Efficacy and Safety of Qibei Jiedu Formula Versus Placebo in Preventing and Managing Acute Radiation Dermatitis in Breast Cancer Patients: A Prospective, Double-blind, Randomized Controlled Trial

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I. Research Background and Objectives

1.1 Research Background

As the most prevalent malignant tumor among women globally, breast cancer is showing a continuous increase in disease burden [1]. The latest epidemiological data from the China National Cancer Center in 2024 indicate that the standardized incidence rate of breast cancer in China has reached 40 per 100,000, ranking first among female malignant tumors, with the onset age being approximately 10 years earlier than in Western countries, demonstrating a significant trend toward younger patients [2]. This disease not only severely threatens patients 'lives and health but also imposes a heavy dual burden on patients' families and the social healthcare system due to its long treatment cycle and high costs. Modern breast cancer treatment has established a comprehensive therapeutic model based on surgery, combined with radiotherapy, chemotherapy, endocrine therapy, and targeted therapy through multidisciplinary collaboration. Among these, radiotherapy serves as a key means for local control, with approximately 70% of breast cancer patients requiring radiotherapy intervention.Extensive clinical evidence has demonstrated that standardized radiotherapy can significantly reduce the local recurrence rate and improve the 5-year survival rate to over 85% [3]. However, while radiation effectively kills tumor cells, it inevitably causes damage to normal tissues, leading to treatment-related toxicities that pose a major clinical challenge.

Acute radiation dermatitis, as the most common adverse reaction of radiotherapy, is pathologically characterized by an inflammatory cascade reaction in skin tissues induced by ionizing radiation. Clinical data indicate that over 95% of breast cancer patients undergoing radiotherapy experience varying degrees of skin damage, manifested as progressively worsening erythema, edema, and desquamation [4].According to the CTCAE grading criteria, grade 1-2 dermatitis may cause patients discomfort such as pruritus and burning pain, significantly affecting quality of life. Severe dermatitis of grade 3 or higher may lead to secondary complications such as skin ulcers and bacterial infections, forcing approximately 15-20% of patients to adjust their radiotherapy regimens, which directly impacts tumor control efficacy [5]. The prevention and management of these complications have become critical clinical challenges in the field of breast cancer radiotherapy.

The pathogenesis of acute radiation dermatitis involves multifactorial interactions, with a

complex pathophysiological process. At the molecular level, ionizing radiation directly damages the DNA structure of basal cells and hair follicle cells in the skin, leading to programmed cell death through activation of the p53-dependent apoptosis pathway. Concurrently, radiation disrupts the dermal microvascular system, causing endothelial cell injury and increased capillary permeability, which results in local tissue ischemia and hypoxia. This subsequently triggers the activation of inflammatory signaling pathways such as NF-κB, promoting the massive release of pro-inflammatory factors like IL-6, thereby inducing a sustained inflammatory response [6,7]. Clinical practice has demonstrated that the risk of radiation dermatitis is closely associated with multiple critical factors. In terms of treatment, the total radiation dose (particularly>40Gy) significantly increases the risk, influenced by factors such as fractionated dose, irradiation field size, and radiotherapy techniques. On the patient side, elderly individuals are more prone to impaired skin repair capacity, and comorbidities such as diabetes mellitus also elevate the incidence and severity of acute radiation dermatitis [6,8]. Currently, clinical management of acute radiation dermatitis remains challenging. Conventional treatments primarily employ symptomatic strategies, including topical corticosteroids to suppress inflammatory responses, antibiotic ointments to prevent secondary infections, and hyaluronic acid-containing moisturizers to repair the skin barrier. However, these methods have significant limitations: long-term use of glucocorticoids may lead to adverse effects such as skin atrophy and telangiectasia; antibiotic misuse can cause dysbiosis and drug resistance; and simple moisturization therapy often fails to interrupt the inflammatory cascade [8]. In recent years, with a deeper understanding of the molecular mechanisms of radiation dermatitis, novel therapeutic strategies have emerged. Recombinant human epidermal growth factor (rhEGF) can accelerate wound healing by promoting keratinocyte proliferation [9]; low-intensity laser therapy (LLLT) can modulate local immune function and reduce inflammatory responses [10]; mesenchymal stem cell exosomes have also demonstrated promising tissue repair potential [11]. However, these innovative therapies are still largely in clinical trial stages, and issues such as efficacy stability, treatment costs, and long-term safety require further validation. This situation highlights the urgent need to develop safer and more effective prevention and treatment strategies.

Traditional Chinese Medicine (TCM) has extensive experience and unique advantages in

