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Chong Li

Chinese Academy of Sciences, China

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Oncology Treatment Discovery

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Opportunistic CT Screening for Osteoporosis in Postmenopausal Women: Background, Challenges, and Evidence Gaps

Shiyu Zhong¹, Ting Zheng¹, Liuqing Yang², Xiangrong Deng³, Bangcai Han⁴, Suting Ye⁵, Wenmin Li³, Yinghua Wu^{6*}

¹College of Medical and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, Sichuan, China

²Department of Ultrasound, the First Hospital of Jilin University, Changchun 130021, Jilin, China

³Department of Radiology, Chongzhou Traditional Chinese Medicine Hospital, Chengdu 611200, Sichuan, China

⁴Department of Radiology, Suzhou BOE Hospital, Suzhou 130021, Jiangsu, China

⁵Department of Function Inspection, Sichuan Integrative Medicine Hospital, Chengdu 610041, Sichuan, China

⁶PhD Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610072, Sichuan, China

*Corresponding author: Yinghua Wu, wyh@cdutcm.edu.cn

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Abstract: Postmenopausal women represent the highest-risk population for osteoporosis (OP), with a prevalence exceeding 32.5%. The resultant fragility fractures are associated with devastating disability, mortality, and a substantial socioeconomic burden. Dual-energy X-ray absorptiometry (DXA), the diagnostic gold standard, is insufficient for large-scale screening due to limited equipment availability, low screening coverage, and poor awareness. Opportunistic screening using CT attenuation values (Hounsfield Units, HU) from routine scans has emerged as a promising alternative, offering the potential for widespread without additional radiation or cost. However, translating this strategy to the core target population of postmenopausal women reveals three critical evidence gaps: (1) a lack of genetic causal evidence specific to postmenopausal women, making it difficult to establish a definitive link between HU decline and osteoporosis; (2) high heterogeneity in diagnostic studies, with a lack of pooled diagnostic parameters exclusive to this group, potentially leading to misclassification with existing general-population thresholds; and (3) the absence of a screening model built entirely on literature parameters from postmenopausal women, hindering individualized risk stratification. This review systematically examines the disease burden of OP in postmenopausal women, the limitations of DXA screening, the principles and progress of opportunistic CT, and critically analyzes these three key gaps to underscore the necessity and urgency for a comprehensive chain of evidence, from causal mechanisms to clinical application.

Keywords: Postmenopausal women; Osteoporosis; Opportunistic screening; CT attenuation value; Hounsfield unit; DXA

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1. Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Often termed a “silent epidemic” due to its asymptomatic progression until fracture, its most severe clinical outcome is fragility fractures, typically occurring at the hip, spine, and wrist. Hip fractures, in particular, are associated with mortality rates exceeding 20% within the first year and profound long-term disability in survivors ^[1,2].

From a public health perspective, identifying an efficient, economical, and widely accessible screening strategy for early identification and intervention in high-risk populations is paramount. This review will first detail the specific burden of osteoporosis in postmenopausal women, then outline the critical failures of current DXA-based screening, before exploring the potential and pitfalls of opportunistic CT. Finally, it will systematically identify and analyze three fundamental evidence gaps that must be addressed to translate this promising technique into effective clinical practice for the highest-risk group

2. Osteoporosis in postmenopausal women: A pressing public health challenge

2.1. Epidemiological burden

Postmenopausal women bear the most significant burden of osteoporosis. According to the 2018 China Osteoporosis Epidemiology Survey, the prevalence of OP in postmenopausal women over 40 was 32.5%, compared to just 6.9% in men of the same age. This disparity widens with age, affecting 51.6% of women over 65. It is estimated that of the approximately 90 million individuals with OP in China, around 70 million (nearly 80%) are women, with postmenopausal women constituting the vast majority ^[2,3]. This pattern is mirrored globally, where low bone mineral density (BMD) in postmenopausal women contributes significantly to years lived with disability and mortality worldwide ^[4,5].

Table 1. Prevalence of osteoporosis in Chinese women by age group

Age Group	Prevalence (%)	Source
40–49	16.0	China OP Epidemiological Survey, 2018
50–59	18.4	China OP Epidemiological Survey, 2018
60–69	37.5	China OP Epidemiological Survey, 2018
70–79	52.9	China OP Epidemiological Survey, 2018
≥ 80	68.0	China OP Epidemiological Survey, 2018

2.2. Catastrophic consequences of fragility fractures

The consequences of fragility fractures are severe. Hip fracture patients face a 20–25% mortality rate within the first year, often due to complications from immobilization such as pneumonia, venous thromboembolism, and infection. Among survivors, approximately 50% experience permanent disability, and only 20% return to their pre-fracture level of function ^[4]. Vertebral fractures lead to height loss, kyphosis, chronic pain, and reduced quality of life. The economic burden is equally staggering, with the cost of managing osteoporotic fractures projected to reach hundreds of billions in China alone by 2050 ^[6].

2.3. Core pathophysiology: The role of estrogen deficiency

The fundamental driver of this heightened risk is the sharp decline in estrogen during menopause. Estrogen

plays a crucial role in suppressing bone remodeling and maintaining a balance between osteoblast and osteoclast activity. Its deficiency leads to increased osteoclast activity and accelerated bone resorption, particularly affecting trabecular-rich sites like the vertebrae and distal radius. Bone loss can reach up to 7% per year in the immediate postmenopausal period, far exceeding the gradual decline seen in aging men ^[7].

3. The screening dilemma: Why DXA fails to meet the need

Despite being the gold standard, DXA-based screening is failing to reach the majority of at-risk postmenopausal women, with testing rates persistently below 10% in many regions, including China ^[8]. This failure stems from three interconnected barriers.

3.1. Low screening coverage and awareness

Awareness of osteoporosis as a preventable disease is critically low. Many women perceive themselves as healthy in the absence of pain. Studies show low knowledge scores among middle-aged women, which directly correlates with a lack of proactive screening behavior ^[9]. Unlike established programs for cancers, osteoporosis screening lacks similar policy support and public health infrastructure.

3.2. Severe shortage of DXA equipment

DXA machines are expensive, require specialized operators and facilities, and are therefore concentrated in larger urban hospitals. In rural and primary care settings, where a significant portion of the population resides, DXA availability is extremely limited, often with fewer than one machine per 100,000 elderly individuals ^[9]. This geographic and financial inaccessibility creates a major bottleneck.

3.3. Limitations of alternative screening tools

While quantitative ultrasound (QUS) is portable and inexpensive, its low sensitivity (< 60%) for detecting asymptomatic OP and its inability to provide a diagnostic T-score limit its utility. An abnormal QUS result still necessitates a confirmatory DXA scan, creating a two-step process that often leads to loss of follow-up ^[10].

Table 2. Comparison of screening/diagnostic modalities for osteoporosis

Modality	Key Advantages	Key Disadvantages	Role in Screening
DXA	Gold standard; Provides T-score for diagnosis.	High cost, limited availability, requires specialized staff.	Primary diagnostic tool, poor for population screening.
QUS	Portable, low-cost, no radiation.	Low sensitivity for OP; Cannot provide diagnostic T-score.	Triage tool; cannot replace DXA.
Opportunistic CT (HU)	Uses existing scans; No extra cost/radiation; Widely available.	No standardized thresholds; Influenced by technical factors.	High potential for passive population screening.

4. Opportunistic CT attenuation: A new direction for screening

4.1. Scientific basis: HU as a proxy for BMD

CT attenuation values (Hounsfield Units, HU) quantify the radiodensity of tissues. Numerous studies have demonstrated a strong, significant positive correlation between trabecular bone HU in the lumbar vertebrae and BMD measured by DXA or quantitative CT (QCT), with correlation coefficients (r) often exceeding

0.6 for DXA and reaching as high as 0.95 for QCT^[10]. This forms the scientific rationale for using HU as a surrogate marker of bone density.

4.2. The concept of opportunistic CT

Formalized by Pickhardt et al.^[9], opportunistic CT screening refers to the practice of leveraging existing CT scans (performed for reasons such as abdominal pain, trauma, or oncology follow-up) to measure vertebral HU and assess osteoporosis risk. Its transformative potential lies in its ability to generate significant public health value from existing clinical data at no additional cost or radiation exposure to the patient. It represents a form of “passive” screening on a massive scale^[11].

4.3. Technical considerations and confounders

For reliable and reproducible measurements, several technical factors must be standardized:

- (1) Scan Parameters: Tube voltage (kVp) significantly affects HU. Lower kVp results in higher HU. Consistency is key, and kVp-specific thresholds may be needed.
- (2) Region of Interest (ROI): Measurements should be taken from the trabecular bone in the mid-vertebral body, carefully avoiding the cortex, posterior venous plexus, bone islands, or focal lesions like hemangiomas or fractures^[12]. Inclusion of cortical bone or osteophytes will falsely elevate HU values.
- (3) Contrast Media: Intravenous contrast significantly increases measured HU values, making it unsuitable for direct application of thresholds derived from non-contrast scans. If contrast scans must be used, correction factors are required^[13].
- (4) Patient Factors: Bone marrow composition, particularly increased fatty infiltration in postmenopausal women, can lower HU values, a factor that must be considered when applying general thresholds^[14].

