constipation, 8 nausea, 4 vomiting, 8 dizziness, 13 somnolence, 4 urinary difficulty, 4 pruritus. No statistically significant difference in adverse event rates.

4.3.1.6 Spleen-Kidney Yang Deficiency Pattern - **Symptoms:** Cold or aching pain at local bone metastasis sites, worsened by cold and relieved by warmth; poor appetite, loose stools, sore weak lower back and knees; aversion to cold, cold limbs, clear abundant urine or nocturia; chronic diarrhea or dawn diarrhea; fatigue, loose muscles; pale swollen tongue with white slippery coating; deep slow weak pulse. - **Treatment Principle:** Boost qi, strengthen spleen, warm kidney, and disperse cold. - **Formula:** Bawei Shenqi Pill [43] (Evidence level: 1A; Recommendation strength: Grade I) (*Jingui Yaolue*): Gandihuang, Shanyao, Shanyurou, Zexie, Fuling, Mudanpi, Guizhi, Fuzi. - **Patent Medicines:** Quanduzhong Capsules [44] (National Drug Approval No. Z20055116) (Evidence level: 1B; Recommendation strength: Grade II); Xianling Gubao Capsules [45] (National Drug Approval No. Z20025337) (Evidence level: 1A; Recommendation strength: Grade I). - **Safety:** No adverse events were reported in included studies on Quanduzhong or Xianling Gubao Capsules.

4.3.1.7 Kidney Deficiency with Upright Qi Depletion and Stasis-Toxin Coagulation Pattern - **Symptoms:** Painful nodules at bone metastasis sites, sore weak lower back and knees, fatigue, dizziness, tinnitus, spontaneous and night sweats, irritability, insomnia, forgetfulness; pale red or purple dark tongue with petechiae, thin white or scanty coating; thin rapid or deep wiry pulse. - **Treatment Principle:** Tonify kidney and support upright qi, transform stasis, disperse nodules, resolve toxins, and relieve pain. - **Formula:** Recommended: Modified Yishen Gukang Formula [46] (Evidence level: 1B; Recommendation strength: Grade II): Shudihuang, Banzhilian, Shanyao, Jiushanyurou, Baihuasheshecao, Chaojiangcan, Mudanpi, Fuling, Zexie, Gusuibu. - **Safety:** One study [47] reported adverse events: Yishen Gukang group had 1 somnolence, 5 constipation, 3 nausea/vomiting; control group had 4 dizziness, 2 somnolence, 13 constipation, 9 nausea/vomiting. The Yishen Gukang group had significantly fewer adverse events ($P<0.05$). - **Patent Medicines:** Yishen Qutong Granules [48-49] (Evidence level: 1B; Recommendation strength: Grade II); Zhuanggu Zhitong Capsules [50-51] (National Drug Approval No. Z20050118) (Evidence level: 1B; Recommendation strength: Grade II). - **Safety:** Two studies [48-49] reported adverse events for Yishen Qutong Granules: one [49] had no adverse

events; the other [48] reported 1 somnolence, 5 constipation, 3 nausea/vomiting in the treatment group versus 4 dizziness, 2 somnolence, 13 constipation, 9 nausea/vomiting in the control group ($P<0.05$). For Zhuanggu Zhitong Capsules [50-51], adverse event rate was 4.85% (2 nausea, 1 flushing, 1 leg cramp, 1 palpitation) versus 12.62% in control (4 nausea, 3 flushing, 1 headache, 3 leg cramps, 1 palpitation, 1 rash) ($P<0.05$).

4.3.2 Acupuncture Treatment (Evidence level: 1B; Recommendation strength: Grade II) Indications: Cancer pain in secondary malignant bone tumor patients; patients undergoing chemotherapy or radiotherapy [52].

Treatment Approach: For cancer pain, use local tender point needling combined with meridian-based point selection: Baihui and Hegu for head pain; Feishu and Danzhong for chest pain; Zusanli and Qimen for abdominal pain; Jianjing or Jianyu for shoulder pain; Shenshu and Weizhong for spine/lower back pain; Huantiao and Biguan for pelvic pain; Yanglingquan and Sanyinjiao for lower limb pain. For post-chemoradiotherapy patients, use Dazhu, Xuanzhong, Zusanli, and Ashi points as main points, with Fenglong, Xuehai, and Sanyinjiao as adjunct points.

Course: Once daily, 15-minute needle retention [53-57], with 3-5 days constituting one treatment course.

4.3.3 Acupoint Injection (Evidence level: 1B; Recommendation strength: Grade II) Indications: Patients with secondary malignant bone tumors [58].

