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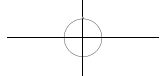
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Research Progress on the Mechanism of Action of Huangqin (*Scutellaria baicalensis*) in the Treatment of Lung Cancer

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Abstract: This article summarizes recent domestic literature on the use of Huangqin (*Scutellaria baicalensis*) in the treatment of lung cancer. It reviews the mechanism of action of Huangqin in treating lung cancer from six aspects: inhibiting the growth of lung cancer cells, inducing apoptosis of lung cancer cells, inducing autophagy of lung cancer cells, inhibiting the migration of lung cancer cells, promoting the differentiation of lung cancer cells, and improving immune function. The aim is to provide a reference for the material basis and further research on the anti-inflammatory and anti-tumor efficacy of Huangqin.

Keywords: Huangqin; Lung Cancer; Mechanism of Action; Inhibiting the Growth of Lung Cancer Cells

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1. Introduction

Lung cancer is one of the most common malignancies worldwide and has the highest incidence and mortality rates in China. Currently, there are many drugs available for the clinical treatment of lung cancer, but their efficacy is not ideal. Therefore, it is particularly important to study new treatment methods. Traditional Chinese medicine has unique advantages in tumor treatment, which can exert anti-tumor effects through mechanisms such as inhibiting tumor cell proliferation, inducing apoptosis, or promoting tumor cell differentiation. Huangqin is a commonly used Chinese herbal medicine^[1,2]. In recent years, with the deepening of people's understanding of traditional Chinese medicine theory and related modern scientific knowledge, the use of Huangqin in the treatment of lung cancer has received increasing attention. Its mechanism of action involves immune regulation, induction of cell apoptosis, enhancement of body immunity, and other aspects, which have become new research hotspots^[3,4].

2. Inhibiting the growth of lung cancer cells

Research has shown that Huangqin extract can reduce the expression levels of proliferation-related genes (such as P16, CCND2, c-Myc) and regulate the expression of protein kinase A (PKA) in lung cancer cell lines, thereby inhibiting the growth of lung cancer cells ^[5]. Studies have found that the ethanol extract of Huangqin can induce G2 phase arrest and inhibit proliferation in A549 and H460 cell lines ^[6]. Another study showed that the main component of Huangqin, flavonoids, inhibited the proliferation of human lung adenocarcinoma NCI-H89 cells by down-regulating the expression of Akt and Bim genes in the PI3K/AKT pathway ^[7]. Additionally, it has been found that Huangqin and its effective components can increase SOD activity in the blood of lung cancer patients, increase superoxide dismutase (SOD) activity, decrease malondialdehyde (MDA) content, and increase glutathione peroxidase (GSH-Px) activity. This protective effect is related to improving the immune function in lung cancer patients ^[8]. The above results indicate that Huangqin has a certain inhibitory effect on lung cancer cells, possibly through the regulation of oxidative stress and inflammatory responses.

3. Inducing apoptosis in lung cancer cells

Oxidative stress and inflammatory responses in lung cancer tissues can cause mitochondrial dysfunction, leading to cell apoptosis. Research has shown that *Scutellaria baicalensis* can significantly increase the apoptosis rate of various tumor-associated macrophage lines and human lung cancer cell lines ^[9].

Sun Guanghui treated H295R and A549 cells with different concentrations of baicalein and detected changes in intracellular reactive oxygen species (ROS), calcium ion concentration, and mitochondrial apoptosis marker gene expression using flow cytometry. The results showed that low concentrations of baicalein could induce mitochondrial apoptosis in both lung cancer cell lines, while high concentrations of baicalein showed the opposite effect. It is speculated that this may be related to the role of the extracellular matrix protein VHL in regulating mitochondrial membrane potential ^[10].

In addition, studies have found that *Scutellaria baicalensis* extract (80% ethanol solution) can promote apoptosis in the human non-small cell lung cancer primary cell line A549. In this experiment, Annexin V-FITC/PI double staining was used to determine cell apoptosis ^[11]. The results showed that after baicalein intervention, the expression levels of p62 and caspase-3 in A549 cells increased, while Bax expression decreased, suggesting that *Scutellaria baicalensis* can induce cell apoptosis.

Furthermore, a novel antioxidant, quercetin-3 (QQ3), has been isolated from *Scutellaria baicalensis* using chemical methods, and it has been confirmed to effectively inhibit the growth of human lung cancer cell lines H1299, H460, NCI-N87, MCF-7, PC-9, HeLa, and HL-60 in a dose-dependent manner, accompanied by an increase in the rate of cell apoptosis ^[12]. QQ3 can induce activation of the p53 and caspase pathways in H1299 and H460 cells in vitro, leading to increased intracellular ROS and Ca²⁺ content, mitochondrial damage, and ultimately tumor cell apoptosis ^[13]. In vivo, QQ3 can upregulate the activity of the Nrf2 pathway, enhance the activity of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), reduce the production of reactive oxygen species, enhance the synthesis of glutathione in cells, reduce damage caused by oxygen free radicals, and finally achieve anti-tumor effects ^[14].

It can be seen that *Scutellaria baicalensis* and its active ingredients can cause intracellular ROS generation, activate the PI3K/AKT signaling pathway, upregulate Nrf2 transcription, induce target gene expression, and finally lead to cell apoptosis.

4. Inducing autophagy in lung cancer cells

Mammalian target of rapamycin (mTOR), as a key signaling hub regulating autophagy, plays a dual role in lung cancer cell proliferation: promoting growth under normal physiological conditions, while inducing excessive autophagy leading to cell death under drug intervention^[15]. Studies have shown that baicalin can induce autophagy in lung cancer cells by regulating the AMPK/mTOR signaling pathway, thereby inhibiting lung cancer cell proliferation and promoting apoptosis^[16]. Furthermore, research has indicated that baicalin can also inhibit the Nrf2/GPX4 signaling axis in lung cancer cells, inducing ferroptosis and autophagy synergistically, demonstrating potential in reversing lung cancer drug resistance^[17].

5. Inhibition of lung cancer cell migration

Inflammatory factors in the lung cancer microenvironment are key factors inducing malignant progression and metastasis of the tumor. In an inflammatory microenvironment, the extracellular matrix (ECM) undergoes remodeling, which may alter the ECM structure and lead to its degradation or reorganization. This makes the ECM loose, weakens its adhesion function, and reduces its barrier effect on tumor cell migration.

Research has found that *Scutellaria* can inhibit the migration of alveolar epithelial cell line A549 and reduce the expression of extracellular matrix metalloproteinase 9 (MMP-9) and matrix metalloproteinase 13 (MMP-13)^[18]. Additionally, the ethanol extract of *Scutellaria* can significantly reduce the expression of migration-related proteins α -SMA, FN, Vimentin, and N-cadherin in lung cancer A549 cells, suggesting that *Scutellaria* can effectively inhibit the migration of lung cancer cells^[19]. This may be related to the ability of *Scutellaria* extracts to up-regulate the expression of fibroblast growth factor 21 (FGF-21). FGF21 is a proinflammatory cytokine secreted by hepatocytes that mediates the activation of immune cells and promotes the differentiation of macrophages into M2 type, which has anti-inflammatory, cell migration inhibitory, and angiogenesis inhibitory effects^[20]. Therefore, *Scutellaria* reduces lung inflammatory responses in NSCLC patients by up-regulating FGF-21 expression, enhances the anti-inflammatory activity of NSCLC cells, and thereby inhibits NSCLC cell migration.

It has also been reported that the water extract of *Scutellaria* can inhibit the migration of NSCLC cells by regulating the balance of MMP-2/9 and TIMP-2/8^[20]. Additionally, some scholars believe that *Scutellaria* can also reduce the expression levels of COX-2 and ICAM-1, and inhibit the expression of basement membrane-like protein (BAP) derived from human lung cancer tissue. These results suggest that *Scutellaria* can inhibit the migration of NSCLC cells while inhibiting ERK phosphorylation^[21].

Currently, the mechanism of action of *Scutellaria* in inhibiting NSCLC cell migration is still not fully understood. However, the above studies have demonstrated that *Scutellaria*, as an anti-inflammatory drug, can prevent NSCLC cell migration by inhibiting the expression of MMP-9 and TIMP-2/8. Thus, the inhibition of lung cancer cell migration by *Scutellaria* may be the result of multiple mechanisms working together, and the specific mechanism of action needs further investigation.

6. Promoting differentiation of lung cancer cells

Cancer stem cells are the main cause of drug resistance in lung cancer, and inducing their differentiation can increase their sensitivity to chemotherapy drugs. Studies have shown that *Scutellaria baicalensis* has the effect of promoting the transformation of normal cells into tumor cells^[22]. For example, in vitro experiments have found

that the water extract of *Scutellaria baicalensis* promotes the invasion and metastasis of lung cancer cells by down-regulating the expression of CXCR4 on the surface of cancer stem cells, up-regulating the expression of matrix metalloproteinase 2 (MMP-2) and vascular endothelial growth factor (VEGF), and enhancing their migration ability ^[23]. Further research has found that *Scutellaria baicalensis* can regulate the secretion levels of various inflammatory factors such as IL-6, IL-23, TNF- α , IL-12, IL-17, IFN- γ , GM-CSF, and MIP-2 in the supernatant of human lung adenocarcinoma A549 cells by activating the TGF- β 1/Smad3 signaling pathway. This may be one of the important mechanisms by which it promotes tumor cell differentiation ^[24].

At the same time, some scholars believe that *Scutellaria baicalensis* can induce apoptosis of lung cancer stem cells. By constructing a nude mouse xenograft model, it was observed that flavonoids can inhibit the colony formation of human non-small cell lung cancer A549 cells. Through immunofluorescence detection, it was found that *Scutellaria baicalensis* can reduce the phosphorylation of p-ERK protein, which in turn causes the accumulation of p53 in the nucleus, ultimately leading to cell apoptosis ^[25]. In addition, researchers have also found that flavonoids not only increase the apoptosis rate of lung cancer cells, but also reduce the expression levels of TGF- β 1, CCND1, cyclinD, cyclinE, P53, and pRb proteins, effectively inducing the differentiation of lung cancer cells into normal lung tissue ^[26]. Therefore, *Scutellaria baicalensis* achieves cancer-promoting differentiation by regulating the expression of inflammation-related molecules.

In summary, *Scutellaria baicalensis*, as a common Chinese herbal medicine, has received widespread attention for its anti-tumor mechanism, but the specific mechanism of action has not been fully elucidated, especially in terms of molecular biology research, which requires further in-depth study. Currently, research on the anti-inflammatory effects of *Scutellaria baicalensis* is mostly focused on different types of inflammation, and its exact pharmacological mechanism remains unclear. Although the direct therapeutic effect of *Scutellaria baicalensis* on lung cancer is very limited, its regulatory effect on the human immune system deserves further exploration.

7. Enhancing immune function

Scutellariae Radix can also play an immune-enhancing role in the treatment of lung cancer by regulating various immune pathways. Baicalin can promote the differentiation and activation of T cells in the body, thereby increasing the CD4⁺/CD8⁺ ratio and enhancing the immune status of patients with non-small cell lung cancer ^[27]. Studies have also found that baicalein can upregulate the activity of NK cells and the phagocytic function of macrophages, participate in the regulation of cytokine expression such as IFN- γ and IL-2, and improve the immunosuppressive state in the lung cancer microenvironment ^[28]. At the same time, research has pointed out that components of *Scutellariae Radix* can inhibit the expression of immunosuppressive factors such as PD-L1 through the PI3K/Akt/NF- κ B pathway, thereby enhancing the ability to control tumor immune escape ^[29]. From cells to animal models, from in vitro to clinical settings, *Scutellariae Radix* and its derivatives are building a complex mechanism network of “immune activation - immune regulation - anti-tumor“, becoming a useful complement to immunotherapy for lung cancer.

8. Summary

Lung cancer, as the most common cancer in China, remains a challenging area of medical research in terms of

treatment and prognosis. Clinical trials have shown that *Scutellaria baicalensis* (Huang Qin in Chinese) has a good therapeutic effect on various tumors, especially lung cancer. It has been used in clinical lung cancer treatment and is characterized by its safety and few side effects. Currently, the mechanism of action of *Scutellaria baicalensis* in the treatment of lung cancer mainly focuses on inhibiting the growth of lung cancer cells, inducing apoptosis and autophagy of lung cancer cells, inhibiting migration of lung cancer cells, promoting the differentiation of lung cancer cells, and improving the body's immune function. However, these mechanisms are not yet fully understood and require further exploration.

The above literature shows that *Scutellaria baicalensis* compounds and their components exert anticancer effects by inducing tumor cell apoptosis or inhibiting cell migration. However, it is difficult to achieve complete inhibition of cancer cell growth with a single component or ingredient, and combination therapy is needed. This is also one of the development directions of traditional Chinese medicine antitumor drugs. In addition, *Scutellaria baicalensis* can also exert antitumor effects by regulating the body's immune function, possibly due to the activation of specific signaling pathways. Therefore, using gene knockout animal models combined with gene microarray technology to analyze the anti-inflammatory basis of *Scutellaria baicalensis* and its impact on the expression of related proteins during the development of lung cancer is expected to elucidate its antitumor mechanism. Meanwhile, modern pharmacological studies have confirmed that *Scutellaria baicalensis* and its effective fractions can reduce inflammatory reactions, resolve lung tissue edema, reduce fibrosis, promote lymphocyte homing to the lungs, increase the level of T cell subsets in peripheral blood and bronchoalveolar lavage fluid, and enhance the immune response in mice with acute lung injury. Therefore, combining traditional Chinese and Western medical theories to comprehensively elaborate on the mechanism of action of *Scutellaria baicalensis* in the treatment of lung cancer is important for establishing new tumor diagnosis and treatment methods and achieving precision medicine for lung cancer.

Disclosure statement

The authors declare no conflict of interest.

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Clinical Efficacy Analysis of Buyang Huanwu Tang in Preventing and Treating Postoperative Recurrence of Advanced Adenomatous Polyps in the Large Intestine

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Abstract: *Objective:* To investigate the efficacy of Buyang Huanwu Decoction in preventing the recurrence of advanced colonic adenomatous polyps after surgery. *Methods:* A total of 160 patients who underwent endoscopic treatment for advanced adenomatous polyps of the large intestine at the First People's Hospital of Jintan, Changzhou, between March 2022 and March 2024 were enrolled in this study. The patients were randomly divided into an intervention group and a control group using a random number table. The control group received routine postoperative care, while the intervention group received Buyang Huanwu Decoction, starting one month after surgery. The decoction was administered warm, twice daily (200 ml per dose), one dose per day, for a total treatment duration of three months. *Results:* Before the intervention, there were no significant differences between the two groups in terms of TCM syndrome scores, and serum levels of G-17, IL-18, IL-6, COX2, and CRP ($P > 0.05$). After the intervention, both groups showed a decrease in TCM syndrome scores and serum levels of G-17, IL-18, IL-6, COX2, and CRP compared to pre-intervention values. The intervention group demonstrated a significantly greater reduction ($P < 0.05$). Three months after the intervention, there was no significant difference in polyp recurrence rates between the two groups ($P > 0.05$). However, six and twelve months after the intervention, the recurrence rates in the intervention group were significantly lower than those in the control group ($P < 0.05$). The incidence of adverse reactions was compared between two groups of patients. The intervention group had an incidence of 12.5%, while the control group had an incidence of 6.25%, with no statistically significant difference ($P > 0.05$). *Conclusion:* Buyang Huanwu Decoction has significant efficacy in preventing the recurrence of advanced colonic adenomatous polyps after surgery. It improves TCM syndrome scores, reduces oncogenic and inflammatory factors, significantly lowers postoperative polyp recurrence rates, and demonstrates good safety. It is a promising treatment for clinical promotion and application.

Keywords: Buyang Huanwu Decoction; Adenomatous polyps; Colorectal adenoma; Traditional Chinese Medicine syndrome score

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1. Introduction

Adenomatous polyps of the large intestine are considered precancerous lesions for colorectal cancer, and their progression typically follows a gradual “adenoma-carcinoma” sequence ^[1]. In recent years, with the increasing incidence of colorectal cancer, early detection and removal of adenomatous polyps have become important measures to reduce the incidence of colorectal cancer. However, the recurrence rate of polyps after surgery remains high ^[2]. The existing postoperative management plan mainly focuses on regular follow-up and lifestyle interventions, but the actual implementation rate and effectiveness of these measures are limited. Drug intervention, as an important means of preventing recurrence after surgery, mainly focuses on the application of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. However, the long-term use of NSAIDs may cause adverse reactions such as gastrointestinal bleeding, limiting their widespread application in prevention ^[3,4]. Therefore, exploring safe and effective postoperative recurrence prevention measures, especially intervention programs for high-risk progressive adenomatous polyps, has important clinical value. As an important part of traditional Chinese medicine, Chinese herbal medicine has achieved good results in the field of cancer prevention and treatment and has accumulated rich experience. Buyang Huanwu Decoction is a classic prescription created by Wang Qingren, a medical expert in the Qing Dynasty. In recent years, significant progress has been made in the research of cerebrovascular disease, chronic inflammation, and cancer prevention and treatment ^[5-8]. The author has achieved good results in preventing the recurrence of postoperative advanced adenomatous polyps of the large intestine with Buyang Huanwu Decoction. The report is as follows.

2. Clinical data

2.1. General information

160 patients who underwent endoscopic treatment for advanced adenomatous polyps of the large intestine in the gastroenterology department of Changzhou Jintan First People’s Hospital from March 2022 to March 2024 were selected as the research subjects. They were randomly divided into an intervention group and a control group using a random number table, with 80 patients in each group. Among them, there were 36 males and 24 females in the intervention group, with an average age of 53.28 ± 6.52 years old. In the control group, there were 38 males and 22 females, with an average age of 53.33 ± 6.48 years old. There was no statistically significant difference in general information between the two groups ($P > 0.05$), indicating comparability. This experiment was approved by the Medical Ethics Committee of Changzhou Jintan First People’s Hospital (Approval No.: 2022006).

2.2. Diagnostic criteria

- (1) Western medicine diagnostic criteria: The diagnosis of colorectal adenomatous polyps refers to “The Consensus on Pathological Diagnosis of Gastrointestinal Adenomas and Benign Epithelial Polyps” ^[9]. Colonoscopy and pathology suggest a diagnosis.
- (2) TCM diagnostic criteria: Refer to the “National Administration of Traditional Chinese Medicine’s TCM Diagnosis and Treatment Plan for Colorectal Polyps (Colon Polyps)” ^[10] to develop. The main symptoms include abdominal pain, changes in bowel movements or stool characteristics, difficulty in defecation, hematochezia, abdominal distension, etc. Combined with tongue imagery, the tongue is dark red, the tongue coating is thin and white, and the pulse is taut or astringent. The main dialectic is (Qi deficiency and blood stasis syndrome).

2.3. Inclusion and exclusion criteria

Inclusion criteria: (1) Age between 18 and 75 years old, no gender restriction. (2) Diagnosed with colorectal polyps through endoscopy and have undergone complete endoscopic resection. (3) Postoperatively confirmed by pathology as having advanced adenomatous polyps of the large intestine (adenoma diameter ≥ 10 mm; villous structure $> 25\%$ (including tubular villous adenoma); accompanied by high-grade intraepithelial neoplasia; or number of adenomas ≥ 3), and have undergone complete endoscopic resection. (4) Good patient compliance, voluntarily signing the informed consent form.

Exclusion criteria: (1) Those with a history of other gastrointestinal tumors or malignant diseases. (2) Postoperative presence of serious complications (such as perforation, massive bleeding, etc.) or long-term use of immunosuppressants, non-steroidal anti-inflammatory drugs. (3) Those with severe cardiac, liver, or kidney dysfunction or other life-threatening chronic diseases. (4) Those allergic to the ingredients of Buyang Huanwu Decoction or with a history of adverse drug reactions. (5) Pregnant or lactating women. (6) Those participating in other clinical trials or unable to guarantee cooperation during the study period.

3. Treatment methods

Control group: Routine postoperative management measures were provided, including dietary guidance, hemostasis, analgesia, and anti-infection treatment. Intervention Group: On the basis of the control group, Buyang Huanwu Decoction was administered one month after surgery. The medicinal composition and dosage of Buyang Huanwu Decoction are: Astragalus 30 g, Angelica 10 g, Chuanxiong 6 g, Dilong 6 g, Chishao 10 g, Taoren 10 g, Honghua 6 g. Add 1500 mL of water to the above medicinal materials, soak for 30 minutes, then simmer over low heat for about 40 minutes, take the liquid medicine to 400 mL, and take it warm twice a day, morning and evening, 200 mL each time. One dose per day for 3 consecutive months. Strictly follow the medicinal material handling specifications during the cooking process to ensure the full release of medicinal effects, while regularly monitoring patient compliance and adverse reactions to ensure the safety and effectiveness of the intervention.

4. Observation indicators

- (1) TCM syndrome score: A scoring table was developed based on references ^[11]. TCM syndromes such as abdominal pain, bowel frequency, constipation, hematochezia, dry mouth and bitter taste, anal burning, and physical heaviness were scored as 0, 1, 2, and 3 based on the absence, mild, moderate, and severe levels of symptoms, respectively. The total score is the sum of the scores of each TCM syndrome.
- (2) Determination by Enzyme-Linked Immunosorbent Assay (ELISA): Kits were purchased from Shanghai Saipaisen Biotechnology Co., Ltd. The levels of G-17 and IL-18 were measured before and 12 weeks after intervention.
- (3) Serum Inflammatory Factors: The levels of IL-6, COX2, and CRP were measured before and 12 weeks after intervention.
- (4) Polyp recurrence rates at 3, 6, and 12 months after intervention ^[12–14].
- (5) Comparison of adverse reactions.

4.1. Statistical methods

Data were analyzed using SPSS 26.0 software. Count data were expressed as cases (%), and the chi-square test was used for comparison. Measurement data were expressed as mean \pm standard deviation (SD), and the *t*-test was performed. $P < 0.05$ was considered statistically significant.

4.2. Results

4.2.1. Comparison of TCM syndrome scores between the two groups

There was no significant difference in TCM syndrome scores between the two groups before intervention ($P > 0.05$). After intervention, the TCM syndrome scores (abdominal pain, bowel frequency, constipation, dry mouth and bitter taste) and total scores of both groups were lower than before intervention, and the reduction in the intervention group was greater. The difference was statistically significant ($P < 0.05$).

Table 1. Comparison of TCM syndrome scores between two groups of patients (mean \pm SD)

Syndrome	Group	Before intervention	After intervention	Within-group <i>t</i> -value	Within-group <i>P</i> -value	Between-group <i>t</i> -value	Between-group <i>P</i> -value
Abdominal pain	Control group	1.93 \pm 0.68	1.54 \pm 0.61	3.819	< 0.001	0.452	0.652
	Intervention group	1.98 \pm 0.72	1.24 \pm 0.45	7.795	< 0.001	3.540	0.001
Stool frequency	Control group	1.89 \pm 0.57	1.65 \pm 0.49	3.450	0.001	-0.214	0.831
	Intervention group	1.87 \pm 0.61	1.23 \pm 0.34	8.197	< 0.001	6.230	< 0.001
Constipation	Control group	1.37 \pm 0.38	1.21 \pm 0.23	3.222	0.002	-0.316	0.753
	Intervention group	1.39 \pm 0.42	0.98 \pm 0.18	8.025	< 0.001	7.404	< 0.001
Hematochezia	Control group	1.55 \pm 0.43	1.21 \pm 0.28	6.025	< 0.001	-0.378	0.736
	Intervention group	1.53 \pm 0.31	1.26 \pm 0.33	5.334	< 0.001	1.033	0.303
Dry & bitter mouth	Control group	1.31 \pm 0.31	1.11 \pm 0.19	4.920	< 0.001	-0.412	0.689
	Intervention group	1.33 \pm 0.32	0.85 \pm 0.16	12.371	< 0.001	9.452	< 0.001
Total score	Control group	7.12 \pm 2.14	6.25 \pm 1.86	2.744	0.007	0.087	0.931
	Intervention group	7.15 \pm 2.21	5.62 \pm 1.42	5.210	< 0.001	2.408	0.017

4.2.2. Comparison of serum G-17 and IL-18 levels between the two groups of patients

Before intervention, there was no significant difference in serum G-17 and IL-18 levels between the two groups of patients ($P > 0.05$). After intervention, the serum G-17 and IL-18 levels in both groups decreased compared to before intervention, and the intervention group showed a greater reduction. The difference was statistically significant ($P < 0.05$).

Table 2. Comparison of serum G-17 and IL-18 levels between the two groups of patients (mean \pm SD)

Group	G-17 (pmol/L)				IL-18 (pg/mL)			
	Before Intervention	After Intervention			Before Intervention	After Intervention		
Control group ($n = 80$)	26.28 \pm 5.38	16.87 \pm 2.78	t	13.803	528.29 \pm 53.42	254.82 \pm 19.39	t	43.040
			p	< 0.001			p	< 0.001
Intervention group ($n = 80$)	26.23 \pm 5.41	10.82 \pm 1.98	t	23.925	519.32 \pm 52.52	143.59 \pm 13.92	t	61.852
			p	< 0.001			p	< 0.001
t	0.059	15.855			1.071	41.680		
p	0.953	< 0.001			0.286	< 0.001		

4.2.3. Comparison of serum IL-6, COX2, and CRP levels between the two groups of patients

Before intervention, there was no significant difference in serum IL-6, COX2, and CRP levels between the two groups ($P > 0.05$). After intervention, the serum IL-6, COX2, and CRP levels in both groups decreased compared to before intervention, and the intervention group showed a greater reduction. The difference was statistically significant ($P < 0.05$).

Table 3. Comparison of serum IL-6 and COX2 levels between the two groups

Group	IL-6 (pg/mL)				COX2 (pg/mL)			
	Before intervention	After intervention			Before intervention	After intervention		
Control group ($n = 80$)	15.32 \pm 3.57	12.76 \pm 2.34	t	5.364	8.29 \pm 1.52	7.21 \pm 1.38	t	4.705
			p	< 0.001			p	< 0.001
Intervention group ($n = 80$)	15.28 \pm 3.61	8.28 \pm 1.87	t	15.340	8.35 \pm 1.47	4.15 \pm 0.92	t	21.662
			p	< 0.001			p	< 0.001
t	0.072	15.237			0.254	17.852		
p	0.943	< 0.001			0.800	< 0.001		

Table 3. Comparison of serum CRP levels between the two groups

Group	CRP (mg/L)			
	Before intervention	After intervention		
Control group ($n = 80$)	9.73 \pm 2.21	6.21 \pm 1.74	t	11.193
			p	< 0.001
Intervention group ($n = 80$)	9.82 \pm 2.28	4.31 \pm 1.43	t	18.311
			p	< 0.001
t	0.254	7.545		
p	0.8	< 0.001		

4.2.4. Comparison of polyp recurrence rates between the two groups of patients

Three months after intervention, there was no significant difference in polyp recurrence rates between the two groups ($P > 0.05$). However, the polyp recurrence rates in the intervention group were significantly lower than those in the control group at 6 and 12 months after intervention. The difference was statistically significant ($P < 0.05$).

Table 4. Comparison of polyp recurrence rates between the two groups

Group	Recurrence cases (Rate/Cases, %)		
	After 3 months	After 6 months	After 12 months
Control group ($n = 80$)	3 (3.75)	9 (11.25)	14 (17.5)
Intervention group ($n = 80$)	2 (2.5)	2 (2.5)	4 (5)
χ^2	0.21	4.78	6.26
P	0.650	0.028	0.012

4.2.5. Comparison of adverse reaction rates between the two groups of patients

No liver or kidney damage was observed in either group. In the intervention group, 5 patients experienced nausea and vomiting, and 5 patients developed a rash. The incidence of adverse reactions was 12.5%. All patients recovered after symptomatic treatment without discontinuing medication. In the control group, 2 patients experienced nausea and vomiting, and 3 patients developed a rash. The incidence of adverse reactions was 6.25%. All patients recovered after symptomatic treatment. There was no statistically significant difference in the incidence of adverse reactions between the two groups ($\chi^2 = 1.84$, $P = 0.175$).

5. Discussion

The term “polyp” first appeared in the ancient Chinese medical text “Ling Shu: Evil Qi, Zang-Fu Organs, and Disease Manifestations,” which states, “When the lung meridian is excessively tense, it causes convulsions; when slightly tense, it causes lung heat and cold, lethargy, coughing up blood, and pain in the waist, back, and chest, or nasal polyps causing obstruction.” Both nasal polyps and colonic polyps share a high degree of overlap in their pathological characteristics, as they are both protrusions of tissue mucosa growing into the lumen. Therefore, some scholars^[15] have proposed “large intestine polyp” as a traditional Chinese medicine disease name based on the naming conventions of Chinese medicine. Advanced adenomatous polyps of the large intestine, which are usually larger and have a longer duration, are precancerous lesions of colorectal cancer. The main pathological factors in Chinese medicine are phlegm and blood stasis. Where do phlegm and blood stasis come from? Referring to the theory of collateral diseases, Ye Tianshi stated in his “Medical Records of Clinical Guidelines: Accumulation” that “initially, there is Qi stagnation in the meridians, and over time, there is blood stasis and heat entering the collaterals.” In his “Medical Records of Clinical Guidelines: Masses,” he also noted that “prolonged illness enters the collaterals, affecting both Qi and blood,” and he believed that collateral diseases can be divided into excess and deficiency types.

For excess types, gentle dredging and pungent herbs for purgation are recommended; for deficiency types, tonifying and dredging the collaterals is recommended. Wang Qingren had a deep understanding of the theory of collateral diseases and created the Buyang Huanwu Decoction, which tonifies Qi and activates blood, resolves blood stasis, and dredges the collaterals. Various factors, such as external pathogens, unclean diet, and emotional

imbalances, can cause a series of conditions, such as spleen and stomach damp-heat, liver Qi stagnation, and intestinal obstruction. Initially, there is “Qi stagnation in the meridians,” and over time, Qi stagnation and blood stasis occur, along with Qi stagnation and dampness obstruction. With the depletion of healthy Qi, phlegm and blood stasis intermingle, and “prolonged illness enters the collaterals,” manifesting as advanced adenomatous polyps of the large intestine. The core of Buyang Huanwu Decoction is “tonifying Qi and activating blood,” which can improve local blood circulation, promote tissue repair, and exert anti-tumor effects by regulating immune function and inhibiting chronic inflammation. Modern research has found that the occurrence and recurrence of colorectal adenomas are closely related to chronic inflammation and immune disorders, and the herbs in Buyang Huanwu Decoction, such as *Astragalus membranaceus* and *Angelica sinensis*, have significant anti-inflammatory and immunomodulatory effects ^[16,17]. For example, polysaccharides and flavonoids in *Astragalus membranaceus* can protect the intestinal mucosal barrier by inhibiting inflammatory factors and free radical levels, while *Angelica sinensis* and Chuanxiong can slow down malignant changes in the tumor microenvironment by improving microcirculation and inhibiting platelet aggregation. These mechanisms together support the role of Buyang Huanwu Decoction in preventing and treating the recurrence of advanced adenomatous polyps of the large intestine after surgery.

Modern pharmacological research on traditional Chinese medicine has shown that Buyang Huanwu Decoction (BYHWD) exhibits various biological effects such as anti-inflammation, anti-oxidation, immune modulation, and microcirculation improvement. This provides a theoretical basis for its application in preventing the recurrence of advanced adenomatous polyps in the large intestine after surgery. Furthermore, the treatment concept of “strengthening the body’s resistance to eliminate pathogenic factors” in traditional Chinese medicine aligns with the goals of “improving the intestinal microenvironment” and “enhancing immune function” in modern medicine. This also offers the possibility of involving traditional Chinese medicine in the prevention of precancerous lesions. However, the clinical efficacy of BYHWD in preventing the recurrence of advanced adenomatous polyps in the large intestine after surgery remains unclear. Therefore, this study aims to clarify the efficacy and safety of BYHWD in the prevention of recurrence through clinical research. The results indicate that compared with conventional postoperative management measures, BYHWD significantly reduces postoperative TCM syndrome scores and improves symptoms such as abdominal pain and abnormal bowel frequency.

Additionally, patients in the intervention group showed significant reductions in levels of cancer-promoting factors (such as G-17 and IL-18) and serum inflammatory factors (such as IL-6, COX2, and CRP) after the intervention. The recurrence rate of polyps was also significantly lower in the intervention group compared to the control group at the 12-month follow-up. These findings suggest that BYHWD not only has significant advantages in symptom improvement but may also reduce the risk of polyp recurrence after surgery through various mechanisms, such as anti-inflammation and inhibition of cancer-promoting factors. This is consistent with the traditional efficacy and modern pharmacological research results of BYHWD ^[18,19], providing a new potential intervention strategy for postoperative management. This study is the first to systematically explore the role of BYHWD in preventing the recurrence of advanced adenomatous polyps in the large intestine after surgery, offering a new research perspective and clinical evidence in this field.

The role of BYHWD in reducing recurrence rates may be closely related to its multi-target regulatory mechanism. This study found that cancer-promoting factors (G-17 and IL-18) significantly decreased in patients after BYHWD intervention. As a gastrointestinal hormone, G-17 is closely associated with the occurrence and development of colorectal cancer, and its decreased level may indicate a reduced risk of progression of

precancerous lesions in the intestine ^[20,21]. IL-18, on the other hand, is a pro-inflammatory cytokine whose role in inflammatory bowel disease and the tumor microenvironment has been widely studied. The reduction in IL-18 levels in this study further validates the anti-inflammatory effect of BYHWD ^[22]. Furthermore, BYHWD significantly improves patient symptoms and the intestinal environment, suggesting that it may provide a new approach for preventing postoperative recurrence by improving the intestinal microenvironment.

6. Conclusion

In summary, this study initially confirms the efficacy and safety of BYHWD in preventing the recurrence of advanced adenomatous polyps in the large intestine after surgery. It offers a new option for managing high-risk populations after surgery and is worthy of clinical promotion. However, further multicenter, large-sample randomized controlled trials are needed to verify its long-term efficacy and mechanism. Additionally, modern research methods such as gut microbiota and metabolomics can be combined to deeply explore the molecular mechanisms of BYHWD's intervention in colorectal precancerous lesions and improve its action network.

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Disclosure statement

The authors declare no conflict of interest.

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Effects of Modified Shenqi Dihuang Decoction Combined with Calcium Dobesilate on TCM Syndrome Scores in Patients with Diabetic Nephropathy

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Abstract: *Objective:* To evaluate the therapeutic effect of Shenqi Dihuang Decoction combined with calcium dobesilate on patients with diabetic nephropathy (DKD). *Methods:* 90 patients with DKD who visited the hospital from March 2024 to March 2025 were selected as samples and randomly divided into two groups. Group A was treated with Shenqi Dihuang Decoction combined with calcium dobesilate, while Group B was treated with calcium dobesilate alone. The efficacy, syndrome scores, blood glucose levels, and renal function indicators were compared between the two groups. *Results:* The efficacy of DKD treatment in Group A was higher than that in Group B ($P < 0.05$). The syndrome scores in Group A were lower than those in Group B ($P < 0.05$). The 2-hour postprandial blood glucose (PBG), fasting blood glucose (FBG), and glycated hemoglobin (HbA1c) levels in Group A were lower than those in Group B ($P < 0.05$). The serum creatinine (SCr), urinary microalbumin, urinary albumin excretion rate (UAER), and β_2 -microglobulin (β_2 -MG) levels in Group A were also lower than those in Group B ($P < 0.05$). *Conclusion:* The treatment of DKD with Shenqi Dihuang Decoction combined with calcium dobesilate can stabilize blood glucose levels, improve renal function, and reduce syndrome scores, which is highly effective and feasible.

Keywords: Diabetic nephropathy; Calcium dobesilate; Shenqi Dihuang Decoction; Syndrome score

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1. Introduction

DKD has a high incidence rate among diabetic complications. Under the stimulation of glucose metabolism disorders, patients experience abnormal expression of cytokines in their bodies, leading to abnormal accumulation of glomerular mesangial matrix and thickening of the capillary basement membrane in the kidneys. Over time, the glomerular filtration membrane is damaged, and the glomeruli gradually become sclerosed. Early diagnosis and treatment of DKD are essential to prevent further damage to renal function, which can lead to chronic renal failure

and even threaten the lives of patients with DKD. Initially, patients with DKD may experience a mild increase in protein levels in their urine, which gradually progresses to proteinuria as the disease advances ^[1]. Therefore, the focus of DKD treatment is to reverse microalbuminuria. Western medicine, such as calcium dobesilate, can improve arterial blood flow and reduce the burden on the kidneys, but the effect of monotherapy on improving renal function is limited. In traditional Chinese medicine, DKD is categorized as “kidney consumption” or “kidney tuberculosis,” and it is believed to be related to qi and blood deficiency and yin and fluid depletion. Treatment typically involves formulas that nourish both the spleen and kidneys, replenish Yin, and boost Qi, such as Shenqi Dihuang Decoction. Based on this, this article explores the efficacy of Shenqi Dihuang Decoction combined with calcium dobesilate using a sample of 90 patients with DKD who visited the hospital from March 2024 to March 2025.