5. Critical research gaps and the rationale for this study

While the potential of opportunistic CT is immense, a systematic review of the literature reveals three interconnected evidence gaps that specifically hinder its application to postmenopausal women. Addressing these gaps requires a comprehensive research approach.

(1) Gap 1: Lack of Causal Genetic Evidence in Postmenopausal Women

All current studies correlating HU with BMD or fractures are observational, which are susceptible to confounding and cannot prove causality. Mendelian randomization (MR) uses genetic variants as instrumental variables to strengthen causal inference. While MR studies have confirmed a causal link between low BMD and osteoporosis using genome-wide association study (GWAS) data^[14], they have not specifically focused on spine CT attenuation values in postmenopausal women. Although genetic correlations exist between BMD at different skeletal sites (e.g., heel and spine), directly extrapolating findings to this specific phenotype and population is methodologically unsound. A targeted MR study is needed to provide robust causal evidence that genetically predicted lower spinal HU is a direct cause of osteoporosis risk in this group.

(2) Gap 2: Heterogeneity in Diagnostic Studies and Lack of Pooled Data for Postmenopausal Women

Existing diagnostic meta-analyses on CT values for osteoporosis typically pool data from mixed populations (men, premenopausal women, postmenopausal women)^[13]. The pooled sensitivity, specificity, and derived thresholds are therefore not optimized for postmenopausal women. Their

unique pathophysiology, particularly increased marrow fat, likely means their HU distribution differs. Applying a generic threshold could lead to systematic over- or under-diagnosis. A dedicated diagnostic meta-analysis, strictly limited to studies reporting data on postmenopausal women, is required to generate pooled diagnostic accuracy parameters and propose an evidence-based HU threshold specific to this population.

(3) **Gap 3: Absence of a Screening Model Built on Postmenopausal Women-Specific Parameters**

Current fracture risk assessment tools (e.g., FRAX, Garvan) are derived from general population cohorts and lack variables critical to postmenopausal women, such as age at menopause, years since menopause, or parity ^[12]. Models incorporating CT values are similarly built on mixed cohorts. An ideal, personalized screening model for this group should be constructed using epidemiological parameters (e.g., baseline prevalence, risk factor effect sizes) derived exclusively from postmenopausal women. It should integrate key variables—including CT attenuation value, age, years since menopause, prior fracture history, and low BMI—to provide accurate, individualized risk stratification. No such model currently exists.

Table 3. Summary of key evidence gaps and proposed research directions

Research Gap	Specific Problem in Postmenopausal Women	Proposed Research Direction
1. Causal Evidence	Lack of proof that low spinal HU causes OP in this group.	Perform a two-sample Mendelian randomization study using GWAS data specific to spinal BMD/OP in women.
2. Diagnostic Threshold	No pooled diagnostic parameters (sensitivity/specificity) or HU threshold exists for this group.	Conduct a diagnostic meta-analysis of studies limited to postmenopausal women to derive a pooled threshold.
3. Screening Model	No risk stratification model is built using parameters solely from this population.	Develop and validate a new screening model using predictor variables and baseline risk from postmenopausal female cohorts.

6. Conclusion and future directions

Opportunistic CT screening for osteoporosis in postmenopausal women holds tremendous promise to overcome the significant limitations of current DXA-based approaches. By harnessing ubiquitous imaging data, it offers a path towards truly large-scale, passive identification of at-risk individuals. However, the strategy cannot be responsibly implemented in this specific population until the three key evidence gaps identified in this review are addressed.

A systematic research program is urgently needed. First, causal evidence must be established using genetic epidemiology methods like Mendelian randomization. Second, rigorous diagnostic synthesis through a population-specific meta-analysis must provide a reliable, evidence-based HU threshold. Finally, this foundational evidence must be integrated into a novel, clinically useful screening model that provides individualized risk probabilities for postmenopausal women. Filling these gaps is not merely an academic exercise; it is a critical prerequisite for translating a promising concept into a safe, effective, and equitable public health strategy to combat the devastating burden of osteoporosis in the highest-risk population.

7. Analytical pathway

To systematically address the three interconnected evidence gaps hindering the clinical translation of

opportunistic CT screening for osteoporosis in postmenopausal women, we propose a sequential, three-phase analytical pathway. This design moves from establishing causal mechanism, to synthesizing diagnostic evidence, and finally to developing a clinical application tool.

7.1. Phase 1: Causal validation

- (1) Objective: To determine if genetically predicted lower spinal CT attenuation values are a causal risk factor for osteoporosis in women.
- (2) Methodology: A two-sample Mendelian Randomization (MR) study will be conducted.
- (3) Data Source: The largest available genome-wide association study (GWAS) summary statistics for 1) lumbar spine bone mineral density (as a proxy for HU) and 2) osteoporosis (fracture) will be utilized. Preference will be given to datasets stratified by or predominantly composed of women.
- (4) Analysis: The inverse-variance weighted (IVW) method will be the primary analysis, with sensitivity analyses (MR-Egger, weighted median) to test for and correct potential pleiotropy.
- (5) Expected Outcome: Confirmation of a significant causal effect, providing the genetic etiological foundation for using spinal attenuation as a screening target in this population.

7.2. Phase 2: Diagnostic synthesis

- (1) Objective: To derive a pooled, evidence-based diagnostic threshold (HU value) for identifying osteoporosis specifically in postmenopausal women.
- (2) Methodology: A comprehensive diagnostic test accuracy (DTA) meta-analysis will be performed.
- (3) Inclusion Criteria: Studies must report HU measurements (index test) and DXA T-scores (reference standard) specifically for a postmenopausal female population, or provide disaggregated data for this subgroup.
- (4) Analysis: A bivariate random-effects model will be used to pool sensitivity, specificity, and construct a summary receiver operating characteristic (SROC) curve. Meta-regression will explore sources of heterogeneity (e.g., CT technical parameters).
- (5) Expected Outcome: A statistically robust, population-specific HU threshold with corresponding pooled sensitivity and specificity, offering a reliable diagnostic benchmark for clinical use.

7.3. Phase 3: Model development

- (1) Objective: To construct and internally validate a clinical screening model for individualized osteoporosis risk prediction in postmenopausal women.
- (2) Methodology: A prediction model study will be developed using data from a large, well-characterized cohort of postmenopausal women.
- (3) Predictors: The model will integrate the HU threshold identified in Phase 2 with key clinical risk factors prevalent in this population (e.g., age, years since menopause, BMI, prior fracture history).
- (4) Analysis: Multivariable logistic regression will be used to develop the model. Performance will be assessed through calibration (Hosmer-Lemeshow test, calibration plot) and discrimination (Area Under the Curve, AUC). Internal validation will be performed using bootstrapping techniques.
- (5) Expected Outcome: A user-friendly, evidence-based screening tool (e.g., a nomogram or risk score) that provides an individual's absolute probability of having osteoporosis, enabling targeted DXA referral and intervention.

Disclosure statement

The authors declare no conflict of interest.

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Clinical Manifestations and Pathological Diagnosis of Anastomosing Hemangioma

Qingtao Shi, Huilei Qiu, Shuzhe Deng

Department of Oncopathology, Harbin Medical University Cancer Hospital, Harbin 150081, Heilongjiang, China

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Abstract: *Objective:* To explore the clinical manifestations, histopathological features and differential diagnosis of anastomosing hemangioma. *Methods:* Histopathological observation and immunohistochemical study were performed on 3 cases of anastomosing hemangioma. *Results:* Among the 3 cases, 2 occurred in the adrenal gland and 1 in the mediastinum. The tumor had a thin fibrous capsule, with interlacing and anastomosing vascular-like arrangement. The vessel walls were irregular, with varying numbers of wall cells and uneven thickness, only a single layer of cells in the thin areas, while dense cell regions with abundant cells forming thick trabeculae. The cells were small with a low nuclear-cytoplasmic ratio, abundant eosinophilic cytoplasm, small round nuclei, thin nuclear membranes, fine chromatin and inconspicuous nucleoli. Eosinophilic edematous and fibrinoid stroma were visible. A small number of scattered irregular thick-walled blood vessels were found in the tumor; some areas resembled splenic medulla, some contained abundant edematous and hyaline stroma, and some endothelial cells could be hobnail-shaped. *Conclusion:* Anastomosing hemangioma is a newly reported benign vascular tumor, which is relatively rare. It generally has no obvious clinical symptoms and is occasionally found during physical examination. Due to the significant anastomosing arrangement of neoplastic blood vessels, it is easily misdiagnosed as angiosarcoma.

Keywords: Anastomosing hemangioma; Histopathology; Diagnosis

Online publication: June 30, 2026

1. Introduction

Anastomosing hemangioma (AH) is a recently reported benign vascular tumor that is relatively rare and not extensively documented in the literature. Due to its characteristic anastomosing and interlacing arrangement of neoplastic blood vessels, it is prone to misdiagnosis as angiosarcoma. To avoid overtreatment, it is essential to understand its clinical and pathological features. We collected three cases of anastomosing hemangioma encountered during routine external examinations at our hospital from 2017 to 2025. By analyzing their clinical manifestations, gross appearances of specimens, histological features, and immunohistochemical expression patterns, we aimed to summarize their clinicopathological characteristics. With a grasp of these key points, accurate diagnoses can generally be made.