Treatment Approach: Point selection: Zusanli, Xuanzhong, Dazhu, Xuehai, Taixi, Ashi, Houxi, Ququan [59]. Main point: Xuanzhong. Adjunct points: Kongzui for lung cancer bone metastasis; Zhongdu for liver, breast, thyroid, or prostate cancer; Liangqiu for gastric cancer; Diji for intestinal cancer; Zhubin for kidney or bladder cancer. Medications: Compound Danshen Injection [60] or morphine [58] can be used.

Course: 1 mL per point, once every 2 days.

4.3.4 Music Therapy (Evidence level: 1B; Recommendation strength: Grade II) Indications: Secondary malignant bone tumor patients with negative emotions (anxiety, fear, depression) or insomnia [61].

Treatment Approach: Based on Five Elements theory, select Gong, Shang, Jiao, Zhi, or Yu mode music corresponding to the patient' s constitution according to the "homologous resonance" principle. For mixed patterns, adjust musical modes accordingly. Position patients comfortably in a quiet, softly lit room with irrelevant sounds and lights turned off. Maintain volume at 30-45 dB for patient comfort. Play music twice daily (morning and afternoon), approximately 30 minutes per session, with 3-5 pieces per session [62-67].

See Table 1 for detailed music therapy recommendations and Figure 1 [Figure 1: see original paper] for Five Elements pattern differentiation.

4.4 Western Medicine Treatment

4.4.1 Overview This section references the *ESMO Clinical Practice Guidelines: Bone Health in Cancer* (2020 edition) [7], *NCCN Guidelines: Prostate Cancer* (2021 edition) [26], and *Expert Consensus on Refractory Cancer Pain* (CRPC, 2017 edition, Interpretation III: Bone Metastasis Pain) [9].

Western interventions for secondary malignant bone tumors include pharmacological and non-pharmacological strategies. Pharmacological approaches combine cytotoxic chemotherapy, bone-targeted agents (bisphosphonates, denosumab), NSAIDs, and opioid analgesics. Non-pharmacological approaches involve radiotherapy and surgical management. Clinical practice requires comprehensive assessment of patients' systemic condition and lesion characteristics to develop individualized protocols that maximize pain relief and improve quality of life.

4.4.2 Pharmacological Treatment 4.4.2.1 Bone Protection Drugs: These target osteoclasts, osteoblasts, and the bone microenvironment. Osteoclast-targeting agents include bisphosphonates, denosumab, dasatinib, odanacatib, and everolimus. Osteoblast-targeting agents include atrasentan. Systematic reviews show denosumab and bisphosphonates have significant efficacy [68].

Recommendation: Initiate bone protection drugs at bone metastasis diagnosis and continue throughout treatment, even in asymptomatic patients [69]. Zoledronic acid: 4 mg intravenous infusion over >15 minutes, once every 4 weeks, with calcium and vitamin D supplementation. Denosumab: 120 mg subcutaneous injection (upper arm, thigh, or abdomen), once every 4 weeks [70].

4.4.2.2 Opioid Analgesics: Pain from secondary malignant bone tumors includes persistent pain at rest, spontaneous breakthrough pain, and movement-evoked breakthrough pain [71]. Resting bone pain is assessed using standard cancer pain evaluation; spontaneous and evoked pain can be assessed using breakthrough pain methods [72].

The WHO three-step analgesic ladder is followed. Mild pain: Step 1 with non-opioids (NSAIDs). Moderate pain: Step 2 with weak opioids (codeine, tramadol) ± NSAIDs. Severe pain: Step 3 with strong opioids (morphine, oxycodone). Adjuvant medications can be used at each step. Short-acting morphine is dosed at 10%-20% of the previous 24-hour total; if needed >3 times daily, retitrate the analgesic dose. See Figure 2 [Figure 2: see original paper] for the treatment algorithm.

4.4.3 Non-Pharmacological Treatment 4.4.3.1 Radiotherapy: Highly effective for secondary malignant bone tumors, with reported local external beam response rates of approximately 85%, with complete pain relief in half of patients. Pain relief typically occurs rapidly, with >50% of patients benefiting within 1-2 weeks [73]. I-131 is used for follicular thyroid cancer bone metastasis [74]; 89Sr, 153Sm, and 223RaCl2 are also commonly used [75]. A randomized controlled study showed median overall survival of 14.9 months with 223Ra versus 11.3 months with placebo; median time to first SRE was longer with 223Ra (15.6 vs 9.8 months, HR=0.66, 95%CI=0.52-0.83, P<0.001), and 223Ra reduced the need for external beam radiotherapy for bone pain (HR=0.52, 95%CI=0.53-0.85) [76].

Recommended dose fractionation for previously unirradiated painful bone metastases: 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or single 8 Gy dose [77].