2. Materials and methods

2.1. Materials

90 patients with DKD who visited the hospital from March 2024 to March 2025 were selected as samples and randomly divided into groups A and B using a lottery method. The baseline data of DKD in Group A were compared with those in Group B, showing no significant differences ($P > 0.05$). See Table 1.

Table 1. Analysis of the baseline characteristics of the patients with DKD

Group	<i>n</i>	Gender (%)		Age (years)		Disease duration (years)	
		Male	Female	Range	Mean ± SD	Range	Mean ± SD
Group A	45	20 (44.44%)	25 (55.56%)	39–63	45.44 ± 1.89	1–3	1.85 ± 0.42
Group B	45	21 (46.67%)	24 (53.33%)	38–62	45.41 ± 1.91	1–4	1.89 ± 0.39
χ^2/t	-	0.0448	0.0749	0.4682			
<i>P</i> -value	-	0.8324	0.9405	0.6408			

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Meet the criteria for diabetic kidney disease (DKD) as defined in the “Expert Consensus on Clinical Diagnosis of Diabetic Kidney Disease in Chinese Adults” ^[2] and the “2011 Guidelines for the Prevention and Treatment of Diabetic Nephropathy in Traditional Chinese Medicine” ^[3]; (2) Signed informed consent; (3) Presence of symptoms such as turbid urine, shortness of breath, fatigue, etc. Exclusion criteria: (1) Congenital renal dysfunction; (2) Malignant tumors; (3) Other hyperglycemia-related complications.

2.3. Treatment methods

Group A received combined treatment with Shenqi Dihuang Decoction. The prescription is as follows: 30 g each of Dangshen (*Codonopsis pilosula*), Huangqi (*Astragalus membranaceus*), and Danshen (*Salvia miltiorrhiza*); 20 g of Shudi (*Rehmannia glutinosa*); 15 g each of Chuanxiong (*Ligusticum chuanxiong*), Danggui (*Angelica sinensis*), Shengshanyao (*Dioscorea opposita*), Shanyu (*Cornus officinalis*), and Zexie (*Alismatis rhizoma*); 10 g each of Fuling (*Poria cocos*) and Danpi (*Paeonia suffruticosa*). Dialectical prescriptions are as follows: For those with dampness and phlegm, add Cangzhu (*Atractylodes lancea*) and Huoxiang (*Pogostemon cablin*); for those with yin deficiency, add Mohanlian (*Eclipta prostrata*) and Nuzhenzi (*Ligustrum lucidum*); for those with yang

deficiency, add Yinyanghuo (*Epimedium brevicornum*) and Zhifuzi (*Aconitum carmichaeli*). All herbs are decocted in water, and 300 mL of juice is taken, warm, morning and evening. The medication is administered for 3 months.

Group B orally administered Calcium Dobesilate Capsules (Shanghai Zhaohui Pharmaceutical Co., Ltd.; National Medical Approval Number H20030088; 0.5 g). A single oral administration of 0.5 g, once a day, switched to twice a day after 1 month of medication. The medication is administered for a total of 3 months.

2.4. Observation indicators

- (1) Efficacy: Disappearance of DKD symptoms and normalization of UAER is considered effective; reduction of DKD symptoms and a decrease in UAER by more than 50% is considered effective; no significant change in DKD symptoms and UAER is considered ineffective.
- (2) Symptom score: Based on symptoms of excessive eating and drinking, spontaneous sweating and night sweats, fatigue, and swelling of the face and feet, scores are assigned from 0–3 according to none, mild, moderate, and severe.
- (3) Blood glucose: PBG, FBG, and HbA1c indicators are detected using an automatic biochemical analyzer.
- (4) Renal function: SCr is detected by the creatinine enzymatic method, urinary microalbumin is detected by immunoturbidimetric assay, urinary albumin and creatinine are quantitatively measured by an automatic biochemical analyzer to calculate UAER, and β 2-MG is detected by immunoturbidimetric assay.

2.5. Statistical analysis

Data is processed using SPSS 23.0, with chi-square test used for counting data (recorded as a percentage) and *t*-test used for measurement data, recorded as mean \pm standard deviation (SD). Statistical significance is determined at $P < 0.05$.

3. Results

3.1. Therapeutic effect of DKD

The therapeutic effect of DKD in Group A was higher than that in Group B, $P < 0.05$. See **Table 2**.

Table 2. Comparison of therapeutic effect of DKD patients (*n*, %)

Group	Markedly effective	Effective	Ineffective	Effective rate
Group A (<i>n</i> = 45)	36 (80.00%)	8 (17.78%)	1 (2.22%)	44 (97.78%)
Group B (<i>n</i> = 45)	28 (62.22%)	10 (22.22%)	7 (15.56%)	38 (84.44%)
χ^2	-	-	-	4.9390
<i>P</i> -value	-	-	-	0.0263

3.2. Syndrome scores of DKD

After treatment, the syndrome score of Group A was lower than that of Group B, $P < 0.05$. See **Table 3**.

Table 3. Comparison of syndrome scores of DKD patients (mean \pm SD)

Group	Polyphagia/Polydipsia (scores)		Spontaneous/Night sweating (scores)		Fatigue/Lassitude (scores)		Facial/Pedal edema (scores)	
	Pre-tx	Post-tx	Pre-tx	Post-tx	Pre-tx	Post-tx	Pre-tx	Post-tx
Group A ($n = 45$)	2.49 \pm 0.26	0.61 \pm 0.18	2.44 \pm 0.27	0.58 \pm 0.16	2.47 \pm 0.21	0.57 \pm 0.18	2.42 \pm 0.25	0.61 \pm 0.19
Group B ($n = 45$)	2.47 \pm 0.28	1.33 \pm 0.21	2.48 \pm 0.26	1.35 \pm 0.23	2.45 \pm 0.22	1.36 \pm 0.21	2.39 \pm 0.27	1.38 \pm 0.23
<i>t</i>	0.3511	17.4626	0.7159	18.4358	0.4411	19.1603	0.5469	17.3142
<i>P</i>	0.7263	0.0000	0.4760	0.0000	0.6602	0.0000	0.5858	0.0000

3.3. Blood glucose levels of DKD

After treatment, the levels of PBG, FBG, and HbA1c in Group A were lower than those in Group B, $P < 0.05$. See **Table 4**.

Table 4. Comparison of blood glucose levels of DKD patients (mean \pm SD)

Group	PBG (mmol/L)		FBG (mmol/L)		HbA1c (%)	
	Pre-tx	Post-tx	Pre-tx	Post-tx	Pre-tx	Post-tx
Group A ($n = 45$)	9.36 \pm 1.26	4.88 \pm 0.51	12.41 \pm 1.72	5.51 \pm 1.09	10.41 \pm 1.42	6.19 \pm 0.88
Group B ($n = 45$)	9.38 \pm 1.28	6.14 \pm 0.69	12.43 \pm 1.75	7.33 \pm 1.43	10.43 \pm 1.39	7.48 \pm 1.16
<i>t</i>	0.0747	9.8510	0.0547	6.7901	0.0675	5.9433
<i>P</i>	0.9406	0.0000	0.9565	0.0000	0.9463	0.0000

3.4. Renal function indices of DKD

After treatment, SCr, urine microalbumin, UAER, and β 2-MG in Group A were lower than those in Group B, $P < 0.05$. See **Table 5**.

Table 5. Comparison of renal function indices of DKD patients (mean \pm SD)

Group	SCr (μ mol/L)		24h urinary microalbumin (mg)		UAER (μ g/min)		β 2-MG (μ g/L)	
	Pre-tx	Post-tx	Pre-tx	Post-tx	Pre-tx	Post-tx	Pre-tx	Post-tx
Group A ($n = 45$)	88.14 \pm 6.42	81.14 \pm 3.25	258.44 \pm 6.29	64.25 \pm 3.21	11.88 \pm 3.25	6.11 \pm 1.25	0.46 \pm 0.08	0.21 \pm 0.02
Group B ($n = 45$)	88.12 \pm 6.39	86.22 \pm 4.11	258.41 \pm 6.31	96.22 \pm 4.68	11.92 \pm 3.21	8.01 \pm 2.36	0.45 \pm 0.07	0.28 \pm 0.04
<i>t</i>	0.0148	6.5037	0.0226	37.7900	0.0587	4.7726	0.6311	10.5000
<i>P</i>	0.9882	0.0000	0.9820	0.0000	0.9533	0.0000	0.5296	0.0000

4. Discussion

The pathogenesis of DKD is not yet clear, and relevant scholars believe that it is related to multiple factors such as metabolism, genetics, and living environment. It is more common in obese and middle-aged, and elderly people ^[4]. In the early stages of DKD, patients do not exhibit specific nephropathy symptoms. A few patients may experience increased glomerular filtration rate and hemodynamic abnormalities. Strenuous exercise or stress reactions may

lead to transient hyperglycemia. As DKD progresses, patients gradually develop symptoms such as foamy urine, edema, anemia, and elevated blood pressure. In severe cases, microvascular complications such as dizziness, palpitations, blurred vision, and acid-base imbalance may occur. DKD is often treated clinically with medication, and calcium dobesilate is commonly used. It can correct microvascular lesions, reduce urinary protein metabolism, and when taken as prescribed, it can dilute the blood, prevent hypercoagulability, optimize renal function, and slow the progression of DKD. However, the effect of calcium dobesilate alone on optimizing renal function is limited. Chinese medicine scholars have conducted in-depth analysis of DKD and categorized it as “kidney fatigue” and “deficiency fatigue”. They believe that the pathogenesis of this disease is a deficiency of both Qi and Yin. Therefore, to achieve both symptomatic and root treatment, therapies that nourish essence, tonify the kidneys, and nourish yin should be adopted [5].

Based on the data analysis in this article, the efficacy of treatment for DKD in Group A is higher than that in Group B, and the syndrome score is lower than that in Group B, with $P < 0.05$. The reason for this is analyzed as follows: calcium dobesilate belongs to a vasculoprotective agent that, when orally administered into the human body, can dilute the blood, optimize microcirculation, and reduce the production of vasoactive substances. Moreover, patients with DKD who comply with medical advice and take medication can also downregulate UACR, inhibit the expression of vascular endothelial growth factor in the body, accelerate the regeneration of damaged kidney tissue, and thereby slow down the progression of kidney disease [6]. On this basis, combined with Shenqi Dihuang Decoction, the prescription includes *Radix codonopsis*, which nourishes the lungs, spleen, and Qi, *Astragalus membranaceus*, which reduces swelling and promotes urination, elevates yang and tonifies Qi, *Salviae miltiorrhizae radix* and *Rhizoma*, which relieves pain, soothes meridians, eliminates blood stasis, and promotes blood circulation, *Rehmanniae radix praeparata*, which nourishes the marrow and essence, nourishes Yin and nourishes blood, *Chuanxiong Rhizoma*, which relieves pain, dispels wind, and promotes blood circulation, *Angelicae sinensis radix*, which regulates menstruation, promotes blood circulation, and relieves pain, *Dioscoreae rhizoma*, which benefits the kidneys, spleen, astringes essence, tonifies the kidneys, nourishes the stomach, and tonifies the spleen, *Corni fructus*, which benefits the kidneys, nourishes Yin, collects essence, and stabilizes the kidneys, *Alismatis rhizoma*, which drains fire, clears heat, promotes urination, and eliminates dampness, *Poria*, which promotes urination and tonifies the spleen, and *Moutan cortex*, which eliminates blood stasis, cools blood, and clears heat. The combined use of these herbs in the prescription can achieve the effects of nourishing the spleen and kidneys, nourishing Yin and benefiting Qi, resulting in the rapid resolution of DKD symptoms [7].

According to traditional Chinese medicine scholars, patients with DKD are considered to have a deficiency of both qi and yin as the root cause, while the manifestation is internal accumulation of dampness and turbidity, and blood stasis obstructing the meridians. Over time, this leads to dysfunction of the internal organs, inability to normally output glycogen, imbalance of the blood glucose regulation system, and elevation of FBG. Additionally, abnormalities in the transportation and metabolism of water and grain essence in the body can further increase FBG. Poor dietary habits can exacerbate the burden on the spleen and stomach, or organ dysfunction can lead to insufficient insulin secretion, or internal accumulation of dampness and turbidity, and blood stasis obstructing the meridians can cause poor blood circulation, or long-term emotional stagnation can lead to disordered blood circulation, all of which can result in elevated FBG. Chronically high blood glucose levels can lead to deficiency of both qi and yin, imbalance of yin and yang, further damage to internal organs, and repeated vicious cycles, resulting in elevated HbA1c [8]. The data presented in this article show that the levels of PBG, FBG, and HbA1c in Group A DKD patients are lower than those in Group B, with $P < 0.05$. The reason for this is analyzed as

follows: combined treatment with Shenqi Dihuang Decoction includes active ingredients such as saponins and polysaccharides in *Radix codonopsis* and *Astragalus membranaceus*, which can alleviate insulin resistance, accelerate glucose absorption in the body, and thereby correct metabolic disorders. The synergistic effect of the herbs strengthens the function of nourishing Qi and Yin, restores the balance of Yin and Yang, and stabilizes blood circulation, resulting in a greater reduction in blood glucose levels. The active ingredients in *Dioscoreae rhizoma* can have anti-inflammatory, antioxidant, and protective effects on islet function, inhibiting damage to islet function caused by hyperglycemia. The active ingredients in *Salviae miltiorrhizae radix* and *Rhizoma* can regulate blood lipids and reduce the risk of cardiovascular disease, which is beneficial for stabilizing blood glucose. The active ingredients in *Chuanxiong rhizoma* can accelerate microcirculation, restore tissue oxygenation, and enhance the sensitivity of body tissues to insulin, resulting in more stable blood glucose levels ^[9]. The combined use of the western medicine calcium dobesilate and Shenqi Dihuang Decoction exerts synergistic effects, including anti-inflammatory and antioxidant properties, and can rapidly repair damaged kidney tissue, which is beneficial for long-term stabilization of blood glucose levels in patients with DKD ^[10].

Patients with DKD who are continuously in a state of hyperglycemia can develop endogenous blood stasis, which can damage kidney cells, disrupt the glomerular filtration barrier, and increase urine protein levels. Additionally, kidney damage can lead to the leakage of water and grain essence, long-term loss of essence, and downward flow into the bladder, resulting in elevated UAER. Deficiency of kidney yuán and damage to yin and yang can impair kidney nourishment, reduce glomerular filtration function, and increase the accumulation of substances such as creatinine in the body, leading to elevated SCr. Impaired renal tubular function can result in reduced reabsorption of β 2-MG and increased excretion in urine, or renal blood stasis can obstruct the renal meridians and continuously damage renal tubular function, also affecting β 2-MG metabolism. Alternatively, during the progression of DKD, patients may experience accumulation of dampness and heat in the body, leading to the formation of phlegm and obstruction, which can further aggravate renal tubular damage, manifesting as elevated β 2-MG levels ^[11]. The final set of data presented in this article shows that SCr, urine microalbumin, UAER, and β 2-MG levels in Group A are lower than those in Group B, with $P < 0.05$. The reason for this is analyzed as follows: treatment of DKD with Shenqi Dihuang Decoction includes ingredients such as *Poria* and *Rehmanniae radix praeparata*, which inhibit oxidative reactions, reduce glomerular function damage, and protect the filtration barrier, thereby reducing urine protein levels and preventing water and sodium retention. The components of *Radix codonopsis* can have antioxidant and lipid-regulating effects, slowing down kidney cell death. When combined with *Poria*, it enhances the antioxidant response and reduces oxidative stress-induced damage to healthy kidney function, facilitating kidney function recovery. The active ingredients in *Alismatis rhizoma* can optimize the body's metabolic function and protect islet cells, stabilizing blood glucose levels. When combined with *Dioscoreae rhizoma*, it enhances antioxidant effects and corrects glucose metabolism disorders, reducing the harmful effects of hyperglycemia and improving the prognosis of patients with DKD ^[12].

5. Conclusion

In summary, the combination of western medicine calcium dobesilate and Shenqi Dihuang Decoction for the treatment of patients with DKD demonstrates excellent efficacy, with stable blood glucose levels, improved renal function indicators, and reduced syndrome scores, indicating its value for widespread application.

Disclosure statement

The authors declare no conflict of interest.

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Sleeve Lobectomy Versus Pneumonectomy for Non-Small Cell Lung Cancer: A Meta-Analysis

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Abstract: *Background:* Sleeve lobectomy (SL) presents an attractive option compared to pneumonectomy (PN) for patients with central or locally advanced non-small cell lung cancer (NSCLC). This study aimed to assess the advantages of SL over PN for NSCLC via a meta-analysis. *Methods:* We performed a systematic review and cumulative analysis of comparative studies that reported both postoperative and survival outcomes for SL and PN. This was accomplished through a thorough search of electronic databases, including PubMed, EMBASE, and the Cochrane library, from inception to April 2023. *Results:* A total of 5727 patients (SL: 1945; PN: 3782) from thirty-one studies were analyzed. The meta-analysis focused on perioperative mortality, local recurrence, and overall survival. The SL group exhibited a significantly lower rate of perioperative mortality (OR = 0.43, 95% CI = 0.32–0.60, $P < 0.0001$). However, no significant difference was observed in local recurrence rates between SL and PN (OR = 1.25; 95% CI, 0.92 to 1.69; $P = 0.16$). Additionally, the survival rates at 1 year and 5 years in the SL cohort (1-year: 0.14, 95% CI: 0.12 to 0.17, $p < 0.0001$; 5-year: 2.15, 95% CI: 1.77 to 2.61, $p < 0.0001$) along with the survival in patients with pN0 or pN1 at 5 years (OR = 0.13, 95% CI 0.04 to 0.22; $P = 0.006$) were notably superior compared to those undergoing PN. *Conclusions:* Sleeve lobectomy should be regarded as a viable alternative to pneumonectomy for treating NSCLC.

Keywords: Non-small cell lung cancer; Sleeve lobectomy; Pneumonectomy; Meta-analysis

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1. Introduction

Lung cancer is the main cause of cancer-related mortality in many parts of the world, and is associated with

dismal prognosis in part due to lymphatic spread and early metastasis ^[1]. Even with the generous improvements in multimodality therapy, surgical resection remains the most effective method to control non-small cell lung cancer (NSCLC), through the complete removal of the lung tumor and the nearby lymph nodes. Pneumonectomy (PN) has traditionally been considered the gold standard for the treatment of central or locally advanced NSCLC ^[2]. However, PN is the most extensive pulmonary resection and a challenge for surgeons. It is associated with a high occurrence of postoperative complications and poor quality of life resulting from cardiopulmonary dysfunction postoperatively ^[3].

Sleeve lobectomy (SL) is a surgical technique designed to preserve lung parenchyma while fully removing tumors that infiltrate the bronchial openings and the main bronchus. It was first introduced by Price-Thomas in 1947 and first performed by Allison in 1952 ^[4]. Since this pioneering study, a growing body of evidence suggests SL as an alternative to PN for NSCLC patients. There have been reports that SL has an advantage in terms of better preservation of lung function without increasing postoperative mortality, even in patients who have undergone chemotherapy or neoadjuvant radiation therapy ^[2,5]. Moreover, some preliminary reports showed that locoregional recurrences and long-term survival of SL are comparable to PN ^[6-8]. Despite the multitude of reported equal outcomes in retrospective observational studies or meta-analyses that included patients operated on many years ago, the controversy of SL within the thoracic community has continued ^[9,10]. This controversy may be attributed to the more demanding techniques and, therefore the need for more experience in addition to the possibility of increased risk of locoregional tumor dissemination. Nevertheless, SL is increasingly used for central or locally advanced NSCLC by thoracic surgeons.

The purpose of this study was to carry out an updated systematic review and meta-analysis based on the earliest to most recent published studies to determine whether SL is an adequate modality for central or locally advanced disease. Through comparison of mortality, locoregional recurrences, and survival between SL and PN. A meta-analysis conducted in accordance with the timeline of publication updates the treatment effect estimate whenever new research findings are released. This approach allows for monitoring the gradual accumulation of evidence over time.

2. Methods

2.1. Search strategy

A systematic electronic search was conducted utilizing PubMed, EMBASE, and the Cochrane Library, spanning from their establishment up until April 2023. The search was restricted to articles published in English. To ensure a thorough collection of relevant studies, we employed a combination of terms, including “sleeve lobectomy,” “pulmonary artery reconstruction,” “pulmonary artery-sleeve resection,” as well as “bronchoplastic resection,” “bronchoplasty,” “bronchovascular sleeve resection,” “sleeve lung resections,” and “pneumonectomy” along with “non-small cell lung cancer” or the abbreviation “NSCLC” across all fields. Two researchers, Xuewei Chen and Xin Zhang, executed the literature search independently and subsequently verified their results against one another. The analysis also incorporated unpublished data, those available solely in abstract form, and articles that were not full-length. Furthermore, the reference lists of all identified articles were examined to uncover additional relevant studies.

2.2. Study eligibility

Eligible studies for this systematic review and meta-analysis included patient cohorts that underwent SL and PN. In cases where institutions released duplicate studies with larger patient numbers or extended follow-up periods, only the most comprehensive reports were considered for quantitative evaluation at each time point. All included publications focused exclusively on human subjects. Abstracts, case reports, conference presentations, editorials, and expert opinions were not included. Review articles were excluded to avoid potential publication bias and the possibility of result duplication. Additionally, studies with fewer than 10 patients in both comparable groups were also disregarded.

2.3. Data extraction and critical appraisal

The full-text articles were reviewed, and data were extracted by two independent authors (Junjun Fu and Xuewei Chen). Discrepancies between the two reviewers were resolved by discussion and consensus. Extracted data included: publication details (first author, study country of origin, publication year, and sample size), patient clinical characteristics and demographics, histologic type of tumor, and distribution of tumor stage. Outcomes included perioperative mortality, locoregional recurrences, overall survival, and the difference of survival at 1 and 5 years between the 2 groups. The results were reviewed by two senior investigators (Yingxin Chen and Xuewei Chen).

2.4. Statistical analysis

We conducted a meta-analysis to evaluate clinical outcomes, using the odds ratio (OR) as the principal metric. These values were sourced directly from the original articles when available. In cases where the hazard ratio (HR) and 95% confidence interval (CI) were not provided, we employed Engauge Digitizer version 4.1 (<http://sourceforge.net/projects/digitizer/>) to extract data from Kaplan-Meier curves. The outcomes for each trial with dichotomous data were represented as odds ratios (OR) along with 95% confidence intervals. A significance level of $p < 0.05$ was established for all evaluated outcomes. Data pooling for the meta-analysis was executed using both fixed-effect and random-effect models. When outcomes from both models were available, we reported the statistics from the random-effects model. To determine statistical heterogeneity for each analysis, the chi-squared (χ^2) and I^2 tests were employed. The I^2 statistic was utilized to convey the proportion of total variation among studies attributed to heterogeneity rather than random chance, and standard heterogeneity tests were conducted. An I^2 value exceeding 50% indicated considerable heterogeneity. Fixed-effects models were applied when no heterogeneity was detected ($p > 0.10$, or $p \leq 0.10$ but $I^2 \leq 50\%$); in contrast, the random-effects model was utilized otherwise. Sensitivity analyses were carried out to assess the robustness of the meta-analysis results based on study quality. We evaluated publication bias using Egger's method and illustrated it with Begg's funnel plot. Throughout all analyses, a 2-tailed p -value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using Review Manager 5.4 software.

3. Results

3.1. Literature search and study characteristics

From our initial literature search, a total of 1347 studies were obtained from PubMed, EMBASE and Cochrane Library. **Figure 1** illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

flow chart for study inclusion and exclusion. After manually screening the titles and abstracts, 1315 articles were excluded (review articles, abstracts, experimental research, duplicate reports and studies irrelevant to the current research objectives). The remaining 32 relevant studies were acquired for full-text review and full assessment, leaving 30 studies that met the inclusion criteria and were included in the final meta-analysis (**Figure 1**).

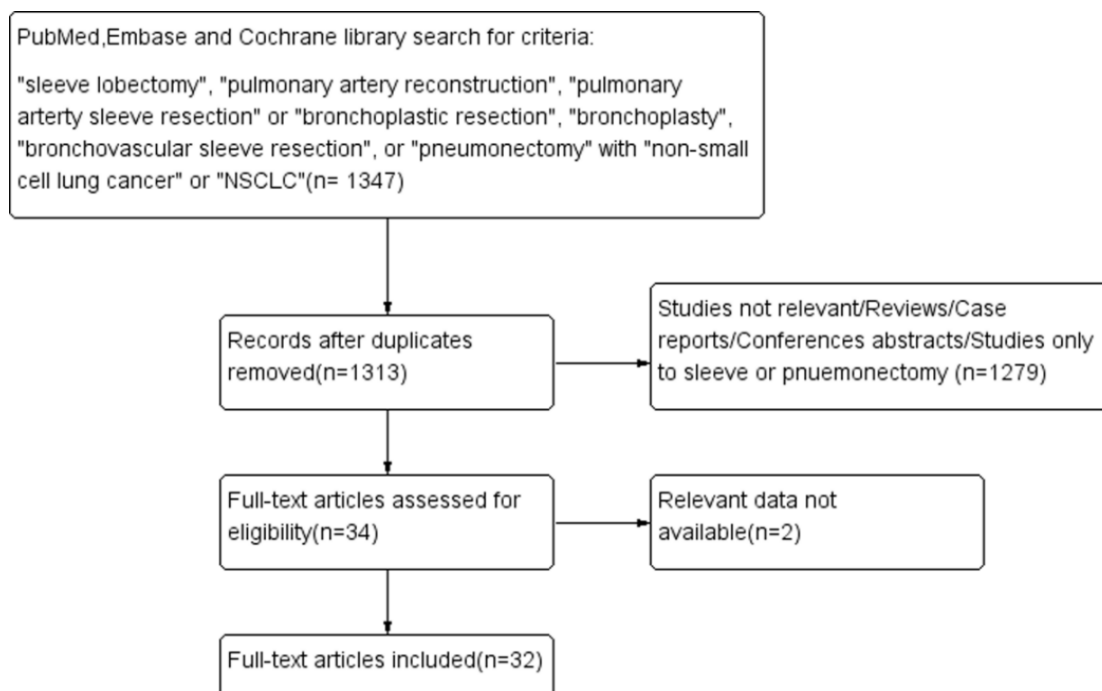


Figure 1. The flow diagram for study selection in this meta-analysis.

Among the 30 studies that were published, one was prospective while the remaining 29 were retrospective. No randomized controlled trials have been documented. Within these studies, comparisons were made involving 5,697 patients diagnosed with NSCLC, of which 1,933 underwent sleeve lobectomy (SL) and 3,764 had pneumonectomy (PN). The baseline characteristics from all included clinical trials can be found in **Table 1**. A significant difference was observed in the stage distribution between the SL group and the PN group (stages I, 32.1%; II, 38.6%; and III, 29.3% for SL; stages I, 19.6%; II, 33.2%, and III, 47.2% for PN, $p < 0.001$), with a higher proportion of early-stage NSCLC (stages I and II) in the SL group. The sex ratio between the two groups showed no significant variation (male/female, 81.2%/18.6% for SL, and 81.6%/18.4% for PN). Information regarding age distributions for the two surgical approach groups was not reported in the available literature. Nonetheless, the average age was similar across the groups (63.4 years for SL; 62.1 years for PN, $P = 0.06$).

Assessment of perioperative mortality rates was reported in all thirty studies (**Figure 2**). The overall mortality rate was 2.56% in the SL group and 6.04% in the PN group. The meta-analysis showed lower mortality in the SL group compared with the PN group (OR = 0.43, 95% CI = 0.32–0.60, $P < 0.0001$) and there was no heterogeneity among the pooled studies.

Table 1. Summary of the main characteristics of the included studies

Authors	Country	Year	Study design	Number		Mean age		Male/female		Stage I		Stage II		Stage III/IV	
				SL	PN	SL	PN	SL	PN	SL (%)	PN (%)	SL (%)	PN (%)	SL (%)	PN (%)
Gaissert	USA	1996	R	72	56	63.4	60.8	56/16	42/14	29(40.3)	9(16.1)	31(43.0)	25(44.6)	12(16.7)	22(39.3)
Yoshino	Japan	1997	R	29	29	60.6	58.2	26/3	23/6	9(31.0)	9(31.0)	12(41.4)	12(41.4)	8(27.6)	8(27.6)
Suen	USA	1999	R	58	142	63.7	66.5	41/17	81/61	18(31.0)	37(26.1)	28(48.3)	46(32.4)	12(20.7)	59(41.5)
Okada	Japan	2000	R	60	60	60.9	60.6	52/8	53/7	U	U	U	U	U	U
Ghiribelli	Italy	2002	R	38	127	65.0	62.4	36/2	102/25	16(42.1)	29(22.8)	10(26.3)	43(33.9)	12(31.6)	55(43.3)
Martin	UK	2002	P	38	81	65.0	63.0	27/11	63/18	10(26.3)	10(12.3)	16(42.1)	32(39.5)	12(31.6)	39(48.2)
Deslauriers	Canada	2004	R	184	1046	60.0	60.7	152/32	827/219	82(44.6)	164(15.7)	72(39.1)	361(34.5)	30(16.3)	521(49.8)
Bagan	France	2005	R	66	151	60.7	58.2	58/8	138/13	40(60.6)	35(23.2)	14(21.2)	35(23.2)	12(18.2)	81(53.6)
Ludwig	Germany	2005	R	116	194	62.0	59.0	U	U	31(26.7)	32(16.5)	41(35.4)	52(26.8)	44(37.9)	110(56.7)
Kim	Korea	2005	R	49	49	58.7	58.1	44/5	46/3	14(28.6)	24(49.0)	20(40.8)	13(26.5)	15(30.6)	12(24.5)
Lausberg	Germany	2005	R	171	63	62.1	60.9	136/35	56/7	33(19.3)	7(11.1)	80(46.8)	32(50.8)	58(33.9)	24(38.1)
Jiménez	Spain	2006	R	35	220	62.0	62.0	34/1	205/15	U	U	U	U	U	U
Takeda	Japan	2006	R	62	110	61.1	59.3	46/16	92/18	26(41.9)	24(21.8)	19(30.7)	14(12.7)	17(27.4)	72(65.5)
Kawaguchi	Japan	2008	R	26	34	68.0	59.0	18/8	30/4	7(26.9)	7(20.6)	8(30.8)	11(32.4)	11(42.3)	16(47.0)
Melloul	Switzerland	2008	R	69	78	U	U	U	U	15(21.7)	28(35.9)	30(43.5)	21(26.9)	24(34.8)	29(37.2)
Balduyck	Belgium	2008	P	10	20	65.3	63.3	U	U	2(20.0)	3(15.0)	1(10.0)	9(45.0)	7(70.0)	8(40.0)
Hanagiri	Japan	2009	R	24	72	65.1	64.7	18/6	61/11	5(20.8)	5(6.9)	8(33.3)	13(18.1)	11(45.9)	54(75.0)
Xie	China	2009	R	93	571	U	U	74/19	482/89	U	U	U	U	U	U
Parissis	Ireland	2009	R	79	129	64.5	65.5	54/25	91/38	U	U	U	U	U	U
Park	Korea	2010	R	105	105	61.3	62.2	99/6	98/7	44(41.9)	43(41.0)	32(30.5)	36(34.3)	29(27.6)	26(24.7)
Gomez-Caro	Spain	2011	R	55	21	63.5	62.4	51/4	18/3	33(60.0)	7(33.3)	20(36.4)	13(61.9)	2(3.6)	1(4.8)
Bölükbas	Germany	2011	R	31	29	73.6	74.2	25/6	25/4	5(16.1)	2(6.9)	17(54.8)	10(34.5)	9(29.1)	17(58.6)
Lee	Korea	2011	R	19	20	62.1	64.3	15/4	16/4	5(26.3)	8(40.0)	8(42.1)	5(25.0)	6(31.6)	7(35.0)
Maurizi	Italy	2013	R	39	39	63.0	59.2	28/11	30/9	17(43.6)	6(15.4)	10(25.6)	15(38.5)	8(20.5)	18(46.1)
Berry	USA	2014	R	35	52	63.5	60.9	21/14	36/16	0	0	22(62.9)	32(61.5)	13(37.1)	20(38.5)
Cusumano	Italy	2014	R	51	68	63.0	59.7	28/23	54/14	27(52.9)	26(38.2)	11(21.6)	18(26.5)	13(25.5)	24(35.3)
Pan	China	2014	R	70	35	72.9	72.8	63/7	33/2	14(20.0)	5(14.3)	35(50.0)	9(25.7)	21(30.0)	21(60.0)
Tagawa	Japan	2015	R	151	54	63.8	62.8	122/29	42/12	43(28.5)	2(3.7)	47(31.1)	7(13.0)	60(39.7)	44(81.5)
Andersson	Finland	2015	R	40	67	61.5	60.0	29/11	49/18	8(20.0)	16(23.9)	19(47.5)	26(38.8)	13(32.5)	25(37.3)
Ma	China	2016	R	58	42	58.5	57.8	50/8	40/2	0	0	30(51.7)	18(42.9)	28(48.3)	24(57.1)
Higuchi	Japan	2018	R	12	18	68.7	66.1	12/0	16/2	3	3	5	6	4	9
Total				1945	3782	63.6	62.2	1451/335	2833/639	536	541	647	914	491	1301

R:Retrospective P:Prospective U:Unknown

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R: Retrospective, P: Prospective, U: Unknown

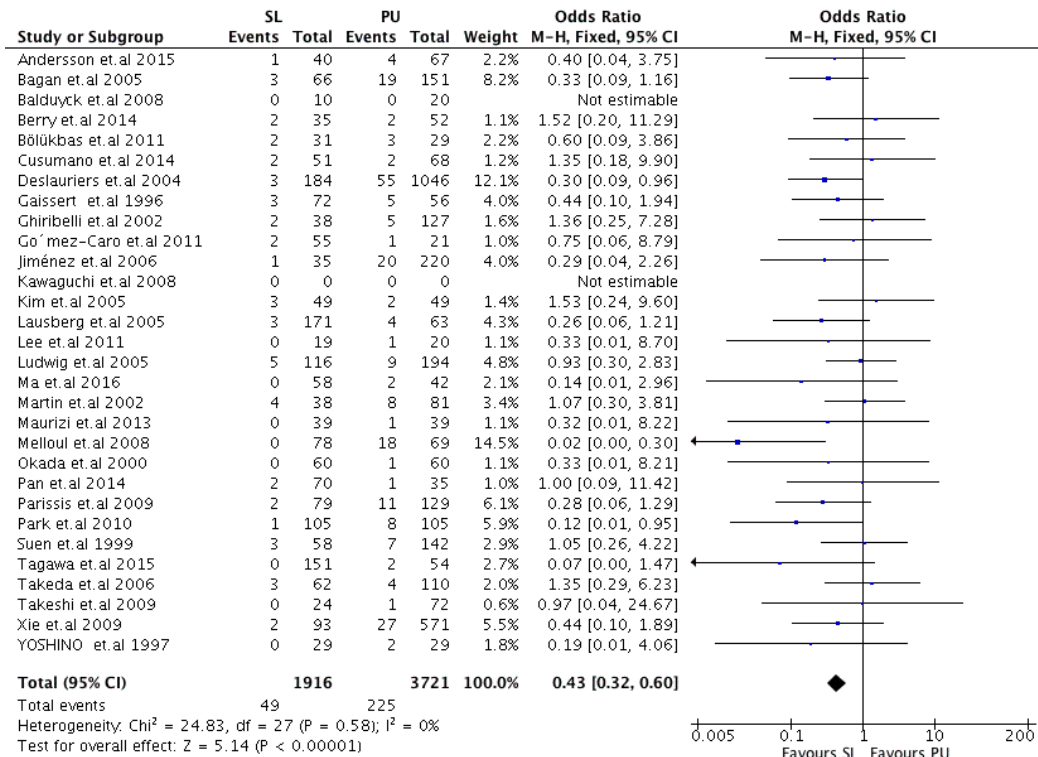


Figure 2. The meta-analysis of perioperative mortality rate between SL and PN group.

3.2. Assessment of locoregional recurrences

Eighteen studies reported the incidence of locoregional recurrences [2,3,5,6,8,11–23]. The meta-analysis showed the locoregional recurrence in SL was 12.2% compared with 8.98% in PN and demonstrated that there was no significant statistical difference in locoregional recurrences (OR = 1.25; 95% CI, 0.92 to 1.69; $P = 0.16$) between the two groups (**Figure 3**) or heterogeneity ($I^2 = 0\%$) among the studies. The cumulative meta-analysis accumulated the studies according to publication year and showed no evidence of increased recurrence rates.