2. Materials and Methods

2.1. General Information

The three cases of anastomosing hemangioma were sourced from external examination cases at the Pathology Department of the Affiliated Tumor Hospital of Harbin Medical University between 2017 and 2025. There were two females and one male, with a male-to-female ratio of 1:2. The patients' ages ranged from 45 to 62 years old, with an average age of 57 years old. Two tumors were located in the adrenal glands, and one was in the mediastinum.

2.2. Methods

Histological observations and immunohistochemical analyses were performed on the three cases of anastomosing hemangioma. Specimens were fixed in 10% formalin, routinely dehydrated, embedded in paraffin, sectioned at 4–5 μm thickness, and stained with routine hematoxylin and eosin (HE) for light microscopy. Antibodies, including FLi1, ERG, CD31, CD34, CK, PAX-8, and CA-9, were purchased from Fuzhou Maixin Biotechnology Co., Ltd.

3. Results

3.1. Clinical manifestations

Anastomosing hemangiomas predominantly occur in solid organs, most commonly in the urogenital system, such as the kidneys, adrenal glands, testes, and ovaries, but can also be found in the liver and gastrointestinal tract. The clinical manifestations of the cases in this study are as follows:

- (1) Case 1: A 45-year-old female presented with a left adrenal mass discovered during a physical examination. She was in good general condition, alert, and cooperative during the examination. An external ultrasound showed a solid hypoechoic nodule in the left adrenal region, measuring approximately 34 mm $\times$ 29 mm, with clear borders and uneven internal echo. CT at our hospital revealed a left adrenal mass. Ultrasound showed a nodular mass in the left adrenal gland. After completing relevant examinations, she underwent surgical treatment, nutritional support, anti-inflammatory therapy, and symptomatic treatment.
- (2) Case 2: A 64-year-old male was admitted with a “lung mass discovered during a physical examination two weeks ago.” He did not have cough, sputum production, fever, night sweats, chest pain, dyspnea, or shortness of breath. Chest CT revealed a mass adjacent to the aortic arch in the upper-middle mediastinum, with micronodules in the upper lobes of both lungs. A PET report indicated a mass in the left upper mediastinum with possible local necrosis and a high-density nodule in the upper pole of the right kidney. The preliminary diagnosis was mediastinal tumor.
- (3) Case 3: A 62-year-old female was admitted with a “left retroperitoneal tumor discovered during a physical examination one month ago.” CT one month before admission showed a cystic-solid mass in the left retroperitoneum, measuring approximately 38 mm $\times$ 31 mm, with lobulated margins, uneven internal density, and significant enhancement of the solid component on contrast-enhanced scans. The boundaries with the left adrenal gland and left renal vein were unclear locally. During the course of the disease, she had normal diet and sleep, good mental state, normal bowel movements, and no significant weight loss.

3.2. Gross appearances of specimens

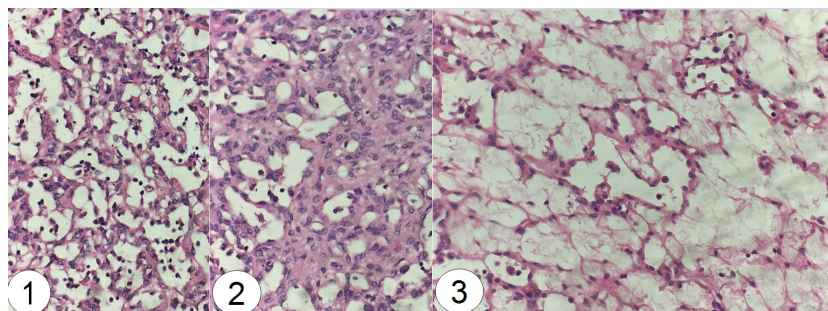
- (1) Case 1: The left adrenal gland specimen measured 40 mm × 40 mm × 20 mm. Upon sectioning, a translucent, grayish-yellow mass measuring 15 mm in length was observed, with a soft texture.
- (2) Case 2: The submitted mediastinal mass was nodular, measuring 35 mm × 22 mm × 15 mm. The central cut surface was light brown and glossy, with dark red, hemorrhagic margins. The mass was soft and encapsulated.
- (3) Case 3: The submitted left adrenal gland specimen measured 70 mm × 50 mm × 40 mm. A nodular mass measuring 30 mm in length was observed on the cut surface, with a grayish-red, soft texture and relatively clear borders.

3.3. Microscopic findings

The histological features of the three tumors were generally similar. Some areas of the masses had a thin fibrous capsule, while others lacked a capsule but had clear boundaries with the surrounding tissue, without obvious “infiltrative” growth. The tumors were generally lobulated, with typical areas as well as loose and dense regions. The most prominent and characteristic feature was the tightly arranged, interconnected capillary lumens forming cell walls, with vascular walls composed of a single layer of cells. Some endothelial cells were hobnail-shaped, and some areas resembled the red pulp of the spleen. In the loose regions, the cellular and tissue structures were similar, but the vascular spaces were widened, with pink edema and fibrinous matrix visible inside. The dense regions had abundant cells, irregular vascular walls, and multilayered wall cells, sometimes arranged in thick cord-like structures. Some areas had hyaline stroma, and some cases had large areas of pink, edematous, acellular regions. Some regions had vascular walls connected in a network-like pattern, and some areas were accompanied by abundant collagenous stroma. Microthrombi were often visible within the vascular lumens. Scattered, few irregular, thick-walled blood vessels were seen within the tumors. The cells were small, with a low nuclear-to-cytoplasmic ratio, abundant eosinophilic cytoplasm, small, round nuclei, thin nuclear membranes, fine chromatin, and inconspicuous nucleoli. There was no obvious atypia, and mitotic figures were rare. Some cases showed extramedullary hematopoiesis and adipose metaplasia.

3.4. Immunohistochemistry

Tumor cells diffusely expressed FLi1, ERG, CD31, and CD34. When differentiating from vascular-rich renal cell carcinoma, additional staining with CK, PAX-8, and CA-9 was performed, all of which were negative.



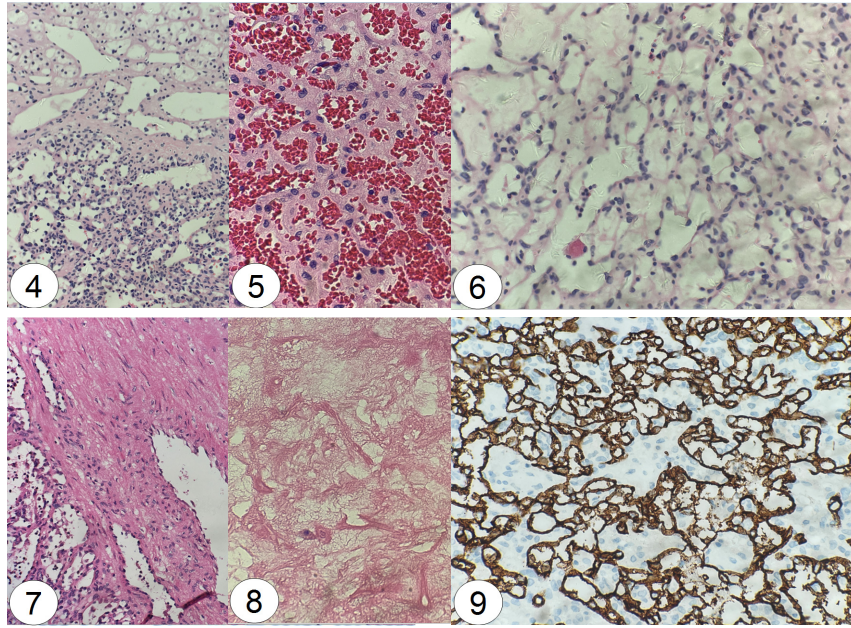


Figure 1. Typical morphology of anastomosing hemangioma (AH), with tightly packed, interconnected, and communicating capillary lumens forming the vessel walls;**Figure 2.** Dense cellular area;**Figure 3.** Loose cellular area;**Figure 4.** The upper part of the image shows normal adrenal tissue, while the lower part shows AH tumor tissue, with a clear boundary between the two;**Figure 5.** Prominent thrombosis;**Figure 6.** Vessel walls connected in a reticular pattern;**Figure 7.** Irregular thick-walled large vessels;**Figure 8.** Extensive pink-stained edematous acellular areas;**Figure 9.** Diffuse strong positivity for CD34 staining.