treating radiation dermatitis. TCM posits that the occurrence of acute radiation dermatitis can be classified under the categories of "drug toxicity" and "drug eruption" [12,13]. The core pathogenesis is "deficiency of both qi and yin, with mutual accumulation of stasis and toxicity." Treatment should focus on replenishing qi and nourishing yin, dispelling wind and activating blood circulation, as well as detoxifying and resolving turbidity. The Qibei Jiedu Formula is a compound herbal formula based on the TCM theory of "strengthening the body's defenses, removing stasis, and detoxifying." Its main components include Astragalus membranaceus, Rehmannia glutinosa, Hedyotis diffusa, Gleditsia sinensis, Euphorbia hirta, Lithospermum erythrorhizon, Tribulus terrestris, stir-fried Shenqu, and raw licorice. The herbal formula is composed of Astragalus membranaceus as the principal herb, which tonifies qi, strengthens defensive qi, and supports toxin elimination to promote tissue regeneration; Rehmannia glutinosa for cooling blood and promoting fluid production; Hedyotis diffusa for detoxification and abscess resolution; Gleditsia sinensis for wound healing and turbid fluid resolution; and Cynanchum wilfordii for wind-dispelling, collaterals dredging, and dysentery relief, collectively serving as ministerial herbs. Lithospermum erythrorhizon assists Rehmannia glutinosa and Hedyotis diffusa in cooling blood and detoxification, while Tribulus terrestris supports Gleditsia sinensis and Cynanchum wilfordii in liver regulation, wind-dispelling, and rash resolution. Fried Shenqu (Saccharomyces cerevisiae) aids digestion and harmonizes the stomach, while serving as a counterbalance to prevent cold-induced stomach injury. Glycyrrhiza uralensis acts as the messenger herb, tonifying qi, detoxifying, and harmonizing the other herbs. Preliminary clinical observations and small-sample studies suggest that the Astragalus and Tribulus Detoxification Formula demonstrates significant clinical value in treating moderate-to-severe acute radiation dermatitis through synergistic effects of toxin support and tissue regeneration, dampness absorption and wound healing, and blood-activating and wind-dispelling. This formula not only effectively alleviates acute symptoms such as skin erythema, exudation, and pain but also promotes the repair and regeneration of damaged skin, significantly improving patients' quality of life. Therefore, our research team plans to initiate a small-scale exploratory clinical trial, primarily aiming to provide preliminary efficacy and safety data for subsequent large-scale clinical studies. The results will guide the estimation of effect sizes and hypothesis generation for future trials, laying the foundation for rigorous large-sample, multicenter randomized controlled clinical trials

to scientifically evaluate the efficacy, dose-response relationship, and long-term safety of this formula, thereby providing higher-level evidence-based medicine for its clinical application.

1.2 Research Objective

1.2.1 Evaluate the preventive and therapeutic effects of Qibei Jiedu Formula on acute radiation dermatitis in breast cancer patients, including the incidence of grade 2 or higher radiation dermatitis, wound healing time, and symptom relief.

1.2.2 Observation of the safety of Qibei Jiedu Formula.

1.2.3 Investigate the potential role of Qibei Jiedu Formula in improving patients' quality of life.

1.2.4 Exploring the potential mechanisms of Qibei Jiedu Decoction in the prevention and treatment of acute radiation dermatitis in breast cancer patients (through exploratory indicators such as inflammatory factors and skin microbiota).

1.2.5 This study is a small-scale exploratory clinical trial designed to obtain preliminary efficacy and safety data from 60 subjects, evaluating the "loading effect" of Qibei Jiedu Formula on "standard basic treatment". It aims to provide effect size estimation and hypothesis generation basis for subsequent large-scale studies, rather than to draw confirmatory conclusions.

II. Research Protocol

2.1 Case Source

A total of 60 breast cancer patients who met the inclusion and exclusion criteria and were admitted to the radiotherapy ward of the Cancer Hospital of the Chinese Academy of Medical Sciences from October 2025 to December 2026 were enrolled in the study.

2.2 Diagnostic Criteria

2.2.1 Western Medical Diagnostic Criteria

① Diagnostic criteria for breast cancer: Refer to the "CSCO Guidelines for the Diagnosis and Treatment of Breast Cancer" (2024 edition) [14].

②Radiation dermatitis: According to the grading criteria of the Common Toxicity Criteria for Adverse Events (CTCAE 5.0) in the United States, the radiation dermatitis in this study was classified as follows:

Table 1 CTCAE 5.0 Grading Criteria for Radiodermatitis

classify	clinical manifestation
Level 1	Mild erythema or dry desquamation
Level 2	Moderate to severe erythema; patchy moist desquamation, mostly localized to wrinkles and folds; moderate edema
Level 3	Wet desquamation is not limited to wrinkles and folds; it may also result from minor injuries or friction-induced bleeding.
Level 4	Life-threatening; skin necrosis or true-layer ulceration; bleeding from the affected area; requires skin grafting

2.2.2 Traditional Chinese Medicine Diagnostic Criteria

The TCM syndrome scale was developed with reference to the Clinical Research Guidelines for New Traditional Chinese Medicine Drugs (2002 Edition) [15], the Diagnosis and Treatment Guidelines for Malignant Tumors in Traditional Chinese Medicine [16], and Traditional Chinese Medicine Surgery [17].

Based on the patient's symptoms, when two of the two primary symptoms listed in the table are present, or one primary symptom accompanied by two secondary symptoms, and both primary and secondary symptoms simultaneously meet any of the following conditions, the syndrome can be diagnosed as "Qi-Yin Deficiency with Stasis-Toxin Interconnection Syndrome":

①Main symptoms: fatigue, chest tightness and shortness of breath, heat in the palms, soles and chest, dry mouth and throat; Main symptoms: localized pain, skin and nails

① Main symptoms: fatigue, chest tightness and shortness of breath, heat in the palms, soles and chest, dry mouth and throat; Secondary symptoms: dark lips, nails and complexion, subcutaneous ecchymosis

② Main symptoms: localized pain, skin and nail disorders + secondary symptoms; fever with sweating, irritability and insomnia, scanty dark urine, dry and hard stools

Table 2 Scale for Syndrome of Deficiency of Both Qi and Yin with Mutual Combination of Stasis and Toxin