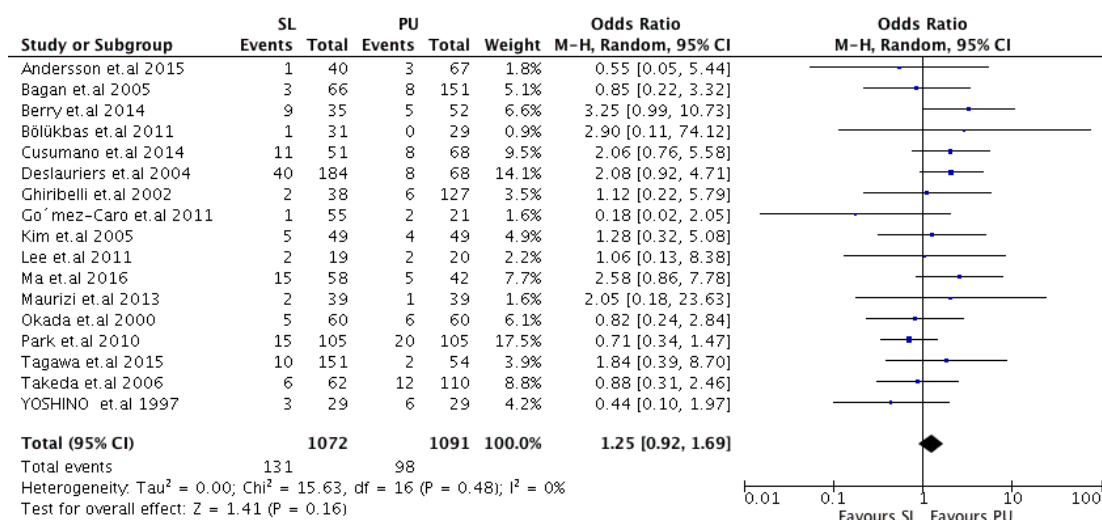


Figure 3. The meta-analysis of locoregional recurrences between SL and PN group.

3.3. Overall survival at 1 and 5 years

The survival difference at one year was derived from a total of 23 studies for examination. For the five-year survival difference, data were gathered from 22 studies. The odds ratios (ORs) consistently favored the SL group, showing significant results at both one year (0.14, 95% CI: 0.12 to 0.17, $p < 0.0001$, **Figure 4**) and five years (2.15, 95% CI: 1.77 to 2.61, $p < 0.0001$, **Figure 5**) regarding overall survival. The analysis revealed that the survival rates at one and five years were greater for the SL group compared to the PN group. Furthermore, there was no evidence of statistical heterogeneity among the included studies (one year: $I^2 = 17\%$, five years: $I^2 = 38\%$). For the cumulative meta-analysis, studies were organized chronologically according to their publication year. This analysis confirmed a significant difference in survival rates at both one and five years between the SL and PN groups.

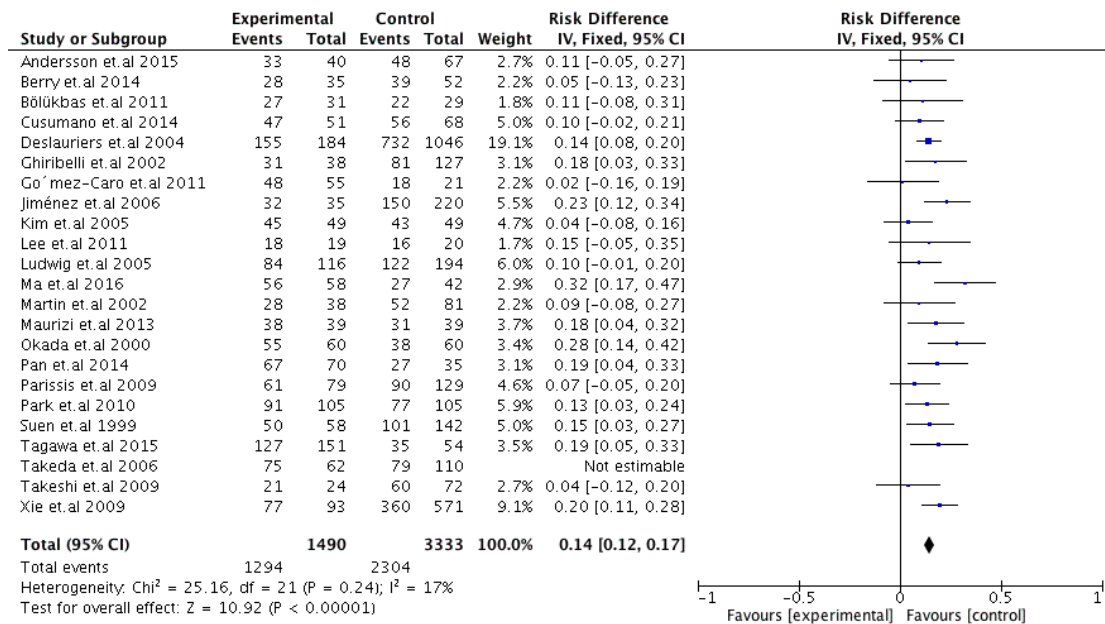


Figure 4. The meta-analysis of overall survival at 1 years between SL and PN group.

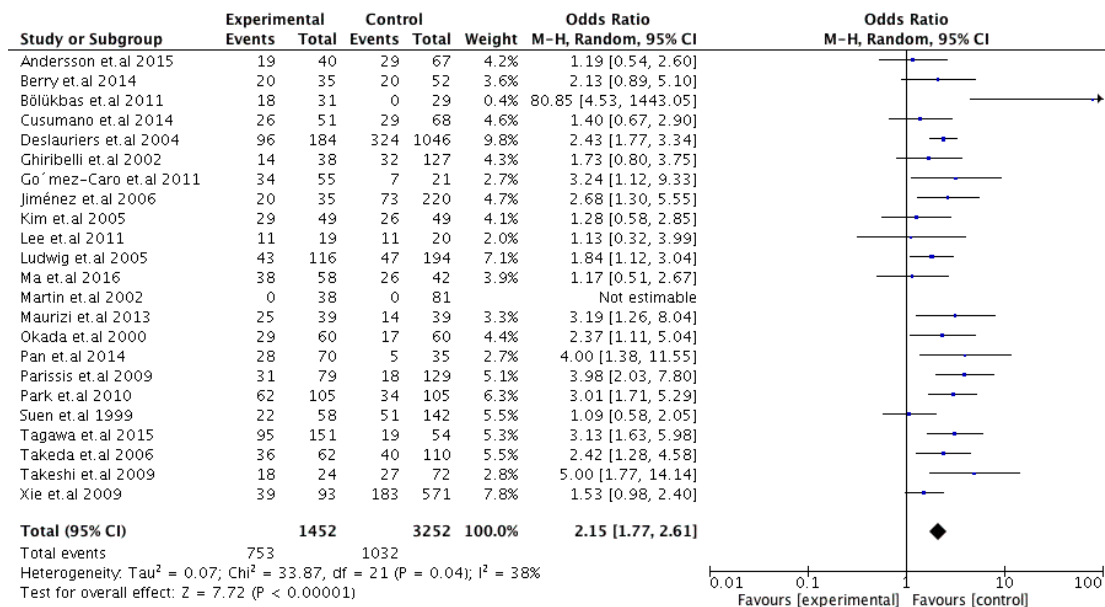


Figure 5. The meta-analysis of overall survival at 5 years between SL and PN group.

3.4. Differences of survival in patients with pN0 or pN1 and pN2 at 1 and 5 years

A total of five studies have reported on the survival rates of patients categorized as pN0 or pN1 over 1 and 5 years^[5,12,15,17,24], illustrated in **Figure 6** and **Figure 7**. The meta-analysis revealed a notable survival advantage for patients with pN0 or pN1 at the 5-year mark (odds ratio = 0.13, 95% confidence interval 0.04 to 0.22; $P = 0.006$) when comparing SL to PN, showing no heterogeneity ($I^2 = 17\%$) among the analyzed studies. Additionally, the survival difference at 1 year for patients with pN0 or pN1 between both groups was also significant (odds ratio = 0.13, 95% confidence interval 0.04 to 0.22; $P = 0.003$), although significant heterogeneity was present across studies ($I^2 = 79\%$).

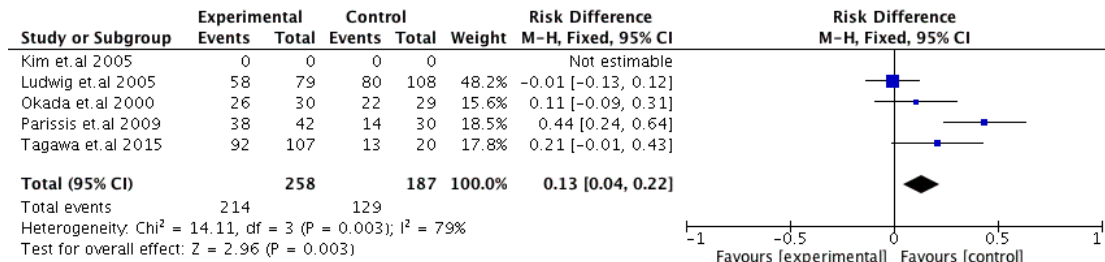


Figure 6. The meta-analysis of in patients with pN0 or pN1 at 1 years between SL and PN group.

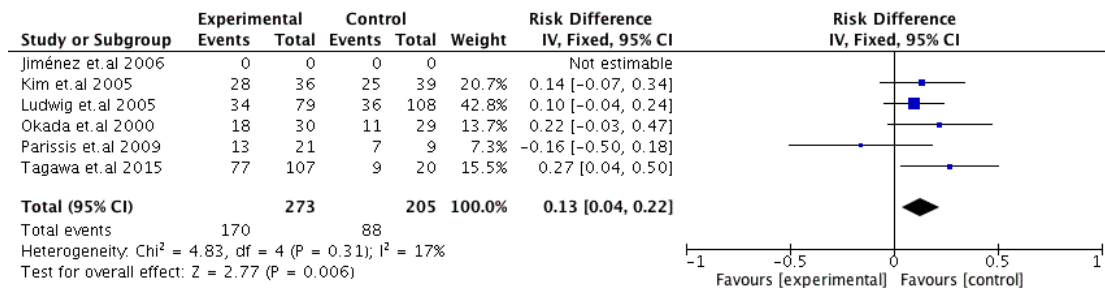


Figure 7. The meta-analysis of in patients with pN0 or pN1 at 5 years between SL and PN group.

Four studies compared the difference of survival in patients with pN2 at 1 and 5 years, respectively (1-year: OR = 1.90, 95% CI: 1.05 to 3.43, $P = 0.03$; 5-year: OR = 0.07, 95% CI: -0.05 to 0.19, $P = 0.24$; **Figure 8** and **Figure 9**).

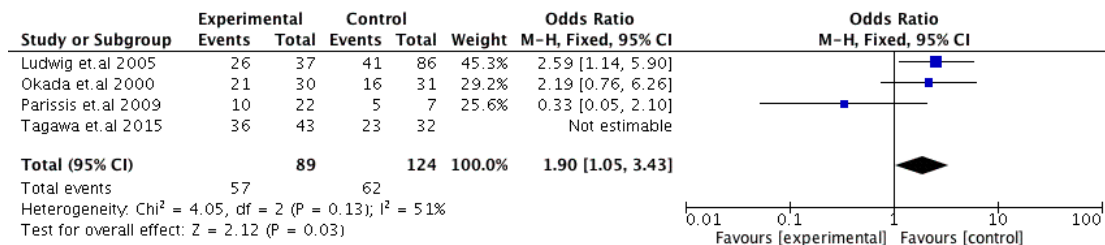


Figure 8. The meta-analysis of in patients with pN2 at 1 years between SL and PN group.

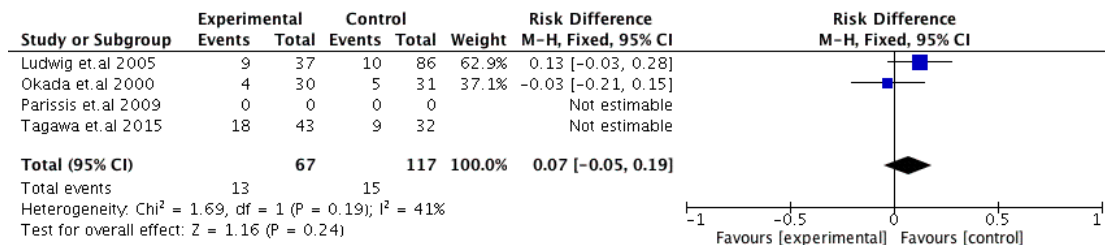


Figure 9. The meta-analysis of in patients with pN2 at 5 years between the SL and PN group.

3.5. Publication bias

The evaluation of publication bias utilized Begg's funnel plot and Egger's test across all findings. The funnel plots depicting the HR after SL and PN in the treatment of NSCLC exhibited signs of asymmetry, indicating potential publication bias. Additionally, Egger's test was conducted to offer statistical support for the symmetry of the funnel plots. However, the outcomes did not indicate any substantial evidence of publication bias.

4. Discussion

SL was initially introduced for NSCLC patients who were unable to tolerate a PN due to compromised lung function. The complexity of SL has been suggested to be associated with a high prevalence of bronchial anastomotic complications or high operative mortality and the incidence of local failure, compared with PN [25,26]. With increased experience in SL, this was progressively employed by most thoracic surgeons. It has been reported that SL offers a better quality of life than PN [27]. However, it is still important to answer the fundamental question of the adequacy of SL in satisfying surgical oncologic principles, as manifested by similar recurrence and survival results compared with PN. Numerous studies on SL were published, but no randomized controlled trials have compared SL and PN groups with respect to short-term outcomes or oncologic impact. In addition, many of these studies had limited sample sizes, making it difficult to draw definitive conclusions. Therefore, a cumulative meta-analysis provides an ideal statistical tool to increase the power of the comparisons and provide the best evidence currently available. Our data suggest that SL represents a valuable alternative surgical technique, with an acceptable risk of perioperative mortality and encouraging long-term outcomes, compared with PN. The use of the SL in NSCLC has expanded slowly. The main reason for the hesitation in performing SL is the uncertain oncologic efficacy, particularly regarding its potential for recurrence, when compared with PN. Tumor postoperative recurrence is the leading cause of late death in NSCLC patients. Concerns over the greater possibility of recurrence in SL might be related to technical reasons in the surgical management, or the risk of leaving residual tumor at the surgical margin [3,20,28].

Numerous investigations that compare segmental lobectomy (SL) and pneumonectomy (PN) suggest that survival rates following SL are generally similar to or may even exceed those after PN, contingent upon achieving a complete tumor resection. In the current meta-analysis, individuals who underwent SL displayed superior overall survival (OS) rates and enhanced 1- and 5-year survival compared to those who received PN. These results imply that SL effectively manages central or locally advanced lung cancer, allowing preservation of unaffected lung lobes, and indicate that SL could serve as a viable alternative to PN for non-small cell lung cancer (NSCLC). Nonetheless, one might contend that the apparent survival advantage associated with the SL technique could largely stem from the notable variation in cancer stage distributions between the SL and PN cohorts. A substantial portion of patients undergoing PN presented with more advanced tumor stages, particularly stage III. The connection between lymph node involvement and survival remains a topic of debate. In various studies, lymph node engagement by the tumor is often cited as a significantly adverse prognostic indicator concerning survival. Given the prevalent use of the SL technique, examining the outcomes related to survival and lymph node involvement among patients treated with either SL or PN is particularly pertinent. It is widely acknowledged that SL generally yields similar or improved outcomes compared to PN for patients with N0 or N1 disease; however, for those with N2 disease, PN tends to be the preferable option. A statistical evaluation conducted by Okada et al. revealed a notable difference that favored SL for patients with N0 or N1 disease. Conversely, a study by Kim

et al. reported that the 3-year and 5-year survival rates in patients with N0 or N1 disease did not reach statistical significance.

Furthermore, Okada et al. observed that there were no significant variations in survival outcomes for patients with N2 disease, even though the findings tended to favor SL. Our meta-analysis identified a noteworthy difference in 5-year survival rates between patients with pN0 or N1 who underwent SL and those who received PN, while the survival rate for those with pN2 disease did not show any significant difference. Additionally, at 1 year, the survival rates between SL and PN for patients categorized as either pN0-pN1 or pN2 did not reach statistical significance. These results indicate that SL continues to provide survival rates comparable to those for individuals with N2 disease. In light of the association analysis, these outcomes imply that even for advanced-stage tumors, a more extensive procedure like PN may not be the optimal option and does not inherently lead to better survival rates. Therefore, it can be concluded that nodal status ought not to be regarded as a strong justification against the adoption of SL.

Limitations inherent to this type of analysis must be taken into account when evaluating its significance for informing clinical practice. To begin with, our search was restricted to a few specific databases, and we only considered literature published in English, potentially introducing bias that could affect the findings. Additionally, due to the lung-conserving benefits of sleeve resection, conducting a randomized controlled trial presents challenges; consequently, further prospective studies are recommended. Moreover, the majority of comparative studies included in our review were nonrandomized and retrospective, which could influence the outcomes of our analysis. Furthermore, there was a notable disparity in stage distribution between the SL and PN groups, which could yield unreliable results favoring SL. The influence of a learning curve is a recognized phenomenon that occurs with the introduction of new complex procedures; however, we could not evaluate how this factor impacted our procedure. Lastly, some hazard ratio estimates were derived from the available data or Kaplan-Meier survival curves, relying on extrapolation and assumptions regarding censoring patterns. Lastly, inconsistencies were observed in the follow-up durations across the selected studies.

5. Conclusion

In conclusion, existing research indicates that surgical lobectomy (SL) is both viable and safe for certain patients, without raising mortality rates when compared to partial nephrectomy (PN). It may represent a legitimate alternative if conducted in accredited centers for non-small cell lung cancer (NSCLC) treatment. The SL and PN approaches for NSCLC showed similar outcomes in terms of local regional recurrence, although SL appeared to yield lower survival rates than those associated with PN. Nevertheless, in light of the variability among the studies and the intrinsic limitations of data derived from retrospective analyses, the findings of this meta-analysis must be approached with caution. Additional research is necessary to further clarify the role of SL in managing NSCLC.

Disclosure statement

The authors declare no conflict of interest.

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Impact of Pharmaceutical Care Model on Rational Use of Antibiotics in Ophthalmology Perioperative Period

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Abstract: *Objective:* To analyze the positive impact of pharmaceutical care in the ophthalmology perioperative period on the rational use of antibiotics. *Methods:* A total of 115 patients who underwent ophthalmological surgery between March and June 2023 were selected as the control group, receiving routine medication management. Another 115 patients who underwent ophthalmological surgery between July and October 2023 were selected as the observation group, receiving pharmaceutical care. The rationality of medication use, mastery of medication knowledge, medication compliance, and adverse reaction rates were compared between the two groups. *Results:* The observation group had higher rationality of medication use, higher scores for mastery of medication knowledge, higher medication compliance, and a lower adverse reaction rate compared to the control group ($P < 0.05$). *Conclusion:* The combination of antibiotic therapy and pharmaceutical care in the ophthalmology perioperative period can improve the rationality of medication use, enhance patients' mastery of medication knowledge, increase their medication compliance, and prevent adverse reactions to antibiotics.

Keywords: Ophthalmology; Perioperative period; Pharmaceutical care model; Antibiotics; Rational use

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1. Introduction

Ophthalmic diseases are complex, including retinal detachment, ocular trauma, and cataracts, and their primary treatment method is surgery^[1]. Most ophthalmic surgical patients have type I incisions, and the surgical procedures are relatively complicated. Due to the high sensitivity of the eyes, postoperative infections can easily occur under the invasive influence of surgery. Therefore, it is necessary to use antibiotics rationally during the ophthalmology perioperative period to prevent infections to the fullest extent. However, improper medication use during antibiotic therapy can lead to an imbalance of the ocular flora or bacterial resistance, which can prolong the patient's treatment cycle and affect the overall efficiency of the surgery^[2]. Pharmaceutical care is a new intervention method in the ophthalmology perioperative period that provides professional medication guidance tailored to the

specific situation of the patient, thereby effectively preventing adverse drug reactions. Based on this, the present study selected 230 ophthalmic surgical patients to evaluate the positive impact of pharmaceutical care on the rationality of medication use.

2. Materials and methods

2.1. General information

The ophthalmic surgery period for the control group was from March to June 2023, including 115 patients. Among them, 53 were male and 62 were female; the age ranged from 8 to 60 years, with a mean of (66.30 ± 12.36) years old. The ophthalmic surgery period for the observation group was from July to October 2023, also including 115 patients. Among them, 50 were male and 65 were female; the age ranged from 7 to 60 years, with a mean of (67.28 ± 11.75) years old. There was no difference in the data between the two groups ($P > 0.05$).

Inclusion criteria: meet the surgical treatment indications; have normal communication skills; meet the indications for antibacterial drug use; have complete clinical data; and are highly informed about the study. Exclusion criteria: presence of mental disorders; preoperative infectious diseases; combined blood or immune system diseases; history of antibacterial drug allergies; and withdrawal from the study.

2.2. Methods

The control group received routine medication management: ophthalmologists reasonably selected the types of antibacterial drugs based on the patient's surgery type, physical condition, and medication history. They provided oral education on medication knowledge, focusing on self-identification and response methods for adverse reactions, to ensure the rationality of antibacterial drug use during the perioperative period.

The observation group received pharmaceutical services:

- (1) Establishment of a pharmaceutical service team: The team was led by a pharmacist and included ophthalmic healthcare workers as members. The pharmacist provided professional training to all team members, covering the necessity of using antibacterial drugs during the perioperative period, the mechanism of antibacterial drugs, drug compatibility principles, contraindications for medication, etc. This ensured that all team members were proficient in medication knowledge before starting their duties. Weekly team meetings were organized to discuss the correct methods and precautions for administering antibacterial therapy during the ophthalmic perioperative period, enabling team members to continuously learn new knowledge.
- (2) Pharmacist assessment: The pharmacist participated in the patient's admission assessment process to comprehensively understand their eye disease type, surgery name, history of antibacterial drug use, and other information, screening for medication risk factors.
- (3) Medication guidance: When dispensing antibacterial drugs to patients, the pharmacist explained storage conditions, usage and dosage, timing of administration, and common adverse reactions. They inquired about the patient's understanding of relevant matters, provided targeted answers to medication questions, and ensured that the patient fully grasped the medication knowledge. Emphasis was placed on explaining precautions during medication use, such as the need to clean hands before applying viscous eye ointment to avoid infection caused by dirty hands touching the eyes.
- (4) Review of medication regimens: The pharmacist participated in the entire process when ophthalmologists

prescribed antibacterial drugs, reviewing the formulation and dosage of the antibacterial drugs in the prescription to prevent misprescription due to similar formulations or dosages of different drugs.

- (5) Ward rounds service: The pharmacist and clinician conducted ward rounds together, 1-2 times per week, to assess the patient's current status of antibacterial drug use on-site and provide pharmaceutical knowledge education to healthcare workers and patients. Graphic manuals or video playbacks were used to explain relevant knowledge, ensuring that both healthcare workers and patients clearly understood the key points.
- (6) Prescription review: A prescription review activity was conducted weekly, focusing on the indications, timing of administration, and duration of use of antibacterial drugs. Prescription issues were pointed out, and doctors were guided to correct the prescription content on-site. Simultaneously, the prescription review results were incorporated into the monthly assessment system, using a reward and punishment mechanism to enhance doctors' sense of responsibility.
- (7) Information intervention: The ophthalmology department introduced an information system to develop real-time statistical reports for type I incisions. These reports included common types of antibacterial drugs, frequency of use, intensity of use, consumption and frequency of medication use, and the probability of combination therapy, providing detailed records of antibacterial drug usage. Guided by common treatment plans for antibacterial drugs, selective assessment indicators were included. For irrational drug prescriptions, the prescriber was identified and handled through measures such as notification and punishment to enhance their awareness of rational drug use.

2.3. Observation indicators

- (1) Rationality of medication use: Evaluate the indications for medication use, timing of administration, selection of medication types, usage and dosage, and the rationality of the treatment course.
- (2) Medication knowledge mastery: Develop a self-made medication knowledge mastery scale, including items such as medication frequency, administration time, and precautions. Each item is scored out of 100, with higher scores indicating better mastery.
- (3) Medication compliance: Develop a self-made medication compliance survey questionnaire with a score range of 0 to 100. Scores above 80 indicate high compliance, scores between 59 and 80 indicate basic compliance, and scores below 59 indicate non-compliance.
- (4) Adverse reaction rate: Observe the incidence of adverse reactions such as red eyes, decreased vision, and eye pain.

2.4. Statistical analysis

Data processing software is SPSS 28.0. Count data is expressed as (*n*/%) and tested using chi-square test. Measurement data is tested for normal distribution using the Kolmogorov-Smirnov (K-S) test, expressed as mean \pm standard deviation (SD), and compared between groups using independent sample *t*-tests. Paired *t*-tests are used for within-group comparisons. Differences are considered statistically significant at $P < 0.05$.

3. Results

3.1. Comparison of medication rationality between the two groups

The medication rationality of the observation group was higher than that of the control group ($P < 0.05$).

Table 1. Comparison of medication rationality between the two groups (n/%)

Group	Cases	Indication accuracy	Timing accuracy	Drug selection	Dosage accuracy	Treatment duration
Observation	115	95 (82.61%)	110 (95.65%)	96 (83.48%)	115 (100.00%)	82 (71.30%)
Control	115	65 (56.52%)	89 (77.39%)	78 (67.83%)	109 (94.78%)	61 (53.04%)
χ^2		18.482	16.442	7.648	6.161	8.153
<i>p</i> -value		< 0.001	< 0.001	0.006	0.013	0.004

3.2. Comparison of medication knowledge mastery between the two groups

The medication knowledge mastery score of the observation group was higher than that of the control group ($P < 0.05$).

Table 2. Comparison of medication knowledge mastery between the two groups (mean \pm SD, points)

Group	Cases	Administration frequency	Administration timing	Precautions compliance
Observation	115	95.43 \pm 4.55	90.88 \pm 4.35	96.52 \pm 3.24
Control	115	80.63 \pm 7.31	79.86 \pm 6.32	81.24 \pm 8.75
<i>t</i> -value		18.433	15.403	17.562
<i>p</i> -value		< 0.001	< 0.001	< 0.001

3.3. Comparison of medication compliance between the two groups

The medication compliance of the observation group was higher than that of the control group ($P < 0.05$).

Table 3. Comparison of medication compliance between the two groups (n/%)

Group	Cases	Full compliance	Partial compliance	Non-compliance	Total compliance rate
Observation	115	75 (65.22%)	37 (32.17%)	3 (2.61%)	97.39% (112/115)
Control	115	60 (52.17%)	40 (34.78%)	15 (13.04%)	86.95% (100/115)
χ^2					8.679
<i>p</i> -value					0.003

3.4. Comparison of adverse reaction rates between the two groups

The adverse reaction rate of the observation group was lower than that of the control group ($P < 0.05$).

Table 4. Comparison of adverse reaction rates between the two groups (n/%)

Group	Cases	Eye redness	Vision decline	eye pain	Total incidence
Observation	115	1 (0.87%)	1 (0.87%)	1 (0.87%)	2.61% (3/115)
Control	115	3 (2.61%)	3 (2.61%)	4 (3.48%)	8.70% (10/115)
χ^2					3.995
<i>p</i> -value					0.046

4. Discussion

Ophthalmologic surgeries are highly specialized procedures. The intraocular tissues, such as aqueous humor or cornea, possess a natural blood-ocular barrier. However, this barrier can be significantly disrupted by the invasive interference of surgical operations, potentially leading to undesirable consequences like ocular infections. Additionally, ophthalmic surgeries often require extended operating times, leaving the incision exposed to the external environment for prolonged periods, which increases the risk of bacterial infections ^[3,4]. Therefore, antimicrobial agents are commonly administered during the perioperative period in ophthalmology to effectively prevent complications such as postoperative infections. Nevertheless, there are instances of irrational use of antimicrobial drugs during this process. For instance, prolonged use or overuse of these drugs can lead to the development of multiple drug-resistant strains, affecting the efficacy of the medication and even inducing adverse drug reactions. Furthermore, ophthalmic surgeries often require adjuvant therapy with eye drops, and some patients fail to grasp the correct administration technique, leading to improper usage and reduced efficacy of the eye drops ^[5]. Previous studies have revealed that ophthalmologic surgery patients often have inadequate knowledge about medications, influenced by factors like education level and awareness of surgical procedures. Patients may lack understanding of the therapeutic mechanisms, administration methods, and precautions of antimicrobial agents, potentially leading them to alter the dosage of antimicrobial drugs postoperatively, thereby affecting the long-term surgical outcomes ^[6]. Hence, there is a need for pharmaceutical services during the perioperative period in ophthalmology to ensure rational use of antimicrobial agents.

Pharmaceutical care is an intervention led by pharmacists, which can fully utilize pharmacists' professional knowledge of antibacterial drugs, provide rational medication guidance based on the disease conditions and surgical plans of ophthalmic surgery patients, and thereby actively prevent adverse drug reactions and improve the rationality of perioperative medication ^[7]. The results indicate that the observation group exhibited superior medication rationality, higher scores for medication knowledge mastery, and better medication compliance compared to the control group, with a lower adverse reaction rate ($P < 0.05$). This can be attributed to the comprehensive medication guidance provided by the pharmaceutical services team. The pharmacists, who undergo professional training, ensure that all team members have a clear understanding of antimicrobial drugs. Regular team meetings provide a platform for learning, allowing members to stay updated on the latest knowledge regarding antimicrobial agents ^[8]. By conducting a comprehensive assessment of patients' basic conditions, pharmacists can identify risk factors during antimicrobial therapy, thereby determining the direction of pharmaceutical intervention. Within the specific pharmaceutical services, medication guidance offers systematic education on antimicrobial drugs to patients and promptly addresses their individual queries. This enhances patients' understanding of medication usage and precautions, facilitating improved mastery of medication knowledge ^[9].

Additionally, medication guidance corrects patients' misconceptions about antimicrobial drug use, encouraging them to follow medical advice and improve medication compliance. Pharmacist review of antimicrobial prescriptions promptly identifies irregularities, maximizing medication rationality ^[10]. Ward rounds and prescription reviews are common components of pharmaceutical services. Regular pharmacist visits provide insights into patients' current antimicrobial drug use and offer targeted guidance, further enhancing patients' knowledge. Prescription reviews raise awareness among doctors about the reasonableness of prescriptions, reducing adverse reactions to antimicrobial agents. Information-based interventions, a novel approach in pharmaceutical services, utilize information systems to comprehensively summarize antimicrobial drug usage. This allows for the selection of appropriate assessment indicators and the integration of reward and punishment mechanisms to avoid irrational drug use ^[11].

5. Conclusion

In summary, the integration of pharmaceutical services into the use of antimicrobial agents during the perioperative period in ophthalmology not only ensures medication rationality but also improves patients' mastery of medication knowledge and medication compliance. Furthermore, it prevents adverse reactions, demonstrating significant intervention effects.

Disclosure statement

The authors declare no conflict of interest.

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Imaging Manifestations and Pathological Basis of One Case of Alveolar Soft Tissue Sarcoma of the Gluteus Maximus Muscle

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Abstract: Alveolar soft tissue sarcoma is a rare malignant tumor of soft tissue, more common in young women, with deep soft tissues in the limbs and buttocks being the most prevalent sites. There are few reported cases in clinical practice. The clinical manifestations lack specificity and the imaging signs are diverse. This case presents ultrasound, MRI and PET/CT images of alveolar soft tissue sarcoma of the gluteus maximus muscle to enhance readers' understanding and awareness of the imaging signs of this rare disease in order to raise awareness of its diagnosis. The characteristics of this case are summarized and reported in combination with domestic literature.

Keywords: Alveolar soft tissue sarcoma; Gluteus maximus; Magnetic resonance; Positron emission tomography

Online publication: August 7, 2025

1. Introduction

Alveolar soft part sarcoma (ASPS) is a rare malignant soft tissue tumor characterized by an unknown tissue origin and tumor cells arranged in an alveolar or organoid pattern. The disease was first reported by Christopherson *et al.*^[1] in 1952 and is prevalent in adolescent females, with deep muscles or fascia of the extremities being more common. Clinically, it often presents as a slow, painless mass, but due to its metastatic potential, it can spread to the lungs, bones, brain, subcutaneous tissue, etc. At present, radical surgery is the main treatment method, and regular follow-up monitoring of metastasis and recurrence is required after surgery. This article provides reference and assistance for clinical diagnosis and treatment by retrospectively analyzing the diagnosis and treatment process of one patient with gluteus maximus ASPS admitted to the Second People's Hospital of Guangdong Province in October 2024, combined with a literature discussion.

2. Clinical data

2.1. Basic information

The patient, male, 15 years old, was admitted to the hospital due to “a mass found in the right hip for more than half a year.” Physical examination: A 4 cm × 5 cm mass was palpated in the right hip, soft in texture, without tenderness, with acceptable range of motion, and no local skin temperature increase. Over the past six months, the mass has grown slowly and progressively without tenderness, ulceration or nerve compression.

2.2. Imaging examination

2.2.1. Ultrasound examination

A hypoechoic mass, approximately 64 mm × 56 mm × 38 mm in size, with a clear boundary and shallow lobulation, and uneven internal echo was observed under the right hip. The mass was surrounded by tortuous and dilated veins. Color Doppler flow imaging showed abundant strip-shaped blood flow signals within the lesion, and the arterial spectrum was of low resistance type (**Figure 1** and **Figure 2**).

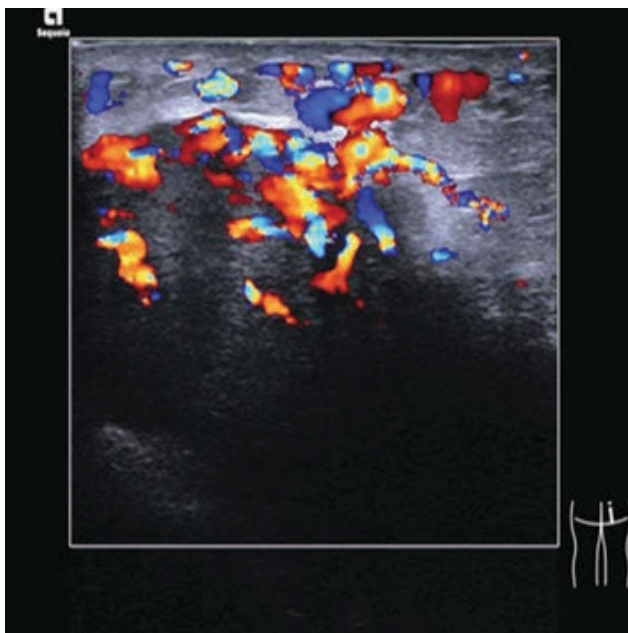


Figure 1. Ultrasonic image.

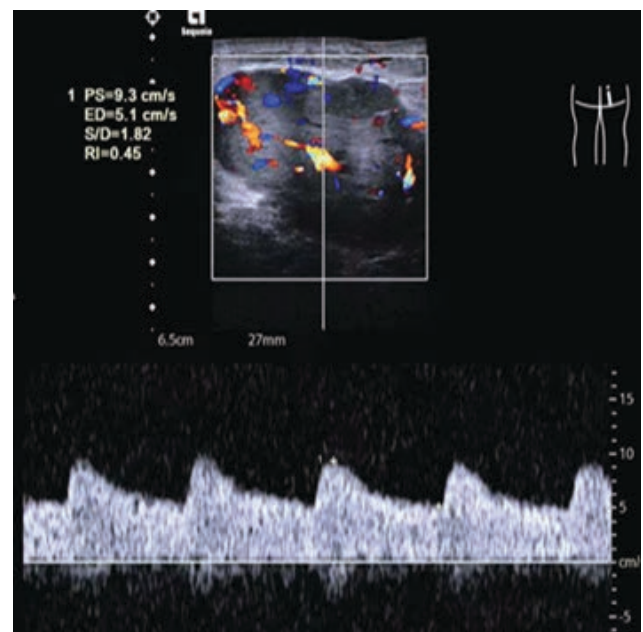


Figure 2. Ultrasonic blood flow spectrum.

2.2.2 Magnetic resonance imaging (MRI)

An abnormal signal space-occupying lesion was seen at the posterior margin of the right gluteus maximus muscle, with a clear boundary, closely related to the gluteus maximus muscle, approximately 38 mm × 71 mm × 68 mm in size. The T1WI sequence shows isosignal, with multiple patchy/cord-like low signals (**Figure 3**). The T2WI/fat inhibition sequence isosignaling, with multiple patchy hypersignaling within (**Figure 4** and **Figure 5**). A high signal in the isosignal area of DWI (Figure 6) and a low signal in ADC (Figure 7) suggest limited diffusion. The isosignal area was significantly enhanced after enhanced scanning, while the intrauterine strip area was not enhanced (**Figure 8**).