4. Discussion

Anastomosing hemangioma (AH), also known as interweaving hemangioma, is a rare benign vascular tumor first described by Montgomery and Epstein ^[1] in 2009. It primarily occurs in parenchymal organs, with the urogenital system, such as the kidneys, adrenal glands, testes, and ovaries, being the most common sites. It can also be found in the liver, gastrointestinal tract, and paraspinal regions ^[2, 3]. Currently, only a few reports have documented AH occurring in the skin and subcutaneous tissues ^[4]. The age range of patients is broad, from 2 to 85 years old (mean age 55.9 years, median age 56 years), with a slight female predominance ^[5]. Clinically, most patients are asymptomatic and are often incidentally discovered during physical examinations. The second case in our series was admitted with a “lung mass discovered during a physical examination two weeks ago.” Chest CT revealed a space-occupying lesion adjacent to the aortic arch in the upper-middle mediastinum, and PET imaging suggested a mass in the left upper mediastinum with possible local necrosis, leading to an initial diagnosis of mediastinal tumor. This indicates that tumors occurring in the lungs and mediastinum can sometimes overlap in imaging findings. The masses are generally small and often present as well-defined nodules. Masses located in parenchymal organs such as the kidneys and adrenal glands rarely have a capsule, but the second case in our series, which occurred in the mediastinum, had a capsule. The primary morphological feature is tightly packed, interconnected, and communicating capillary lumens forming the vessel walls, with a clear boundary and no “infiltrative” growth pattern. Since the growth pattern of interconnected and communicating capillary lumens forming the vessel walls is typical of angiosarcoma, the clear boundary of AH plays a crucial role in accurate diagnosis. The microscopic tissue

morphology of the tumor is generally similar. It usually lacks a capsule but has a clear boundary with the surrounding tissue, often presenting as indistinct, blurred lobules with typical areas, as well as loose and dense regions. The typical areas have vessel walls composed of a single layer of cells; some endothelial cells are hobnail-shaped; some areas resemble the red pulp of the spleen; the loose areas have similar cellular and tissue structures but with widened vascular spaces, containing pink-stained edema and fibrinous matrix; the dense areas are rich in cells with irregular vessel walls, and the vessel wall cells can be multilayered or even arranged in thick trabecular cords; some areas contain hyaline stroma; some cases may have extensive pink-stained and edematous acellular areas; some areas have vessel walls connected in a reticular pattern; some areas may be accompanied by abundant collagen fiber stroma; microthrombi are often visible within the vascular lumens; the cells are small with a low nuclear-to-cytoplasmic ratio, eosinophilic cytoplasm, small, round nuclei with thin nuclear membranes, fine chromatin, inconspicuous nucleoli, no obvious atypia, and rare mitotic figures; some cases may show extramedullary hematopoiesis and adipose metaplasia; when irregular thick-walled vessels are scattered within the tumor, it can be easily confused with renal angiomylipoma ^[6]; immunohistochemical staining shows diffuse strong positivity for vascular endothelial markers such as CD34, CD31, ERG, F8, and Fli-1, while Ki-67 staining indicates low proliferative activity of tumor cells ^[7-8]. The vast majority of AH cases have somatic mutations in the GNAQ or GNAI4 genes, supporting its classification as a neoplastic lesion ^[9-11].

5. Differential diagnosis

- (1) Well-differentiated angiosarcoma: This is the most important differential diagnosis for AH in clinical practice. Well-differentiated angiosarcoma shares significant morphological similarities with AH, sometimes lacking obvious cellular atypia, and including interconnected and interwoven vascular lumens. However, the primary characteristic of well-differentiated angiosarcoma is infiltrative growth into the surrounding normal tissue. Moreover, most well-differentiated angiosarcomas exhibit some degree of cellular atypia, with cells of varying sizes, disorganized arrangement, thick nuclear membranes, clumped chromatin, small nucleoli, frequent multilayered vessel walls, easily visible mitotic figures, and possible necrosis.
- (2) Kaposi sarcoma: AH, with its clear boundary and often visible eosinophilic hyaline bodies, may be confused with Kaposi sarcoma. However, Kaposi sarcoma primarily occurs on the skin of the extremities, presenting as spindle cell fascicles with rare anastomosing or interwoven arrangements, indistinct vascular lumens, and significant extravasation of red blood cells between cells, which can serve as an important diagnostic clue. Additionally, Kaposi sarcoma is generally associated with HIV infection or the use of iatrogenic immunosuppressants. Immunohistochemical staining positive for HHV8 is diagnostic.
- (3) Hobnail hemangioma: This presents with a characteristic biphasic morphology, with significantly dilated, thin-walled vascular lumens lined by prominent hobnail endothelial cells visible in the superficial dermis, and slit-like vascular lumens in the deep dermis, often surrounded by hemosiderin deposition. Hobnail morphology is relatively rare in AH. Furthermore, a hobnail hemangioma primarily occurs on the skin, while an AH primarily occurs in abdominal visceral organs.
- (4) Reticular hemangioendothelioma: This often involves the superficial skin and is composed of slender, branching vascular lumens resembling the rete testis structure; the vascular lumens are

lined by prominent hobnail endothelial cells, similar to some cases of AH; it may form intraluminal papillary structures with hyaline axial changes and is often surrounded by lymphocyte infiltration in the stroma, overlapping with the morphology of Dabska tumor. Hobnail (Dabska reticular) hemangioendothelioma is the preferred term connecting Dabska-type hemangioendothelioma and reticular hemangioendothelioma due to their many overlapping features, particularly the hobnail endothelial cells. Dabska-type hemangioendothelioma was first described in 1969^[12] and is primarily a tumor occurring in the skin and subcutaneous tissues of infants and young children. Reticular-type hemangioendothelioma shares histological similarities with AH but occurs in adults and is characterized by long “reticular” vascular lumens lined by hobnail endothelial cells^[13].

- (5) Renal clear cell renal cell carcinoma: A small number of renal clear cell renal cell carcinomas are highly vascular but have small cells, making an initial diagnosis of a vascular tumor tempting. However, clear cell renal cell carcinoma is characterized by abundant blood sinuses without anastomosing or interwoven vessels. A small number of clear cell renal cell carcinomas may show significant shrinkage and degeneration, presenting with extensive acellular areas, which can be confused with some cases of AH. In such cases, careful search for residual small clear cells or additional sampling to find more typical areas is necessary. Additionally, immunohistochemistry is very helpful in differentiating the two. Clear cell renal cell carcinoma expresses PAX2, PAX8, CD10, and CAIX positively but does not express vascular endothelial markers such as CD34, CD31, and ERG.
- (6) Hemangioblastoma: This primarily occurs in the central nervous system, most commonly in the cerebellum, but can occasionally occur in the kidneys. Hemangioblastoma is characterized by epithelioid stromal cells among abundant capillaries, with vessels lacking interwoven and anastomosing features. Immunohistochemical staining positive for α -inhibin can also aid in differentiating it from AH. According to current research, the biological behavior of AH is benign, with no reports of recurrence or metastasis.

6. Conclusion

Anastomosing hemangioma is a recently discovered rare, benign tumor with only a few reports in the literature and has not yet been included in the latest (fifth) edition of the WHO classification of soft tissue tumors. It commonly occurs in visceral organs, particularly the kidneys and adrenal glands. The primary and most important morphological feature is tightly packed, interconnected, and communicating capillary lumens. Since this interconnected and communicating growth pattern is characteristic of angiosarcoma, inexperienced pathologists may easily misdiagnose it as angiosarcoma. However, the most crucial differentiating point is that AH has a clear boundary and lacks an “infiltrative” growth pattern. Therefore, the clear boundary of AH plays a pivotal role in accurate diagnosis.

Disclosure statement

The authors declare no conflict of interest.

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A Case of Multiple Metastases from Follicular Thyroid Carcinoma Treated with Radioactive Iodine-131 After Lobectomy

Derun Yu¹, Boye Zhou¹, Zhenhu Zhou^{2*}

¹Graduate Department, Shandong First Medical University, Jinan 250117, Shandong, China

²Department of Nuclear Medicine, Liaocheng Hospital Affiliated to Shandong First Medical University (Liaocheng People's Hospital), Liaocheng 252000, Shandong, China

*Corresponding author: Zhenhu Zhou, zhouzhenhu06@163.com

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Abstract: Follicular thyroid carcinoma (FTC) is the second most common type of differentiated thyroid cancer, with a high propensity for hematogenous metastasis, particularly to the lungs and bones. Radioactive iodine-131 (¹³¹I) therapy is traditionally recommended after total thyroidectomy when minimal remnant thyroid tissue is present. However, the necessity of completion thyroidectomy before ¹³¹I therapy in patients who have undergone lobectomy remains controversial. This case report describes a 73-year-old female patient with multiple distant metastases (bones, lungs, lymph nodes, and adrenal gland) that developed eight years after lobectomy for FTC. She received two courses of individualized ¹³¹I therapy (70 mCi and 200 mCi) based on pre-therapeutic assessment of iodine-avidity using ^{99m}TcO₄-thyroid scintigraphy. Following treatment, the patient's pain symptoms significantly improved, and follow-up whole-body iodine scintigraphy with SPECT/CT showed marked reduction in metastatic lesions with osteoblastic repair changes. Serial thyroglobulin levels demonstrated a sustained downward trend. This case suggests that for FTC patients with iodine-avid metastatic disease after lobectomy, ¹³¹I therapy can be safe and effective, even in the presence of significant remnant thyroid tissue, provided that pre-treatment evaluation of iodine uptake capacity is thoroughly performed.