Quantitative Scoring Table for TCM Syndrome Classification					
symptom		**None (0 point)**	**Mild (2 points)**	**Moderate (4 points)**	**Severe (6 points)**
cardinal symptom	**exhaustion**	not have	exertion leads to exhaustion	exertion leads to exhaustion	No movement, no fatigue
	chest tightness	not have	Shortness of	Shortness of	No movement,

	and shortness of breath		breath after activity	breath with slight movement	no shortness
	dysphoria in chestpalms-soles	not have	palmar and plantar hyperthermia	Exposure of limbs beyond clothing	coldness in hands and feet relieved by grasping cold objects
	dry mouth and throat	not have	light	Drinking water can alleviate the symptoms.	drinking without relieving
	localized pain	not have	Occasional occurrence, may resolve spontaneously within 30 minutes	The pain duration is less than 3 hours per day, and tenderness is pronounced upon palpation.	persistent pain, severe pain
	squamous and dry skin	not have	rough and dry skin	rough, dry skin with darkening of color	rough, dry skin with darkening of skin color, accompanied by subcutaneous ecchymoses and petechiae
symptom		**None (0 point)**	**Mild (1 point)**	**Moderate (2 points)**	**Severe (3 points)**
minor symptom	**febrile sweating**	not have	Occasionally	Recurrent chest and back heat flashes	Generalized hot flashes, profuse sweating, frequently occurring
	restless sleep	not have	Occasional irritability with easy awakening during sleep	restless and difficulty falling asleep	Restless and sleepless all night
	lip color	not have	dull coloration of the lip and nail	dark purple coloration of the lip and nail	dull and bluish-purple coloration of the lip and face
	ecchymosis	not have	1 site	2 sites	3 or more sites
	oliguria with reddish urine	not have	yellow urine	yellowish-red urine with a sensation of heat	dull and scanty urine with yellowish-red color and burning

					sensation
	dry stool	not have	dry stool, one per day	Constipation, occurring every two to three days	difficult defecation, once every few days

2.2.3 Drainage Standards

Inclusion criteria:

① Patients with pathologically confirmed unilateral stage I-III non-invasive breast cancer who have undergone breast-conserving surgery or modified radical mastectomy for breast cancer, and who have received or plan to receive standard postoperative adjuvant therapy (according to the latest clinical guidelines);

② Adopt postoperative adjuvant radiotherapy, with the patient scheduled to receive a high-dose fractionation regimen of 40-50 Gy/15 fractions based on the recommended radiation target dose from the National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines and the CSCO Guidelines for the Diagnosis and Treatment of Breast Cancer (2024 edition).

③Conform to the syndrome of deficiency of both qi and yin with mutual accumulation of blood stasis and toxins;

④Karnofsky Performance Score (KPS) ≥70 points;

⑤ Age ≥18 years, female;

⑥Voluntary participation in the study and signing of the informed consent form.

Exclusion criteria:

① Patients with grade 4 radiation dermatitis present at enrollment or developing during the study requiring emergency intervention;

② Received radiotherapy to the breast or chest within the past 3 months;

③ Any skin disease or condition that may interfere with the assessment of radiation dermatitis, such as active infection, atopic dermatitis, psoriasis, vitiligo, active collagen vascular diseases (e.g., scleroderma, systemic lupus erythematosus), or other autoimmune diseases known to significantly alter skin appearance or physiological responses;

④ Pre-treatment liver or kidney dysfunction of grade 2 or above or hematologic toxicity

(meeting the CTCAE 5.0 grading criteria):

⑤ Currently participating in other clinical trials or concurrently using other traditional Chinese medicine preparations;

⑥ Unstable mental state, unable to cooperate with the study;

⑦Pregnant and lactating patients;

⑧ Patients with known hypersensitivity to any component of the Chinese herbal medicines used in this study.

2.2.4 Shedding Criteria

①Poor therapeutic efficacy or adverse reactions that the subject cannot tolerate, making it impossible to continue the trial, and requesting voluntary withdrawal;

② Occurrence of serious adverse events, or concurrent development of other diseases or severe complications during the trial.

2.2.5 Exclusion Criteria

① Poor medication adherence during treatment, with violations of prescribed medication protocols;

② Patients who did not complete the observation period specified in the protocol or whose results were affected by incomplete information.

III. Research Content

3.1 Randomization and Blinding

3.1.1 stochastic

A stratified block randomization design was employed, with a 5-member independent statistical unit (non-research team) from the Cancer Hospital of the Chinese Academy of Medical Sciences responsible for generating and safeguarding the random sequence. The random sequence was generated using SAS 9.4 statistical software and stratified by surgical type (breast-conserving surgery versus modified radical mastectomy). A total of 60 cases were enrolled in this trial, and the 60 patients were allocated 1:1 to the treatment group and control group (30 cases each) using a fixed block design (length=4). The random sequence was sealed in a lightproof envelope and,

along with an emergency unblinding envelope, was entrusted to a 5-member blind management team composed of representatives from the Department of Traditional Chinese Medicine, Statistics, and Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences. The sequence was stored in a dedicated institutional safe. Prior to unblinding, neither the patients, researchers, nor outcome assessors were aware of the group assignments.

3.1.2 Blinding

The study employed a double-blind design, strictly adhering to the "three separations" principle (i.e., independent random sequence generators, clinical implementers, and data statisticians). The treatment group (Qibei Jiedu Formula) and the control group (simulant) were identical in appearance, color, odor, and packaging, with random coding assigned for packaging. Clinical researchers distributed the corresponding coded medications sequentially according to the enrollment order of participants, while independent outcome assessors were responsible for evaluating all subjective indicators. Upon completion of the study, the CRF forms were transferred to statistical personnel for primary unblinding (A/B group analysis), followed by secondary unblinding (official disclosure of group assignments) after statistical analysis was completed. All unblinding procedures were meticulously documented and archived, with oversight by the blind management team.