4.4.3.2 Surgery: Decompression and fixation surgery combined with postoperative radiotherapy may be considered for selected patients with single-level spinal cord compression or spinal instability, excluding those with very short expected survival. Kyphoplasty and vertebroplasty are suitable for osteolytic metastases and spinal instability in patients who cannot tolerate or have no indication for surgery [78]. For long bone metastases, common procedures include screw/plate fixation with or without bone cement, and joint arthroplasty. Selection depends on metastasis location, bone defect extent, and tumor sensitivity to systemic therapy. Principles include: screws preferred for lower limbs, plates for upper limbs; extend fixation length to reduce fracture risk at other sites [79].

4.4.3.3 Hyperthermia: Physical energy is applied to heat tumor tissue to therapeutic temperatures for sustained periods. Based on differential temperature tolerance between normal and cancerous tissue, this achieves direct cancer cell killing, apoptosis induction, immune enhancement, and pain relief without damaging normal tissue. Hyperthermia combined with TCM enhances treatment efficacy [80-82].

4.5 Management of Adverse Reactions

4.5.1 Radiotherapy Adverse Reactions 4.5.1.1 Radiation Enteritis: TCM considers radiation enteritis as root deficiency with branch excess—deficiency primarily involving spleen-kidney deficiency, excess involving damp-heat-stasis intermingling [83]. Treatment focuses on supplementing spleen-kidney, clearing damp-heat, and resolving toxins-stasis, using Wumei Pill combined with Sijunzi Decoction (Evidence level: 1B; Recommendation strength: Grade II) [83]. External TCM methods such as herbal enema, acupuncture, and acupoint injection (Evidence level: 1A; Recommendation strength: Grade I) are also recommended [84].

4.5.1.2 Myelosuppression: TCM considers radiation as having hot-yang toxin properties that damage yin fluids, consume healthy qi, and scorch body fluids. It also damages spleen-stomach function, interfering with qi-blood generation [85]. Treatment focuses on supplementing qi and nourishing blood, strengthening spleen and stomach, and nourishing liver-kidney, using Danggui Buxue Decoction [86] (Evidence level: 1B; Recommendation strength: Grade II), Bazhen Decoction [87-89] (Evidence level: 1B; Recommendation strength: Grade II), Siwu Decoction [90] (Evidence level: 1B; Recommendation strength: Grade II), and Shiquan Dabu Decoction [91] (Evidence level: 1B; Recommendation strength: Grade II).

4.5.1.3 Radiation Dermatitis: Most patients develop skin damage during radiotherapy, manifesting as erythema, ulceration, scarring, hyperpigmentation, and hair loss. Vitamin B12, triethanolamine cream, and recombinant human epidermal growth factor are recommended [92-93]. Acupuncture, fumigation, compresses, plasters, umbilical therapy, physical therapy, and medicinal baths may be used, with Simiao Yong' an Ointment or Oil [94-96] (Evidence level: 1B; Recommendation strength: Grade II), Zicao Ruyi Jinhuang Ointment [97] (Evidence level: 1B; Recommendation strength: Grade II), and Baizhi Aloe Vera Gel [98] (Evidence level: 1B; Recommendation strength: Grade II).

4.5.2 Bone Protection Drug Adverse Reactions 4.5.2.1 Fever: Bisphosphonates commonly cause fever, pain, flu-like symptoms, and hypocalcemia leading to headache, myalgia, and arthralgia. NSAIDs are recommended for symptom relief [99], possibly combined with Guizhi Decoction (Evidence level: 1B; Recommendation strength: Grade II) [100]. For hypocalcemia, calcium gluconate injection and active vitamin D supplementation are recommended [101].

4.5.2.2 Osteonecrosis of the Jaw: The incidence of bisphosphonate-related osteonecrosis of the jaw has increased [102]. Xianfang Huoming Drink [103] (Evidence level: Class 3; Recommendation strength: Grade III) is recommended: Sheng Huangqi 60g, Jinyinhua 60g, Zhe Beimu 10g, Danggui 15g, Tianhuafen 12g, Baizhi 10g, Chenpi 6g, Fangfeng 10g, Zhi Ruxiang 6g, Zhi Moyao 6g, Zaojiaoci 6g, Chishao 30g, Shengyiyiren 30g, Qing Banxia 8g, Jiegeng 10g.

Evidence Grading and Recommendation Strength [104-106]

Evidence Level	Study Design	Quality	Recommendation Strength	Evidence Basis	Consensus	Interpretation
1A	Large-sample RCTs, Meta-analyses	High	I	1A and some 2A	Expert consensus ($ 80 $80% support)	Possibly reasonable, unclear; benefits not less than risks
2B	Non-standardized expert consensus, retrospective case series, historical controls	Low	Not recommended	Any category	Expert consensus	Not recommended, ineffective, should not be implemented; benefits less than risks
3	Case reports, empirical summaries	Low				

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Table 1 and **Figure 1** [Figure 1: see original paper] are referenced in the text but not reproduced here. **Figure 2** [Figure 2: see original paper] illustrates the WHO three-step analgesic ladder for bone metastasis pain management.