Keywords: Follicular thyroid carcinoma; Radioactive iodine-131 therapy; Multiple distant metastases; Remnant thyroid tissue

Online publication: June 30, 2026

1. Introduction

Follicular thyroid carcinoma (FTC) is the second most common type of differentiated thyroid cancer (DTC) after papillary thyroid carcinoma (PTC), accounting for 5%–15% of DTC cases ^[1,2]. The lungs and bones are the most common sites of distant metastasis. For FTC with bone metastases, radioactive iodine-131 (¹³¹I) therapy can significantly alleviate pain symptoms and prolong progression-free survival ^[3]. However,

conventional views hold that ^{131}I therapy is primarily indicated for patients with minimal remnant tissue after total thyroidectomy. With updates in clinical practice and guidelines, this concept has gradually been revised. For DTC patients who have undergone only lobectomy and meet the indications for ^{131}I therapy, or for those who face surgical risks or refuse a second surgery, ^{131}I therapy may be a viable option. This study reports a case of a patient with multiple metastases following lobectomy for follicular thyroid carcinoma, who received individualized sequential ^{131}I therapy based on an assessment of iodine-avidity. Dynamic imaging and thyroglobulin changes were monitored, and a favorable treatment outcome was achieved. The case is reported as follows.

2. Case report

A 73-year-old female patient was hospitalized due to “one year of lumbosacral and right lower extremity pain, aggravated for four months.” Four months prior to admission, the patient visited a local hospital due to worsening lumbosacral and right lower extremity pain. A chest CT revealed multiple pulmonary lesions, and a puncture biopsy indicated metastasis from follicular thyroid carcinoma. Eight years ago, the patient underwent surgical treatment at a local hospital for a “thyroid mass,” with postoperative pathology indicating follicular thyroid carcinoma. No ^{131}I therapy was administered, and the patient was treated with daily regular levothyroxine sodium 50 μg . Laboratory tests upon admission: After two injections of recombinant human thyroid-stimulating hormone, serum thyroid-stimulating hormone (TSH) was 182.91 mIU/L (normal reference range: 0.566–5.91 mIU/L), thyroglobulin (Tg) > 4,920 ng/mL (1.59–50.03 ng/mL), and anti-thyroglobulin antibodies (TgAb) 0.20 mIU/L (< 4 mIU/L). Whole-body bone scintigraphy (**Figure 1**) showed multiple bone metastases. Thyroid ultrasound (**Figure 2**) indicated changes after partial thyroidectomy, with multiple lymph nodes visible in both cervical regions. $^{99\text{mTcO}_4^-}$ thyroid scintigraphy (**Figure 3**) showed residual thyroid tissue and multiple areas of increased radiotracer uptake in the bones and both lungs. After a comprehensive evaluation, the patient underwent two courses of ^{131}I therapy on April 28, 2025, and November 18, 2025, respectively, with relevant examinations performed before and after each treatment to assess the condition. During the first 70 mCi ^{131}I therapy, the patient received intravenous methylprednisolone 40 mg/day.

On the third day, swelling and pain in the neck and right face occurred without dyspnea, considered related to radiation-induced thyroiditis. On the fifth day after treatment, whole-body iodine scintigraphy and SPECT/CT fusion imaging (**Figure 4**) showed residual thyroid tissue after thyroid surgery, multiple lymph node metastases in the right supraclavicular region, right hilum, and mediastinum, lung metastases, left adrenal metastasis, and multiple bone metastases. Fifteen days after the first ^{131}I therapy discharge, the patient’s lumbosacral and right lower extremity pain significantly improved, and mobility gradually recovered, transitioning from wheelchair dependence to independent activity with full self-care ability. Before the second 200 mCi ^{131}I therapy, a repeat $^{99\text{mTcO}_4^-}$ thyroid scintigraphy (**Figure 3**) showed a slightly increased radiotracer uptake in the right thyroid region compared to the previous scan, with disappearance of radiotracer uptake in other metastatic lesions. On the fifth day after the second treatment, repeat whole-body iodine scintigraphy and SPECT/CT fusion imaging showed a significant reduction in multiple metastatic lesions compared to before, indicating a marked improvement in the condition. The patient’s thyroglobulin levels were monitored six times from before the first ^{131}I therapy to after the second treatment

(**Figure 5**), showing an overall downward trend, indicating a favorable biochemical response to treatment. After discharge, the patient's levothyroxine sodium dosage was adjusted to 100 µg daily for regular TSH suppression therapy.

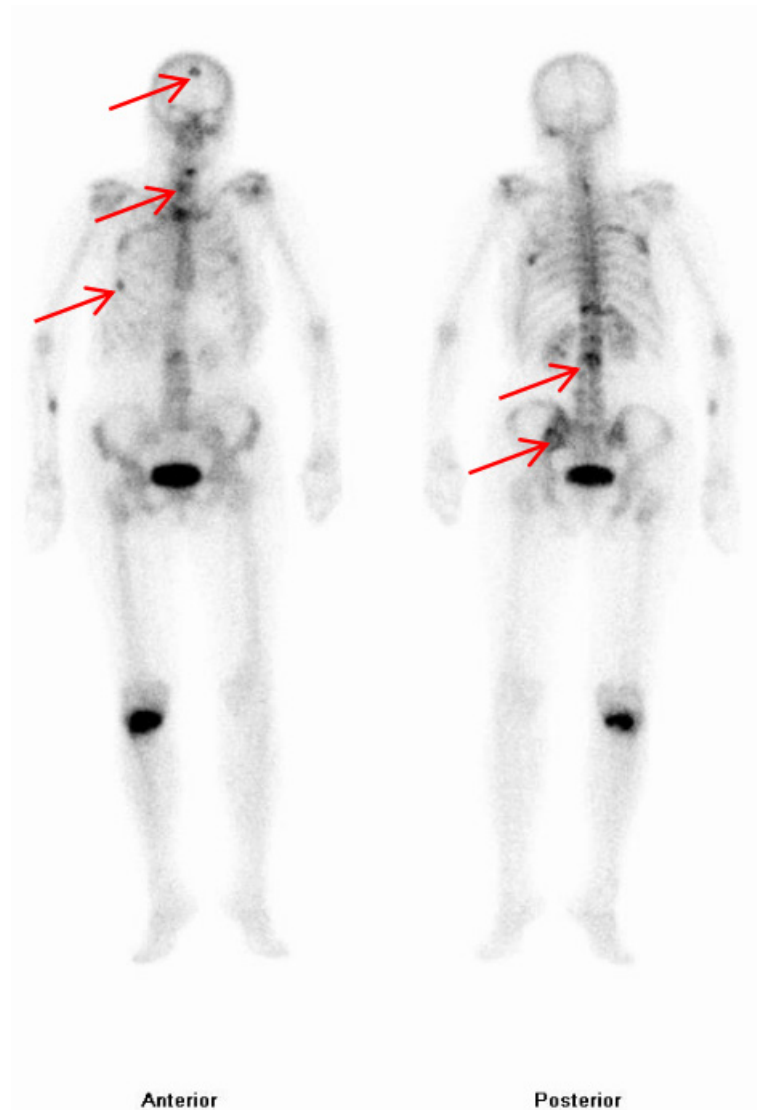


Figure 1. Whole-body bone scintigraphy of a 73-year-old female patient with multiple metastases from follicular thyroid carcinoma (arrows indicate the lesions).

Multiple irregular, abnormal, radioactive foci were observed in the skull, sternum, multiple ribs, spine, pelvis, and bones of the extremities.

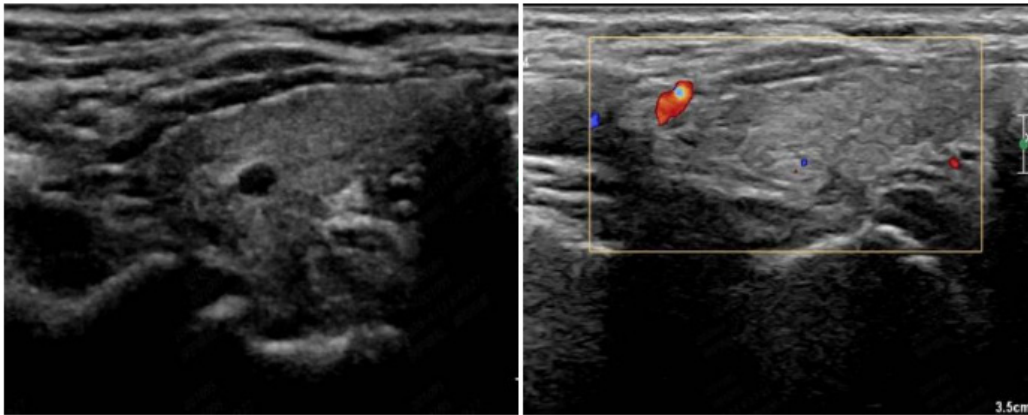


Figure 2. Thyroid color Doppler ultrasound image.