3.2 Treatment Protocol

3.2.1 Therapeutic Agents

Treatment group: Qibei Jiedu Formula (Composition: Astragalus membranaceus 10g, Rehmannia glutinosa 10g, Hedyotis diffusa 10g, Gleditsia sinensis 6g, Euphorbia hirta 10g, Lithospermum erythrorhizon 10g, Tribulus terrestris 10g, Fried Shenqu 10g, Licorice root 5g).

Control group: Placebo, which was identical to the test drug in appearance, dosage form, weight, color, and odor, with the dosage of traditional Chinese medicine being 5% of the original formula.

3.2.2 Intervention Measures

This study is a pragmatic randomized controlled trial. All enrolled patients will receive standard basic treatment formulated by their respective research centers based on current clinical guidelines and routine practices. On this unified basis, patients will be randomly assigned to one of the following two groups:

Treatment group: standard basic treatment + Jibei Jiedu prescription.

Control group: Standard basic treatment + Simulated agent of Jibei Jiedu Decoction (original dose 5%).

(1) Standard basic treatment

Radiotherapy regimen: High-dose fractionation (40-45 Gy/15 fractions).

Skin care: Refers to the routine protocol adopted by the research center to prevent radiation dermatitis (including but not limited to various gel dressings, ointments, or creams). This protocol is determined by the attending physician based on the patient's specific condition and departmental protocols. The specific drug names, administration methods, dosages, and duration of use must be recorded in the case report form.

Stability requirements: To ensure research quality, the skin care regimen for patients should remain as stable as possible after enrollment.

(2) Loading intervention

Subjects began taking Qibei Jiedu Formula or a placebo from the first day of radiotherapy, with one dose per day. Each dose of decoction was divided into two sachets (100 mL/sachet), with one sachet taken at each dose. The treatment was administered twice daily (morning and evening) for three consecutive weeks (21 days, synchronized with radiotherapy).

(3) Rescue Treatment Protocol

When a subject develops grade ≥2 radiation dermatitis (based on CTCAE v5.0 criteria) or reports intolerable pruritus/pain (numerical rating scale [NRS] ≥4), the predefined standardized rescue treatment protocol may be initiated. Investigators should select from the following protocols based on the patient's clinical presentation, with detailed documentation of the initiation date, termination date, and selected protocol category (A or B). In principle, for patients presenting with predominant symptoms of moist desquamation and exudation, protocol A (healing-promoting agents, such as recombinant human epidermal growth factor) should be prioritized. For patients exhibiting severe erythema, pruritus, or burning pain, protocol B (anti-inflammatory agents, such as medium-to low-potency topical corticosteroid creams, e.g., hydrocortisone cream or mometasone furoate cream) should be prioritized.

IV. Outcome Metrics

4.1 General Situation Survey Form

(1) Age: years, mean ± standard deviation

(2) BMI: kg/m², mean ± standard deviation

(3) Smoking history: n (%)

(4) History of diabetes: n (%)

(5) Menopause status: n (%)

(6) KPS score: n (%)

(7) History of chemotherapy: n (%)

(8) History of connective tissue disease or immune disorder: n (%)

(9) Fitzpatrick classification: n (%)

(10) Type of surgery: n (%)

(11) Radiotherapy techniques (IMRT/VMAT): n (%)

(12) Radiation therapy coverage: n (%)

(13) Adjuvant therapy during the trial: n (%)

(14) Planned CT breast volume: cm³, mean ± standard deviation

(15) Cutaneous Dmax (Gy, mean ± standard deviation)

(16) Skin Dmean (Gy, mean ± standard deviation)

(17) Skin V20Gy (% mean ± SD)

(18) Skin V30Gy (% mean ± SD)

(19) Skin V40Gy (% mean ± SD)

(20) Skin V45Gy (% mean ± SD)

4.2 Efficacy Evaluation

4.2.1 Primary outcome measures: incidence of radiation dermatitis

Definition: The proportion of patients who developed CTCAE grade 2 or higher radiation dermatitis during radiotherapy and within 1 month after radiotherapy completion, as confirmed by the investigator.

Assessment method: Incidence = (Number of patients with at least one ≥ grade 2 event recorded / Total number of patients) × 100%.

radiodermatitis	
Level 1	Mild erythema or dry desquamation
Level 2	Moderate to severe erythema; patchy moist desquamation, mostly localized to wrinkles and folds; moderate edema
Level 3	Wet desquamation is not limited to wrinkles and folds; it may also result from minor injuries or friction-induced bleeding.
Level 4	Life-threatening; skin necrosis or true-layer ulceration; bleeding from the affected area; requires skin grafting
Level 5	die

4.2.2 Secondary Outcomes

(1) Median time to first occurrence of radiation dermatitis: the time required for the investigator to confirm the first occurrence of radiation dermatitis meeting CTCAE 5.0 Level 2 criteria.

(2) Median time to wound healing in skin

Definition: The skin wound healing time refers to the duration from the onset of grade 2-3 radiation dermatitis to complete wound healing. According to the CTCAE 5.0 and the "Guidelines for Clinical Research of New Traditional Chinese Medicine Drugs," the grading of radiation dermatitis is evaluated, and the skin wound healing time is defined as the period from the investigator's confirmation and initial recording of ≥grade 2 to recovery to <grade 2 (i.e., grade 0 or 1) [18,19].