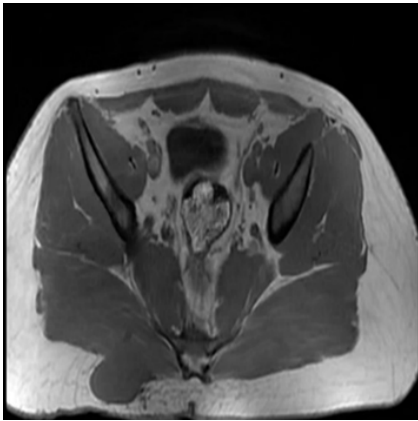


Figure 3. MRI T1WI image.

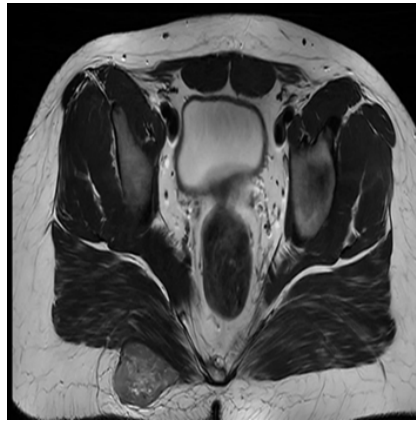


Figure 4. MRI T2WI image.

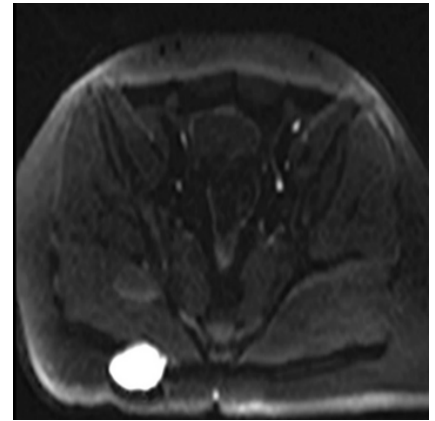


Figure 5. MRI T2-weighted imaging with fat suppression.

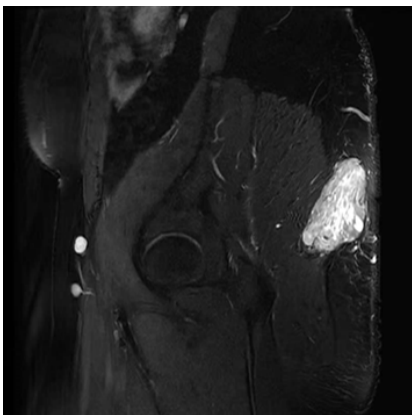


Figure 6. Diffusion weighted imaging, DWI.

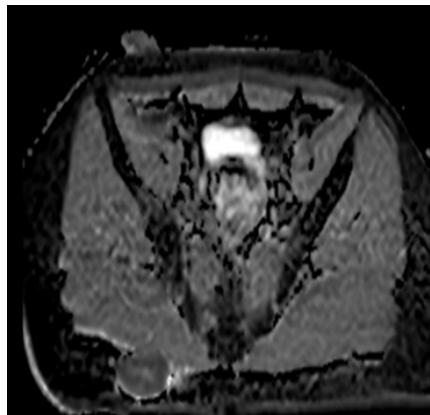


Figure 7. Apparent Diffusion Coefficient, ADC.

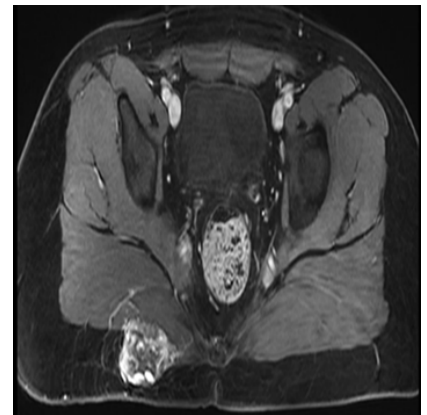


Figure 8. MRI enhanced scan image.

2.2.3. Positron emission computed tomography (PET/CT)

A soft tissue density mass was seen in the right buttock, with an indistinct boundary from the gluteus maximus on one side, approximately 50 mm × 27 mm × 65 mm in size, with abnormal FDG concentration, SUVmax of about 5.0. Multiple tortuous vascular shadows were seen subcutaneously in the lumbococcygeal region (**Figure 9** and **Figure 10**).

Based on the patient's age, medical history and imaging manifestations, mesenchymal malignant tumor was considered, with surgical indications, and surgery was proposed.



Figure 9. Plain CT scan image

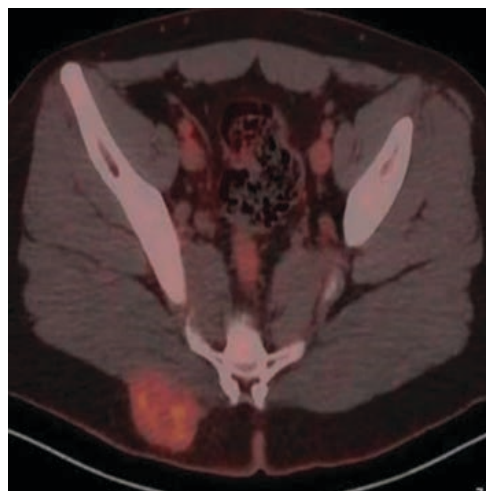


Figure 10. PET-CT image

2.3. Puncture and postoperative pathological results

The tumor tissue is arranged in an acinar pattern, with a rich network of slit-like capillaries in between. The cytoplasm of polygonal or large round tumor cells is rich in red staining, and some have nucleoli. Mitotic signs are rarely seen. Immunohistochemistry: CK/pan (-) EMA (-) Desmin (scattered few +) SMA (+) MyoD1 (-) Myogenin (-) TFE3 (+) S-100 (-) HMB45 (-) Melan-A (-) CD34 (interstitial vascular endothelium +) Ki-67 (about 3% to 5%+). Special staining: reticular fibers (showing acinar structures), D-PAS (showing a few PAS positive crystals in the cytoplasm), the lesion is considered to be alveolar soft part sarcoma (ASPS) (**Figure 11** and **Figure 12**).

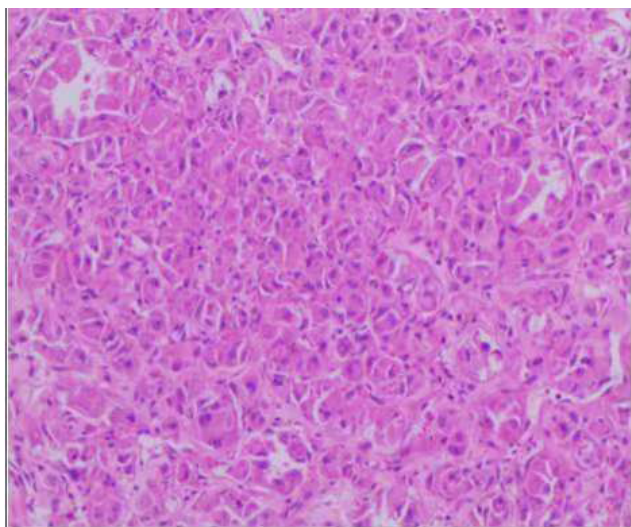


Figure 11. Puncture pathology.

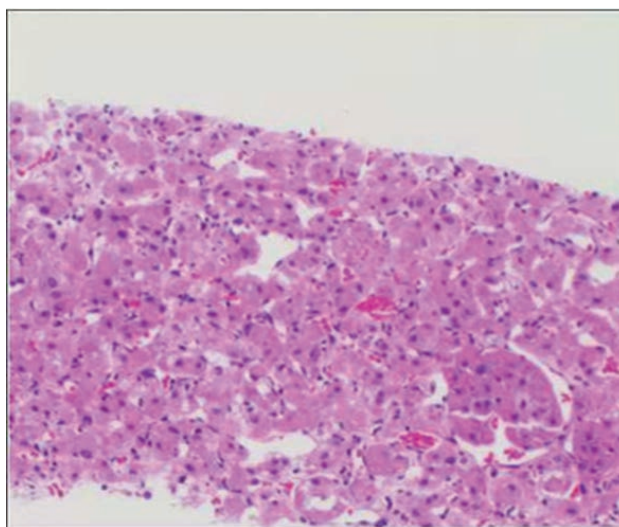


Figure 12. Postoperative pathological image.

3. Discussion

ASPS are malignant tumors with undetermined differentiation as defined in the 2020 WHO histological classification of soft tissue and bone tumors. Epidemiological studies have shown that the disease has a significant

gender bias and is more common in women aged 15–35 years old, especially in the deep muscles of the lower extremities and the buttocks. At the first diagnosis, the mass is often large, the tumor is deep, usually in the intermuscular space or between the muscle and the bone, and is not easily detected at an early stage ^[2]. ASPS grow slowly and often present as painless, progressively increasing masses, and are thus called “silent tumors.” Although the histological grade is mostly FNCLCC 1-2, the rate of metastasis is relatively high, about 20 to 40 percent, most often to the lungs (about 42 to 65 percent), followed by the brain and bones ^[3]. The treatment strategy for ASPS is extensive resection, and postoperative chemotherapy may be crucial for long-term survival.

3.1. Imaging findings

On CT images, ASPS typically present as slightly low-density masses with relatively clear boundaries. CT scans can clearly show the location, size, and shape of the tumor, and whether there are features such as calcification, bleeding, or adjacent bone destruction. However, CT has limited value for qualitative diagnosis of tumors.

3.2. The diagnosis of ASPS relies more on MRI

MRI imaging features: On T1WI, ASPS often shows isosignal or slightly hypersignal, and their signal characteristics are closely related to the abundance of blood components within the tumor and the relatively slow blood flow ^[4]. In some cases, small patchy necrotic foci can be observed within the tumor, presenting as low-signal areas on T1WI and high-signal areas on T2WI ^[5]. On T2WI, the lesion often shows uneven high signal, reflecting the heterogeneity of vascular structure and the diversity of cellular components within the tumor, and the characteristic empty vascular shadow is significant within and around the tumor ^[6]. Dynamic contrast-enhanced scans showed significant heterogeneous enhancement of the lesion, and the enhancement mechanism involved the combined effect of dense vascular networks, arteriovenous fistulas, and larger “blood pool” volumes ^[7]. DWI showed a significant reduction in the apparent diffusion coefficient (ADC) value, suggesting the dual effect of high cell density and abundant buried tube structure in the tumor, which is positively correlated with the malignancy of the tumor ^[8].

3.3. Pathological features

ASPS are typically structured with characteristic alveolar or nest-like arrangements, and the cytoplasm is rich in PAS staining positive anti-amylase rhombic or rod-like crystals. Immunoeexpression analysis showed strong positive expression of TFE3 in tumor cell nuclei, which has now become the gold standard for diagnosis ^[9]. At the molecular pathological level, ASPSCR1-TFE3 gene fusion is its specific molecular marker, and this genetic anomaly leads to the characteristic sinusiform vascular network structure in the tumor stroma by activating angiogenesis-related pathways (such as VEGF, MET). These vascular abnormalities are significantly associated with the therapeutic sensitivity of anti-angiogenic drugs, providing an important basis for molecular targeted therapy ^[10].

3.4. Differential diagnosis

ASPS need to be differentiated from the following soft tissue tumors:

- (1) Muscle or intramuscular hemangioma: significantly high signal on T2WI (“bulb sign”) with clear boundaries; Common venous stones or calcified components are seen on CT, with significant nodular enhancement after enhancement, and the pathological basis is vascular endothelial cell proliferation and

thrombotic organization^[11].

- (2) Arteriovenous malformations: Dominated by vascular masses, with less solid components, and the image shows “earthworm-like” empty shadows formed by the thick supplying arteries and draining veins^[12].
- (3) Synovial sarcoma: It is more common in young adults (20–24 years old), and is often seen in the deep soft tissues beside the joint (such as the knee joint, foot); Imaging manifestations are mostly marginal calcification and necrotic cystic lesion areas, lack of ASPS characteristic empty vessels, and enhancement in patchy moderate enhancement.
- (4) Myxomyfibrosarcoma: More common in the elderly (> 60 years old), mostly located beneath the superficial fascia; MRI shows “double low signal” (low signal on both T1WI and T2WI), and the pathology is mainly composed of collagen fiber bundles and mucinous matrix. After enhancement, the fiber components are significantly enhanced, and the mucinous area shows delayed enhancement^[13].

4. Summary

ASPS is a rare malignant tumor with low incidence and diverse clinical manifestations, making accurate preoperative diagnosis quite challenging. Currently, the preoperative diagnosis of ASPS mainly relies on imaging examinations, but the imaging manifestations lack specificity and are easily confused with other soft tissue tumors, resulting in a high rate of misdiagnosis. Therefore, there is an urgent need to further summarize and refine the imaging features of ASPS by accumulating more cases to provide a more reliable basis for a clear preoperative diagnosis in the future.

Disclosure statement

The authors declare no conflict of interest.

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Research Progress in Emergency Treatment for Patients with Cerebral Hemorrhage

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Abstract: As a severe neurological disease, cerebral hemorrhage is dangerous and progresses rapidly, with high disability and fatality rates. Its occurrence seriously harms patients' lives and health, and also causes a heavy social burden. Timely diagnosis and treatment of cerebral hemorrhage are essential for improving patients' prognosis. This article reviews the research progress in emergency treatment for patients with cerebral hemorrhage, providing a basis for diagnosis and treatment.

Keywords: Cerebral hemorrhage; Assessment; Diagnosis; Examination; Treatment

Online publication: August 7, 2025

1. Introduction

Cerebral hemorrhage, or primary non-traumatic parenchymal hemorrhage, accounts for 20–30% of acute strokes. It is characterized by high incidence, disability, and mortality rates. Epidemiological data show that there are 350,000 to 550,000 new cases annually in China, and the incidence rate increases significantly with age, reaching (120–180)/100,000 among people aged 45–75^[1]. The core etiology is hypertension combined with cerebral arteriolar sclerosis, accounting for about 60–70% of cases, followed by cerebral aneurysms (10–15%), arteriovenous malformations (5–10%), and coagulation dysfunction^[2]. The influencing factors are diverse, such as age, gender, uncontrolled hypertension, long-term alcohol abuse, smoking, etc. About 40–60% of survivors of cerebral hemorrhage suffer from neurological impairments such as hemiplegia and aphasia, and the long-term care dependence rate for severe patients exceeds 70%, posing continuous pressure on families and the social medical system^[3]. Early identification of abnormal blood pressure and control of risk factors are key strategies to reduce the disease burden. Timely diagnosis and treatment are crucial for reducing brain damage and improving the prognosis of patients with cerebral hemorrhage.

2. Early assessment of cerebral hemorrhage

2.1. Early imaging examination and laboratory testing

2.1.1. Imaging examination

Cranial CT and MRI can distinguish between cerebral hemorrhage, cerebral infarction, and primary or secondary space-occupying lesions. Compared to conventional MRI, CT examination has higher sensitivity in diagnosing edema. Therefore, in the early assessment of patients with cerebral hemorrhage, CT examination can be preferred to determine the patient's clinical manifestations, bleeding site and volume, and the presence of intraventricular hemorrhage and subarachnoid hemorrhage. To clarify the intracranial hemorrhage, especially for young patients with no history of hypertension and uncommon sites of cerebral hemorrhage, head MRI, head magnetic resonance angiography (MRA), or digital subtraction angiography (DSA) can be performed. The first classification based on the etiology of cerebral hemorrhage was released in 2012, indicating that the etiologies include drug-induced, hypertension, amyloid vascular disease, systemic diseases, structural etiologies, and unknown etiologies. This classification can provide a basis for determining the etiology of clinical cerebral hemorrhage and assessing patient prognosis.

2.1.2. Laboratory testing

There are many laboratory tests, including complete blood count, serum glucose, serum electrolytes, liver function, CRP, coagulation function, international normalized ratio, etc. Toxicology testing can be performed when drug abuse is suspected. Besides, patients' vital signs should be monitored using electrocardiographic monitoring.

2.2. Scales related to cerebral hemorrhage

2.2.1. Glasgow Coma Scale (GCS)

Since its introduction in 1974, the Glasgow Coma Scale (GCS) has become the most widely used quantitative assessment tool for coma severity in the world. This scale establishes a 15-point evaluation system based on three dimensions: eye-opening response (1–4 points), verbal response (1–5 points), and motor response (1–6 points). It boasts three core features: standardized operation, cross-cultural universality, and dynamic monitoring value. The GCS establishes objective quantitative criteria, providing an accurate basis for clinical decision-making through grading. The feasibility and professionalism of the scale design are strong. Currently, GCS has been included in 85% of stroke diagnosis and treatment guidelines in China, becoming a standard tool for assessing neurological function in patients with acute brain injury. The GCS score is widely used in the assessment of acute cerebral hemorrhage status, providing a basis for medical staff to assess the patient's condition early and helping to formulate timely response measures. However, the GCS score is not applicable to some patients, including children under 3 years old, patients with mental illness, communication disorders, or hearing loss. Applying this score to such patients may affect the accuracy of the assessment results. Additionally, the scoring can be influenced by the scorer's subjective consciousness, and the use of related drugs may also affect the assessment results.

2.2.2. Intracerebral Hemorrhage (ICH) clinical grading score

The ICH score is a grading system specifically designed for spontaneous intracerebral hemorrhage. It is simple to operate and highly practical, capable of predicting the risk of death within one month for patients with cerebral hemorrhage. In the early stages of cerebral hemorrhage, assessing the patient's clinical condition using the ICH score can provide a reference for clinicians to formulate treatment plans. However, the ICH score has certain

limitations, as some of its indicators have limited applicability among different global populations.

2.2.3. National Institutes of Health Stroke Scale (NIHSS) score

As a commonly used method to evaluate neurological impairment in stroke patients, the NIHSS score is calculated by summarizing the scores of 15 parameters. The patient's condition is inversely correlated with this score. The NIHSS score can not only assess the severity of stroke patients but also evaluate their treatment effectiveness. Research has shown that among the risk factors for poor prognosis in patients with cerebral hemorrhage, an NIHSS score of 20 or higher is one of the risk factors, suggesting that NIHSS can be used to assess the prognosis of patients with cerebral hemorrhage ^[4].

3. Emergency treatment of cerebral hemorrhage

3.1. Blood pressure management

Hypertension is not only one of the main causes of cerebral hemorrhage, but can also be induced by cerebral hemorrhage. Hypertension can affect the edema around the hematoma in patients with cerebral hemorrhage and may cause recent rebleeding. Among the factors contributing to a poor prognosis in patients with cerebral hemorrhage, hypertension is a significant one. Therefore, managing the patient's blood pressure is crucial. There is a positive correlation between elevated blood pressure and hematoma expansion in patients with cerebral hemorrhage. Effective blood pressure-lowering treatment during the acute phase can prevent hematoma expansion and improve the patient's prognosis. Guidelines recommend that hypertensive patients should use intravenous medication to control their systolic and diastolic blood pressure below 160 mmHg and 90 mmHg, respectively. Early intensive blood pressure lowering in patients has higher efficacy and safety compared to target blood pressure lowering. Studies by Liu Chang *et al.* ^[5] have shown that intensive blood pressure lowering treatment for hypertensive cerebral hemorrhage patients can reduce the risk of hematoma expansion, which is significantly positive for improving the patient's prognosis. Wang Yu *et al.*'s ^[6] research results indicate that using urapidil for intensive blood pressure lowering in cerebral hemorrhage patients can effectively control blood pressure and delay hematoma expansion.

3.2. Intervention for antiplatelet drug-related cerebral hemorrhage

In the early stages of spontaneous cerebral hemorrhage, neurological damage caused by the expansion of the hematoma or the intensification of edema around the hematoma is significant, which can have a notable impact on the patient's prognosis. Especially in acute cerebral hemorrhage, where the hematoma expands rapidly and often appears early, it is crucial to adopt scientific and standardized methods to limit its expansion to prevent further damage to the patient. Antiplatelet drugs, commonly used for various diseases, including stroke, are increasingly widespread. Although these drugs play a vital role in disease treatment, they also have side effects. Overuse can inhibit platelet function, potentially increasing the risk of bleeding events. Multiple studies have been conducted in China on whether to use platelet transfusion in the acute phase of cerebral hemorrhage, but this issue remains controversial. Commonly used antiplatelet drugs such as aspirin and clopidogrel have irreversible inhibitory effects on platelets, leading many scholars to shift their treatment goals to reversing platelet function. A phase III clinical trial involving 190 patients who developed symptoms within 6 hours was divided into a platelet transfusion group and a standard treatment group. The results showed that the fatality rate in the platelet transfusion group was

higher than that in the control group^[7]. Thus, platelet transfusion should be performed cautiously in the treatment of cerebral hemorrhage.

3.3. Intervention for anticoagulant drug-related cerebral hemorrhage

With the global increase in patients with thrombotic diseases such as atrial fibrillation and venous thrombosis, the incidence of anticoagulant drug-related cerebral hemorrhage (including vitamin K antagonists and novel oral anticoagulants) has shown a significant upward trend. The annual risk of bleeding for those receiving warfarin therapy ranges from 0.3% to 2.4%. Although the incidence of cerebral hemorrhage associated with novel oral anticoagulants is lower than that of warfarin, it is higher in certain patient groups, such as elderly patients and those with chronic kidney disease. Anticoagulant drug-related cerebral hemorrhage has unique clinical characteristics, including a hematoma expansion rate higher than 35% and a 24-hour mortality rate exceeding 25%. Due to abnormal coagulation function, the effectiveness of conventional hemostatic treatment is limited, and survivors are more likely to experience moderate to severe neurological dysfunction compared to non-anticoagulant-related cases. For warfarin-related cerebral hemorrhage, if the patient's international normalized ratio (INR) is below 1.3 within 4 hours of onset and their systolic blood pressure is controlled below 160 mmHg, the risk of intracranial hematoma expansion can be reduced. The reversal of warfarin's anticoagulant effect mainly focuses on supplementing coagulation factors, with options including fresh frozen plasma, prothrombin complex concentrates, vitamin K, and recombinant activated coagulation factor VII. Studies have shown that tranexamic acid is effective in treating cerebral hemorrhage caused by non-vitamin K antagonist oral anticoagulants^[8]. For anticoagulant drug-related cerebral hemorrhage, anticoagulant reversal agents should be used as early as possible, provided the patient's condition allows.

3.4. Use of hemostatic agents

Studies have explored whether recombinant human coagulation factor VIIa can be used for the treatment of cerebral hemorrhage. The results showed that the emergency use of hemostatic drugs in patients did not prevent hematoma expansion and did not improve patient functional outcomes^[9]. Some scholars have also pointed out that the application of tranexamic acid in patients with cerebral hemorrhage can prevent hematoma enlargement and improve hematoma area. It contains thrombin-like substances that can promote platelet aggregation, quickly stop bleeding at the site of cerebral hemorrhage, and prevent rebleeding^[10]. However, there are few studies on the use and dosage of hemostatic drugs in patients with cerebral hemorrhage, which requires further exploration.

3.5. Intervention for common complications

Complications of cerebral hemorrhage can aggravate the patient's condition and increase the risk of mortality, so timely intervention is needed for the complications that occur. For patients with fever, prompt cooling measures should be taken to restore normal body temperature. The patient's swallowing function should be evaluated to prevent aspiration and aspiration pneumonia, paying attention to the patient's posture. If the patient is at risk of gastrointestinal bleeding, gastric mucosal protective agents can be administered, strengthening patient observation and watching for active bleeding. For severe patients requiring mechanical ventilation, real-time monitoring of the patient's condition should be implemented to avoid acute respiratory distress syndrome.

4. Conclusion

Cerebral hemorrhage is a rapidly changing and dangerous condition. Early diagnosis and timely treatment are crucial for improving the patient's condition and prognosis. Currently, emergency treatment for cerebral hemorrhage patients mainly involves targeted therapeutic measures and symptomatic treatment based on patient examination and condition. However, there is a lack of standardized treatment processes and standard treatment plans. To ensure treatment effectiveness and improve patient prognosis, it is necessary to explore effective treatment methods and establish standardized treatment processes and plans.

Disclosure statement

The authors declare no conflict of interest.

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Study on the Preparation of Doxorubicin Hydrochloride Liposomes and Their Therapeutic Effect on Liver Cancer

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Abstract: *Objective:* This study aimed to prepare doxorubicin hydrochloride liposomes and explore their application value in patients with liver cancer. *Methods:* Doxorubicin hydrochloride liposomes were prepared using the ammonium sulfate gradient method. Doxorubicin, as a broad-spectrum antitumor drug, has significant toxic and side effects after toxicological investigation. After preparing DOX-Lip, single-factor analysis was used to analyze the effects of solution pH, number of ultrafiltration, oil-water ratio, incubation temperature, and time on the encapsulation efficiency of doxorubicin hydrochloride liposomes. The process was optimized through orthogonal experiments and then applied clinically. 110 patients with liver cancer were selected as the research subjects to verify the drug's effectiveness. *Results:* The results of this study showed that under optimal process conditions, the prepared doxorubicin hydrochloride liposomes were evenly distributed, similar to spherical shapes, with an average particle size of 85–87 nm and a Zeta potential of 15–16 mV, indicating good encapsulation efficiency. The application of these liposomes to clinical treatment of liver cancer demonstrated good therapeutic effects and could effectively promote favorable patient prognosis. *Conclusion:* The doxorubicin hydrochloride liposomes prepared through process optimization exhibit strong stability and pronounced sustained-release characteristics, providing a solid foundation for the treatment of liver cancer.

Keywords: Doxorubicin hydrochloride; Liposomes; Drug preparation; Liver cancer; Clinical efficacy

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1. Introduction

Liver cancer is a common malignant tumor in clinical practice, with high morbidity and mortality rates, mainly dominated by hepatocellular carcinoma ^[1]. There are no obvious clinical symptoms in the early stages of the disease, but in the middle and late stages, patients may experience pronounced right upper quadrant abdominal pain and aversion to greasy foods ^[2]. Some patients may also experience weight loss and lower extremity edema,

which seriously threatens their health. Currently, the main therapeutic drugs for hepatocellular carcinoma include fluorouracil, etc. [3], which can inhibit the development of tumor cells but also have certain side effects. Based on this, this study prepared doxorubicin hydrochloride liposomes using the ammonium sulfate gradient method, achieving an encapsulation efficiency exceeding 95%, which effectively solved the problem of low encapsulation efficiency. Furthermore, patients with liver cancer who visited our hospital from October 2023 to October 2024 were selected as research subjects to explore the application effects of doxorubicin hydrochloride liposomes in the treatment of liver cancer, as detailed below.

2. Materials and methods

2.1. Reagents and instruments

Reagents: Doxorubicin hydrochloride (Ouyi Pharmaceutical Co., Ltd. of Shijiazhuang Pharmaceutical Group), hydrogenated soy phosphatidylcholine (Hubei Wei's Chemical Reagent Co., Ltd.), pegylated phosphatidylethanolamine (Jiangsu Southeast Nano Materials Co., Ltd.), cholesterol (Anhui Kebao Bioengineering Co., Ltd.), ammonium sulfate (Shandong Jinruida Biochemical Co., Ltd.), histidine (Zhengzhou Yuhe Food Additive Co., Ltd.), sucrose (Zhengzhou Dewang Chemical Industry Co., Ltd.), ethanol (Anhui Shuanghui Biological Industry Co., Ltd.), isopropanol (Shandong Xuchen Chemical Technology Co., Ltd.), ammonium chloride (Shandong Lubei Chemical Co., Ltd.), sodium chloride (Shouguang Chenlong Chemical Co., Ltd.).

Instruments: Particle size analyzer (Beijing Yaou Depeng Technology Co., Ltd.), electronic balance (Kunshan Lugong Precision Instrument Co., Ltd.), constant temperature heating magnetic stirrer (Zhengzhou Shiji Shuangke Experimental Instrument Co., Ltd.), constant temperature water bath shaking tank (Changzhou Gaode Instrument Manufacturing Co., Ltd.), cryo-transmission electron microscope (Shuimu Keyi Technology Co., Ltd.).

2.2. DOX Measurement method

2.2.1. Chromatographic conditions

The specific chromatographic conditions are set as follows: Chromatographic column: XDB-C18 (4.6×250 mm); Mobile phase: 0.28% sodium dodecyl sulfate solution - methanol - acetonitrile; Wavelength: 254 nm; Flow rate: $1.0 \text{ mL} \cdot \text{min}^{-1}$; Column temperature: 30°C .

2.2.2. Specificity test

Select the control solution, and compete for the drug-loaded liposomes and blank liposomes, dilute with methanol, then take the supernatant, and analyze it according to the chromatographic conditions to investigate its specificity. Subsequently, the linear relationship was investigated. Precision measurement involves the vector configuration of DOX reference substances to form a standard storage solution with a concentration of $0.2 \text{ mg} \cdot \text{mL}^{-1}$. Then, a certain amount of solution was taken to prepare solutions with concentrations of 14, 16, 20, 24, and $26 \text{ } \mu\text{g} \cdot \text{mL}^{-1}$, respectively, and analyzed according to the corresponding conditions, and the corresponding standard curve was drawn.

2.2.3. Preparation of doxorubicin hydrochloride liposomes

Prepare doxorubicin hydrochloride liposomes by the ammonium sulfate gradient method. Dissolve lipid components such as hydrogenated soy phosphatidylcholine, cholesterol, and pegylated phosphatidylethanolamine

in organic solvents to form a lipid solution ^[4]. Use a rotary evaporator or thin-film dispersion method to remove organic solvents and form a lipid film. Prepare an ammonium sulfate solution and use it to hydrate the lipid film to obtain a suspension containing blank liposomes. Use a high-pressure homogenizer or extruder to prepare the blank liposome suspension into liposomes with uniform particle size. Use tangential flow technology or column chromatography to remove ammonium sulfate outside the liposomes, forming an ammonium sulfate gradient inside and outside the phospholipid membrane ^[5]. Dissolve doxorubicin hydrochloride in an appropriate solvent to prepare a drug solution. Under heating conditions, mix the drug solution with blank liposomes to allow the drug to diffuse into the liposomes driven by the ammonium sulfate concentration gradient. Post-processing: Use methods such as dialysis or ultrafiltration to remove unencapsulated drugs and impurities. Add excipients such as sugar and buffers to adjust the stability and pH of the liposomes. Sterilize by filtration, and dispense to obtain the finished product ^[6].

2.2.4. Liposome characterization

For particle size distribution, take the corresponding amount of doxorubicin hydrochloride liposome solution, place it in the sample cell, and measure the Zeta potential using a particle size analyzer. For morphological determination, observe the morphology of liposomes using an electron microscope. Select a certain amount of doxorubicin hydrochloride liposomes, place them on a copper grid, and observe their morphology after freezing. For encapsulation efficiency testing, use a glucose gel filtration method to detect doxorubicin hydrochloride liposomes. The calculation methods are shown in formulas 1 and 2.

$$\text{Encapsulation Efficiency} = ([DOX]_{\text{Encapsulated}} / [DOX]_{\text{Total}}) \times 100\% \quad (\text{Formula 1})$$

$$\text{Recovery Rate} = ([DOX]_{\text{Encapsulated}} + [DOX]_{\text{Free}}) / [DOX]_{\text{Total}} \times 100\% \quad (\text{Formula 2})$$

2.2.5. Single factor analysis method

Using DOX encapsulation efficiency as the observation index, factor analysis was performed on the pH of the ammonium sulfate solution, oil-water ratio, extrusion times, ultrafiltration times, incubation temperature, and incubation time.

2.3. Statistical methods

The statistical data involved in this study were processed and calculated using SPSS 21.00 software. Chi-square test was selected for measurement data, and *t*-test was used for counting data. When the calculation result shows $P < 0.05$, it means that the difference is statistically significant.

3. Results

3.1. Establishment of content determination method

In the specificity test, detection was carried out according to chromatographic conditions. Under such chromatographic conditions, the reference solution and the drug-loaded liposomes reached the maximum absorption peak at 254 nm, and the blank liposomes did not show a chromatographic peak at the same retention time, indicating high specificity. See **Figure 1** for details.

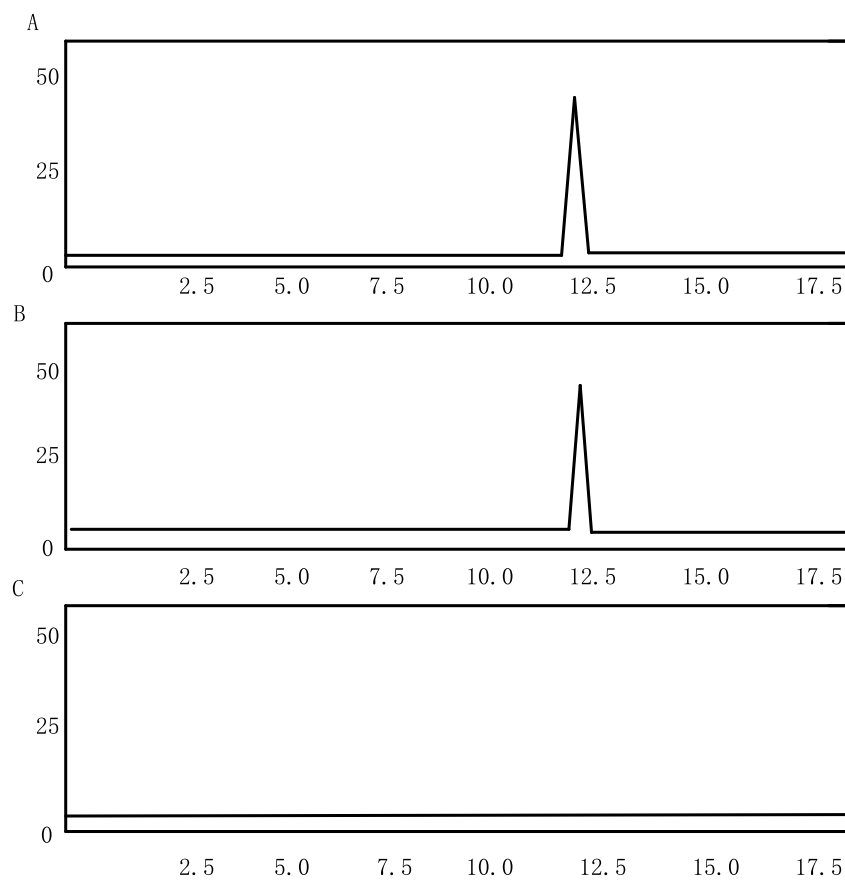


Figure 1. Results of specific chromatogram.

3.2. Recovery test

The configured solution was analyzed by chromatographic conditions, and the study results found that the recovery rates were all above 95%, meeting the HPLC content requirements.

3.3. Single factor analysis

Through single-factor analysis, it was found that ammonium sulfate solution is one of the main influencing factors of liposome encapsulation efficiency. When the pH value increases, there is no significant change trend in the encapsulation efficiency of liposomes. As the number of ultrafiltrations increases, the encapsulation efficiency of liposomes mainly shows a trend of increasing first and then decreasing. When the oil-water ratio is 1:6–1:10, as the oil-water ratio decreases, but the volume of ethanol is small, the concentration of the filter paper solution increases, and the particle size also increases. Therefore, the oil-water ratio is set to 1:10. As the number of extrusions increases, the particle size decreases. After 8-10 extrusions, there are no significant changes in sample particle size and encapsulation efficiency. Therefore, the number of extrusions is set to 10. Through orthogonal experiments, the preparation process of optimized liposomes was discovered. See **Table 1** for details.

Table 1. Analysis of orthogonal experiment results

Trial	Factor A	Factor B	Factor C	Factor D	Encapsulation efficiency
1	1	1	1	1	85.62
2	1	2	2	2	91.33
3	1	3	2	3	97.46
4	2	1	2	3	80.64
5	2	2	3	1	93.75
6	2	3	1	2	91.52
7	3	1	3	2	73.21
8	3	2	1	3	82.27
9	3	3	2	1	90.89
K1	274.25	239.50	259.43	270.28	-
K2	265.98	267.33	262.88	256.07	-
K3	246.39	279.88	264.41	260.38	-
k1	91.50	79.80	86.48	90.10	-
k2	88.65	89.14	87.60	85.36	-
k3	82.14	93.30	88.15	86.80	-
R	9.36	13.49	1.68	4.74	-

3.4. Analysis of application effects

Compared with the control group, the total effective rate of treatment in the observation group was significantly higher, and the difference was statistically significant ($P < 0.05$). See **Table 2** for details.