The size and shape of the right thyroid lobe are acceptable, and its surface is relatively smooth. Multiple lymph nodes with echogenicity can be detected on both sides of the neck. The larger ones are located in level II, with clear borders and relatively clear corticomedullary differentiation. CDFI (Color Doppler Flow Imaging) shows a small amount of blood flow signals within them.

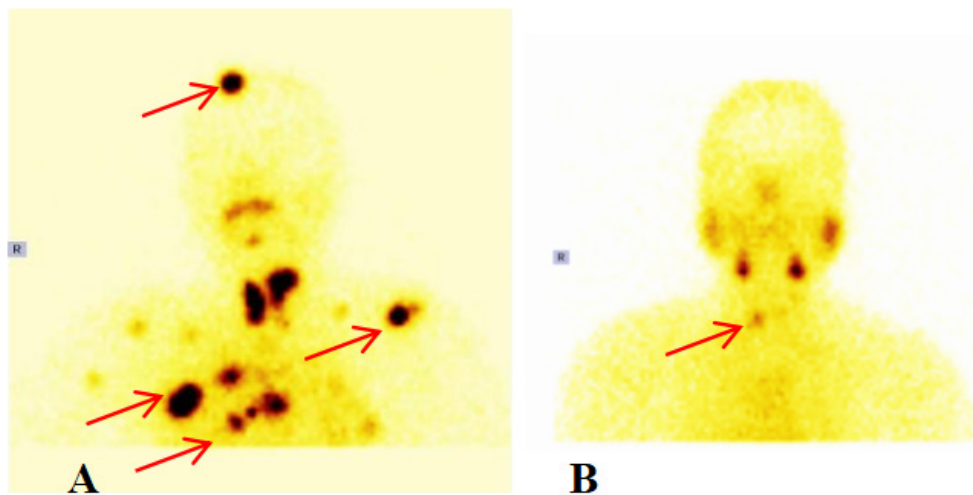


Figure 3. $^{99m}\text{TcO}_4$ - thyroid function imaging scans before two rounds of ^{131}I therapy (lesions indicated by arrows).

Image A is the first $^{99m}\text{TcO}_4$ - thyroid function imaging scan, showing multiple areas of increased radioactivity in the vertex of the skull, thyroid region, both shoulders, and chest. Image B is the second $^{99m}\text{TcO}_4$ - thyroid function imaging scan, revealing a slightly hyperactive radioactive area in the right thyroid region; the parotid glands, submandibular glands, and oral cavity are also visualized.

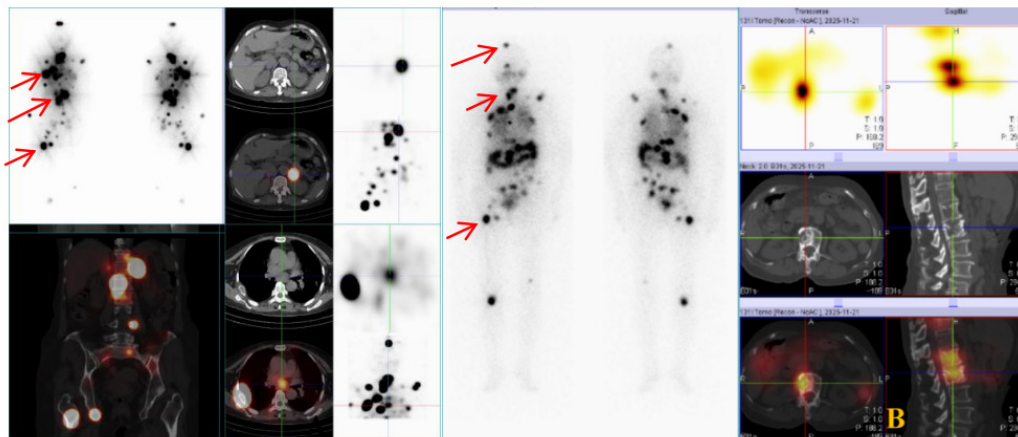


Figure 4. Whole-body iodine scintigraphy and SPECT/CT fusion images obtained on day 5 after each of the two courses of ^{131}I therapy (arrows indicate lesions).(A): Whole-body iodine scintigraphy and SPECT/CT fusion images after the first course of ^{131}I therapy. Multiple foci of increased radioactivity uptake are visible in the head, neck, thorax, abdomen, pelvis, and extremities. Multiple osteolytic destructive lesions with markedly increased radioactivity are seen in the frontal bone, spine, scapulae, ribs, pelvis, and extremity bones.(B): Whole-body iodine scintigraphy and SPECT/CT fusion images after the second course of ^{131}I therapy. Multiple foci of increased radioactivity uptake are still visible in the head, neck, thorax, abdomen, pelvis, and extremities. Compared with the previous iodine scan, the remnant thyroid tissue in the right thyroid lobe has decreased in volume and density, with reduced radioiodine uptake. The previously noted multiple bilateral pulmonary metastases, metastatic lymph nodes in the right supraclavicular region and right hilar region, as well as the adrenal metastasis, have markedly decreased in size, with no significant increase in radioactivity. The multiple osteolytic destructive lesions in the skull, spine, scapulae, ribs, pelvis, and extremity bones show predominantly osteoblastic repair changes on this scan. Some lesions show a slight size reduction, although increased radioactivity (indicating post-therapeutic repair changes) is still observed.

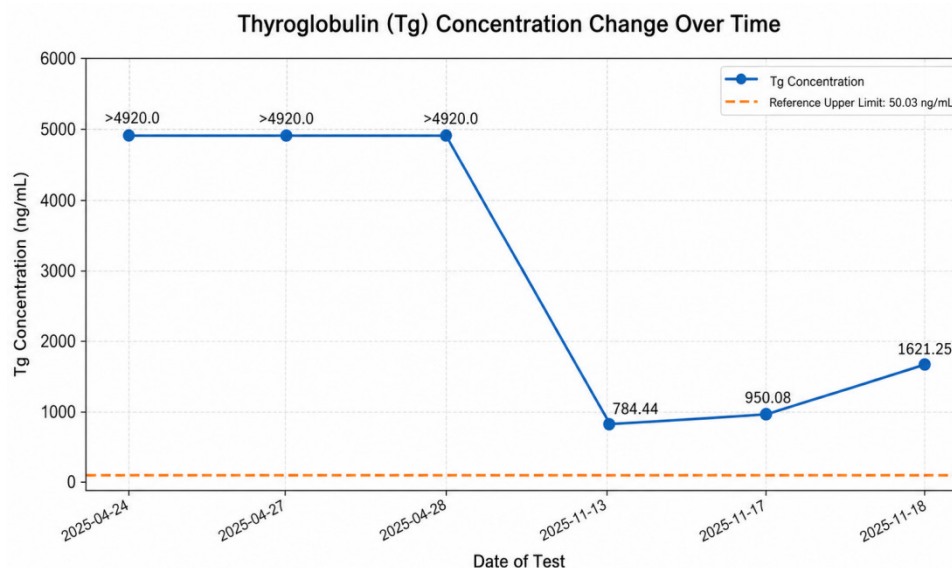


Figure 5. Graph of the changes in thyroglobulin levels.

3. Discussion

Follicular thyroid carcinoma (FTC) is the second most common type of differentiated thyroid carcinoma (DTC) after papillary thyroid carcinoma (PTC), accounting for 5–15% of DTC cases ^[1,2]. Unlike PTC, FTC is closely associated with vascular invasion and distant metastasis, with the lungs and bones being the most common sites of distant metastasis. For FTC patients with bone metastases, ¹³¹I therapy can significantly alleviate pain symptoms and prolong progression-free survival ^[3].

For a long time, there has been a misconception in clinical practice that ¹³¹I therapy cannot be performed after lobectomy of the thyroid gland, and that total thyroidectomy is a prerequisite for ¹³¹I therapy. This concept stems from the traditional theoretical basis of ¹³¹I ablation therapy, that residual thyroid tissue is minimal after total thyroidectomy, allowing ¹³¹I to more effectively ablate residual tissue and treat metastases. However, this concept is being overturned by modern guidelines and clinical practice. The 2025 edition of the CSCO guidelines for the diagnosis and treatment of thyroid carcinomas of follicular epithelial origin clearly state that for DTC patients who have undergone only unilateral lobectomy and have indications for ¹³¹I therapy, and where surgery poses risks or the patient refuses a second operation, ¹³¹I therapy can be performed ^[4]. In this case, the patient developed multiple distant metastases after a lobectomy. Before the first ¹³¹I therapy, a ^{99m}Tc thyroid scan showed multiple areas of intense uptake throughout the body, indicating highly active metastatic lesions. After treatment, the scan showed that the metastatic lesions had accumulated a significant amount of ¹³¹I, suggesting a favorable therapeutic response. Before the second treatment, a ^{99m}Tc thyroid scan showed that the lesions did not take up the imaging agent, indicating a reduced cancer cell burden or activity within the lesions. After the second ¹³¹I therapy, the scan showed a significant reduction in metastatic lesions throughout the body. This series of dynamic changes indicates that even with a significant amount of residual thyroid tissue, as long as the metastatic lesions retain iodine uptake capacity, ¹³¹I therapy can still achieve favorable therapeutic outcomes. Therefore, the surgical approach is not a criterion for selecting patients for ¹³¹I therapy. The decision to administer ¹³¹I therapy should be based on an assessment of postoperative recurrence risk stratification and the iodine uptake capacity of the lesions.