(3) Radioactive Dermatitis Symptom Rating Scale (RISRAS):

RISRAS (Total score 0-36)					
Researcher section (total score 0-24)					
spiloplaxia	0□ Normal skin	1□ light pink	2□ kermesinus	3□ bright red	4□ royal purple
dry desquamation	0□ Normal skin	1□ < 25%	2□ 25-50%	3□ 50-75%	4□ > 75%
wet desquamation	0□	1.5□	3.0□	4.5□	6□

	Normal skin	< 25%	25-50%	50-75%	> 75%
necrosis	0□ Normal skin	2.5□ < 25%	5.0□ 25-50%	7.5□ 50-75%	10□ > 75%
remarks	Dry desquamation, wet desquamation, and necrosis were assessed based on the proportion of the irradiated field area affected by dermatitis.				
Patient section (total score 0-12)					
symptom		in no shape	appreciably	somewhat	very serious
Is there any pain, discomfort, or sensitivity in the treated area?		0□	1□	2□	3□
Is the skin in the treatment area itchy?		0□	1□	2□	3□
Is there a burning sensation in the treated area?		0□	1□	2□	3□
To what extent do your skin reactions and symptoms affect your daily life?		0□	1□	2□	3□

(4) Quality of Life Assessment

a. Breast Cancer-Specific Questionnaire (EORTC QLQ-BR23)

1 point means none, 2 points mean a little, 3 points mean some, and 4 points mean a lot				
Over the past week (past 7 days)				
1. Why are you thirsty?	□1	□2	□3	□4
2. Do you notice any unusual taste in your food or drinks?	□1	□2	□3	□4
3. Do you experience eye pain, stinging, or tearing?	□1	□2	□3	□4
4. Do you experience hair loss?	□1	□2	□3	□4
5. You must answer this question if you experience hair loss: Do you feel distressed by hair loss?	□1	□2	□3	□4
6. Do you feel unwell or physically uncomfortable?	□1	□2	□3	□4

7. Do you experience hot flashes?	□1	□2	□3	□4
8. Do you have a headache?	□1	□2	□3	□4
9. Do you feel that your physical appearance has become less attractive due to your illness or treatment?	□1	□2	□3	□4
10. Do you feel that your illness or treatment has diminished your femininity?	□1	□2	□3	□4
11. Do you find it uncomfortable to watch yourself naked?	□1	□2	□3	□4
12. Are you dissatisfied with your body appearance?	□1	□2	□3	□4
13. Are you concerned about your future health?	□1	□2	□3	□4
Over the past four weeks (28 days)				
14. How interested are you in sex?	□1	□2	□3	□4
15. How active is your sexual life? (Have you had sexual intercourse or not?)	□1	□2	□3	□4
16. You only need to answer this question if you have had sexual intercourse in the past four weeks: How do you feel about the pleasure of sexual intercourse?	□1	□2	□3	□4
In the past week (past 7 days)				
17. Do you experience pain in your arm or shoulder?	□1	□2	□3	□4
18. Do you have swelling in your arm or hand?	□1	□2	□3	□4
19. Do you have difficulty raising or extending your arm?	□1	□2	□3	□4
20. Is there pain in the affected breast area?	□1	□2	□3	□4
21. Is there swelling in the affected breast area?	□1	□2	□3	□4
22. Is the affected breast area hypersensitive?	□1	□2	□3	□4
23. Are there any dermatological issues (e.g., pruritus, xerosis, desquamation) in the affected breast area? This	□1	□2	□3	□4

alteration involves more than one-quarter of the mammary gland tissue.				

b.Dermatology Quality of Life Index Questionnaire (DLQI)

Dermatology Quality of Life Index Scale				
	Very serious	serious	light	not have
1. Have you experienced severe pruritus or pain symptoms on your skin during the past week?	□3	□2	□1	□0
2. Over the past week, how many times have your skin lesions made you aware of or experienced feelings of "embarrassment," "frustration," or "sadness"?	□3	□2	□1	□0
3. To what extent have your skin lesions affected your shopping, household chores, or gardening activities over the past week?	□3	□2	□1	□0
4. Have you chosen different or special clothing or shoes due to skin discomfort in the past week?	□3	□2	□1	□0
5. To what extent have your skin lesions affected your social or recreational activities during the past week?	□3	□2	□1	□0
6. To what extent has your skin lesion affected your ability to engage in physical activities over the past week?	□3	□2	□1	□0
7. Have your skin lesions interfered with work or study in the past week? □No □Yes If yes: How much do your skin problems affect your work or study?	□3	□2	□1	□0
8. To what extent have your skin lesions caused distress to your companions, close friends, or family members over the past week?	□3	□2	□1	□0

9. To what extent have your skin lesions caused difficulties in sexual intercourse during the past week?	□3	□2	□1	□0
10. Does your skin condition cause inconvenience in daily life?	□3	□2	□1	□0

(5) Skin Reflection Spectrophotometry (SRS) measurement:

During each follow-up visit and on the day of the end of the traditional Chinese medicine (TCM) treatment course, the measurement instrument was a colorimeter (CR-10 Plus, Konica Minolta, Tokyo, Japan). This device has been validated for non-invasive and objective assessment of radiation dermatitis (RD). Measurements were taken three times at different random locations in each quadrant of both breasts (a total of 4 quadrants), with the mean value used to minimize error. The CIE L*a*b* standard chromaticity system was employed: L*: brightness value (0−100), where lower values indicate deeper skin pigmentation. a*: red-green axis value, with higher positive values suggesting more pronounced erythema (RD). b*: yellow-blue axis value, which serves as a secondary indicator in the evaluation of acute radiation dermatitis [20－22]. The changes in chromaticity values of the affected skin from baseline at different time points (ΔL*, Δa*, Δb*) were statistically analyzed. Measurements were only taken at the beginning of the study (baseline) and at the end of radiotherapy (day 21) on the unaffected skin to exclude the influence of significant systemic skin changes on the trial results.