Table 2. Comparison of clinical efficacy results between the two groups

Group	Cases	Markedly effective, n(%)	Effective, n(%)	Ineffective, n(%)	Total effective rate, n(%)
Control group	55	18 (32.73)	27 (49.09)	10 (18.18)	45 (81.82)
Observation group	55	21 (38.18)	32 (58.18)	2 (3.64)	53 (96.36)
χ^2	-	-	-	-	5.986
P	-	-	-	-	0.014

4. Discussion

Doxorubicin hydrochloride, also known as Adriamycin hydrochloride, has a relatively broad antibacterial spectrum. However, during the treatment process, doxorubicin hydrochloride also exhibits certain drug resistance [7], limiting its clinical application. Relevant studies have directly pointed out that doxorubicin hydrochloride liposomes, as a nano-drug preparation, can be prepared by the ammonium sulfate gradient method with an encapsulation efficiency exceeding 95% [8]. Moreover, doxorubicin hydrochloride liposomes have a certain inhibitory effect on RNA and DNA synthesis and play a significant role in liver cancer cells. Due to the influence of liposomes, they can not only prolong the half-life of the drug but also reduce its side effects, thereby controlling

the disease ^[9]. As a novel drug carrier, liposomes have shown great potential in the field of drug delivery since their discovery in the 1970s, owing to their unique biocompatibility, degradability, and targeting ability. Liposomes are composed of phospholipid bilayers that can encapsulate hydrophilic or hydrophobic drugs and deliver them precisely to tumor tissues through passive or active targeting ^[10]. Additionally, liposomes can extend the circulation time of drugs in the bloodstream, reduce exposure to non-target tissues, thereby reducing toxicity and improving efficacy.

Based on this, the present study prepared doxorubicin hydrochloride liposomes using the ammonium sulfate gradient method and applied them in clinical settings. The results indicated that the final determined process involved an oil-water ratio of 1:10, an extrusion time of 8, a fusion pH of 5 for ammonium sulfate, a temperature of 55 °C, and an incubation time of 20 minutes. The prepared doxorubicin hydrochloride liposomes exhibited good processability. Clinical validation revealed that they could effectively improve clinical efficacy.

5. Conclusion

In summary, doxorubicin hydrochloride liposomes can be prepared using the ammonium sulfate gradient method and applied in clinical settings to enhance clinical efficacy. However, further clarification of the correlation between drug release in vitro and in vivo is needed to ensure the consistency between doxorubicin hydrochloride liposomes and RLD.

Disclosure statement

The authors declare no conflict of interest.

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Neoadjuvant Therapy with Alectinib for Non-Small Cell Lung Cancer with Pleural Metastasis: A Case Report

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Abstract: *Background:* The prognosis of stage IV non-small cell lung cancer (NSCLC) with pleural metastasis is poor, with a 5-year survival rate of only 2% to 4% for patients, with the median survival was 9.5-11.5 months. According to the “NCCN Lung Cancer Guidelines,” stage IV NSCLC lung cancer is a contraindication for surgery. It is recommended to adopt a standard treatment plan mainly based on chemotherapy or targeted therapy with EGFR-TKIs. However, Neoadjuvant therapy with alectinib for non-small cell lung cancer with pleural metastasis is rarely reported. *Case presentation:* A 41-year-old Asian male patient presented with a persistent cough for one month. A chest computed tomography (CT) scan conducted two years prior revealed that a nodular radiative anomalous concentrated shadow was observed in the inferior tongue segment of the upper lobe of the left lung, approximately $2.2 \times 1.6 \times 1.2$ cm in size, with a SUVmax of about 5.5. Two small nodular shadows were seen beside the disease in the inferior lingual segment of the upper lobe of the left lung, with the larger one having a diameter of approximately 0.6 cm. Multiple lymph node metastases in the left hilum and mediastinum; Multiple metastases of the left pleura and a small amount of pleural effusion on the left side. The patient began to receive 2 courses of chemotherapy and targeted therapy (pemetrexed+ carboplatin+crizotinib) and 1 course of chemotherapy and other targeted therapy (pemetrexed+ carboplatin+ alectinib). The result of re-examination of CT demonstrated that peripheral lung cancer in the lower lingual segment of the left upper lung is approximately 0.8×0.9 cm in size, slightly smaller than before. A thoracoscopic lobectomy was performed, and the pulmonary bulla was removed concurrently. Pathological examination confirmed non-small cell lung carcinoma (NSCLC) in the mass. Patient discharged on the 7th day after the operation and received 2 courses of chemotherapy (pemetrexed + carboplatin) and had been receiving alectinib targeted drug treatment all along for over 5 years. However, the patient stopped taking the medicine on his own for half a year. Though in the recent CT examination, the result demonstrated no recurrence and metastasis and the patient has been clinically cured. Unfortunately, the results of brain magnetic resonance imaging suggested that multiple brain metastases of lung cancer occurred, and the patient began taking the third-generation ALK-targeted drug lorlatinib. *Conclusions:* The patient with stage IV non-small cell lung cancer (NSCLC) presenting with pleural

metastasis received neoadjuvant alectinib therapy and underwent thoracoscopic lobectomy, which resulted in significant therapeutic effects and fulfilled the criteria for clinical cure. This case highlights the potential for improved preventative strategies and treatment approaches in similar patients.

Keywords: NSCLC; Pleural metastasis; Neoadjuvant alectinib therapy; Alectinib

Online publication: August 5, 2025

1. Introduction

Lung cancer is the malignant tumor with the highest incidence and mortality rates in China and worldwide, accounting for approximately 22.7% of all malignant tumor deaths. Among them, non-small cell lung cancer (non-small cell lung cancer). Deaths from NSCLC account for approximately 85% of all lung cancer deaths ^[1]. The 8th edition of the TNM staging of lung cancer by the Union for International Cancer Control (UICC) classifies pleural metastasis as stage IV (M1a). The 5-year survival rate of patients with stage IV NSCLC is only 2% to 4%, while the median survival period of M1a patients is 9.5 to 11.5 months, with a very poor prognosis. In principle, surgical intervention is not recommended ^[1]. According to the “NCCN Lung Cancer Guidelines”, stage IV NSCLC lung cancer is a contraindication for surgery. It is recommended to adopt a standard treatment plan mainly based on chemotherapy or targeted therapy ^[1]. Whether surgical treatment is necessary is not clearly stated. However, a large number of studies have shown that in patients with non-small cell lung cancer and dry pleural metastasis, surgical resection of the primary tumor is beneficial. Ichinose Y *et al.* first reported in 2001 that tumor resection has a good therapeutic effect on the prognosis of NSCLC patients with local pleural metastasis, with 3-year and 5-year survival rates of 31.8% and 22.8%, respectively ^[2]. Studies have shown that complete resection of the primary tumor, being female, and having a lower N stage are favorable prognostic factors ^[3–7]. Resection of the primary lesion may locally control the progression of the disease. At the same time, chemotherapy or targeted therapy can delay the progression of the disease, thus significantly prolonging the survival period of patients.

Since the sensitivity of tyrosine kinase inhibitors (TKIs) to epidermal growth factor receptor mutations was discovered, the treatment strategies for NSCLC have undergone significant changes. At present, the “NCCN Lung Cancer Guidelines” recommend EGFR-TKIs as the first-line treatment for advanced NSCLC, which has received extensive clinical support ^[1]. Multiple studies have shown that EGFR-Tkis, as first-line treatment drugs, can significantly improve the survival rate of NSCLC patients with EGFR mutation positivity and dry pleural metastasis ^[8–10]. Greenhalgh *et al.* demonstrated that the use of TKIs in patients with EGFR mutation-positive localized metastatic NSCLC could significantly prolong the overall survival rate and progression-free survival of the patients ^[11]. The study found that there was no significant difference in the efficacy of multi-drug combination compared with single-drug targeted therapy. Li Y *et al.* analyzed the US Electronic Health database and found that for patients with advanced NSCLC, the time interval between two treatments was significantly longer for those treated with EGFR-TKIs compared with those treated with other first-line systemic therapies ^[12].

This indirectly indicates that for DPD patients with EGFR mutation-positive, TKIs have higher cytotoxicity. However, other targeted therapy drug such as alectinib is rarely reported in the advanced NSCLC with pleural metastasis. Alectinib represents a second-generation inhibitor of the ALK tyrosine kinase ^[13]. By specifically targeting and inhibiting the function of ALK fusion proteins, it interferes with downstream signaling pathways, which in turn reduces the proliferation of tumor cells and promotes apoptosis. The drug’s approved use is explicitly for individuals

with ALK-positive locally advanced or metastatic non-small cell lung cancer. Before its administration, it is essential to confirm the presence of ALK fusion through genetic testing methods such as FISH, PCR, or NGS ^[14]. This medication is acknowledged as a primary therapeutic option for adults diagnosed with ALK-positive non-small cell lung cancer (NSCLC) and is also employed as a second-line treatment for patients who have already been treated with crizotinib ^[15].

2. Case presentation

A 41-year-old Asian male patient presented with a persistent cough for one month. A chest computed tomography (CT) scan demonstrated that a nodular radiative anomalous concentrated shadow was observed in the inferior tongue segment of the upper lobe of the left lung, approximately $2.2 \times 1.6 \times 1.2$ cm in size, with a SUVmax of about 5.5. Two small nodular shadows were seen beside the disease in the inferior lingual segment of the upper lobe of the left lung, with the larger one having a diameter of approximately 0.6 cm. Multiple lymph node metastases in the left hilum and mediastinum; Multiple metastases of the left pleura and a small amount of pleural effusion on the left side (**Figure 1A**). The patient reported no additional symptoms or smoking history. Laboratory investigations at admission included lung tumor marker analysis, which showed an elevated carcinoembryonic antigen (CEA) level of 83.9 ng/mL (reference value ≤ 5.00 ng/mL). Routine blood tests and coagulation function tests were within normal limits. Contrast-enhanced chest CT demonstrated that a solid nodule shadow was seen in the lower tongue segment of the left upper lung. A small cavity was observed within the lesion, approximately 1.3×1.0 cm in size, with uneven density, irregular shape, and lobulation. Spicules and pleural traction could be seen at the edge. After enhancement, there was an obvious uneven enhancement. ALK mutation testing was performed, and the result was positive. The CT values before and after enhancement were approximately 25/49 HU. A solid small nodule shadow was seen beside the lesion, with a diameter of about 6mm and a clear boundary. To further evaluate the possibility of lung cancer, a whole-body ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) scan (**Figure 1B–1D**).

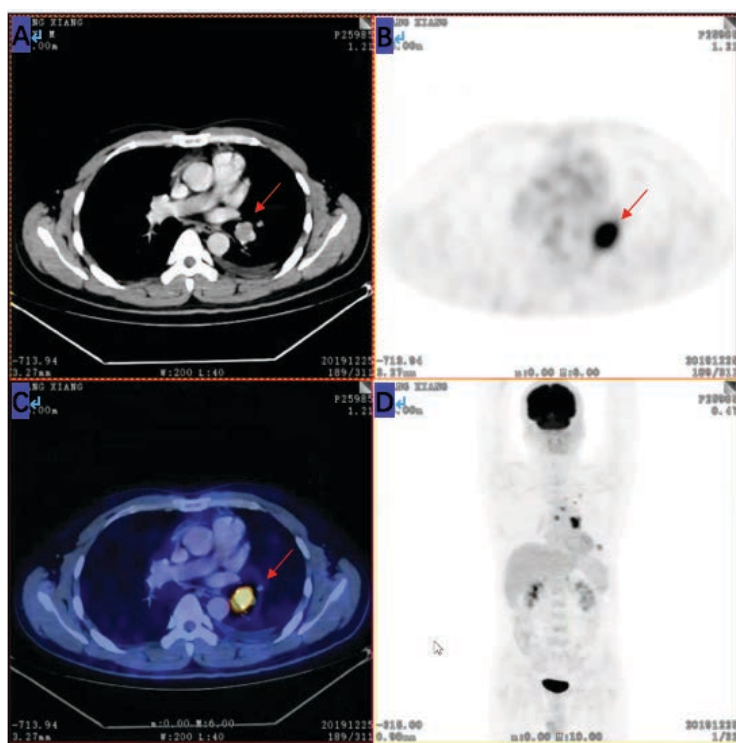


Figure 1. (A) Chest CT image demonstrating a high-density mass (red arrow) located the inferior tongue segment of the upper lobe of the left lung. (B–D) Whole-body ¹⁸F-FDG PET image showing increased FDG uptake in the mass (red arrow).

The PET scan revealed that a nodular radiative anomalous concentrated shadow was observed in the inferior tongue segment of the upper lobe of the left lung, approximately $2.2 \times 1.6 \times 1.2$ cm in size, with a SUVmax of about 5.5. On CT, a soft tissue density nodular shadow was seen in the above area, with a relatively clear boundary, lobulated edge, adjacent to the pleural cavity, and the density within it was relatively uniform. Enhanced scanning showed enhancement. Two small nodular shadows were seen beside the lower lingual segment of the upper lobe of the left lung in this disease. The larger one was about 0.6cm in diameter, and no radioactive abnormal concentration was observed. The left oblique fissure pleura is thickened, and no radioactive abnormal concentration is observed. Small patchy ground-glass density shadows were seen in the dorsal segment of the lower lobe of the left lung, and no radioactive anomaly concentration was observed. A few patchy cord-like shadows were seen in the posterior basal segment of the lower lobe of the left lung, and no radioactive anomaly concentration was observed. Several nodular radioactive abnormal concentrated shadows were seen in the left hilum and mediastinum (4L7), with the maximum approximately 2.7×2.0 cm. The SUVmax was about 12.7. CT showed several lymph node shadows in the above areas, with clear boundaries. No definite abnormal density shadows or radioactive concentration lesions were observed in the trachea and the main bronchi on both sides. Multiple nodular thickening was observed in the left pleura, showing radioactive abnormal concentration, with a SUVmax of approximately 3.4. A small amount of fluid density shadow was seen in the left thoracic cavity, while no effusion was observed in the right thoracic cavity. Mild physiological radioactive concentration in the myocardium. No obvious mass, lumen enlargement, or radioactive abnormal concentration was observed in the esophagus. The patient firstly received 2 courses of chemotherapy and targeted therapy (pemetrexed + carboplatin + crizotinib). The result of re-examination of CT revealed that the nodule size showed no significant change (Data not shown). Subsequently, the patient received 1 course of chemotherapy and other targeted therapy (pemetrexed + carboplatin + alectinib). The result of re-examination of CT demonstrated that peripheral lung cancer in the lower lingual segment of the left upper lung is approximately 0.8×0.9 cm in size, slightly smaller than before (**Figure 2**).

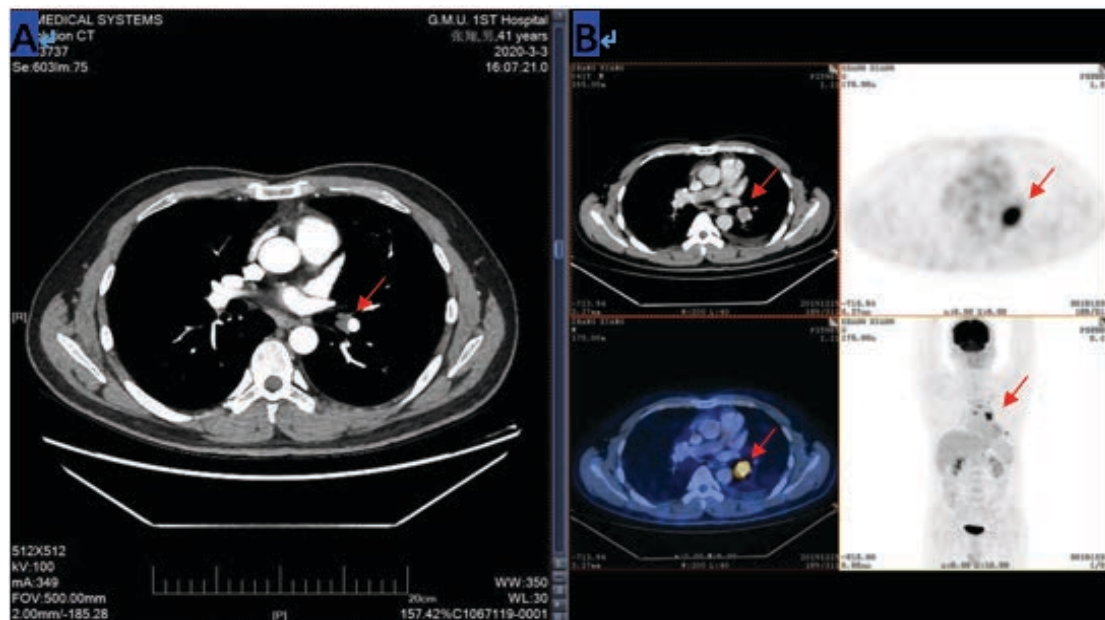


Figure 2. (A) Chest CT image demonstrating a high-density mass (red arrow) located the inferior tongue segment of the upper lobe of the left lung. (B) Whole-body ^{18}F -FDG PET image showing increased FDG uptake in the mass (red arrow).

A thoracoscopic lobectomy was performed, and the pulmonary bulla was removed concurrently. Pathological examination confirmed non-small cell lung carcinoma (NSCLC) in the mass (**Figure 3**).

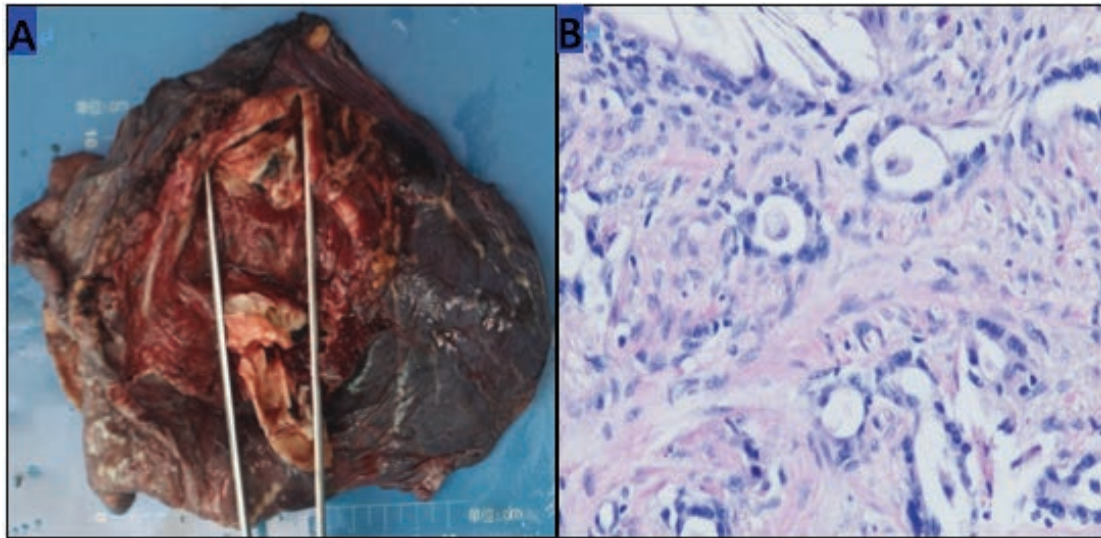


Figure 3. (A) The excised left lung over 10 cm contained a mass 40 mm × 26 mm × 22 mm. (B) Histological examination of the specimen revealed invasive lung adenocarcinoma (hematoxylin and eosin [H&E] staining, × 400).

The result of re-examination of CT demonstrated a total resection of the left lung (**Figure 4**). Patient was discharged on the 7th day after the operation and received 2 courses of chemotherapy (pemetrexed+ carboplatin) and had been receiving alectinib targeted drug treatment all along in the recent 5 years. However, the patient stopped taking the medicine on his own for half a year. Though in the recent CT examination, the result demonstrated no recurrence and metastasis and the patient has been clinically cured. Unfortunately, the results of brain magnetic resonance imaging suggested that multiple brain metastases of lung cancer occurred, the patient began taking the third-generation ALK-targeted drug lorlatinib.

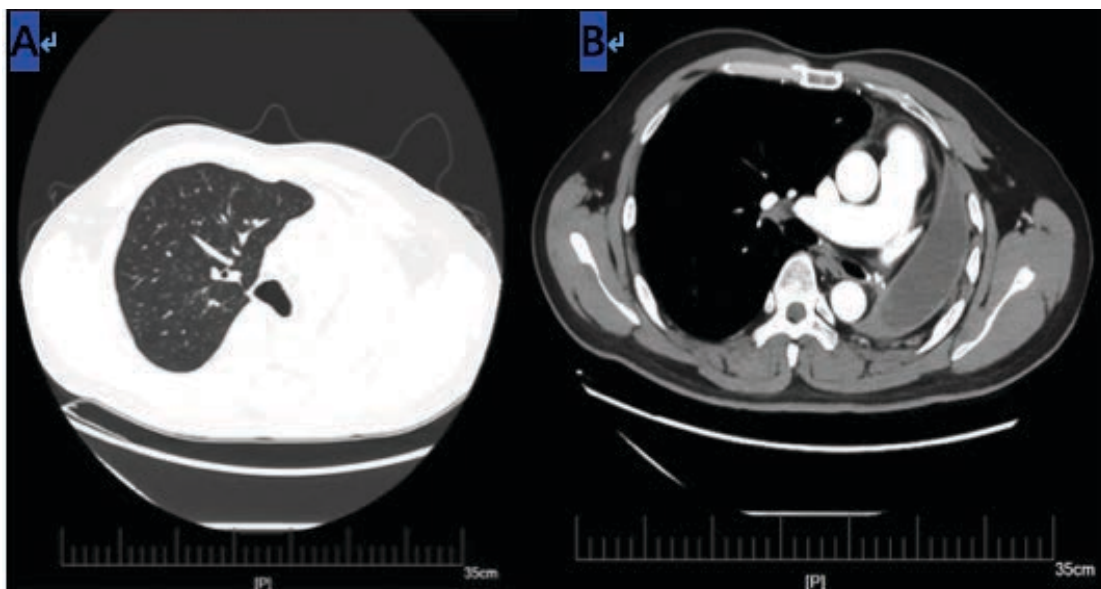


Figure 4. (A) The Chest CT image after thoracoscopic lobectomy. (A) Lung window; (B) Mediastinal window.

3. Discussion and Conclusions

Pleural dissemination is one of the important metastasis modes of non-small cell lung cancer and also one of the factors associated with a poor prognosis. UICC uniformly incorporates pleural dissemination into M1a, but pleural dissemination is not a single disease entity but a general term for a series of diseases, ranging from localized pleural nodules to malignant pleural effusion. The survival rate over five years for individuals diagnosed with stage IV non-small cell lung cancer (NSCLC) ranges between 2% and 4%. Additionally, the median survival duration for patients with metastatic illness is approximately 9.5 to 11.5 months, indicating a highly unfavorable prognosis. Generally, surgical procedures are not advised. The “NCCN Lung Cancer Guidelines” designate stage IV NSCLC as inappropriate for surgical intervention. Instead, a conventional treatment approach that focuses primarily on chemotherapy or targeted therapy is suggested. With the advancement of technology, the impact of gene mutations on the pleural metastasis of lung cancer has gradually been revealed.

Currently, the “NCCN Lung Cancer Guidelines” advise the use of EGFR-TKIs as the primary therapeutic option for advanced NSCLC, a recommendation backed by substantial clinical evidence¹. Numerous research studies indicate that EGFR-TKIs, when used as first-line treatment agents, can greatly enhance the survival rates of NSCLC patients who are positive for EGFR mutations and have dry pleural metastasis^[16–19]. Alectinib is a second-generation ALK tyrosine kinase inhibitor. By targeting and inhibiting the activity of ALK fusion proteins, it blocks downstream signaling pathways, thereby suppressing tumor cell proliferation and inducing apoptosis. Its indication is clearly defined as ALK-positive locally advanced or metastatic non-small cell lung cancer. It should be used after confirming the ALK fusion status through genetic testing (such as FISH, PCR or NGS). It is recognized as a primary treatment option for adult individuals diagnosed with ALK-positive non-small cell lung cancer (NSCLC) and is utilized as a second-line therapy in patients who have already undergone treatment with crizotinib. Literature indicates that it notably extends progression-free survival when compared to chemotherapy in patients dealing with advanced non-small cell lung cancer. Similar to a previous case report, which described a 24-year-old woman with malignant massive pleural effusion caused by ALK rearranged pulmonary adenocarcinoma with pleural and pericardial metastasis receiving alectinib rescue therapy, the present case received alectinib targeted drug treatment during the perioperative period and all along in the recent 5 years. In the recent CT examination, the result demonstrated no recurrence and metastasis and the patient has been clinically cured. This novel attempt may offer new perspectives and directions for the neoadjuvant therapy on non-small cell lung cancer patients with pleural metastasis.

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Research Progress on Integrated Chinese and Western Medicine Nursing Techniques in the Perioperative Period of Thyroid Cancer

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Abstract: Nursing care during the perioperative period of thyroid cancer plays a crucial role in the recovery of patients. With the development of medical technology, Western medicine nursing techniques have matured in the perioperative period, including preoperative risk assessment and airway management, intraoperative neuromonitoring nursing coordination, postoperative drainage, and incision management. However, single Western medicine nursing often cannot fully meet the multifaceted needs of patients, especially in emotional nursing and the management of postoperative adverse reactions. The involvement of traditional Chinese medicine nursing techniques provides an effective complement to nursing work. Through integrated Chinese and Western medicine nursing, it is possible not only to improve patients' preoperative anxiety and postoperative nausea and vomiting but also to effectively manage postoperative pain, enhancing the overall comfort and recovery speed of patients.

Keywords: Integrated Chinese and Western medicine nursing techniques; Thyroid cancer; Perioperative period; Research progress

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1. Introduction

Thyroid cancer is a common endocrine malignancy in clinical practice. The quality of perioperative nursing care directly affects the quality of postoperative recovery and prognosis of patients. Preoperative, intraoperative, and postoperative nursing care are essential for good postoperative recovery and quality of life. Although Western medicine nursing techniques for thyroid cancer have been fully and effectively applied, such as preoperative risk assessment and airway management to reduce surgical risks, intraoperative neuromonitoring nursing coordination to ensure surgical safety, and new techniques for postoperative drainage and incision management to facilitate wound healing and prevent surgical site infections, traditional Western medicine nursing techniques still have

limitations in controlling surgical risks, intraoperative responses, and postoperative management. In particular, there are significant deficiencies in adjusting patients' mental state and controlling postoperative adverse reactions. Traditional Chinese medicine nursing techniques can effectively fill this gap. Therefore, improving perioperative nursing care for thyroid cancer patients by combining Chinese and Western medicine nursing techniques has become a current research direction in nursing science.

2. Special requirements for perioperative nursing of thyroid cancer

Perioperative nursing for thyroid cancer is a systematic management of the surgical nursing process, involving both physiological and psychological issues. Unlike other cancers, thyroid cancer patients often have stronger concerns about the decrease in body hormones after surgery. As nursing staff, it is necessary to not only consider physiological recovery issues but also take into account hormone regulation to avoid problems such as hypocalcemia and thyroid dysfunction. Nursing is no longer just a technical issue; it involves more care and companionship from the nursing staff. During the treatment process, patients often experience mixed emotions of tension and anxiety, especially when facing total thyroidectomy. Patients generally have fears about changes in their physiological condition ^[1]. Therefore, perioperative nursing should not only focus on preoperative preparations and intraoperative cooperation but also emphasize psychological nursing and emotional communication. Nursing staff need to listen to patients' concerns with a gentle attitude, provide psychological comfort, and help them correctly understand the treatment process and surgery to reduce psychological anxiety and burden. Considering various physiological and psychological issues, perioperative nursing for thyroid cancer is a lasting process of trust-building and emotional maintenance. The success of nursing is not only due to technical factors but also relies on establishing a good relationship with patients through increased trust.

3. Application progress of Western nursing techniques in the perioperative period

3.1. Preoperative risk assessment and airway management

Preoperative risk assessment and airway management are also important aspects of perioperative nursing for thyroid cancer, which are crucial for patient safety during surgery. Given the complex anatomical sites involved in the clinical treatment of thyroid cancer, a detailed preoperative assessment of patients is particularly important. This is not a simple evaluation of patients' basic diseases but a comprehensive consideration of various factors such as patients' basic disease status, respiratory conditions, and high-risk factors of the airway. A careful preoperative assessment can provide more assistance for intraoperative airway evaluation, especially for patients with comorbidities. In terms of airway management, medical staff need to closely cooperate with anesthesiologists. For elderly patients, obese patients, and patients with pharyngeal deformities who have high-risk airway diseases, nursing staff should manage high-risk factors of the airway before surgery to reduce the incidence of intraoperative airway obstruction ^[2]. Additionally, preoperative inspection of airway management devices, such as laryngeal masks and endotracheal tubes, should be improved to prevent difficulties in emergency treatment of airway obstruction during surgery. Through careful management and monitoring of patients' airways, the incidence of airway problems during surgery can be effectively reduced, thereby lowering intraoperative risks and facilitating postoperative recovery.

3.2. Intraoperative neuromonitoring nursing coordination

Intraoperative neuromonitoring is an important technique during thyroid cancer surgery, especially for monitoring the recurrent laryngeal nerve. Damage to the recurrent laryngeal nerve can lead to serious consequences such as loss of voice and difficulty breathing for the patient after surgery. Therefore, protecting this nerve should be a key focus for surgeons during the operation. Intraoperative neuromonitoring is an important task for nurses, who need to cooperate with surgeons to monitor the nerves. If there is a malfunction in the neuromonitoring equipment during surgery, nurses should respond promptly. Neuromonitoring is not only an operational technique for monitoring nerve equipment, but also a surgical technique to protect patients' lives. Nurses must closely cooperate with surgeons to monitor intraoperative nerve conditions and make timely emergency responses in case of abnormalities. Additionally, preoperative and postoperative neurological function assessments cannot be ignored. Nurses need to observe patients' neurological functions, such as speech and respiratory functions, until they recover. Intraoperative neuromonitoring not only guarantees surgical precision but also guarantees the quality of life of patients after surgery ^[3].

3.3. New techniques for postoperative drainage and incision management

Postoperative drainage and incision care are the focus of perioperative nursing for thyroid cancer patients. In complex surgical cases, new surgical and nursing methods can further accelerate patient recovery and avoid complications. Traditional drainage using a drainage tube is effective, but it has disadvantages such as poor drainage and potential incision infection risks. The use of new technologies such as negative pressure drainage techniques, has shown significant drainage effects with fewer postoperative complications. For incision care, it is no longer limited to changing dressings, but involves more personalized and high-tech interventions. For example, the application of antibacterial dressings can effectively prevent incision infections, and transparent dressings facilitate observation of the incision and prompt handling of abnormalities. Nurses should observe the postoperative drainage tube and incision status, paying attention to any abnormalities in the nature and quantity of drainage fluid. Effective postoperative drainage and incision care ensure smooth recovery, shorten hospital stays, and improve patients' quality of life.

3.4. ERAS (Enhanced Recovery After Surgery) nursing pathway

The promotion of the ERAS nursing pathway in recent years has been an innovation in perioperative nursing work. ERAS nursing pathway advocates multidisciplinary and multiprofessional collaboration, insists on patient-centered care, takes care of the overall state of patients, and strives to achieve the fastest recovery for patients. The ERAS nursing philosophy is based on reducing preoperative, intraoperative, and postoperative interventions to ensure optimal treatment effects, shorten hospital stays, and reduce the trauma caused by surgery. Clinical nurses are an important component of the ERAS nursing pathway. Besides being responsible for traditional nursing work, they also need to assist physicians in implementing clinically personalized nursing treatment plans ^[4]. In the ERAS nursing pathway, patients are prepared psychologically before surgery, provided with adequate preoperative education and guidance, informed about surgical procedures and postoperative care, and educated on psychological knowledge, so that they are aware of their condition and have a clear self-perception and understanding of thyroid tumor resection. During the critical intraoperative period, they assist the anesthesiologist to ensure the implementation of intraoperative anesthesia, postoperative analgesia, and nutritional status. After surgery, patients continue to be observed to promote rapid recovery, such as early exercise and scientific and reasonable nutritional

support, to help them regain self-care ability as soon as possible. The application of the ERAS pathway enables thyroid cancer patients to recover faster after surgery, improves their comprehensive treatment experience, and ensures the effectiveness of comprehensive clinical treatment.

4. Optimized practice of integrated traditional Chinese and Western medicine nursing

4.1. Application of traditional Chinese medicine (TCM) emotional nursing in preoperative anxiety intervention

Thyroid cancer patients often experience tension, anxiety, and fear before surgery due to concerns about the operation. This not only increases their physical burden before the procedure but also hinders their postoperative recovery. As an intervention method, TCM emotional nursing can improve patients' emotional stress by adjusting their mindset, helping them smoothly prepare for surgery. The core of TCM emotional nursing is syndrome differentiation treatment, which is mainly based on the Yin-Yang and five elements theory of TCM. It focuses on harmonizing Qi and blood, heart and spleen, stomach, etc., and dredging liver Qi stagnation according to the patient's physiological and emotional state, thus ensuring a stable and positive mindset. Practical emotional nursing intervention methods can include Tui Na (Chinese massage), massage, and auricular point pressing with beans. These methods help patients relax their bodies and minds and promote the adjustment of their internal environment. Tui Na and massage can stimulate specific acupoints, meridians, and collaterals to relax the body tightness and tension caused by anxiety, facilitating a comfortable mood and a more stable preoperative state. The auricular point pressing with beans, a characteristic of TCM, can regulate the patient's central nervous system by stimulating specific acupoints on the ears, keeping them calm and peaceful, and maintaining a stable and positive preoperative emotional state. Combining TCM emotional nursing and other methods helps patients stabilize their mindset, timely and effectively controls their preoperative anxiety issues, enables them to face surgical treatment positively and calmly, reduces unnecessary fear due to emotional tension, and facilitates smoother postoperative recovery^[5].

4.2. Acupoint application for prevention and treatment of postoperative nausea and vomiting

Postoperative nausea and vomiting are common perioperative complications. Intraoperative medication, drug side effects, and surgical procedures can cause significant changes in the patient's physiological state, leading to extreme discomfort. Acupoint application in traditional Chinese medicine is a simple and feasible method to intervene in the above situation. By selecting specific meridians and acupoints for postoperative patients and applying Chinese herbal patches, it can regulate the patient's gastrointestinal function and provide relief from postoperative nausea and vomiting. For example, Neiguan and Shenmen acupoints are often chosen for medication administration, which can dredge meridians and regulate Qi movement. After surgery, nursing staff can select appropriate acupoints for patients based on their physical constitution and condition for application. The applied medication can regulate the patient's gastrointestinal tract, improve their constitution by adjusting Qi and blood, and promote postoperative recovery. The selection of herbs for the medication has strict requirements, using herbs with the effect of warming the stomach and regulating Qi. These herbs, after proper processing, can penetrate the skin and enter the meridians and acupoints to achieve the desired regulatory effect. This method is simple

to operate and highly acceptable to patients, avoiding the use of excessive Western medication and reducing drug-related damage to the body. Acupoint application is not only a local treatment but also involves systemic regulation, achieving the effect of conditioning the patient's body.

4.3. Application of auricular acupressure in postoperative pain management

Perioperative pain management, including intraoperative and postoperative pain control, is a crucial aspect of nursing care for thyroid cancer patients. Adequate postoperative analgesia not only improves patient comfort but also reduces postoperative complications, alleviates the psychological burden on patients' families, enhances treatment compliance, and mitigates medical disputes. Auricular acupressure, a traditional Chinese medicine therapy, stimulates nerve reflex zones corresponding to specific acupoints on the ears. This stimulation dredges meridians, promotes Qi and blood circulation, treats pain, exerts neuro-integrative regulatory functions, provides analgesia and anti-inflammatory effects, and reduces nerve excitement. Through multiple mechanisms, auricular acupressure effectively reduces postoperative pain. The benefits of auricular acupressure in postoperative pain relief are evident:

- (1) It reduces the need for postoperative analgesic drugs, thereby minimizing side effects and improving patients' quality of life.
- (2) Auricular acupoints converge numerous meridians and acupoints, stimulating relevant ear acupoints to facilitate self-healing and pain relief through bodily regulation.
- (3) As a non-pharmacological analgesic method, auricular acupressure is simple, convenient, and well-tolerated by patients. It involves applying pressure to specific ear acupoints using small bean-like objects, allowing patients to continue experiencing pain relief postoperatively.
- (4) For patients concerned about drug side effects or allergies, auricular acupressure offers a safe, effective, non-invasive alternative that reduces complications associated with analgesic drug use.