In this case, the initial dose of ¹³¹I therapy was 70 mCi, determined primarily based on pre-treatment thyroid scans and iodine uptake rate measurements. This dose adequately assessed the iodine uptake capacity of the lesions and the volume of residual tissue, ensuring treatment safety. Since the patient had undergone a lobectomy, there was a significant amount of residual thyroid tissue, and a larger dose might have caused edema in the residual tissue at the thyroid bed, compressing the trachea and leading to dyspnea and edema risks. From a therapeutic perspective, within half a month after the first ¹³¹I therapy, the patient's pain symptoms were significantly alleviated. After the second treatment, the scan showed a marked reduction in metastatic lesions, indicating a favorable therapeutic response. This suggests that the dosing regimen achieved a reasonable balance between safety and efficacy. Recent studies have also confirmed that a thorough pre-treatment assessment of residual thyroid volume and iodine uptake function helps significantly reduce the incidence of complications such as radioactive thyroiditis while ensuring therapeutic efficacy ^[5].

4. Conclusion

The therapeutic outcomes of this case indicate that: (1) Metastatic lesions of follicular thyroid carcinoma have good iodine uptake capacity, making them ideal targets for ¹³¹I therapy; (2) ¹³¹I therapy after lobectomy is not only feasible but also has favorable therapeutic effects on distant metastatic lesions; (3) Accurate

pre-treatment assessment of the amount and iodine uptake capacity of residual thyroid tissue is crucial for ensuring treatment safety.

Disclosure statement

The authors declare no conflict of interest.

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Construction and Validation of a Prognostic Model for Hepatocellular Carcinoma Based on Hypoxia-Related lncRNAs

Yahan Ren*

Biotherapy Center, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510630, Guangdong, China

*Corresponding author: Yahan Ren, 15670256960@163.com

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Abstract: *Objective:* To explore the correlation between hypoxia-related long non-coding RNA (lncRNA) and the prognosis of hepatocellular carcinoma (HCC) patients, and to construct and validate a prognostic risk model based on hypoxia-related lncRNA. *Method:* Obtain RNA transcriptome sequencing data and clinical follow-up data of HCC patients from the Cancer Genome Atlas (TCGA) database. Based on the HALLMARK-HYPOXIA gene set in the Molecular Signature Database (MSigDB), Spearman correlation analysis was used to screen hypoxia-related lncRNAs. Further, single-factor Cox proportional hazards regression, Least Absolute Shrinkage and Selection Operator (LASSO) - Cox regression, and multiple-factor Cox regression were used to screen for key lncRNAs associated with HCC prognosis, and a risk scoring model was constructed based on these results. According to the median risk score, patients were divided into high-risk and low-risk groups. Kaplan Meier survival analysis was used to compare the overall survival differences between the two groups, and the discriminant ability and clinical application value of the model were evaluated through a time-dependent receiver operating characteristic (ROC) curve and consistency index (C-index). Further combining clinical pathological characteristics for univariate and multivariate Cox regression analysis, screening for independent prognostic factors, and constructing a column chart prediction model. *Result:* A total of 367 HCC patients were included. Finally, 14 hypoxia related lncRNAs closely related to the prognosis of HCC were screened, namely MAPKAPK5-AS1, KDM4A-AS1, LINC00674, HCG15, NEAT1, EIF3J-AS1, BSG-AS1, FRMD6-AS1, HMMR-AS1, MRV11-AS1, SZT2-AS1, SLC1A5-AS, CPS1-IT1 And AC115619, and based on this, construct a prognostic risk scoring model. The Kaplan Meier survival analysis results showed that the overall survival rate of high-risk group patients was lower than that of the low-risk group, and the difference was statistically significant ($P < 0.01$). ROC curve analysis showed that the area under the curve (AUC) of the model for predicting the survival of HCC patients at 1, 3, and 5 years was 0.59, 0.61, and 0.65, respectively, indicating that the model has good survival prediction performance. Multivariate Cox regression analysis showed that age, T stage, and risk score were independent risk factors affecting the prognosis of HCC patients ($P < 0.05$). The Nomogram model was constructed on this basis. The calibration curve results confirm that the model has good predictive value for the 1, 3, and 5-year survival probabilities of HCC patients. *Conclusion:* 14 hypoxia-related lncRNAs are closely related to the prognosis of HCC patients. The risk scoring model constructed based on them has good prognostic stratification and survival prediction ability, and can

provide a reference for individualized risk assessment and clinical decision-making of HCC patients.

Keywords: Hypoxia; lncRNAs; Hepatocellular carcinoma; Prognostic model

Online publication: June 30, 2026

1. Introduction

Primary liver cancer still poses a heavy burden of morbidity and mortality worldwide. GLOBOCAN 2020 data show that liver cancer ranks third in global cancer deaths, accounting for approximately 8.3% of all cancer deaths. In 2020, there were approximately 905700 new cases of liver cancer and 830200 deaths worldwide. Hepatocellular carcinoma (HCC) is the most common histological type of primary liver cancer, accounting for approximately 75% to 90%. Due to its insidious onset, significant tumor heterogeneity, and unsatisfactory overall survival outcomes, its clinical management still faces significant challenges^[1-3]. In recent years, further research has shown that HCC exhibits significant individual differences in molecular subtyping, tumor immune microenvironment, and treatment response, suggesting that relying solely on traditional clinical indicators such as TNM staging often makes it difficult to fully achieve refined prognostic risk stratification^[4,5]. Hypoxia is one of the important characteristics of the solid tumor microenvironment. Abnormal angiogenesis and high metabolic status in tumors can lead to insufficient local oxygen supply, which in turn activates hypoxia-inducible factor (HIF) related pathways and promotes malignant biological processes such as angiogenesis, glycolysis reprogramming, invasion and metastasis, and treatment resistance. There is a close relationship between hypoxia and acquired resistance to sorafenib in HCC^[6-7]. At the same time, increasing evidence suggests that long non-coding RNAs (lncRNAs) are widely involved in key processes such as cell proliferation, apoptosis, invasion and metastasis, and immune escape during the development of HCC. Some lncRNAs also have the potential to serve as diagnostic and prognostic biomarkers^[8,9]. Based on this, this study aims to screen hypoxia-related lncRNAs using a publicly available database system, construct and validate a prognostic risk model for HCC, in order to provide a reference for risk stratification and personalized treatment decision-making in patients.

2. Materials and methods

2.1. Data download and filtering

2.1.1. TCGA-LIHC data source and download

The transcriptome and clinical follow-up data from the TCGA database can be obtained through (<https://portal.gdc.cancer.gov/>). Traceable download and preprocessing through R/Bioconductor's TCGAbiolinks package. This study included a total of 367 patients with hepatocellular carcinoma. The baseline characteristics showed that there were 194 cases of age > 60 years old and 173 cases of age ≤ 60 years old; There were 248 males and 119 females. The T stage was mainly the T1 stage (181 cases), followed by the T2 stage (92 cases) and the T3 stage (78 cases), with 13 cases in the T4 stage and 3 cases missing. In the N stage, there were 249 cases in the N0 stage, 4 cases in the N1 stage, and 114 cases were missing. In the M stage, there were 264 cases in the M0 stage, 3 cases in the M1 stage, and 100 cases were missing.

2.2. Screening of hypoxia-related lncRNAs

Use the HALLMARK-HYPOXIA gene set from the MSigDB Hallmark set. Calculate the Spearman correlation coefficient between lncRNA and hypoxia genes using $|\text{Rho}| > 0.3$ and $P < 0.001$. Screening for hypoxia-related lncRNAs.

2.3. Preliminary screening of prognostic hypoxia-related lncRNAs

Using overall survival (OS) as the primary endpoint, a univariate Cox proportional hazards regression model was employed to analyze the relationship between hypoxia-related lncRNAs and OS in HCC patients. Hazard ratio (HR), 95% confidence interval (CI), and P-value were calculated. Using $P < 0.05$ as the screening criterion, hypoxia lncRNAs significantly correlated with patient prognosis were included in the subsequent Least Absolute Shrinkage and Selection Operator (LASSO) Cox regression analysis.

2.4. Construction of risk scoring model

Based on the results of single-factor Cox regression screening, the LASSO Cox regression model was used to further reduce the dimensionality of candidate hypoxia-related lncRNAs. By introducing a penalty function to compress regression coefficients, we can reduce collinearity between variables and avoid overfitting of the model. Using the cross-validation method to determine the optimal penalty parameter λ value, and selecting key lncRNAs based on the non-zero regression coefficient corresponding to the optimal λ value. Subsequently, the lncRNAs selected by LASSO were included in a multivariate Cox proportional hazards regression model to determine the final lncRNAs and their regression coefficients to be included in the prognostic model. Based on this, a risk score formula was constructed: Risk score = $\sum (\beta_i \times \text{Exp}_i)$, where β_i is the regression coefficient of each variable and Exp_i is the expression level of the corresponding variable. Quantify the prognostic risk of patients based on risk scoring.