(6) TCM syndrome scoring (Qi-Yin deficiency and blood stasis-toxin intermingling syndrome): A TCM syndrome scoring scale was established based on the "Guidelines for Clinical Research of New Traditional Chinese Medicine Drugs" (2002 edition), "Diagnosis and Treatment Guidelines for Malignant Tumors in Traditional Chinese Medicine," and "Traditional Chinese Medicine Surgery." The therapeutic efficacy was evaluated by analyzing the changes in syndrome scores at different treatment stages, as detailed in Table 2.

The therapeutic efficacy was evaluated using the Traditional Chinese Medicine (TCM) syndrome score improvement rate method (syndrome score improvement rate = (difference in scores before and after treatment / pre-treatment score) × 100%). The results were classified into four grades: complete cure (syndrome score reduction rate ≥ 95%), marked efficacy (70% ≤

syndrome score reduction rate <95%), effective (30% ≤ syndrome score reduction rate <70%), and ineffective (syndrome score reduction rate <30%).

The total effective rate = [(Number of cured + effective + significantly effective cases) / Total number of cases] × 100%.

4.2.3 Exploratory Indicators

（1）Inflammatory markers (TNF-α, IL-6, IL-10, IL-8, etc.): Collect 5 mL of blood from the median cubital vein of the patient, store in a separation rubber tube (yellow cap), and determine the inflammatory levels using enzyme-linked immunosorbent assay (ELISA). (Is covered by medical insurance?)

（2）Skin microbiota analysis: Using sterile cotton swabs, wipe the 5cm×5cm skin surface along the center and periphery of the irradiation field (with a 2cm non-irradiated area at the edge as control). Divide the target area into four rectangular zones from top to bottom, maintaining moderate contact between the swab tip and skin. Perform at least five reciprocating swabs per zone. After completing one zone, rotate the swab 90 degrees before proceeding to the next zone to ensure adequate microbial sample coverage. Immediately store the swabs in preservation solution and conduct skin microbiota analysis using 16S rRNA gene sequencing technology.

（3）Lymphocyte subpopulation analysis: Collect 5 mL of blood from the median cubital vein of the patient and store it in an EDTA anticoagulant tube (purple cap). Perform flow cytometry to detect the distribution of lymphocyte subpopulations in peripheral blood.

4.3 Safety Evaluation

(1) Laboratory tests: This study will evaluate laboratory test indicators of all subjects using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 5.0. Laboratory abnormalities meeting any of the following criteria will be defined as "clinically significant abnormalities" and recorded, tracked, and managed as adverse events:

a) Non-hematologic abnormalities meeting CTCAE 5.0 Level 2 or higher (e.g., hepatic or renal dysfunction);

b) Hematologic abnormalities meeting CTCAE 5.0 grade 3 or higher (e.g., neutropenia, thrombocytopenia);

c) Any laboratory abnormalities that necessitated discontinuation of the study intervention, dose adjustment, or targeted medical interventions (e.g., leukocyte-elevating agents, hepatoprotective agents, etc.), regardless of their CTCAE classification.

(2) Adverse Events (AEs) and Adverse Drug Reactions (ADRs): Throughout the trial period, all adverse events/adverse drug reactions will be closely monitored and recorded. Particular attention will be paid to their nature, severity, timing, duration, relevance to the investigational drug (using a 5-level association evaluation: definite, very likely, probable, probably unrelated, unrelated), management measures, and outcomes. This study will conduct a pooled analysis of the overall incidence of adverse events/adverse drug reactions, with special reporting on the incidence of grade ≥3 adverse events and cases leading to study withdrawal.

V. Trial Protocol and Follow-up Plan

All randomized patient visit evaluation time points are shown in Table 5.

Table 5 Visit Flowchart

step	period	Filter period	stage of therapy					follow-up period	
	study follow-up	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Key Event Record after Discharge	Follow-up 1
	Study date (days)	-7 to 0 days	7±2 days	10±2 days	14±2 days	17±2 days	21±2 days	22 to 47 days	49±3 days
1	Sign the informed consent form	√							
2	Brief Summary of the Subject's Medical Record	√							
3	Inclusion and Exclusion Criteria	√							
4 Clinical and Safety Evaluation	Vital signs/Electrocardiogram (ECG)	√							
	Complete blood count/Liver and kidney function tests	√					√		√
	Drug dispensing	√							
	Drug recovery						√		
6 Skin and End-point	Radiation Dermatitis Grading/RISRAS Score	√ (baseline)	√	√	√	√	√	(Based on weekly card evaluations)	√

Indicators	Skin reflection spectrophotometry	√ (base line)	√	√	√	√	√		√
	Symptom Tracking Weekly Card						√ (provide)	√ (Patient records)	√ (retrieve)
	Quality of Life Assessment/Traditional Chinese Medicine Syndrome Evaluation	√ (base line)			√		√		√
7 Biological Sample Collection	Blood sample (lymphocyte cytokine subsets, multiplex cytokine assay)	√ (base line)					√ (postradiotherapy)		
	Skin swab	√ (base line)					√ (postradiotherapy)		
8	fill in CRF	√	√	√	√	√	√	√ (event-driven)	√
Shared Page	Concomitant medication								
	Emergency treatment								
	adverse event								
	protocol bias								
Review page									

VI. Statistical Analysis

6.1 Follow-up

Primary follow-up is conducted in the hospital, supplemented by telephone or WeChat follow-ups.