4.4. Evidence-based construction of integrated traditional Chinese and Western medicine nursing care plan

The application of integrated traditional Chinese and Western medicine nursing care models in the perioperative period of thyroid cancer represents a significant trend in the development of modern medicine. By integrating the holistic approach of traditional Chinese medicine with advanced scientific and technological methods of Western medicine, this model provides patients with comprehensive and individualized nursing care plans. Theoretically, integrated traditional Chinese and Western medicine nursing care must be supported by rich and effective clinical practice experience, as well as modern scientific evidence, to ensure the safety and efficacy of treatment. The implementation of this nursing care model must take into account the actual situation of patients, combining therapies such as Chinese herbal medicine, acupuncture, and massage with Western medical treatments, including surgery, anesthesia, and medication. In the rehabilitation phase after thyroid cancer surgery, Western medical surgical treatment can address the pathological disease, while herbal medicine can accelerate the patient's recovery process by regulating Qi and blood and promoting the function of internal organs according to traditional Chinese medicine principles. Traditional Chinese medicine nursing care plays a role in managing pain, anxiety, and immune function recovery, and the integrated treatment of traditional Chinese and Western medicine can effectively improve patients' overall health and well-being.

5. Conclusion

In summary, the adoption of integrated traditional Chinese and Western medicine nursing techniques during the perioperative period of thyroid cancer can not only compensate for the limitations of Western medicine nursing techniques alone, but also further improve the overall quality of nursing care for patients during this period. Traditional Chinese medicine nursing techniques, such as emotional regulation and acupuncture at specific acupoints, can help manage patients' preoperative anxiety, postoperative nausea and vomiting, and pain. Western medicine nursing techniques play a positive role in predicting surgical risks, monitoring neural function, and postoperative care. In the future, it is expected that further research on integrated traditional Chinese and Western medicine nursing models will lead to more comprehensive and humanized care for patients during the perioperative period of thyroid cancer, promoting rapid recovery and a good quality of life after surgery.

Disclosure statement

The authors declare no conflict of interest.

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Early Curative Effect Observation of Shenqi Hexue Decoction in the Treatment of Qi Blood Deficiency Syndrome after PKP for Thoracolumbar Metastases with Pathological Vertebral Fractures

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Abstract: *Objective:* After percutaneous kyphoplasty (PKP), patients with pathological vertebral fractures of thoracolumbar metastases often have Qi and blood deficiency syndrome and hidden blood loss, resulting in postoperative debilitation syndrome. This study aimed to evaluate the clinical efficacy and mechanism of Shenqi Hexue Decoction on early postoperative recovery of such patients. *Methods:* 36 Patients were randomly divided into an experimental group (Shenqi Hexue Decoction + conventional treatment) and a control group (conventional treatment). The changes of hemoglobin (HB), Karnofsky functional status (KPS) score, and TCM syndrome score on the 1st, 4th, and 7th day after operation were observed. *Results:* The HB value of the experimental group was significantly higher than that of the control group on the 4th and 7th days after operation ($p < 0.01$), and the maximum decline value of HB decreased by 42.1% ($p < 0.001$); The improvement rate of KPS score in the experimental group was 94.4% on the 7th day after operation, which was significantly better than 66.7% in the control group ($p < 0.05$). The total effective rate of TCM syndrome efficacy was 94.4% in the experimental group and 72.2% in the control group ($p < 0.05$); No drug-related serious adverse reactions were found. *Conclusion:* Shenqi Hexue decoction can effectively improve the anemia state and activity ability of patients with Qi blood deficiency syndrome in the early stage after PKP, and its possible mechanism involves multi-target regulation such as hematopoietic regulation, microcirculation improvement and inflammation inhibition, with good safety.

Keywords: Thoracolumbar metastases; Qi and blood deficiency syndrome; Shenqi Hexue Decoction; Curative effect

Online publication: August 8, 2025

1. Introduction

Bone is the third most common site of metastasis for malignant tumors, with thoracolumbar metastases accounting for 60%-80% of bone metastases ^[1]. Pathological vertebral fractures can cause severe pain, neurological dysfunction, and limited mobility, which can lead to paraplegia ^[2]. Percutaneous kyphoplasty (PKP), as a minimally invasive surgery, can effectively stabilize the vertebral body and relieve pain ^[3]. However, clinical observations have found that patients often experience “postoperative frailty syndrome” manifestations such as progressive anemia and decreased mobility after PKP, but without significant external bleeding, which is referred to as “occult blood loss”. Studies have shown that the amount of occult blood loss after orthopedic surgery can reach 2-3 times that of overt blood loss, which is more prominent in cancer patients ^[4].

From the perspective of traditional Chinese medicine theory, patients with malignant tumors inherently have a deficiency of healthy Qi ^[5]. Surgical trauma further depletes Qi and blood, leading to a syndrome of Qi and blood deficiency, as “Qi cannot generate blood, and blood cannot carry Qi” ^[6]. According to “Medical Formula Examination,” this formula is prescribed for those with a deficiency of both Qi and blood. Qi is the father of all bones and muscles, while blood is the mother. They must not be deprived of nourishment.” The specific manifestations include a lusterless complexion, lack of energy and desire to speak, fatigue, palpitations and insomnia, pale tongue with a weak pulse, and other symptoms, which are highly consistent with the postoperative frailty syndrome described in modern medicine.

Shenqi Hexue Decoction is derived from the modification of Bazhen Decoction from “Ruizhu Tang’s Experienced Formulas,” incorporating the principles of Danggui Buxue Decoction and Xuefu Zhuyu Decoction ^[7]. The complete formula consists of 30 g of Huangqi (Astragalus), 15 g of Renshen (Ginseng), 15 g of Danggui (Angelica), 30 g of Baizhu (Atractylodes), 30 g of Fuling (Poria), 30 g of Baishao (Paeoniae), 15 g of Shengdihuang (Rehmanniae), 15 g of Chuanxiong (Ligustici), 10 g of Taoren (Persicae), 15 g of Xuduan (Dipsaci), 10 g of ZhiQiao (Citri), 10 g of Jiegeng (Platycodi), 10 g of Sharen (Amomi), and 10 g of Zhigancao (Glycyrrhizae). It has the effect of “tonifying Qi and harmonizing blood, removing blood stasis and dredging meridians.” Modern pharmacological studies have shown that polysaccharides from Huangqi and ginsenosides from Renshen can promote the proliferation of hematopoietic stem cells ^[8], polysaccharides from Danggui can increase peripheral blood cell counts ^[9], total glucosides of paeony can regulate immune function ^[10], and tetramethylpyrazine from Chuanxiong can improve microcirculation ^[11].

The multi-disciplinary treatment (MDT) model has become the standard management strategy for bone metastases. The MDT team for bone metastases integrates expert resources from orthopedics, oncology, radiotherapy, and integrated Chinese and Western medicine departments ^[12]. In this context, this study aims to scientifically evaluate the clinical efficacy of Shenqi Hexue Decoction for Qi and blood deficiency syndrome after PKP surgery, providing a basis for optimizing perioperative management.

2. Materials and methods

2.1. Study design

A retrospective randomized controlled analysis was conducted, adhering to the relevant guidelines of the hospital ethics committee. Patient and medical record data were objective, authentic, and the dataset was essentially complete.

2.2. Study subjects

A retrospective analysis was performed on 36 patients with thoracolumbar metastatic tumors accompanied by pathological vertebral fractures who were treated between January 2020 and December 2023. All patients underwent single-segment PKP surgery. After accessing medical records, the included patients were divided into an experimental group and a control group, with 18 cases in each group based on the study methodology.

Inclusion criteria: (1) The primary lesion was confirmed by tissue biopsy, and single thoracolumbar metastasis (T5-L5 segment) was diagnosed by imaging (MRI/CT/PET-CT); (2) Vertebral compression fracture (compression rate 30–70%); (3) Meeting the diagnostic criteria for Qi and blood deficiency syndrome (referencing the 2022 edition of “Guiding Principles for Clinical Research of New Chinese Medicines”): Main symptoms: fatigue and sallow complexion; Secondary symptoms: dizziness, palpitations and shortness of breath, poor appetite, pale tongue with white coating, and weak pulse; (4) Age between 65 and 75 years.

Exclusion criteria: (1) Coagulation dysfunction (INR > 1.5, PLT < $80 \times 10^9/L$); (2) Severe liver and kidney dysfunction (Child-Pugh Class C, eGFR < 30 mL/min); (3) Spinal infection or active systemic infection; (4) Psychiatric disorders or cognitive impairments; (5) Expected survival < 3 months (assessed by Tokuhashi score ≤ 8).

2.3. Treatment methods

Control group: Routine treatment after PKP surgery.

- (1) Anti-bone resorption: Intravenous infusion of zoledronic acid 4 mg (once monthly).
- (2) Empirical prophylactic infection control.
- (3) Empirical nutritional support.
- (4) Rehabilitation training: Bed rest for 24 hours after surgery, overall turning every 2 hours, wearing protective gear and ambulating with functional training after 24 hours.

Experimental group: Routine treatment + oral administration of ShenQi Hexue Decoction starting 6 hours after surgery.

- (1) Medication composition: Astragalus 30 g, Ginseng 15 g, Angelica 15 g, Atractylodes 30 g, Poria 30 g, Paeoniae 30 g, Rehmanniae 15 g, Chuanxiong 15 g, Persicae 10 g, Dipsaci 15 g, Aurantii 10 g, Platycodi 10 g, Amomi 10 g, Glycyrrhizae 10 g.
- (2) Preparation method: Chinese herbal pieces were uniformly decocted by the hospital’s designated decoction pharmacy and concentrated into 200 mL \times 3 bags per dose.
- (3) Usage and dosage: 200 mL/1 bag per time, 3 times a day, taken warm after meals, continuously for 7 days.
- (4) Symptomatic modifications: For poor appetite, add Eupatorii 10 g and Atractylodis 15 g; for constipation, add Cannabisi 15 g; for insomnia, add Polygoni Multiflori 15 g.

2.4. Observation indicators

- (1) Hemoglobin (Hb): Venous blood samples were collected before surgery and on the 1st, 4th, and 7th days after surgery for testing (using the Sysmex XN-1000 fully automated blood analyzer).
- (2) Activity status score: The Karnofsky Performance Status (KPS) was used to evaluate activity capacity on the 1st, 4th, and 7th days after surgery.
- (3) Traditional Chinese Medicine (TCM) syndrome score: A scale was developed based on the 2022 edition of the “Guiding Principles for Clinical Research of New Drugs of Traditional Chinese Medicine.” It includes 5 primary symptoms (fatigue, sallow complexion, dizziness and vertigo, palpitations and shortness of breath, poor appetite, 0–6 points per item) and 3 secondary symptoms (spontaneous sweating, numbness

of hands and feet, insomnia, 0–3 points per item), with a total score ranging from 0–39 points.

(4) Clinical recovery: Syndrome score reduction $\geq 95\%$.

(5) Significant effect: Score reduction $\geq 70\%$.

(6) Effective: Score reduction $\geq 30\%$.

(7) Ineffective: Score reduction $< 30\%$.

(8) Safety evaluation: Adverse reactions such as nausea, vomiting, and diarrhea were recorded, and liver and kidney function (ALT, Cr) were monitored.

2.5. Statistical methods

Data were analyzed using SPSS 25.0 software. Measurement data were expressed as mean \pm standard deviation (SD) and comparisons between groups were performed using the *t*-test. Repeated measures ANOVA was used for repeated measurement data. Count data were expressed as rates (%), and comparisons were made using the χ^2 test or Fisher's exact test. A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of baseline data

There were no statistically significant differences in age, gender, primary tumor type, fracture segment, preoperative Hb, and KPS scores between the two groups ($P > 0.05$), indicating comparability (**Table 1**).

Table 1. Comparison of baseline data between the two groups

Item	Experimental group (<i>n</i> = 18)	Control group (<i>n</i> = 18)	Statistical value	<i>P</i> -value
Age (years)	67.8 \pm 3.2	68.3 \pm 2.9	<i>t</i> = 0.521	0.605
Gender (Male/Female)	10/8	9/9	χ^2 = 0.118	0.731
Primary tumor Type				
- Lung cancer	7	6		
- Breast cancer	5	6		
- Prostate cancer	4	4		
- Renal cancer	2	2	χ^2 = 0.273	0.965
Fracture level				
- Thoracic (T5-T10)	11	10		
- Lumbar (L1-L5)	7	8	χ^2 = 0.128	0.721
Pre-op Hb (g/L)	112.6 \pm 11.2	114.8 \pm 10.7	<i>t</i> = 0.632	0.532
Pre-op KPS Score	61.7 \pm 6.3	60.9 \pm 5.8	<i>t</i> = 0.427	0.672

3.2. Hemoglobin changes

The Hb levels in both groups showed a trend of decreasing first and then increasing after surgery, but the decrease in the experimental group was significantly lower than that in the control group ($F = 18.37$, $P < 0.001$) (**Table 2**):

(1) On the 1st day after surgery: There was no significant difference in Hb between the two groups ($P > 0.05$);

(2) On the 4th day after surgery: The Hb level in the experimental group (102.5 \pm 8.7 g/L) was significantly

higher than that in the control group (94.3 ± 9.2 g/L)($t = 2.873$, $P = 0.007$);

(3) On the 7th day after surgery: The Hb level in the experimental group rose to (110.6 ± 9.4 g/L), significantly higher than that in the control group (100.8 ± 8.9 g/L)($t = 3.274$, $P = 0.002$);

(4) Maximum Hb decrease: The experimental group (15.3 ± 4.2 g/L) showed a 42.1% decrease compared to the control group (26.5 ± 5.1 g/L)($t = 7.112$, $P < 0.001$).

Table 2. Comparison of postoperative hemoglobin changes between the two groups of patients (g/L, mean \pm SD)

Group	Pre-op	Post-op day 1	Post-op day 4	Post-op day 7	Maximum Hb decline
Test group	112.6 ± 11.2	105.8 ± 9.3	$102.5 \pm 8.7^* \blacktriangle$	$110.6 \pm 9.4^{**} \blacktriangle \blacktriangle$	$15.3 \pm 4.2^{**}$
Control group	114.8 ± 10.7	104.7 ± 10.1	94.3 ± 9.2	100.8 ± 8.9	26.5 ± 5.1

Note: Compared with the control group, $*P < 0.05$, $**P < 0.01$; compared with 1 day after surgery, $\blacktriangle P < 0.05$, $\blacktriangle \blacktriangle P < 0.01$

3.3. Karnofsky Performance Status (KPS) score

The recovery of post-surgical activity in the experimental group was significantly better than that in the control group ($F = 12.84$, $P < 0.001$)(Table 3):

(1) On the 1st day after surgery: The KPS scores of both groups were relatively low (experimental group 53.6 ± 5.2 , control group 52.8 ± 4.9 , $P > 0.05$);

(2) On the 4th day after surgery: The KPS score of the experimental group (68.4 ± 6.3) was significantly higher than that of the control group (62.7 ± 5.8)($t = 2.954$, $P = 0.006$);

(3) On the 7th day after surgery: The KPS score of the experimental group (78.9 ± 7.1) was significantly higher than that of the control group (70.3 ± 6.5)($t = 3.864$, $P < 0.001$);

(4) Improvement rate (increase of ≥ 10 points): The experimental group was 94.4% (17/18), and the control group was 66.7% (12/18), with a significant difference ($\chi^2 = 4.433$, $P = 0.035$).

Table 3. Comparison of post-surgical KPS scores between the two groups (score, mean \pm SD)

Group	Post-op day 1	Post-op day 4	Post-op day 7	Improvement rate (%)
Test group	53.6 ± 5.2	$68.4 \pm 6.3^{**} \blacktriangle \blacktriangle$	$78.9 \pm 7.1^{**} \blacktriangle \blacktriangle$	94.4*
Control group	52.8 ± 4.9	62.7 ± 5.8	$70.3 \pm 6.5 \blacktriangle \blacktriangle$	66.7

Note: Compared with the control group, $*P < 0.05$, $**P < 0.01$; compared with 1 day after surgery, $\blacktriangle \blacktriangle P < 0.01$

3.4. Therapeutic effect of TCM syndromes

The improvement of TCM syndromes in the experimental group was significantly better than that in the control group (Table 4):

(1) TCM syndrome score: The score on the 7th day after surgery in the experimental group (8.5 ± 2.7) was significantly lower than that in the control group (14.6 ± 3.8) ($t = 5.682$, $P < 0.001$)

(2) Total effective rate: The experimental group was 94.4% (17/18: 2 cases of clinical recovery, 8 cases of marked effectiveness, 7 cases of effectiveness), while the control group was 72.2% (13/18: 5 cases of marked effectiveness, 8 cases of effectiveness, 5 cases of ineffectiveness), with significant differences ($\chi^2 = 4.433$, $P = 0.035$)

Table 4. Comparison of therapeutic effect of TCM syndromes between the two groups on the 7th day after surgery

Group	n	Clinical cure	Markedly effective	Effective	Ineffective	Total effective rate (%)
Test group	18	2	8	7	1	94.4*
Control group	18	0	5	8	5	72.2

Note: Compared with the control group, * $P < 0.05$ *

3.5. Safety Evaluation

No serious adverse reactions occurred in both groups: (1) 2 cases in the experimental group experienced mild nausea (which resolved spontaneously without intervention); (2) 1 case in the control group had constipation (relieved with glycerin enema); (3) Liver and kidney function indicators were all within the normal range.

4. Discussion

4.1. Mechanism of Shenqi Hexue Decoction in reducing hidden blood loss

This study found that the decrease in Hb in the experimental group was 42.1% lower than that in the control group ($P < 0.001$), which is consistent with Zou Wenzhen's research conclusions on Bazhen Decoction^[13]. The mechanism of action of ShenQi Hexue Decoction may involve the following three aspects (**Figure 1**).

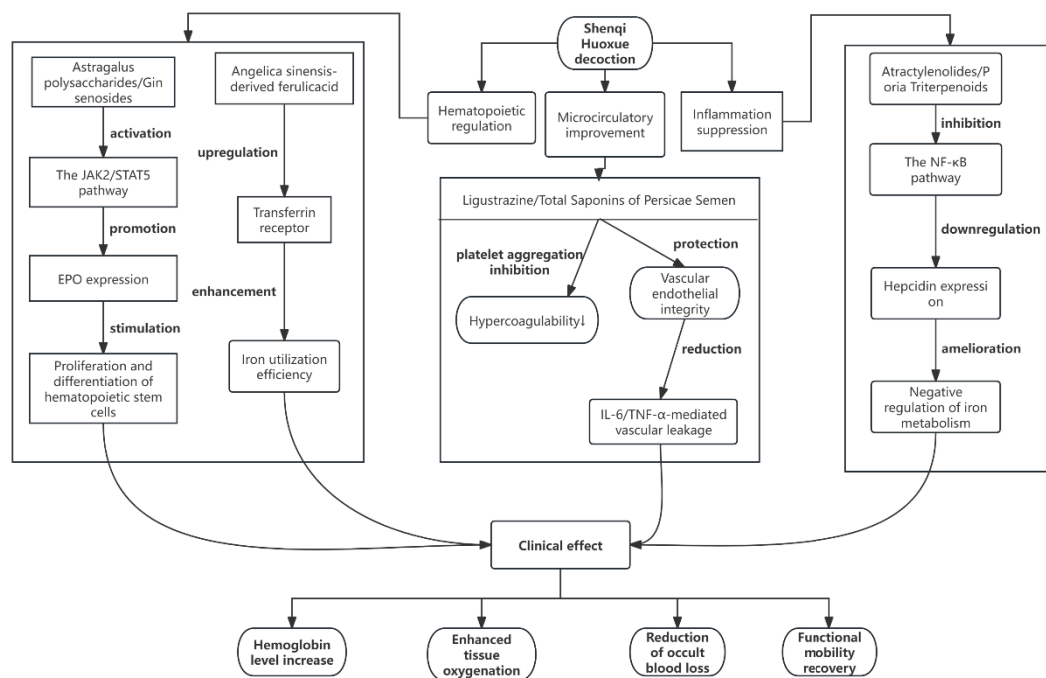


Figure 1. Schematic diagram of the potential mechanism of SHENQI Hexue Decoction.

- (1) Promoting hematopoietic regulation: Astragalus polysaccharides and ginsenoside Rg1 in the prescription can activate the JAK2/STAT5 signaling pathway, promote the expression of erythropoietin (EPO), and stimulate the proliferation and differentiation of bone marrow hematopoietic stem cells^[14]. Ferulic acid in

Angelica sinensis can enhance the utilization efficiency of iron ions and improve the iron deficiency state of tumor anemia by up-regulating the expression of transferrin receptor^[15].

- (2) Improving microcirculation disturbance: Tetramethylpyrazine and total saponins of peach kernel have anti-platelet aggregation effects, reduce blood hypercoagulability, and protect the integrity of vascular endothelium, reducing inflammation factors (IL-6, TNF- α) mediated vascular leakage^[16]. This is consistent with the effect of “removing blood stasis and dredging meridians” in Shenqi Hexue Decoction, which can reduce blood stagnation in tissue spaces^[17,18].
- (3) Reducing inflammatory consumption: Atractylenolide and pachyman triterpenes can inhibit the NF- κ B inflammatory pathway, down-regulate the expression of hepcidin, relieve its negative regulation of iron metabolism, and reduce iron utilization disorders in inflammatory anemia^[19,20].

4.2. Effects of Qi and blood double nourishing method on postoperative functional recovery

This study showed that the KPS score of the experimental group was significantly higher than that of the control group on the 7th day after surgery ($P < 0.01$), and the total effective rate of TCM syndromes was 94.4% ($P < 0.05$), reflecting the clinical effect of “tangible blood comes from invisible Qi”:

- (1) Improving tissue oxygen supply and energy metabolism: The increase in Hb level directly enhances oxygen transport capacity and improves skeletal muscle hypoxia. Catalpol in *Rehmannia glutinosa* can activate the HIF-1 α pathway, promote glycolysis and angiogenesis, and increase tissue oxygen utilization^[21]. Asperosaponin VI can promote the synthesis of Bone Morphogenetic Protein (BMP) and accelerate fracture healing^[22], laying a foundation for early functional exercise.
- (2) Regulating neuro-muscular function: Paeoniflorin can reduce the incidence of muscle spasms by regulating GABAergic neurotransmission^[23]. Ginsenoside Rg3 can cross the blood-brain barrier, act on the hypothalamus-pituitary-adrenal axis, regulate the balance of 5-HT/DA neurotransmitters, and improve symptoms such as “lack of energy, lazy speech, and mental fatigue”^[24,25].
- (3) Reducing cancer-related fatigue: Shenqi Hexue Decoction improves immune function by increasing the CD4+/CD8+ ratio and NK cell activity. Both Zou Wenzhen’s clinical research and Liu Hui’s Meta-analysis have confirmed that Bazhen Decoction and similar prescriptions can significantly improve the immune function and activity scores of cancer patients^[13,26].

4.3. Positioning and value of traditional Chinese medicine in the MDT model

The MDT model for bone metastases has been operating maturely in many medical institutions at home and abroad, integrating expert resources from orthopedics, oncology, radiotherapy, and integrated Chinese and Western medicine departments. Under this framework, the application value of ShenQi Hexue Decoction is reflected in the following aspects:

- (1) Precise symptom management: Targeting the specific syndrome of “Qi and blood deficiency” after surgery, modular processing of symptoms is achieved through syndrome differentiation and treatment. For example, in this study, the addition of Peilan and Cangzhu for appetite loss stimulates the spleen and improves appetite; the addition of Huoma Ren for constipation moistens the intestines and promotes bowel movement, reflecting the strategy of “corresponding formulas and syndromes”. Studies by Fang Hua and others have confirmed that modified Bazhen Decoction can reduce the incidence of digestive

tract reactions in chemotherapy patients and improve their quality of life^[27,28].

- (2) Synergistic efficacy enhancement and risk control: Shenqi Hexue Decoction can reduce the myelosuppression of targeted drugs and improve peripheral blood counts. Studies by Zhao Han and others have found that ginsenoside Rg3 can increase anti-tumor effects by activating the MAPK/ERK pathway to promote the killing effect of CD8+ T lymphocytes^[29], reducing the risk of tumor metastasis. At the same time, blood-activating components such as Taoren and Chuanxiong can improve blood hypercoagulability and prevent deep vein thrombosis (DVT)^[30,31].
- (3) Facilitating the implementation of Rapid Rehabilitation Surgery (ERAS): By reducing hidden blood loss, improving anemia and physical condition, patients can get out of bed and move around on the first day after surgery, just like patients with osteoporotic vertebral pathological fractures. This significantly shortens the length of hospital stay and reduces medical costs.

4.4. Research limitations

This study has the following limitations: (1) Small sample size: Only 36 patients were included from a single center, which may affect the generalizability of the results; (2) Short observation period: The study only observed patients up to 7 days after surgery, lacking medium- and long-term follow-up data; (3) Insufficient exploration of mechanisms: Changes in hematopoietic regulatory factors such as EPO and hepcidin were not detected; (4) No evaluation of tumor prognosis: The effect of the drug on tumor progression was not observed. Future research directions should focus on large-sample multicenter studies, extending follow-up time, and deeply exploring the regulatory mechanism of “Yiqi Shengxue” through molecular biology techniques such as single-cell sequencing. At the same time, it is necessary to evaluate the impact of traditional Chinese medicine compounds on the tumor microenvironment and clarify their precise positioning in MDT.

5. Conclusion

This study confirms that SHENQI Hexue Decoction can effectively improve the hidden blood loss caused by early Qi and blood deficiency syndrome after PKP surgery for patients with thoracolumbar metastatic tumors, enhance postoperative functional activity, and alleviate pathological syndromes of traditional Chinese medicine with good safety. Its mechanism of action involves multi-target regulation such as hematopoietic control, microcirculation improvement, and inflammation inhibition. Under the MDT model for bone metastases, this formula can be used as an important component of integrated Chinese and Western medicine treatment, providing new ideas for optimizing perioperative management of cancer patients.

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Disclosure statement

The authors declare no conflict of interest.

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Advances in Diagnosis and Clinical Management Strategies for Liver Trauma

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Abstract: Liver trauma, a common and severe surgical emergency, refers to injuries caused by various external forces acting on the liver. The causes of liver trauma are diverse, with direct external impacts such as traffic accidents, falls from heights, and violent collisions being frequent contributors. Additionally, iatrogenic procedures like improper liver biopsy techniques may also lead to liver trauma. Clinically, symptoms vary depending on the severity and extent of injury. Mild cases might present with localized symptoms like right upper abdominal pain and tenderness, while severe cases could result in massive intra-abdominal bleeding accompanied by shock symptoms, including pallor, rapid heart rate, and hypotension, along with gastrointestinal manifestations such as nausea and vomiting. Treatment approaches differ significantly: For minor injuries, conservative management typically involves bed rest, close monitoring of vital signs, hemostasis, and anti-infection measures. In critical scenarios involving liver rupture or massive hemorrhage, immediate surgical intervention is required to repair liver damage and control bleeding.

Keywords: Liver trauma; Diagnosis; Clinical treatment strategy

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1. Introduction

The etiology of liver trauma encompasses multiple dimensions. Regarding causative factors, traffic accidents, falls from heights, violent conflicts, and industrial accidents may all contribute to liver injuries. In terms of risk factors, excessive alcohol consumption can impair normal liver function, making the liver more vulnerable to injury when subjected to external impacts. Individuals with pre-existing liver conditions often have structural abnormalities or pathological changes in their liver tissue, significantly increasing the risk of liver damage during similar traumatic events ^[1]. Additionally, high-risk occupational groups such as construction workers and miners face elevated risks of liver trauma due to exposure to hazardous working environments.

2. Pathogenesis and pathophysiology

The pathophysiology of liver trauma is centered on a vicious cycle of hemorrhage-inflammation-metabolic failure. Early intervention should focus on hemostasis, anti-shock measures, and infection prevention, while dynamically assessing hepatic regeneration capacity and systemic multi-system functions to halt disease progression and improve prognosis ^[2].

2.1. Acute hemorrhage and circulatory failure

- (1) Vascular rupture: Damage to the hepatic artery (high-pressure system) and portal vein (high blood flow) causes rapid blood loss, leading to hypovolemic shock.
- (2) Coagulation disorders: Hepatocyte injury reduces synthesis of clotting factors (e.g., II, VII, IX, X), exacerbating bleeding tendencies.

2.2. Inflammatory response and microcirculation disorders

- (1) Cytokine release: Pro-inflammatory factors like TNF- α and IL-6 activate neutrophil infiltration, intensifying tissue edema and microthrombus formation.
- (2) Ischemia-reperfusion injury: Reactive oxygen species (ROS) surge after blood flow restoration, further damaging hepatocyte mitochondrial function.

2.3. Bile exudation and secondary injury

Biliary tract injury: Bile leakage into the peritoneal cavity triggers chemical peritonitis, causing severe abdominal pain and increasing bacterial infection risks.

2.4. Metabolic and detoxification failure

- (1) Glucose metabolism disorders: Depletion of hepatic glycogen reserves leads to hypoglycemia, while impaired lactate clearance causes acidosis.
- (2) Detoxification dysfunction: Accumulation of blood ammonia and bilirubin may induce hepatic encephalopathy (consciousness impairment) or jaundice.

2.5. Complication progression

- (1) Infectious complications: Bile leakage or secondary bacterial infections (e.g., *Escherichia coli*) from necrotic tissues may result in liver abscesses or sepsis.
- (2) Delayed bleeding: Pseudoaneurysm or arteriovenous fistula formation, which may rupture and bleed days to weeks after injury.
- (3) Liver failure: Multiple organ failure, such as coagulation disorder and hepatorenal syndrome, occurs when extensive liver necrosis exceeds regeneration capacity.

3. Diagnosis

Open liver injuries are relatively straightforward to diagnose, but clinicians must also consider the possibility of combined thoracoabdominal trauma. Closed injuries presenting with typical hemorrhagic shock and peritoneal irritation signs, when combined with a history of trauma, can be easily identified. However, patients with

multiple injuries, such as unconsciousness from head trauma, multiple fractures complicated by shock, or elderly individuals with delayed responses due to frailty, require heightened vigilance to avoid missed diagnoses. Patients with cirrhosis or liver cancer may experience hepatic rupture from minor trauma, which demands careful evaluation. The determination of whether closed abdominal injuries involve liver damage significantly impacts the need for open surgery, thus requiring high diagnostic accuracy ^[3].

3.1. Clinical manifestations

Subcapsular hemorrhage and/or liver parenchymal contusion primarily present with hepatic pain and hepatomegaly, with minimal peritoneal irritation signs. The pain gradually subsides as vital signs stabilize. In cases of high-tension subcapsular hematomas, delayed acute abdominal pain and internal bleeding may occur. True rupture is characterized by massive internal bleeding, potentially manifesting as biliary peritonitis with right upper quadrant pain radiating to the right chest and shoulder. The peritonitis progresses from the right upper quadrant to involve the entire abdomen. Severe hemorrhage and biliary peritonitis may occur with major vessel tears, leading to early shock. Some patients with liver trauma may experience hematemesis or melena when blood from damaged liver tissue enters the duodenum via bile ducts.

3.2. Ancillary examinations

3.2.1. Laboratory tests

- (1) Blood tests show leukocytosis with progressive decreases in red blood cell count, hemoglobin, and hematocrit levels.
- (2) Coagulation parameters (prothrombin time, activated partial thromboplastin time) may be prolonged and international normalized ratio (INR) elevated due to impaired liver synthesis of clotting factors.
- (3) Liver function tests reveal significantly elevated ALT and AST levels during hepatocyte injury, particularly after blunt trauma. Elevated bilirubin levels suggest cholestasis or biliary tract injury, especially when total bilirubin and direct bilirubin are high. Renal function tests (blood urea nitrogen and creatinine) may indicate pre-renal renal insufficiency caused by hypovolemia or subsequent multi-organ failure.
- (4) Blood gas analysis shows increased lactate levels, indicating tissue hypoperfusion, metabolic acidosis in shock, or hypovolemic conditions. Blood gas analysis, including pH, BE (alkaline residue), and HCO₃, can reflect metabolic status and help assess the severity of shock.
- (5) Inflammatory markers such as CRP and PCT may be used to monitor infection complications like secondary hepatic abscess or peritonitis.

3.2.2. Imaging examinations ultrasound

- (1) Rapid assessment of intra-abdominal hemorrhage is commonly used for emergency initial screening.
Indications: Preliminary screening for hemodynamically unstable patients.
Advantages: Fast, non-invasive, repeatable, with 85% sensitivity in detecting free fluid in the abdominal cavity.
Limitations: Cannot clearly grade liver injury, may miss minor bleeding or retroperitoneal injuries.
- (2) CT: Contrast-enhanced CT scans (gold standard) can detail liver injury extent, active bleeding, hematomas, cholesteatoma, and assess other abdominal organ injuries.
Diagnostic value: Injury grading: Clarifies AAST classification, identifies depth of liver laceration,

hematoma range, and vascular damage.

Complication screening: Cholesteatoma, pseudoaneurysm, hepatic abscess.

- (3) Angiography: Used for suspected active bleeding or vascular injury, allowing simultaneous embolization therapy.

Indications: CT-predicted active bleeding or suspected vascular injury (e.g., hepatic artery pseudoaneurysm).

Therapeutic value: Simultaneous embolization (gelatin sponge, coil) achieves > 90% hemostasis success rate.

- (4) MRI: Less frequently used but useful for specific conditions like biliary tract injury.

Indications: Suspected bile duct injury (e.g., biliary leakage) or unclear CT findings.

Advantages: Non-radiation, clear visualization of biliary tree structure (MRCP), intrahepatic hematoma evolution (subacute phase).

Limitations: The procedure takes longer and is not suitable for emergency or critically ill patients.

- (5) Diagnostic peritoneal puncture or lavage: For patients with hemodynamic instability, this method can rapidly confirm the presence of intra-abdominal hemorrhage.

Indications: When FAST is negative but clinical suspicion of peritoneal bleeding is high, or when imaging is unavailable.

Positive criteria: Extracting > 10 mL non-clotted blood or detecting red blood cells > 100,000/mm³ in lavage fluid.

Limitations: Cannot pinpoint the source of bleeding, and may yield false negatives due to localized peritumoral hematoma.

4. Treatment

4.1. Traditional surgical approaches

Traditional surgical methods play a crucial role in managing liver trauma, primarily including liver suturing, hepatic resection, and packing procedures. Liver suturing stands as one of the most commonly used techniques, particularly suitable for patients with parenchymal lacerations that do not involve major blood vessels or bile ducts. Studies indicate its adoption rate reaches 51.2% in liver injury cases, especially right lobe injuries. Hepatic resection is indicated for severe parenchymal damage or uncontrollable bleeding, though surgeons must carefully balance surgical invasiveness against postoperative liver compensatory capacity. Packing procedures (such as perihilar packing) are typically employed for hemodynamically unstable patients to control bleeding and buy time for subsequent treatment, though they carry higher complication risks like infection and rebleeding. Additionally, hepatic artery ligation may be considered for specific cases but carries potential long-term complications such as pseudoaneurysms or collateral circulation formation leading to biliary bleeding. The primary advantage of surgical intervention lies in rapid hemorrhage control, which proves critical for hemodynamically unstable or high-grade (AAST IV-V) liver trauma patients. For instance, in penetrating liver injuries with active bleeding, hepatic artery ligation or packing can significantly reduce early mortality rates (22.7%). However, these procedures involve substantial surgical trauma, increased postoperative complications (including hepatic necrosis [16%], bile leakage [1.5%-4.5%], and infection risks), and extended hospital stays (averaging 11 days).

Furthermore, obesity-related higher surgical intervention rates may correlate with anatomical complexity

and slower postoperative recovery. Non-surgical management (NOM) demonstrates success rates of 85%-99% in stable patients, though surgery remains the irreplaceable salvage intervention, particularly when complicated by multi-organ injuries or vascular abnormalities such as hepatic arteriovenous fistulas, requiring multidisciplinary collaboration ^[4].

4.2 Interventional

Therapy Endovascular therapy plays a pivotal role in managing liver trauma and complications, with transarterial embolization (TAE) being a core technique. Clinical evidence shows TAE demonstrates significant efficacy in emergency scenarios including traumatic hepatic artery tears, pseudoaneurysm rupture, and spontaneous hepatic rupture associated with HELLP syndrome. For post-liver transplant pseudoaneurysm rupture, combined embolization with restorative balloon occlusion (REBOA) serves as a transitional treatment, although some patients still face prognostic risks due to multiple organ failure. The core advantage of interventional therapy lies in its minimally invasive nature, avoiding the trauma and prolonged recovery associated with traditional open surgery. For instance, TAE can be performed via percutaneous femoral artery puncture, making it particularly suitable for hemodynamically unstable emergency cases.

However, limitations must be acknowledged:

- (1) The technical threshold is high, requiring interventional radiologists to master vascular anatomy and catheterization skills proficiently, with significant challenges in managing complex scenarios like multi-vessel hemorrhage or combined portal vein thrombosis.
- (2) Certain patients may experience complications such as postembolism hepatic ischemia leading to liver dysfunction or biliary ischemic injury. Furthermore, long-term efficacy is influenced by underlying conditions, such as the higher recurrence risk in patients with malignant tumors following pseudoaneurysm embolization.
- (3) Interventional therapy often requires multidisciplinary collaboration (e.g., trauma surgery and transplant teams) to develop stepwise treatment plans ^[5,6]. Overall, interventional therapy remains a crucial option for hepatic vascular lesions, but strict patient-specific risk assessment is essential.

4.3 Non-surgical strategies

Nonoperative management (NOM) has become the standard treatment for hemodynamically stable blunt liver injuries, particularly for injuries graded I-III according to the American Society of Trauma Surgeons (AAST) classification. Indications include: hemodynamic stability (systolic blood pressure > 90 mmHg), absence of peritoneal irritation signs, and no other emergency laparotomy complications (e.g., bowel perforation) ^[7]. Multiple studies demonstrate that even high-grade (IV-V) liver injuries can be safely managed through NOM under strict monitoring, achieving success rates exceeding 85%. Contraindications include persistent hemodynamic instability, intra-abdominal organ injuries requiring surgical intervention, and imaging evidence of active contrast agent extravasation (indicating arterial bleeding). The core advantage of NOM lies in avoiding surgical trauma and related complications (e.g., infection, adhesive intestinal obstruction), especially reducing secondary trauma in patients with multiple injuries. Angioembolization (AE), a crucial adjunct to neurointerventional surgery (NOM), effectively controls arterial hemorrhage. However, it carries a 43% complication rate, including hepatic infarction, biliary ischemia, and abscess formation. Delayed bleeding, the primary risk of NOM, typically occurs within 72 hours post-injury and may result from incomplete embolization or open collateral circulation. Additionally, NOM requires intensive monitoring (e.g., continuous CT scans and laboratory tests), potentially prolonging hospital

stays. Novel therapeutic approaches like melatonin, which modulates mitochondrial-endothelial contact (MAMs) to reduce post-traumatic liver injury, offer new adjunctive treatment options^[8]. Overall, successful NOM relies on multidisciplinary collaboration (trauma surgery, interventional radiology, ICU) while balancing its dual effects of reducing surgical risks and preventing delayed complications.

5. Complications

5.1. Early posttraumatic liver complications (Within 72 hours post-injury)

Early post-traumatic liver complications are primarily characterized by acute hemorrhage, infection, and organ dysfunction. Hemorrhagic shock is the most lethal complication due to the liver's high blood supply. Tissue tears of grade III or higher or major vascular injuries can cause blood loss exceeding 2000 mL, requiring emergency surgical hemostasis or interventional embolization. Bile leakage occurs in 10–25% of cases, typically caused by ruptured intrahepatic bile ducts. Bile entering the peritoneal cavity may induce chemical peritonitis, presenting with severe abdominal pain, peritoneal irritation signs, and elevated bilirubin levels in bloody ascites. Infectious complications include liver abscesses (5%-10% incidence) and peritoneal infections, with significantly increased risks during open injuries or combined intestinal ruptures. Coagulation disorders result from reduced synthesis of clotting factors (II, VII, IX, X) due to hepatocyte damage, exacerbated by transfusion-induced dilutional coagulopathy. Adjacent organ injuries often involve diaphragmatic rupture, right-sided hemothorax/pneumothorax, or renal contusions, requiring imaging evaluation. This stage demands close monitoring of vital signs, timely fluid resuscitation, broad-spectrum antibiotics, and vigilance for delayed bleeding^[9].

5.2. Late posttraumatic liver complications (2-24 months post-injury)

Late-stage complications are frequently associated with abnormal wound healing, biliary system injury, and hemodynamic changes. Traumatic biliary strictures may cause obstructive jaundice due to scar contraction, requiring ERCP or biliary-enteric anastomosis. Gallbladder tumors manifest as right upper quadrant masses with elevated alkaline phosphatase levels, treatable by percutaneous drainage or surgical resection. Portal hypertension, caused by injury to the hepatic or main portal vein, leads to esophageal and gastric varices with ascites, requiring TIPS (Transjugular Intrahepatic Shunt) or shunt surgery. Hepatic pseudoaneurysms exhibit characteristic “rapid entry and exit” enhancement in contrast-enhanced CT scans during the arterial phase, with a rupture risk as high as 50%, necessitating interventional embolization therapy. Liver failure predominantly occurs in patients with pre-existing liver disease or hepatic resection exceeding 50%, manifesting as jaundice, hepatic encephalopathy, and worsening coagulation parameters. Additionally, some patients develop chronic abdominal pain associated with perihepatic adhesions, localized peritonitis, or traumatic neuropathy. Advanced complications often require multidisciplinary collaboration, combined with imaging follow-ups (ultrasound/CT/MRCP) and liver function monitoring. Timely intervention can significantly improve prognosis^[10,11].

6. Conclusion

Current treatment challenges primarily focus on optimizing individualized decision-making. For instance, while Non-Operational Management (NOM) has become the standard protocol for low-grade liver injury, its application in high-grade injuries remains controversial. Studies indicate that patients with high-grade injuries

may experience complications (such as delayed bleeding and biliary fistula) at 9.7% after NOM, compared to 45.5% in surgical groups. Additionally, interventional therapies like arterial embolization, while effective in controlling bleeding, require advanced techniques and need more evidence regarding long-term outcomes for intrahepatic bile duct injuries. Emerging technologies such as mesenchymal stem cell-derived exosomes (MSC-exos) show potential in reducing hepatic injury inflammation through gut microbiota regulation and metabolites (e.g., 6-methylnicotinamide and glutathione) in animal experiments, though clinical translation requires further validation.

Future research should prioritize developing precision risk stratification tools (integrating injury grading, hemodynamic parameters, and biomarkers) and innovating minimally invasive techniques. For example, the “suspension technique” in robot-assisted hepatectomy can reduce parenchymal traction injuries, while novel hemostatic materials (e.g., extracellular matrix-modified gelatin sponge) demonstrate superior biocompatibility and regenerative capacity in animal models compared to traditional gelatin sponges. For extreme cases (e.g., hepatic artery rupture or post-transplant pseudotumor), optimizing multidisciplinary strategies (including interventional embolization, injury control surgery, and liver transplantation) will further enhance treatment success rates. In general, the treatment of liver trauma is moving towards individualization, minimally invasive and multimodal integration, but more prospective studies are needed to balance efficacy and safety.

Disclosure statement

The authors declare no conflict of interest.

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Clinical Efficacy and Adverse Reactions of VMAT Radiotherapy Combined with Raltitrexed Chemotherapy in the Treatment of Elderly Patients with Esophageal Cancer

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Abstract: *Objective:* To investigate the efficacy and adverse reactions of volumetric modulated arc therapy (VMAT) radiotherapy combined with raltitrexed chemotherapy in the treatment of elderly patients with esophageal cancer. *Methods:* A total of 86 elderly patients with esophageal cancer admitted to our hospital between February 2024 and February 2025 were enrolled in this study and equally divided into two groups: a control group receiving VMAT radiotherapy alone and a study group receiving VMAT radiotherapy combined with raltitrexed chemotherapy, with 43 patients in each group, to compare the therapeutic outcomes between the two treatment approaches. *Results:* The study group demonstrated significantly higher objective remission and disease control rates than the control group ($P < 0.05$). Post-treatment levels of HSP90 α , Cyfra21-1, and CEA were markedly reduced in the study group relative to the control group ($P < 0.05$). Adverse reaction incidence showed no notable difference between the two groups ($P > 0.05$). Quality of life (QOL) scores were significantly elevated in the study group compared to the control group at both 3- and 6-month follow-ups ($P < 0.05$). *Conclusion:* VMAT radiotherapy combined with raltitrexed chemotherapy can improve the short-term efficacy, reduce tumor marker levels, and improve the quality of life of elderly patients with esophageal cancer. The treatment has fewer adverse reactions and better patient tolerance.

Keywords: Esophageal cancer; Elderly; Volumetric modulated arc therapy; Raltitrexed

Online publication: August 7, 2025

1. Introduction

Esophageal cancer is a common clinical gastrointestinal tumor, and its incidence increases with age. Its early symptoms are concealed, and the disease stage is often advanced at diagnosis. Many patients are already unable to undergo surgical treatment. Research shows that about 40–60% of patients are unable to undergo surgical

treatment due to the advanced stage of the disease at diagnosis^[1]. For these patients, radical radiotherapy and chemotherapy have become the main treatment methods. As a new radiotherapy method, volumetric modulated arc therapy (VMAT) kills tumor cells by irradiating the tumor target area. Its measurement distribution effect is good and more precise and flexible, playing an important role in the treatment of solid tumors^[2]. Studies have shown that radiotherapy combined with chemotherapy in the treatment of esophageal cancer can improve radiotherapy sensitivity and patient survival rates^[3]. Based on this, this study explores the effect of VMAT radiotherapy combined with raltitrexed chemotherapy in the treatment of elderly patients with esophageal cancer, as detailed below.

2. Materials and methods

2.1. General information

A total of 86 elderly patients diagnosed with esophageal cancer and admitted to our hospital between February 2024 and February 2025 were enrolled in this study. Based on the treatment approaches, they were categorized into a control group and a study group, each comprising 43 patients. The baseline characteristics of both groups were comparable, with no statistically significant differences ($P > 0.05$), as detailed in **Table 1**.

Table 1. Comparison of general information between the two groups

Group	Cases	Gender (%)		Age (years)	Disease duration (months)	BMI (kg/m ²)	TNM stage	
		Male	Female				II	III
Control	43	24 (55.81%)	19 (44.19%)	79.34 ± 4.32	11.35 ± 4.23	23.66 ± 3.51	25 (58.14%)	18 (41.86%)
Study	43	23 (53.48%)	20 (46.51%)	79.12 ± 4.61	11.23 ± 4.14	23.75 ± 3.62	24 (55.81%)	19 (44.19%)
χ^2/t		0.047	0.228	0.133	0.117	0.047		
P		0.829	0.820	0.894	0.907	0.828		

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Meet the diagnostic criteria^[4] and confirmed by pathological examination; (2) Age is not less than 70 years old; (3) Unable to complete surgery and receiving radiotherapy and chemotherapy for the first time; (4) Estimated survival time is greater than 1 year; (5) Signed informed consent.

Exclusion criteria: (1) Those with esophageal bleeding, erosion, etc.; (2) Those with distant metastasis; (3) Those with severe mental illness and other serious organic diseases; (4) Those with incomplete information.

2.3. Methods

The control group received VMAT radiotherapy alone: Patients were placed in a supine position, with CT enhancement for positioning, a 5mm scanning layer thickness, and delineation based on examination results, including gross tumor volume, clinical target volume, planning target volume, and adjacent tissues and organs. A three-dimensional radiotherapy planning system was used to perform a counterclockwise 358° single-arc VMAT plan (179–181°) for VMAT-treated patients, with a maximum dose rate of 600 MU/min and a 4° sub-field interval. Treatment was administered 5 times per week, with a 21-day cycle, for 2 cycles.

The study group received raltitrexed on the basis of the control group's treatment: 3 mg/m² of the drug was

diluted in 100 mL of normal saline and administered intravenously to patients every 3 weeks, with 2 cycles of treatment during radiotherapy.

2.4. Observation indices

- (1) The short-term outcomes of both groups were evaluated based on complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) ^[5]. The objective response rate was determined by (CR + PR) divided by the total cases, while the disease control rate was calculated as (CR + PR + SD) divided by the total cases.
- (2) Compare the tumor marker levels before and after treatment in the two groups. Fasting venous blood samples were collected to detect heat shock protein 90 α (HSP90 α), cytokeratin fragment 19 antigen 21-1 (Gyfra21-1), and carcinoembryonic antigen (CEA).
- (3) Record adverse reactions during treatment in both groups.
- (4) A 6-month follow-up study assessed the quality of life (QOL) in cancer patients across both groups, comparing baseline measurements taken before treatment with subsequent evaluations at 1, 3, and 6 months post-treatment to analyze changes over time.

2.5. Statistical methods

Data were analyzed using SPSS 24.0 software. Normally distributed measurement data with homogeneous variance were expressed as mean \pm standard deviation (SD), and enumeration data were expressed as percentages (%). T-test and chi-square test (χ^2) were performed accordingly. A P -value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of short-term efficacy between the two groups

The study group demonstrated a significantly greater objective remission rate and disease control rate than the control group ($P < 0.05$), as detailed in **Table 2**.

Table 2. Comparison of short-term efficacy between the two groups [n , (%)]

Group	Cases	CR	PR	SD	PD	Objective response	Disease control
Control	43	12 (27.91%)	13 (30.23%)	10 (23.26%)	8 (18.60%)	25 (58.14%)	35 (81.40%)
Study	43	20 (46.51%)	20 (46.51%)	2 (4.65%)	1 (2.33%)	40 (93.02%)	42 (97.67%)
χ^2						14.176	6.081
P						<0.001	0.014

3.2. Comparison of tumor marker levels before and after treatment in both groups

After treatment, the levels of HSP90 α , Cyfra21-1, and CEA in the study group were significantly lower than those in the control group ($P < 0.05$). See Table 3.

Table 3. Comparison of tumor marker levels before and after treatment in both groups (mean \pm SD, ng/mL)

Group	Cases	HSP90 α (ng/mL)		Cyfra21-1 (ng/mL)		CEA (ng/mL)	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Control	43	110.87 \pm 43.23	72.11 \pm 26.43	6.67 \pm 1.31	3.87 \pm 1.03	6.49 \pm 1.23	3.42 \pm 1.01
Study	43	111.12 \pm 45.24	54.61 \pm 21.23	6.72 \pm 1.18	2.37 \pm 0.64	6.51 \pm 1.16	2.48 \pm 0.56
<i>t</i>		0.026	3.385	0.186	8.111	0.078	5.337
<i>P</i>		0.979	0.001	0.853	<0.001	0.938	<0.001

3.3. Comparison of adverse reactions between the two groups

No statistically significant variation was observed in the occurrence of adverse effects when comparing the two groups ($P > 0.05$), as detailed in **Table 4**.

Table 4. Comparison of adverse reactions between the two groups [*n*, (%)]

Group	Cases	Radiation Esophagitis	Radiation Pneumonitis	Leukopenia	Thrombocytopenia	Gastrointestinal Reactions	Total Incidence
Control	43	4 (9.30%)	4 (9.30%)	36 (83.72%)	36 (83.72%)	3 (6.98%)	17 (39.53%)
Study	43	4 (9.30%)	36 (83.72%)	4 (9.30%)	4 (9.30%)	4 (9.30%)	19 (44.19%)
χ^2							0.191
<i>P</i>							0.662

3.4. Comparison of QOL scores before and after treatment between the two groups

The quality of life (QOL) scores in the study group demonstrated a statistically significant improvement compared to the control group at both the 3-month and 6-month follow-up assessments ($P < 0.05$), as detailed in **Table 5**.

Table 5. Comparison of QOL scores before and after treatment between the two groups (mean \pm SD, scores)

Group	Cases	Baseline	1 month post-treatment	3 months post-treatment	6 months post-treatment
Control	43	75.64 \pm 4.21	72.42 \pm 3.43	77.35 \pm 4.12	78.53 \pm 3.32
Study	43	75.56 \pm 4.31	71.43 \pm 4.32	81.03 \pm 3.24	86.33 \pm 4.34
<i>t</i> -value		0.087	1.177	4.604	9.360
<i>p</i> -value		0.931	0.243	< 0.001	< 0.001

4. Discussion

Surgical treatment is a commonly used therapy for esophageal cancer. However, elderly patients may not tolerate surgery due to their physical condition and underlying diseases; thus, radiotherapy is often chosen as the treatment method ^[6]. As an advanced radiotherapy technique commonly used in clinical practice, Volumetric Modulated Arc Therapy (VMAT) can increase the local dose to the tumor without increasing the dose to critical organs. Its application can effectively shorten treatment time, and it has characteristics such as high

conformality and fewer jumps. It has demonstrated outstanding advantages in the treatment of tumors, including esophageal cancer ^[7]. Studies have shown that VMAT can shorten treatment time for esophageal cancer patients, protect critical organs, and reduce the occurrence of radiation pneumonitis ^[8]. Although VMAT can be effective in the treatment of esophageal cancer, monotherapy with radiotherapy often yields suboptimal results. Yan et al. ^[9] showed that concurrent radiotherapy and chemotherapy can lead to better long-term outcomes, improving local control rates and prolonging survival time for esophageal cancer patients.

As a specific inhibitor of thymidylate synthase (TS), raltitrexed has a higher binding affinity for TS and can competitively block TS activity, disrupting normal DNA replication in tumor cells and causing cell cycle arrest and apoptosis, thereby exerting an anti-tumor effect. Although its efficacy is similar to that of fluorouracil, its mechanism of action is different, and it has a lower incidence of adverse reactions ^[10]. Some scholars have pointed out that raltitrexed has lower cardiotoxicity compared to fluorouracil drugs, making it particularly advantageous for elderly cancer patients, especially those with cardiac insufficiency, as it can reduce the impact on cardiac function ^[11]. In this research, the study group demonstrated a greater objective response rate and disease control rate compared to the control group, along with significantly reduced tumor marker levels post-treatment. This indicates that concurrent VMAT radiotherapy and raltitrexed chemotherapy have good short-term efficacy in elderly esophageal cancer patients, improving disease control and reducing tumor marker levels. The two groups showed comparable rates of adverse effects, with no severe or life-threatening acute radiation toxicities observed, demonstrating that the combination of VMAT radiotherapy and raltitrexed chemotherapy has manageable toxicity and is well-tolerated by patients. The results also showed that the QOL scores of the study group were significantly higher than those of the control group at 3 and 6 months after treatment. Concurrent radiotherapy and chemotherapy can improve disease control, symptoms, prognosis, and quality of life for patients.

5. Conclusion

In summary, VMAT radiotherapy can shorten treatment time and improve tumor control effects, while raltitrexed chemotherapy has definite efficacy and lower adverse reactions. The synchronous treatment of both can improve the short-term efficacy of elderly patients with esophageal cancer, with good disease control effects, and can reduce patients' tumor marker levels, which is beneficial for improving patients' quality of life. Patients have good tolerance, indicating clinical value.

Disclosure statement

The authors declare no conflict of interest.

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The Therapeutic Effects and Safety of Dioscorea Decoction Combined with Coix Seed in Treating Cancer Cachexia (Spleen-kidney Yang Deficiency Syndrome) in Malignant Tumor Patients

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Abstract: *Objective:* To investigate the therapeutic effects and safety of Dioscorea Decoction combined with Coix Seed in treating cancer cachexia (spleen-kidney Yang deficiency syndrome) in malignant tumor patients. *Methods:* A total of 90 patients with cancer cachexia admitted between June 2024 and June 2025 were randomly divided into a control group and a study group (45 cases each) using a random number generator. Both groups received antitumor therapy, oral megestrol acetate capsules, and conventional nutritional intervention. The study group additionally received oral Dioscorea Decoction combined with Coix Seed. Differences in TCM syndrome scores, nutritional indicators (serum albumin, hemoglobin), and adverse reactions were compared before and after treatment. *Results:* Baseline TCM syndrome scores and nutritional indicators were comparable between the two groups before treatment. After treatment, both groups showed significant reductions in TCM syndrome scores and increases in serum albumin and hemoglobin levels. The study group exhibited lower TCM syndrome scores and higher serum albumin and hemoglobin levels than the control group, with statistically significant differences. No significant difference in adverse reaction rates was observed between the two groups. *Conclusion:* Dioscorea Decoction combined with Coix Seed can further improve nutritional status, alleviate clinical symptoms, and demonstrate good safety in treating cancer cachexia patients.

Keywords: Dioscorea Decoction; Coix Seed; Cachexia; Malignant tumor

Online publication: August 7, 2025

1. Introduction

Cancer cachexia is a clinical syndrome characterized by persistent loss of skeletal muscle mass, most commonly seen in patients with lung cancer and digestive system tumors. It is often caused by an imbalance in energy

metabolism due to various reasons and clinically manifests as anorexia, weight loss, etc.^[1] Epidemiological data shows that the incidence and mortality of malignant tumors are on the rise in China. In this context, the incidence of cachexia in patients with advanced malignant tumors can reach up to 80%, severely affecting the quality of life and prognosis of cancer patients and causing at least 22% of cancer deaths^[2]. Conventional Western medicine and nutritional support interventions for cancer cachexia patients have limited effects and single targets, and may also increase the risk of liver and kidney function damage in patients. However, due to the anemia state of cancer cachexia patients, exercise therapy has significant limitations in the treatment of such patients. Therefore, it is necessary to explore a safe and effective method for comprehensive intervention in clinical practice^[3]. Because of this, this study conducted research on 90 patients with cancer cachexia, including from June 2024 to June 2025, intending to investigate the therapeutic effect and safety of Dioscorea Decoction combined with Coix Seed on cancer cachexia (spleen and kidney Yang deficiency syndrome) in patients with malignant tumors.

2. Materials and methods

2.1. General information

Ninety patients with malignant tumor cachexia admitted to our hospital from June 2024 to June 2025 were selected and randomly divided into a control group and a study group, with 45 patients in each group using a computer random number generator. The study group consisted of 24 males and 21 females, aged between 37 and 77 years old, with an average age of (55.65 ± 8.46) years old. The course of disease ranged from 1 to 5 years, with an average of (2.46 ± 0.51) years. Among them, 27 patients were in stage III and 18 patients were in stage IV of TNM tumor staging. The control group consisted of 28 males and 17 females, aged between 35 and 79 years old, with an average age of (56.17 ± 9.34) years old. The course of disease ranged from 1 to 5 years, with an average of (2.73 ± 0.60) years. Among them, 31 patients were in stage III and 14 patients were in stage IV of TNM tumor staging. This study has been approved by the Medical Ethics Committee of XX Hospital, and all patients and their families involved in the trial were informed and signed consent forms.

2.2. Inclusion criteria

- (1) Patients who meet the diagnostic criteria for cancer cachexia^[4];
- (2) Meet the diagnostic criteria for spleen and kidney Yang deficiency syndrome in the “Clinical Terminology of Traditional Chinese Medicine GB2019 Edition”^[5];
- (3) Aged between 18 and 80 years old;
- (4) Complete baseline data.

2.3. Exclusion criteria

- (1) Patients with an estimated survival time of less than 3 months;
- (2) Patients with neurologic anorexia;
- (3) Women during pregnancy and lactation;
- (4) Patients with severe cardiac, liver, kidney diseases or infections;
- (5) Patients with autoimmune diseases;
- (6) Patients with severe benign gastrointestinal diseases;
- (7) Patients with poor compliance. Patients with severe benign gastrointestinal diseases.

2.4. Methods

Both groups of patients received concurrent anti-tumor therapy. They orally took Megestrol Acetate Capsules (Jiangsu Nhwa Pharmaceutical Corporation Limited, National Medical Approval Number H20010553, specification 80 mg/capsule), 160 mg per time, once a day, combined with conventional nutritional intervention, including health education, high-protein and high-nutrition diet, and symptomatic treatments such as enteral nutrition, intravenous injection of fat emulsion, antiemetic, and analgesic when necessary. In addition to the above treatments, the study group was given orally Shuyu Decoction combined with prepared Coix seed (the main ingredients include 23 herbs such as Chinese yam, *Codonopsis pilosula*, *Ophiopogon japonicus*, *Paeonia lactiflora*, and prepared Coix seed, decocted by the pharmacy of XX Hospital), one dose per day, taken once in the morning and once in the evening, for 2 months.

2.5. Observation indicators

2.5.1. TCM syndrome scores

Evaluated before treatment and after 2 months of treatment, respectively. Referring to the relevant standards of the “Guiding Principles for Clinical Research of New Chinese Medicines”^[6], the symptom scores include five aspects: emaciation, poor appetite, shortness of breath, fatigue, and abdominal distension. The higher the score, the more severe the symptoms.

2.5.2. Nutritional indicators

Evaluated before treatment and after 2 months of treatment, respectively. An automatic biochemical analyzer was used to measure patients’ serum albumin levels, and a hematology analyzer was used to measure patients’ hemoglobin levels.

2.5.3. Adverse reactions

The occurrence of adverse reactions such as gastrointestinal side effects, dizziness and headache, and abnormal liver function during the treatment process in both groups was observed.

2.6. Statistical methods

Data analysis was performed using SPSS 19.0 statistical software. After passing the Shapiro-Wilk test for normal distribution, the scores of traditional Chinese medicine (TCM) syndromes and nutritional indicators were expressed as mean \pm standard deviation (SD). Independent sample *t*-tests were used for comparisons between groups. Adverse reactions were expressed as rates (%), and differences between the two groups were compared using the χ^2 test or Fisher’s exact test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of TCM syndrome scores between the two groups

There were no significant differences in TCM syndrome scores between the two groups before treatment (all $P > 0.05$). After treatment, the scores decreased significantly in both groups (all $P < 0.05$), and the scores in the study group were lower than those in the control group, with statistically significant differences (all $P < 0.05$). See **Table 1**.

Table 1. Comparison of TCM syndrome scores between the two groups

Group	n	Weight Loss (kg)		Anorexia Score		Dyspnea Score		Fatigue Score		Abdominal Distension Score	
		Baseline	Post-Tx	Baseline	Post-Tx	Baseline	Post-Tx	Baseline	Post-Tx	Baseline	Post-Tx
Study	45	1.41 ± 0.36	0.79 ± 0.24*	1.21 ± 0.34	0.60 ± 0.14*	1.03 ± 0.32	0.51 ± 0.19*	1.47 ± 0.45	0.92 ± 0.23*	1.52 ± 0.37	0.96 ± 0.35*
Control	45	1.36 ± 0.40	0.94 ± 0.29*	1.27 ± 0.41	0.91 ± 0.25*	1.11 ± 0.39	0.86 ± 0.29*	1.56 ± 0.39	1.17 ± 0.34*	1.45 ± 0.43	1.16 ± 0.44*
<i>t</i> -value		0.623	-2.673	-0.756	-7.258	-1.064	-6.772	-1.014	-4.086	0.828	-2.386
<i>p</i> -value		0.535	0.009	0.452	< 0.001	0.290	< 0.001	0.313	< 0.001	0.410	0.019

Note: Compared with before treatment, **P* < 0.05.

3.2. Comparison of surgical parameters between the two groups

There was no significant difference in serum albumin and hemoglobin levels between the two groups before treatment (all *P* > 0.05). However, after treatment, both groups showed significant increases in these levels (all *P* < 0.05). Moreover, the study group had higher levels of serum albumin and hemoglobin compared to the control group, with a statistically significant difference (all *P* < 0.05). See **Table 2**.

Table 2. Comparison of nutritional indices between the two groups (mean ± SD)

Group	n	Albumin (g/L)		Hemoglobin (g/L)	
		Baseline	Post-Tx	Baseline	Post-Tx
Study	45	36.09 ± 6.58	42.43 ± 8.61*	101.65 ± 14.09	117.42 ± 14.34*
Control	45	34.96 ± 7.13	38.49 ± 6.82*	102.12 ± 13.35	111.06 ± 12.07*
<i>t</i> -value		0.781	2.406	-0.508	2.169
<i>p</i> -value		0.437	0.018	0.613	0.033

Note: Compared with before treatment, **P* < 0.05.

3.3. Comparison of adverse reactions between the two groups

The study group only experienced dizziness and headache in one case each, and gastrointestinal side effects in one case. The control group had one case of gastrointestinal side effects. There was no statistically significant difference in the total incidence of adverse reactions between the two groups (4.44% vs 2.22%, *P* > 0.05). See **Table 3** for details.

Table 3. Comparison of adverse reactions between the two groups (cases)

Group	n	Gastrointestinal reactions (<i>n</i>)	Dizziness/headache (<i>n</i>)	Total incidence (%)
Study	45	1 (2.22%)	1 (2.22%)	2 (4.44%)
Control	45	1 (2.22%)	0	1 (2.22%)
χ^2				0
<i>p</i> -value				1

4. Discussion

From the perspective of traditional Chinese medicine, cachexia can be attributed to “deficiency and debilitation.” Traditional Chinese medicine oncology believes that the pathogenesis of tumor cachexia is similar to that of tumors, which is a mixture of deficiency and excess, with deficiency at the root and excess as the manifestation. For patients with spleen and kidney Yang deficiency syndrome, the treatment should focus on strengthening the body’s resistance to eliminate pathogens and nourishing the spleen and stomach, supplemented by promoting Qi and blood circulation, resolving phlegm, and detoxifying^[7]. In this study, both groups of patients showed significant improvement in traditional Chinese medicine symptom scores and nutritional indicators after corresponding treatment. This is likely due to the use of megestrol acetate as the basic treatment in this study, which can inhibit inflammatory factors released in the tumor microenvironment to reduce systemic inflammatory response on the one hand, and act on the hypothalamus appetite center to increase hunger and food intake, thereby improving patients’ nutritional status on the other hand^[8]. Dioscorea decoction is derived from Dioscorea Pill in “Synopsis of Golden Chamber” by Zhang Zhongjing. It mainly nourishes Qi and blood, dispels wind and eliminates pathogens, and can treat “various deficiencies of debilitation and hundreds of wind-induced diseases”. In this study, it was combined with Coix seed to enhance the effect of strengthening the spleen and promoting dampness elimination. The treatment effects are as follows:

After corresponding treatment, the scores of various traditional Chinese medicine symptoms in the study group were lower than those in the control group, and the levels of serum albumin and hemoglobin were higher than those in the control group, indicating that Dioscoreae Radix Decoction combined with processed Coix seed could further improve the nutritional status and reduce clinical symptoms of patients. Dioscoreae Radix Decoction uses Huai Shan Yao as the monarch drug to tonify the Qi and Yin of the triple warmer and rebuild the source of transformation for the spleen and kidney Yang deficiency syndrome of cachexia. With Si Jun Zi Tang, Si Wu Tang, *Ophiopogonis Radix*, and *Colla Corii Asini* as minister drugs, it can tonify the Qi of the spleen and lungs, assist the monarch drug to invigorate the middle warmer, nourish blood and essence, and nourish the organs. Assisted by drugs such as *Bupleuri Radix*, *Saposhnikovia Radix*, Medicated Leaven, and *Platycodi Radix* to eliminate pathogens and regulate the pivotal function. Finally, *Zingiberis Rhizoma Recens*, *Jujubae Fructus*, and prepared *Glycyrrhizae Radix Rhizoma* are used as envoy drugs to harmonize the various drugs while stimulating the spleen Yang to promote transportation and transformation, tonifying the spleen and nourishing the nutrients^[9]. Processed Coix seed is made by processing Coix seed, which reduces its cold property and increases its function of tonifying the spleen and eliminating dampness. When used in combination with Dioscoreae Radix Decoction, it can break the difficulty of not being able to accept tonifying drugs due to internal dampness and turbidity^[10]. Modern pharmacological experiments have shown that yam polysaccharide can promote fatty acid oxidation and inhibit excessive activation of mTOR, thereby blocking muscle protein breakdown^[11]. Coix seed ester can reduce the activation of the ubiquitin-proteasome pathway and inhibit the expression of muscle atrophy factors (Atrogin-1/MuRF1). In addition, Coix seed has also been shown to reduce caspase-1-mediated IL-18 maturation by inhibiting NLRP3 inflammasome activation, thereby inhibiting inflammatory responses^[12]. On the other hand, yam mucous protein can enhance the integrity of intestinal epithelial tight junctions and promote the repair of intestinal mechanical barriers^[13]. The pachymic acid contained in Poria can reduce intestinal wall edema and improve absorption function by up-regulating the expression of aquaporin AQP3, thereby improving the nutritional status of patients^[14]. There was no significant difference in the incidence of adverse reactions between the two groups of patients in this study, indicating that Dioscoreae Radix Decoction combined with processed Coix seed is safe for

the treatment of cachexia and does not increase the risk of adverse reactions.

5. Conclusion

In summary, the use of *Dioscoreae Radix* Decoction combined with processed Coix seed for the treatment of malignant tumor cachexia patients can further improve their nutritional status, reduce clinical symptoms, and has good safety. It is worthy of further promotion in clinical practice.

Disclosure statement

The authors declare no conflict of interest.

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Research Progress of HER-2 in Colorectal Cancer

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Abstract: Human epidermal growth factor receptor 2 (HER-2) is a transmembrane receptor tyrosine kinase that is overexpressed in various solid tumors and is closely related to tumor invasion, metastasis, and poor prognosis. In recent years, the expression of HER-2 in colorectal cancer and its clinical significance have gradually attracted attention. This article reviews the expression of HER-2 in colorectal cancer, the clinicopathological characteristics of HER-2 positive colorectal cancer, the detection methods of HER-2, and the drug treatment targeting HER-2, to provide references for clinical diagnosis and treatment and research.

Keywords: Human epidermal growth factor receptor 2; Colorectal cancer; Expression; Targeted therapy

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1. Introduction

Colorectal cancer is one of the malignant tumors with high incidence and mortality worldwide. Its pathogenesis has not yet been fully elucidated. Human epidermal growth factor receptor 2 (HER-2) is a transmembrane receptor tyrosine kinase encoded by an oncogene, playing an important regulatory role in cell proliferation, differentiation, and apoptosis. Recent studies have found that HER-2 is overexpressed in various solid tumors, with an expression rate of up to 20% to 30% in breast cancer, and is closely related to tumor invasion, metastasis, and poor prognosis. Currently, drugs targeting HER-2 have become the standard treatment for HER-2-positive breast cancer patients. In contrast, the research on HER-2 in colorectal cancer has been relatively lagging, but has gradually gained attention in recent years.

2. Expression of HER-2 in colorectal cancer

The HER-2 gene is located on the long arm of chromosome 17 (17q12-q21) and is encoded by 28 exons. The HER-2 protein is localized on the cell membrane and consists of three parts: the extracellular region, the

transmembrane region, and the intracellular region. When the ligand binds to the extracellular region, it can induce the dimerization of the HER-2 protein, thereby activating the tyrosine kinase activity in the intracellular region, initiating downstream signaling pathways, and thereby regulating the proliferation, differentiation, migration, and other functions of the cells ^[1].

The expression rate of HER-2 in colorectal cancer tissues varies and shows significant differences. He *et al.* conducted a meta-analysis on 123 colorectal cancer patients and found that the positive expression rate of HER-2 was significantly higher than that in normal tissues adjacent to the cancer ($P < 0.05$). The expression level of HER-2 is closely related to the clinical and pathological parameters of the patients. The combined detection of LGR5 and HER-2 has a high predictive value for the prognosis of patients ^[2]. Chen *et al.* analyzed 35 patients with benign colorectal lesions (benign lesion group) and 36 healthy individuals undergoing physical examinations (normal control group) for colorectal cancer. The serum HER-2 level was related to RAS gene mutations and peripheral nerve invasion in colorectal cancer patients ($P < 0.05$), while the CD44 level was not related to RAS gene mutations and peripheral nerve invasion ($P > 0.05$) ^[3]. The areas under the curve (AUC) for the individual and combined detection of HER-2, CD44, carcinoembryonic antigen (CEA), and carbohydrate antigen (CA19)-9 in the diagnosis of colorectal cancer were 0.779, 0.692, 0.620, 0.634, and 0.837 ^[4], respectively. It can be seen that the expression of HER-2 in colorectal cancer shows significant heterogeneity, and its positive rate is affected by factors such as region, stage, and tissue origin. Overall, it is approximately 5%.

3. HER-2 detection methods

Accurate assessment of HER-2 status in colorectal cancer is of great significance for guiding treatment decisions. Currently, the main methods for HER-2 detection include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and real-time PCR, etc.

3.1. IHC

IHC (Immunohistochemistry) is the preferred method for detecting HER-2 expression. Its principle involves using specific antibodies to bind with the HER-2 protein, and through a color reaction, observing the expression of HER-2 on the tumor cell membrane under a microscope. Commonly used antibodies include HercepTest, 4B5, A0485, etc. Among them, HercepTest is a reagent approved by the FDA for HER-2 detection in colorectal cancer ^[5].

The IHC operation steps include: dewaxing and hydration of paraffin sections, antigen retrieval, incubation with primary antibody, incubation with secondary antibody, DAB staining, and hematoxylin re-staining. The result interpretation requires observation under a high-power microscope, and reference to the HER-2 scoring standard for breast cancer, which is divided into four grades: 0, 1+, 2+, and 3+. The specific interpretation criteria are as follows:

- (1) 0: The tumor cell membranes show no staining at all, or less than 10% of the tumor cell membranes show partial staining;
- (2) 1+: More than 10% of the tumor cell membranes show slight/almost imperceptible staining, with only local coloring on the cell membranes;
- (3) 2+: More than 10% of the tumor cell membranes show mild/moderate staining, with the cell membranes fully colored;
- (4) 3+: More than 10% of the tumor cell membranes show strong/complete circular and uniform staining.