6.2 Statistical Methods

SPSS 29.0 software was used, with a significance level set at $p<0.05$ (two-tailed). All analyses adhered to the intention-to-treat (ITT) principle. For quantitative data, normally distributed values were expressed as mean ± standard deviation, while non-normally distributed values were expressed as median (interquartile range); categorical data were presented as frequency and percentage. Continuous variables were tested for normality using the Shapiro-Wilk test, with independent samples t-test applied to normally distributed data and Mann-Whitney U test to non-normally distributed data. Categorical variables were analyzed using the χ^2 test or

Fisher's exact test (when theoretical frequencies did not meet the χ^2 test requirements). Time-event data (e.g., skin healing time, first onset of dermatitis) were estimated using the Kaplan-Meier method to calculate median time and 95% confidence interval (CI), with intergroup comparisons performed using the Log-rank test. For primary outcome measures (incidence of $\geq$ 2-grade dermatitis), adjusted hazard ratios were calculated primarily using log-binomial regression (or Poisson regression with robust standard errors if convergence was not achieved), supplemented by the χ^2 test for unadjusted intergroup comparisons. Skin microbiota analysis employed QIIME2 to assess alpha diversity (intergroup comparisons using Mann-Whitney U test) and beta diversity (intergroup comparisons using PERMANOVA), with LEfSe analysis used to identify differential genera.

6.3 Statistical Hypotheses

6.3.1 Primary Outcomes Assumptions

(1) Preventive research:

H_0 (null hypothesis): The incidence of grade ≥ 2 radiation dermatitis is equal between the Qibei Detoxification Formula group and the placebo group ($P_1 = P_2$).

H1 (alternative hypothesis): The incidence rates are not equal between the two groups (P1 = P2).

This study will primarily evaluate the point estimate difference in incidence rates between the two groups and its 95% confidence interval (CI). The range of the CI will be used to assess whether there are clinically significant differences, and to provide a basis for sample size calculation for future Phase III studies.

(2) Therapeutic studies:

H_0 : The survival distributions of wound healing time between the two groups are identical.

H1: The survival distributions of the two groups are different.

This study will primarily evaluate the median healing time difference between the two groups, along with their 95% confidence intervals (CIs), and the hazard ratio (HR) and its 95% CI.

6.3.2 Secondary Outcomes Hypotheses

For each secondary endpoint (e.g., overall response rate, scale scores, inflammatory markers,

etc.), similar null hypothesis (H_0) and alternative hypothesis (H_1) of no difference were established, with all tests conducted at a two-tailed α=0.05 level.

6.3.3 Description

The statistical analysis in this study will focus on estimating the magnitude of the effect and its precision, rather than solely on the p-value of hypothesis testing. All preliminary findings will be utilized to guide the design of subsequent confirmatory studies (e.g., sample size calculation, selection of primary endpoints).

VII. Ethical Requirements

7.1 Ethics Review and Compliance

This study strictly adheres to the Helsinki Declaration and relevant clinical research laws, regulations, and standardization protocols of China, and can only be implemented after submission to the hospital's ethics committee for review and approval. If any revisions to the protocol occur during the study, they must be resubmitted to the ethics committee for deliberation and approval before execution. If important new information related to the investigational drug is obtained, the informed consent form should be promptly revised and resubmitted to the ethics committee for review and approval before obtaining the informed consent of the subject or their legal guardian again. All serious adverse events and protocol deviations must be reported to the ethics committee in a timely manner as required.

7.2 Privacy and Confidentiality Measures

Only authorized personnel of this study (researchers and monitors) may access the medical records of participants, and all are obligated to maintain confidentiality. The drug regulatory authority has the right to review clinical trial-related documents. All data processing procedures are conducted through anonymization, with the removal of information that could directly identify individuals. Participant medical information is stored at the National Drug Clinical Trial Institution, ensuring strict information security.

7.3 Informed Consent Procedure

Researchers must fully explain the purpose, nature, expected benefits and potential risks of the study, alternative treatment options, and the rights and obligations of the subjects under the Declaration of Helsinki to the subjects or their legal guardians. Only after ensuring that the

subjects fully understand and voluntarily sign a written informed consent form can they be enrolled in the study and proceed with the relevant procedures.

7.4 Preservation of Research Data

Researchers must properly preserve all study materials, including subject identification documents (for cross-referencing with hospital original records), signed informed consent forms, and all observation record forms. All clinical trial materials should be retained for no less than 5 years after the study concludes.

VIII. Technology Roadmap

VIII. Observation and Analysis of Adverse Events

1. Definition of Adverse Events

Adverse events (AEs) refer to adverse medical events occurring during clinical studies, regardless of their association with the investigational drug.

2. Observation and Documentation of Adverse Events

Researchers should meticulously observe and document the occurrence time, severity, duration, measures taken, and outcomes of all adverse events (AEs), and record them in the Adverse Event Log. For radiation dermatitis, in addition to grading according to the following general criteria, the severity should primarily be professionally assessed based on the CTCAE v5.0 standards.

3. Severity Assessment of Adverse Events

Carefully observe the process, severity, management, and outcome of adverse events (AEs) and record them in the AEs report form. According to the following criteria, the severity of AEs can be classified as mild, moderate, or severe.

✓ Mild: Signs/symptoms are mild, easily tolerated, generally do not affect daily activities, and do not require special treatment.

✓Moderate: Significant signs/symptoms affecting daily activities, requiring targeted medical intervention/treatment.