IHC 0 and 1+ are defined as negative and no further testing is required; IHC 3+ is defined as positive,

indicating overexpression of the HER-2 protein; IHC 2+ is considered a suspected positive and further methods such as FISH should be used to verify the gene amplification situation. The American Society for Clinical Pathology (CAP) recommends that at least the primary or metastatic tumor tissues related to the treatment be tested, and a positive cell ratio of no less than 10% can be used to determine HER-2 overexpression.

3.2. FISH

FISH (Fluorescence In Situ Hybridization) is the gold standard method for detecting HER-2 gene amplification. Its principle is to use DNA probes with fluorescent labels, which specifically bind to the HER-2 gene in the tumor cell nucleus and the centromere region of chromosome 17 (CEP17). By observing the signal intensities of both, it is possible to determine whether the HER-2 gene is amplified ^[6].

The FISH operation steps include: dewaxing and hydration of paraffin sections, baking, DNA denaturation, hybridization, denaturation removal, DAPI re-staining, etc. The commonly used probes include PathVysion, INFORM, PharmDx, etc., all of which are dual-color probes. The red fluorescent dye marking the HER-2 gene is SpectrumOrange, and the green fluorescent dye marking CEP17 is SpectrumGreen.

The result interpretation needs to be conducted under a special fluorescence microscope. For each case, 20 tumor cell nuclei are randomly counted to obtain the signal numbers of HER-2 and CEP17. There are two interpretation indicators:

- (1) The ratio of HER-2/CEP17 (HER-2/CEP17 ratio);
- (2) The copy number of HER-2.

The interpretation criteria are as follows:

- (1) Negative: HER-2/CEP17 ratio < 2.0, and HER-2 copy number < 4.0;
- (2) Suspected positive: HER-2/CEP17 ratio < 2.0, but HER-2 copy number ≥ 4.0 and < 6.0;
- (3) Positive: HER-2/CEP17 ratio ≥ 2.0 or HER-2 copy number ≥ 6.0 .

FISH has the following advantages over IHC:

- (1) It can directly reflect the HER-2 gene amplification status, which is more objective and accurate;
- (2) The results are stable and not affected by factors such as tissue fixation;
- (3) The staining signal can be preserved for a long time, making it convenient for re-reading ^[7].

However, FISH also has certain limitations, such as complex operation, long cycle, high cost, and high requirements for equipment and technology. In addition, due to genetic alterations such as chromosome 17 polysomy, in a few cases, inconsistent HER-2/CEP17 ratio and HER-2 copy number may occur, and careful interpretation is required.

3.3. Real-time quantitative PCR

Real-time quantitative PCR (RT-qPCR) is a DNA quantification method based on PCR, which can rapidly and sensitively detect the copy number of the HER-2 gene. Unlike IHC and FISH, RT-qPCR does not rely on tumor tissue sections. It can directly extract DNA from fresh tissues, frozen tissues, or paraffin-embedded tissues for detection, and has lower requirements for tissue quantity, especially being suitable for cases with few biopsy tissues or ctDNA detection from peripheral blood ^[8].

RT-qPCR uses the Taqman probe method, which enables real-time quantitative detection of the amplification products simultaneously during PCR amplification through specific primers and fluorescently labeled probes. Common internal reference genes include ALB, B2M, G6PDH, etc., which can correct for differences in DNA input and PCR efficiency. By comparing the Ct values of the HER-2 gene and the internal reference gene, the

relative copy number of the HER-2 gene can be calculated.

The RT-qPCR operation steps include: DNA extraction, preparation of the reaction system, real-time quantitative PCR amplification, and result analysis. Currently, there are multiple commercial kits available, such as Cobas 4800 HER-2, Therascreen HER-2 ARMS-PCR, etc., which provide standardized detection procedures and result interpretation. Taking Cobas 4800 HER-2 as an example, with a DNA copy number ≥ 6.0 as the positive judgment standard, the consistency with FISH results is as high as 96%.

Compared with IHC and FISH, RT-qPCR has the following advantages:

- (1) Simple operation, short cycle, high throughput;
- (2) Objective and accurate quantitative results with good repeatability;
- (3) High sensitivity, capable of detecting low-copy-number gene amplification^[9];
- (4) Can utilize paraffin tissue specimens, facilitating retrospective studies;
- (5) Can detect ctDNA in peripheral blood, enabling non-invasive dynamic monitoring.

However, RT-qPCR also has certain limitations, such as being susceptible to factors such as PCR inhibitors in the sample, non-tumor cell contamination, etc., which may lead to false-negative results. In addition, RT-qPCR only reflects the copy number of the HER-2 gene and cannot provide information on HER-2 protein expression, which may have a poor correlation with clinical efficacy.

4. Clinical and pathological characteristics of HER-2 positive colorectal cancer

4.1. Tumor location: HER-2 positivity is more common in rectal cancer, with a higher positive rate than in colon cancer

Multiple studies have shown that the positive rate of HER-2 in rectal cancer is higher than that in colon cancer^[10]. A study involving 105 patients with colorectal cancer found that the difference in HER-2 positivity between rectal cancer and colon cancer may be related to the different anatomical locations, embryonic developmental origins, and molecular biological characteristics of rectal cancer and colon cancer^[11]. Rectal cancer is more susceptible to local microenvironmental influences, such as chronic inflammation and intestinal flora imbalance, which may promote the overexpression of HER-2. Additionally, the prognosis of rectal cancer patients is generally worse than that of colon cancer patients, suggesting that HER-2 may be one of the important factors affecting prognosis.

4.2. Gender: The HER-2 positive rate in females is higher than that in males

Epidemiological data show that the incidence and mortality rates of colorectal cancer exhibit significant gender differences, with female patients having a better prognosis than male patients. Studies have found that the abnormal activation of the mitogen-activated protein kinases (MAPK) signaling pathway plays an important role in the occurrence and development of CRC. In terms of HER-2 expression, the positive rate in female patients is also higher than that in male patients^[12]. Gender-related factors such as estrogen may affect the occurrence and development of colorectal cancer by regulating HER-2 expression. In addition, HER-2 positive breast cancer mostly occurs in pre-menopausal women, suggesting that ovarian function may be involved in regulating the HER-2 signaling pathway. Future research is expected to clarify the molecular mechanism of gender differences and provide new ideas for individualized prevention and treatment of colorectal cancer.

4.3. Histological type: HER-2 positivity is more common in mucinous adenocarcinoma, signet ring cell carcinoma and other special types

The distribution of HER-2 positivity varies among different histological types of colorectal cancer. Generally, the positive rate of HER-2 in mucinous adenocarcinoma and signet ring cell carcinoma, etc., is higher than that in ordinary adenocarcinoma. A study involving 60 patients with colorectal cancer found that the expression of COX-2 in all colorectal tissues was determined by immunohistochemistry, and the correlation between COX-2 expression and clinical pathological features was analyzed. The result showed that the COX-2 positive rate in CRC tissues was 46.67%, significantly higher than 11.67% in normal colorectal tissues ($P < 0.05$)^[13]. These special types often have a poorer prognosis, suggesting that HER-2 may affect prognosis by promoting the secretion of mucus by tumor cells and their differentiation towards a neuroendocrine direction. In addition, the occurrence of these special types may be related to specific genetic alterations, such as MSI-H, CIMP, etc., and these alterations may also have cross-relationships with the HER-2 signaling pathway, which requires further research to confirm.

4.4. Degree of differentiation: The differentiation degree of HER-2 positive patients is generally poor

Tumor differentiation degree is one of the important indicators for judging the malignancy and prognosis. Multiple studies have found that the tumor differentiation degree of HER-2 positive colorectal cancer patients is worse than that of HER-2 negative patients^[14]. Chen Minyang et al. included 80 colorectal cancer patients in their study and showed that the expression level of HER2 was positively correlated with clinical stage, invasion depth, lymph node metastasis, distant metastasis, and pathological features such as differentiation degree. The survival rate of HER-2 positive patients was significantly lower than that of negative patients^[15]. Among them, the lower the differentiation degree, the higher the atypia of tumor cells, and the stronger the proliferative and invasive ability. HER-2 activates downstream PI3K/Akt and MAPK signaling pathways to promote cell cycle progression, inhibit apoptosis, and may lead to tumor cell dedifferentiation. In addition, HER-2 can also upregulate the expression of certain stem cell markers, such as CD44 and CD166, enabling tumor cells to acquire stem cell-like characteristics, thereby accelerating tumor progression.

4.5. TNM staging: The positive rate of HER-2 increases with the elevation of T stage, N stage and M stage

The positive rate of HER-2 is closely related to the TNM staging of colorectal cancer. He *et al.* have shown that HER-2 may promote tumor progression by enhancing the invasive and metastatic ability of tumor cells. HER-2 can induce epithelial-mesenchymal transition, enabling tumor cells to exhibit malignant manifestations such as migration and invasion^[16]. Moreover, HER-2 can promote tumor angiogenesis, disrupt the basement membrane, and provide a pathway for tumor metastasis and spread. Therefore, it is particularly important to conduct HER-2 testing for advanced patients, and those with positive results can benefit from targeted drugs such as trastuzumab.

4.6. Sites of metastasis: HER-2 positive patients are more prone to liver metastasis, followed by lung metastasis and peritoneal metastasis

HER-2 affects the pattern and sites of metastasis in colorectal cancer. Studies have shown that HER-2 positive patients are more likely to develop liver metastasis. A study involving 126 patients with metastatic colorectal cancer revealed that the expressions of her-2 and VEGF proteins were higher in colorectal cancer, and their expressions were closely related to the growth, invasion and metastasis of colorectal cancer, possibly having a synergistic effect^[17]. The combined detection of HER-2 and VEGF expressions in the tissues of colorectal cancer

patients is helpful for evaluating the severity of colorectal cancer and the prognosis of patients, providing certain scientific basis for the early diagnosis and molecular treatment of colorectal cancer in the future^[18]. Thus, HER-2 may promote tumor cell metastasis to the liver through various mechanisms, such as upregulating the expression of matrix metalloproteinases, degrading the extracellular matrix; inducing epithelial-mesenchymal transition, enhancing cell motility; promoting tumor angiogenesis, providing pathways for metastasis, etc. In addition, HER-2 positive patients have a higher risk of lung metastasis and peritoneal metastasis, which may be related to the lymphangiogenesis mediated by HER-2 and the changes in adhesion factor expression.

5. Research on HER-2 as a prognostic predictor for colorectal cancer

HER-2 as a prognostic predictor for colorectal cancer holds significant research value and clinical significance. Numerous studies have shown that HER-2 positivity is closely associated with poor prognosis in patients with colorectal cancer, suggesting that HER-2 may be a potential prognostic marker^[19]. HER-2 participates in the invasion and metastasis process of colorectal cancer through various mechanisms, such as activating downstream signaling pathways, inducing epithelial-mesenchymal transition, and promoting tumor angiogenesis, ultimately leading to a shorter survival period for patients. Systematic evaluation of HER-2 expression status is of great value in predicting the prognosis of colorectal cancer patients and guiding treatment decisions.

However, there are still some controversies and challenges regarding HER-2 as a prognostic marker for colorectal cancer at present. Firstly, the expression frequency of HER-2 in colorectal cancer is relatively low, with a positive rate of approximately 5%, which to some extent limits its clinical application value^[20]; Secondly, different detection methods and interpretation standards lead to significant differences in the positive rate of HER-2, and there is still a lack of unified detection norms; Moreover, the heterogeneity of HER-2 expression may cause false negative results, and the HER-2 status may change during tumor progression, so dynamic monitoring is required.

In addition, HER-2 may also become an important target for the treatment of colorectal cancer. Anti-HER-2 drugs such as trastuzumab have shown good efficacy in the treatment of HER-2 positive breast cancer and gastric cancer, but research in the field of colorectal cancer is still in its infancy. The preliminary results of clinical trials such as HERACLES are encouraging, indicating that trastuzumab combined with chemotherapy or other targeted drugs may bring survival benefits to HER-2 positive, treated advanced colorectal cancer patients. In the future, large-scale, prospective clinical trials are needed to further verify the efficacy and safety of anti-HER-2 treatment in different molecular subtypes and different treatment settings, optimize the dosage regimen and combination strategies, and evaluate its impact on patients' quality of life and medical expenses. In addition, discovering new resistance mechanisms and developing new anti-HER-2 drugs will be the focus of future research.

5.1. Drug treatment targeting HER-2

Trastuzumab is a humanized monoclonal antibody that specifically binds to the extracellular region of HER-2 and blocks the HER-2 signaling pathway, thereby inhibiting the proliferation of tumor cells. A study included 584 patients with HER-2-positive advanced gastric or gastroesophageal junction cancer. The results showed that trastuzumab combined with chemotherapy significantly prolonged the median survival time of patients compared to chemotherapy alone (13.8 months vs. 11.1 months, HR = 0.74, $P = 0.0046$)^[21]. Based on these results, trastuzumab combined with chemotherapy has become the standard first-line treatment for HER-2-positive

advanced gastric cancer.

The HERACLES trial included 27 patients with HER-2-positive metastatic colorectal cancer who received trastuzumab and lapatinib (a small molecule tyrosine kinase inhibitor) in combination therapy. The objective response rate was 30%, the disease control rate was 59%, and the median progression-free survival was 21 weeks. This study confirmed that anti-HER-2 treatment may bring survival benefits to this group of patients ^[22]. Subsequently, the HERACLES-RESCUE trial used trastuzumab combined with TDM-1 (a trastuzumab-emtansine conjugate) to treat HER-2-positive, RAS/BRAF wild-type metastatic colorectal cancer, and the preliminary results were encouraging.

Furthermore, some new antibody drugs targeting HER-2, such as Pertuzumab and MM-111, as well as various small molecule tyrosine kinase inhibitors like Lapatinib, Neratinib, and Pyrotinib, are currently in the clinical trial stage.

6. Conclusion

In conclusion, HER-2 plays a significant role in the occurrence, development and prognosis of colorectal cancer. HER-2 positivity indicates a poorer prognosis for patients, but it also provides new ideas for targeted therapy for this group of patients. Anti-HER-2 drugs such as trastuzumab have shown good efficacy and safety in the treatment of HER-2-positive advanced colorectal cancer, but more clinical trial data are needed for verification. In the future, with the in-depth study of the molecular mechanism of HER-2, the continuous emergence of new drugs, and the optimization of treatment regimens, HER-2 is expected to become one of the most important therapeutic targets for colorectal cancer. At the same time, how to select patients suitable for anti-HER-2 treatment, early identification and reversal of drug resistance will be the key research directions in the future.

In summary, the role of HER-2 in the diagnosis and treatment of colorectal cancer is increasingly prominent. Only by strengthening basic research, standardizing and popularizing HER-2 testing, actively conducting clinical trials can more patients benefit from it, and thereby improve the overall diagnosis and treatment level and patient survival quality of colorectal cancer. It is believed that in the and near future, HER-2 testing will become an important part of the routine diagnosis of colorectal cancer, and anti-HER-2 drugs will benefit more patients in need.

Disclosure statement

The authors declare no conflict of interest.

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Case Study and Literature Review on Diagnosis and Treatment of Advanced Metastasis of Tumor with Unknown Primary Origin

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Abstract: Primary of Unknown Origin Cancer (CUP) is a metastatic tumor whose origin remains undetermined. The reason for this ambiguity in identifying the primary site remains unclear, possibly due to the tumor being too small or growing too slowly, or because the immune system has destroyed the tiny primary lesion. Most CUP patients receive only localized treatment or empirical systemic chemotherapy, leading to poor prognosis and shorter average overall survival. There is currently insufficient evidence-based medical support for the diagnosis and treatment of CUP. This study retrospectively analyzed clinical characteristics, diagnostic methods, treatment approaches, and prognostic outcomes of newly diagnosed CUP patients treated in our department. The findings aim to provide clinical guidance for diagnosis and treatment of CUP, with the goal of reducing diagnostic delays and improving patient outcomes.

Keywords: Primary of Unknown Origin Cancer; Case report; Literature analysis; diagnosis; Cervical lymph nodes

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1. Introduction

Primary of unknown origin tumors refer to metastatic lesions confirmed as malignant through pathological examination, where no anatomical primary site can be identified through detailed medical history review, physical examinations, and diagnostic tests prior to treatment. These tumors account for approximately 1–2% of all malignancies and rank fourth in mortality rates. Most patients with cutaneous upstitched carcinoma (CUP) receive only localized treatment or empirical systemic chemotherapy, resulting in poor prognosis with an average overall survival of 6–9 months. Therefore, early and effective diagnosis combined with targeted therapy holds significant value for improving survival rates among these patients.

2. Case report patient information

A 71-year-old female patient was admitted to the hospital with left supraclavicular lymph node metastatic adenocarcinoma detected 2 years prior and left lower limb pain for 3 months. Two years ago, she developed left supraclavicular lymphadenopathy without apparent cause, measuring approximately 3×2 cm. She was initially evaluated at a county hospital where a left supraclavicular lymph node biopsy was performed. Postoperative pathology (October 25, 2022) revealed: (Left supraclavicular mass) malignant epithelial tumor with carcinomatous features and metastatic potential. For further treatment, she was transferred to a municipal hospital. PET-CT scans indicated:

- (1) Thickened gastric wall in the cardia and fundus with contrast filling defects and heterogeneous hypermetabolism, recommending gastroscopy;
- (2) Multiple hypermetabolic enlarged lymph nodes in the right internal mammary region, left cardiac-diaphragmatic angle, and retroperitoneal area, suggesting metastasis.

Subsequent gastroscopies (December 18, 2022) showed gastric body posterior wall bulging and hiatal hernia. Pathology from gastroscopy (December 20, 2022) demonstrated gastric fundus polyps with chronic inflammation, focal mucosal erosion, and dilated small vessels in the lamina propria; HP (-). Endoscopic ultrasound (December 23, 2022) revealed no significant abnormalities in the cardia and fundus. Review of county hospital pathology slides at municipal hospital (December 26, 2022) confirmed metastatic carcinoma with possible adenocarcinoma, immunohistochemistry showing Her-2 (1+). The patient did not receive additional treatment. Three months ago, the patient developed left lower limb pain that progressively worsened. She sought treatment at a local county hospital. A CT scan (October 3, 2024) revealed a space-occupying lesion adjacent to the left psoas major muscle at L4-L5 levels and multiple retroperitoneal lymph nodes with suspected left iliac vein thrombosis. Subsequent procedures included a left psoas mass biopsy (October 4, 2024) and a left neck mass biopsy. The pathological report from the psoas biopsy (October 6, 2024) indicated metastatic carcinoma. Biopsy specimens from the left lymph node mass (October 6, 2024) showed lymph node metastasis with poorly differentiated adenocarcinoma. The patient was referred to our department for further evaluation. Her weight had decreased by 3 kg over three months. The patient has a history of hypertension for over six years, with peak blood pressure reaching 160/90 mmHg. Metoprolol was intermittently used for control.

A history of type 2 diabetes mellitus (T2DM) for over ten years, with peak blood glucose levels at 9 mmol/L. Regular oral administration of dapagliflozin maintained blood glucose at 5.5–6.3 mmol/L. No history of hepatitis, malaria, tuberculosis, or vaccination. No known allergies, surgeries, blood transfusions, or trauma. Physical examination revealed: T: 36.8 °C; P: 78 bpm; R: 19 bpm; BP: 128/78 mmHg. The abdomen was flat without visible gastrointestinal patterns, peristaltic waves, or abdominal wall varices. Soft abdomen with no tenderness, rebound tenderness, or muscle rigidity. No palpable masses, liver or spleen detected, and negative Murphy's sign. Full abdominal percussion showed tympanic sounds but no shifting dullness. Bowel sounds were 4/min, with no metallic or air-fluid sounds heard. Left lower limb pain presents as radiating pain in the thigh and calf, occasionally with stabbing sensations without burning. No numbness or muscle weakness is present in the left leg.

Imaging findings at admission (**Figure 1**): Contrast-enhanced CT (October 10, 2024): (1) Cerebral atrophy. (2) Multiple lymphadenopathy in the mediastinum, supraclavicular region, and cardiac diaphragmatic angle, with lymph node metastasis not excluded. (3) Esophageal hiatal hernia with localized wall thickening. (4) Irregular right partial ribs. (5) Multiple intra-abdominal and retroperitoneal lymphadenopathy with lymph node metastasis not excluded. (6) Malignant space-occupying lesion in the left psoas muscle area. Upper gastrointestinal radiography (October 10, 2024): No significant abnormalities observed.

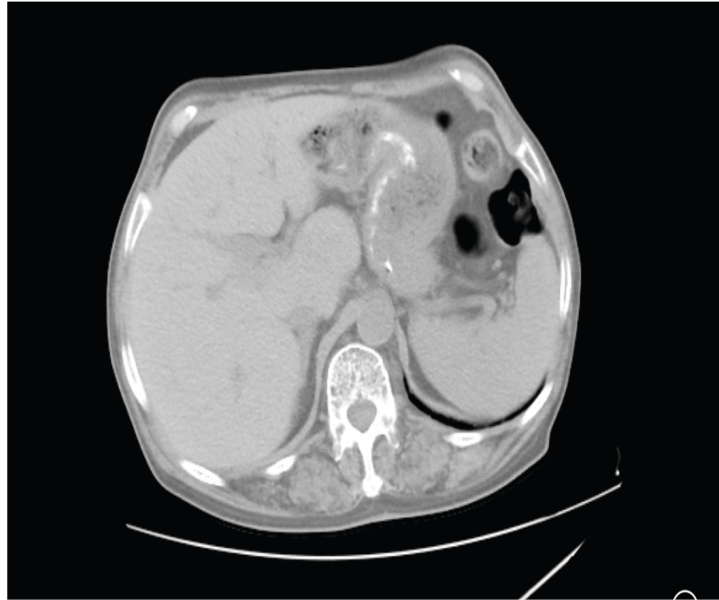


Figure 1: Enhanced CT before chemoradiotherapy.

Breast ultrasound (October 10, 2024): (1) Multiple nodules in the right breast (BI-RADS 3 grade); (2) Nodules in the left breast (BI-RADS 3 grade); (3) Multiple enlarged lymph nodes in the left neck, bilateral supraclavicular regions, and left subclavian area.

Superficial lymph node ultrasound (October 10, 2024): (1) Multiple hypoechoic lesions in the left neck and supraclavicular region, with a larger one measuring approximately 1.91 cm × 1.11 cm showing indistinct portal structure and visible blood flow signals on CDFI. (2) Multiple hypoechoic nodules in the right supraclavicular region, with a larger one measuring approximately 2.68 cm × 1.11 cm showing indistinct portal structure and visible blood flow signals on CDFI. (3) A hypoechoic lesion measuring approximately 5.48 cm × 5.18 cm × 2.57 cm with indistinct borders and irregular morphology in the deep layer of the left psoas muscle, showing unclear demarcation from the muscular layer and visible peripheral blood flow signals on CDFI. (4) Multiple hypoechoic nodules were observed beside the left iliac artery, with the largest measuring approximately 1.90 cm × 1.10 cm in size. The borders remained well-defined and the morphology regular. CDFI imaging revealed minimal blood flow signals.

Gastroscopy (October 11, 2024): Hiatal hernia. Colonoscopy (October 11, 2024): Multiple polyps in the colon. Whole-body bone imaging (**Figure 2**): Localized hypermetabolism of bone salts at L4 and L5. Laboratory tests upon admission: Complete blood count: Red blood cells $3.60 \times 10^{12}/L$; Hemoglobin 94 g/L. Biochemical profile: Glucose 6.84 mmol/L. Tumor marker panel: Glycoantigen 153:134.00 U/mL; Glycoantigen 125:133.10 U/mL; Glycoantigen 724:47.07 U/mL; Neuron-specific enolase: 33.45 ug/L.

Treatment: Our hospital's pathology department reviewed a 2-year-old pathological section from a local county hospital (**Figure 3**), which indicated metastatic adenocarcinoma. Immunohistochemistry will be performed if necessary for definitive diagnosis. BRS-6 pain score: (1) PS score: (2) Following multidisciplinary MDT consultation, we preliminarily considered primary gastric malignancy. The treatment plan includes SOX chemotherapy combined with radiotherapy. Radiotherapy targets include the right psoas major muscle and corresponding retroperitoneal lymph nodes (target areas) as shown by CT localization. Fractionated doses are 180 cGy/F per session, administered 5 times weekly for a total of 28 sessions, with a cumulative dose of 5040 cGy/F.

After completing synchronized chemoradiotherapy, the patient's pain significantly improved. A follow-up CT scan (**Figure 4**) revealed: (1) Multiple lymphadenomas in the mediastinum, supraclavicular region, and cardiac diaphragmatic angle, with partial reduction; (2) Esophageal hiatal hernia with localized wall thickening improvement; (3) Irregular right rib contour; (4) Multiple intra-abdominal and retroperitoneal lymph nodes showing partial shrinkage, with lymph node metastasis not excluded; (5) Reduced left psoas mass lesion, suspected malignancy. The patient experienced no significant gastrointestinal reactions during treatment and was discharged.

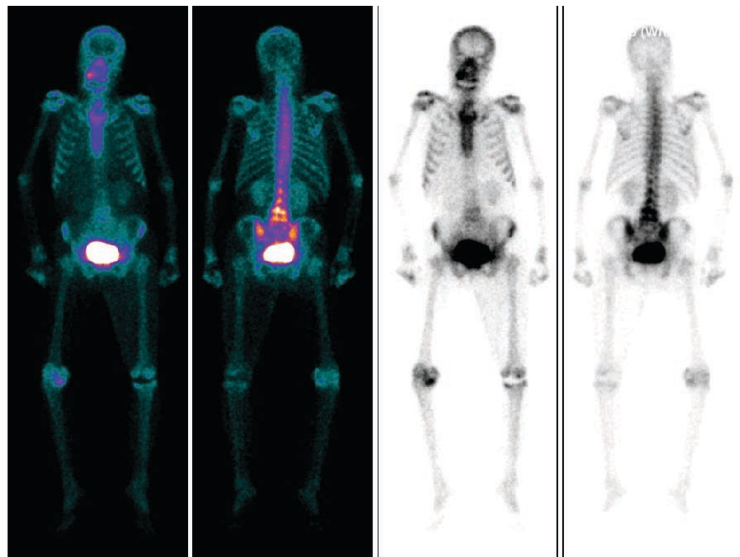


Figure 2: Bone imaging.

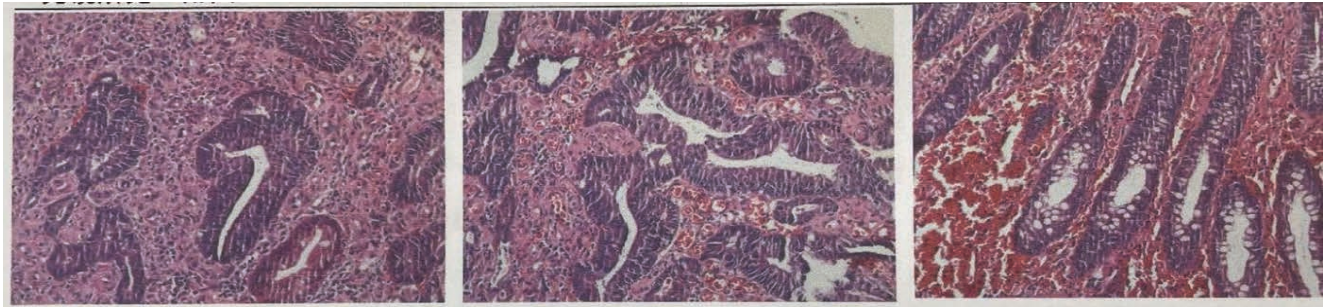


Figure 3: Re-read pathology.

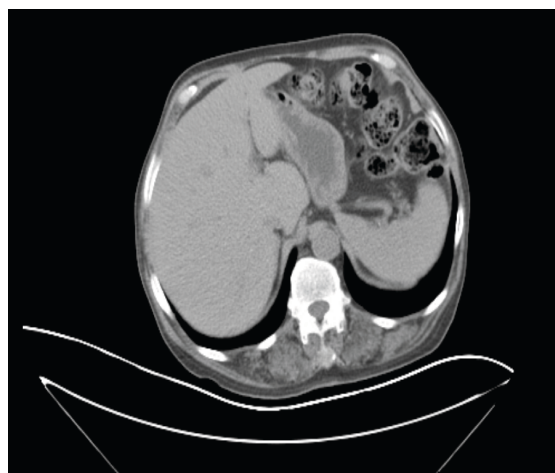


Figure 4: CT after chemoradiotherapy.

Final diagnosis: Primary adenocarcinoma of unknown origin, left cervical lymph node metastasis, left psoas metastasis, gastric primary carcinoma?

Follow-up instructions: Return for continued treatment after 3 weeks.

3. Discussion

Primary of Unknown Origin Cancer (Cancer of Unknown Primary, CUP), also termed cryptogenic carcinoma, refers to metastatic tumors confirmed as malignant through pathological examination, where no anatomical origin can be determined through detailed medical history review, physical examination, and diagnostic tests prior to treatment. Potential causes include: (1) Insufficient detection methods; (2) Inadequate tissue sampling; (3) Removal of the primary tumor; (4) Extensive metastasis obscuring the primary site; (5) Unique dissemination patterns; (6) Small primary tumor or spontaneous regression.

Even autopsy findings show 20–50% of cases lack identifiable primary sites. With an incidence rate of 1–2% among all malignancies ^[1], it ranks fourth in mortality rates ^[2]. Most CUP patients receive only localized therapy or empirical systemic chemotherapy, resulting in a poor prognosis with an average survival of 6–9 months. Early, effective diagnosis and targeted treatment are crucial for improving survival rates. Current diagnostic and therapeutic approaches lack robust evidence-based support ^[3]. Recent advancements in molecular biology and precision medicine have increased global research focus ^[4]. In CUP diagnosis, every clue suggesting a primary site should be carefully evaluated. Comprehensive medical history inquiries and thorough physical examinations are essential to identify potential diagnostic indicators. Imaging modalities include ultrasound, X-ray, computed tomography (CT), magnetic resonance imaging (MRI), emission computed tomography (ECT), and positron emission tomography-computed tomography (PET/CT). The selection of imaging studies should be based on the suspected primary site, with PET/CT being directly performed when indicated. During the diagnosis and treatment of cervical cancer with primary bone metastasis (CUP), endoscopic examination should be selected according to clinical indications to avoid unnecessary testing. In addition to imaging, other diagnostic methods include sentinel lymph node biopsy, evaluation of isolated or localized bone metastases via the prespinous venous plexus, 18F-FES PET/CT (estrogen receptor-targeted molecular imaging), and PET/CT scans using tumor-specific biomarkers.

Furthermore, tumor marker detection—particularly analysis of tumor marker panels—can provide valuable clues for identifying the primary tumor's location or system. Histopathological examination remains the gold standard for CUP diagnosis; if tissue samples are unavailable, immunohistochemical analysis of cellular aggregates may serve as diagnostic evidence. Clinical diagnosis of CUP follows two fundamental principles: first, consider common malignant tumors in China as potential primary carcinomas; second, avoid misdiagnosis or missed diagnosis of tumors with a favorable prognosis or curability. When developing personalized precision medicine treatment plans, it is recommended to conduct next-generation sequencing (NGS), liquid biopsy, and tumor origin gene testing. Additionally, participation in multidisciplinary team (MDT) consultations is advised to achieve comprehensive treatment strategies. Patients are strongly encouraged to enroll in clinical trials or receive targeted therapies based on NGS and tumor origin test results, or adopt empirical treatment. The tumor type should be determined through a comprehensive evaluation of medical history, symptoms, physical examination findings, imaging studies, endoscopic examinations, and pathological analyses. Treatment principles for primary-site unknown tumors:

- (1) If a primary site is identified, follow specific disease guidelines.

- (2) For localized tumors without identifiable origins (e.g., head/neck, supraclavicular, axillary, mediastinal, pulmonary, pleural/peritoneal effusions, abdominal, retroperitoneal, inguinal, bone, brain, or liver tumors), refer to specialized treatment protocols.
- (3) For metastatic tumors without identifiable origins, prioritize symptom management with clinical trial enrollment as the first option, supplemented by empirical chemotherapy and targeted therapy ^[1].

MDT for primary-site unknown tumors: If expert consensus confirms tumor origin, recommend corresponding treatment plans according to current guidelines. If only preliminary suspicion exists, request additional immunohistochemical testing from pathology departments and consider genetic testing to identify tumor origin. It is hoped that such expressions will be clearer and accurate ^[1]. Due to the unique biological characteristics and heterogeneity of childhood upper respiratory tract infections (CUP), conducting clinical trials is challenging, with an overall poor prognosis: median survival duration is less than one year, and the 5-year survival rate is merely 14% ^[5]. To date, no specific treatment protocol has been established as a standard of care. Most CUP patients require empirical chemotherapy, such as taxane or platinum-based regimens ^[6]. Both symptomatic patients with invasive lesions (Eastern United States Clinical Oncology Group [ECOG] PS 1-2) and asymptomatic patients (ECOG PS 0) may consider chemotherapy. Different chemotherapy regimens should be selected based on histological types, and radiotherapy, immunotherapy, and targeted therapy may be added when necessary ^[1]. The cervical lymph nodes not only drain lymph from head and neck organs but also receive drainage from the chest, abdomen, pelvis, and limbs. Therefore, malignant tumors presenting with cervical lymphadenopathy as their initial symptom often have complex primary lesions, making misdiagnosis common ^[7,8].

Common clinical misdiagnosis scenarios include:

- (1) Due to anatomical complexities of small tumors in specific areas like the tonsillar fossa or tongue root, combined with inherent limitations in diagnostic techniques, these conditions are frequently overlooked during physical exams and radiological examinations;
- (2) Primary lesions grow slowly and remain dormant for extended periods, making them difficult to detect, while cervical metastases tend to be larger and appear earlier;
- (3) Primary tumors may undergo immune suppression, causing micro or small diffuse primary cancers to regress while metastatic cancer continues to grow;
- (4) Primary tumor cells may have undergone infarction;
- (5) During metastatic cancer treatment, extensive radiotherapy or chemotherapy may suppress or eliminate sensitive primary tumors, or when primary tumors are small and adjacent to metastases, they might be removed during metastatic lesion surgery ^[9-11].

4. Conclusion

The emergence of novel diagnostic methods such as gene expression profiling, epigenetic analysis, and liquid biopsy, along with technological advancements, has provided new approaches for identifying primary lesions in Cancer of Unknown Primary Site (CUP). These innovations have been validated in clinical trials. Therefore, immunohistochemistry (IHC) should complement these new technologies to enhance diagnostic accuracy for CUP patients. Furthermore, the promising clinical outcomes observed in targeted therapy and immunotherapy trials strongly support the application of traditional chemotherapy regimens. However, further efforts are required to identify predictive biomarkers and establish effective patient classification systems to enable more personalized

treatment strategies. It is crucial to note that primary lesion identification is a prolonged process, with some lesions potentially remaining undetected for months or even years. When suspected new lesions are identified, repeat biopsies are necessary to confirm their status as primary lesions. Regular follow-up visits and close monitoring of disease progression are essential throughout the CUP management process.

Disclosure statement

The authors declare no conflict of interest.

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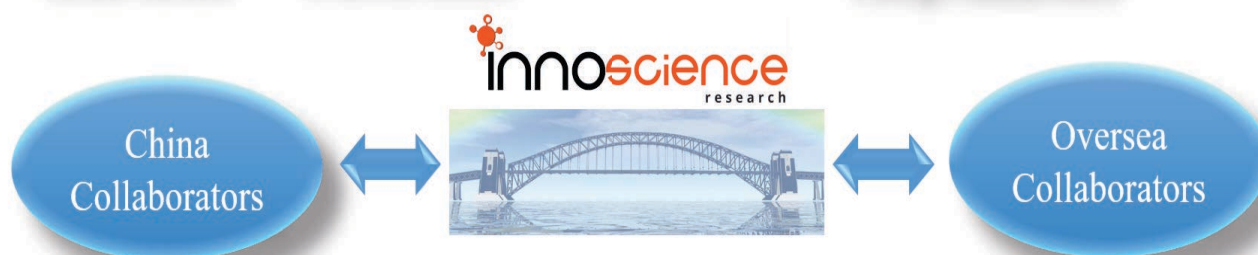
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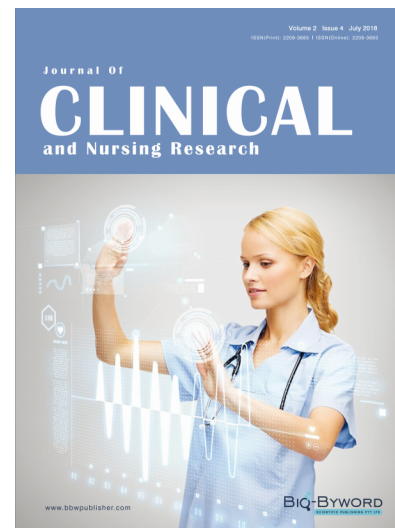
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