✓ Severe: The signs/symptoms are severe, impairing daily activities and requiring active

medical intervention/treatment.

Note: 'Severe' describes the intensity of the event and is not equivalent to 'serious adverse event (SAE)'.

4. Determination and Reporting of Serious Adverse Events (SAE)

A serious adverse event refers to any occurrence that poses significant harm to the patient and/or constitutes a contraindication to continued treatment. In clinical practice, the following events are included:

✓ deadly ；

✓ life-threatening ；

✓ Requires unplanned hospitalization or prolonged hospital stay;

✓Resulting in permanent or significant disability/loss of function in patients;

✓causes congenital malformations or birth defects;

✓ Other significant medical events (not meeting the above criteria but potentially endangering the subject or requiring medical intervention to prevent the aforementioned outcomes).

Reporting procedure: Upon the occurrence of a Serious Adverse Event (SAE), the investigator shall immediately take necessary measures to ensure the safety of the subject and submit a written 'Subject SAE Report Form' to the institutional ethics committee and other relevant departments within 24 hours of notification.

5. Outcomes of Adverse Events and Serious Adverse Events (SAEs)

✓ die ；

✓Not cured/Not remitted;

✓ recure ；

✓Symptoms resolved but sequelae persist;

✓ laxation ；

✓ not quite clear

6. Evaluation of the Correlation Between Adverse Events and Medications

(1) Indicators for determining the causal relationship between adverse events and drugs

✓Whether there is a reasonable temporal sequence between the initiation of medication and the occurrence of adverse events/adverse reactions.

✓ Verify whether the suspected adverse reaction matches any known adverse reaction profile of the drug.

✓ Whether the suspected adverse reaction can be explained by relevant pathological conditions, concomitant medications, concurrent treatment modalities, or previously administered therapies.

✓Can the suspected adverse reaction be alleviated or resolved after discontinuation or dose reduction?

✓ Whether the same reaction reoccurs after re-administration of the suspected drug.

According to the above five indicators, the causal relationship is analyzed as positive, very likely, possible, doubtful and impossible.

(2) Analysis of adverse events and drug-relatedness

	Sure	As likely as not	Possible	Suspicious	Impossible
Have a reasonable chronological order with the medication	+	+	+	+	-
Known types of drug response	+	+	+	+	-
The reaction decreased or disappeared after drug withdrawal	+	+	±	±	-

Reactions were repeated after re-administration	+	?	?	?	-
Cannot be explained by disease, combination, etc ten	+	+	-	±	-
Note: + means positive, - means negative, ±means positive or negative, ? means unclear					

	肯定	很可能	可能	可疑	不可能
与用药有合理的时间顺序	+	+	+	+	-
已知的药物反应类型	+	+	+	+	-
停药后反应减轻或消失	+	+	±	±	-
再次给药后反应反复出现	+	?	?	?	-
无法用疾病、合用药等解释	+	+	-	±	-

说明：+表示肯定　—表示否定　±表示肯定或否定　？表示情况不明

Special Note: The relationship between radiation dermatitis and adverse events in this trial

(1) Dual Attribute Definition: The primary efficacy endpoint of this study was the incidence of grade ≥ 2 radiation dermatitis. Therefore, radiation dermatitis was identified as both an expected event and an efficacy observation indicator in this study.

(2) Safety record requirements: In accordance with the principle of comprehensive subject safety assurance under GCP, all cases of radiation dermatitis occurring during the trial, regardless of severity, must be objectively recorded as adverse events (AEs) for intergroup safety comparison and analysis.

(3) SAE Reporting Principle: If radiation dermatitis meets the protocol-defined criteria for a serious adverse event (SAE) (e.g., resulting in hospitalization or life-threatening conditions), the SAE reporting procedure must be immediately initiated. This procedure is not exempted due to the event being anticipated.

IX. Other Notes

1. Establish a project management team with reasonable division of labor and clear tasks, and appoint a project secretary to facilitate the arrangement of various clinical-related matters.

2. A dedicated archive cabinet should be established to properly store project documentation, facilitating supervision and audits by regulatory authorities.

3. Ensure the authenticity and completeness of research data by promptly and meticulously documenting study cases according to visit points, and timely entering them into the electronic medical record (EMR) system. This facilitates early identification of potential issues in the study and avoids last-minute documentation or entry of study cases.

4. Participation in medical research by individuals with capacity for informed consent must be voluntary. Although consulting family members or community leaders may be appropriate, the subject cannot be enrolled in the medical study unless they have given their free and informed consent.

5. In medical research involving human subjects with capacity for informed consent, each potential participant must be fully informed of the study objectives, methods, funding sources, any potential conflicts of interest, the investigator's affiliation, expected benefits and potential risks of the study, possible discomforts associated with the study, post-study safeguards, and any other research-related matters. Potential participants must be informed of their right to refuse participation in the study or to withdraw their consent at any time without retaliation. Special attention should be paid to the specific information requirements of potential individual subjects and the manner in which such information is communicated. All medical research subjects have the right to be informed of the general outcomes and results of the study.

6. When obtaining informed consent for research participation, physicians should exercise particular caution if the potential subject has a dependent relationship with the physician or may consent under duress. If a potential subject deemed incapable of giving informed consent agrees to participate in the study, the physician must additionally obtain consent from a legally authorized representative. The objections raised by the potential subject should be respected.

7. Physicians must fully inform patients about which aspects of medical treatment are related to the study. Patients' refusal to participate in the study or decision to withdraw should not adversely affect the doctor-patient relationship.

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