2.5. Risk stratification and survival analysis

According to the risk score of each patient, divide them into high-risk and low-risk groups based on the median. The Kaplan Meier method was used to plot the survival curves of two groups of patients, and the Log-rank test was applied to compare the differences in OS between the two groups, in order to evaluate the stratification ability of the constructed model for the prognosis of HCC patients.

2.6. Evaluation of the discriminative power and calibration ability of prognostic models

The time-dependent receiver operating characteristic curve (ROC) was used to evaluate the predictive ability of the risk scoring model for patients' 1, 3, and 5-year survival outcomes, and the area under the curve (AUC) was calculated. Further, use the consistency index (C-index) to evaluate the overall prediction accuracy of the model.

2.7. Independent prognostic factor analysis and column chart construction

To further evaluate the independent prognostic value of risk score, age, gender, tumor stage, tumor grade, and other clinical pathological variables were included in univariate and multivariate Cox proportional hazards regression analysis along with risk score. After screening for statistically significant independent prognostic factors, a column chart prediction model was constructed by integrating risk scores with independent clinical variables for personalized prediction of 1, 3, and 5-year survival probabilities in HCC patients. By calculating

the C-index of the column chart model, drawing the calibration curve and DCA curve, a comprehensive evaluation is conducted on its discrimination, calibration degree, and clinical application value.

2.8. Statistical analysis

All data organization and statistical analysis were completed using R 4.0.2 software. Quantitative data is described and compared using corresponding statistical methods based on the distribution characteristics of the data; Count data is presented in terms of examples and percentages, and comparison between groups is conducted using the χ^2 test or Fisher's exact probability method. Survival analysis was performed using the Kaplan–Meier method to plot survival curves, and the log-rank test was used to compare differences between groups. Using the Cox proportional hazards regression model to analyze the influencing factors of prognosis in patients with hepatocellular carcinoma. The discrimination and predictive performance of the time-dependent subject work characteristic curve, consistency index, and area under the curve evaluation model are evaluated. The difference is statistically significant when $P < 0.05$ is used for bilateral testing.

3. Results

3.1. Screening and risk scoring of hypoxia-related lncRNAs

Using $|\text{Rho}| > 0.3$ and $P < 0.001$ as screening criteria, a total of 213 hypoxia-related lncRNAs were screened. On this basis, further single-factor Cox proportional hazards regression analysis was used to preliminarily screen candidate lncRNAs. The results showed that a total of 36 hypoxia-related lncRNAs were significantly correlated with the prognosis of hepatocellular carcinoma patients ($P < 0.05$). Using the Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis for dimensionality-reduction screening, we identified 16 hypoxia-related lncRNAs that may be associated with the prognosis of hepatocellular carcinoma, as shown in **Figure 1**. Further analysis was conducted by incorporating the aforementioned candidate lncRNAs into a multivariate Cox proportional hazards regression model, resulting in the selection of 14 hypoxia-related lncRNAs that are independently associated with the prognosis of hepatocellular carcinoma, as shown in **Table 1**. Among them, CPS1-IT1 and AC115619 are protective factors, while MAPKAPK5-AS1, KDM4A-AS1, LINC00674, HCG15, NEAT1, EIF3J-AS1, BSG-AS1, FRMD6-AS1, HMMR-AS1, MRV11-AS1, SZT2-AS1, SLC1A5-AS For risk factors. Constructing a risk scoring model based on regression coefficients of various lncRNAs: Risk rating = $0.316 \times \text{Exp}(\text{MAPKAPK5-AS1}) + 0.376 \times \text{Exp}(\text{KDM4A-AS1}) + 0.450 \times \text{Exp}(\text{LINC00674}) + 0.464 \times \text{Exp}(\text{HCG15}) + 0.748 \times \text{Exp}(\text{NEAT1}) + 1.015 \times \text{Exp}(\text{EIF3J-AS1}) + 0.231 \times \text{Exp}(\text{BSG-AS1}) + 0.568 \times \text{Exp}(\text{FRMD6-AS1}) + 0.515 \times \text{Exp}(\text{HMMR-AS1}) + 0.619 \times \text{Exp}(\text{MRV11-AS1}) + 0.652 \times \text{Exp}(\text{SZT2-AS1}) + 0.494 \times \text{Exp}(\text{SLC1A5-AS}) - 0.551 \times \text{Exp}(\text{CPS1-IT1}) - 0.411 \times \text{Exp}(\text{AC115619})$.

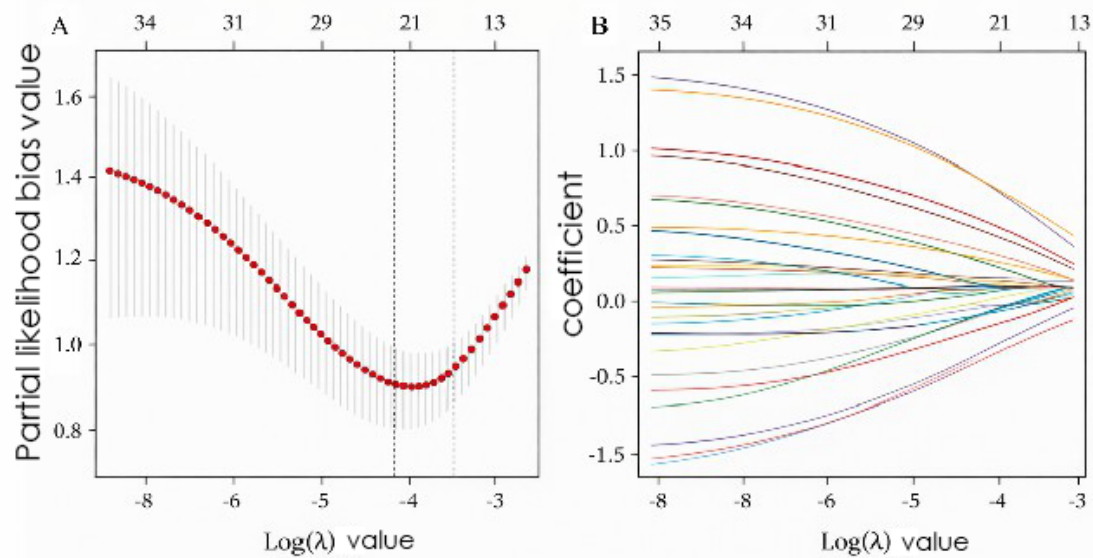


Figure 1. LASSO regression analysis results. A is the partial likelihood bias plot of hypoxia-related lncRNAs, and B is the profile plot of LASSO coefficients.

Table 1. Results of multivariate Cox regression analysis

lncRNA	β value	SE value	Wald χ^2 value	HR value(95% CI)	P value
MAPKAPK5-AS1	0.316	0.088	12.742	1.371 (1.153, 1.631)	< 0.001
KDM4A-AS1	0.376	0.079	22.707	1.456 (1.248, 1.699)	< 0.001
LINC00674	0.45	0.13	11.937	1.568 (1.215, 2.025)	< 0.001
HCG15	0.464	0.118	15.42	1.590 (1.262, 2.004)	< 0.001
NEAT1	0.748	0.137	29.738	2.112 (1.614, 2.763)	< 0.001
EIF3J-AS1	1.015	0.188	29.276	2.759 (1.910, 3.984)	< 0.001
BSG-AS1	0.231	0.095	5.867	1.259 (1.045, 1.518)	0.015
FRMD6-AS1	0.568	0.198	8.205	1.765 (1.197, 2.605)	0.004
HMMR-AS1	0.515	0.17	9.153	1.674 (1.199, 2.337)	0.002
MRV11-AS1	0.619	0.192	10.395	1.857 (1.275, 2.704)	0.001
SZT2-AS1	0.652	0.155	17.638	1.919 (1.416, 2.602)	< 0.001
SLC1A5-AS	0.494	0.147	11.295	1.639 (1.229, 2.186)	< 0.001
CPS1-IT1	-0.551	0.111	24.514	0.576 (0.463, 0.717)	< 0.001
AC115619	-0.411	0.132	9.703	0.663 (0.512, 0.859)	0.002

3.2. Verification of risk assessment

Using a median risk score of 18.28 as the threshold, hepatocellular carcinoma patients were divided into a low-risk group (< 18.28 , $n = 183$) and a high-risk group (≥ 18.28 , $n = 184$) as shown in **Figure 2**. Kaplan Meier survival analysis showed that the survival rate of high-risk group patients was lower than that of the low-risk group, and the difference was statistically significant ($HR = 2.31$, $P < 0.001$), as shown in **Figure**

3. The C-index of the risk-scoring model is 0.836, indicating good prognostic performance. Time dependent ROC curve analysis showed that the AUC predicted by this risk score for the 1-year, 3-year, and 5-year survival of hepatocellular carcinoma patients were 0.59 (95% CI: 0.551-0.672, $P < 0.05$), 0.61 (95% CI: 0.564-0.685, $P < 0.05$), and 0.65 (95% CI: 0.601-0.708, $P < 0.05$), respectively. **Figure 4** indicates that the model has good survival prediction performance.

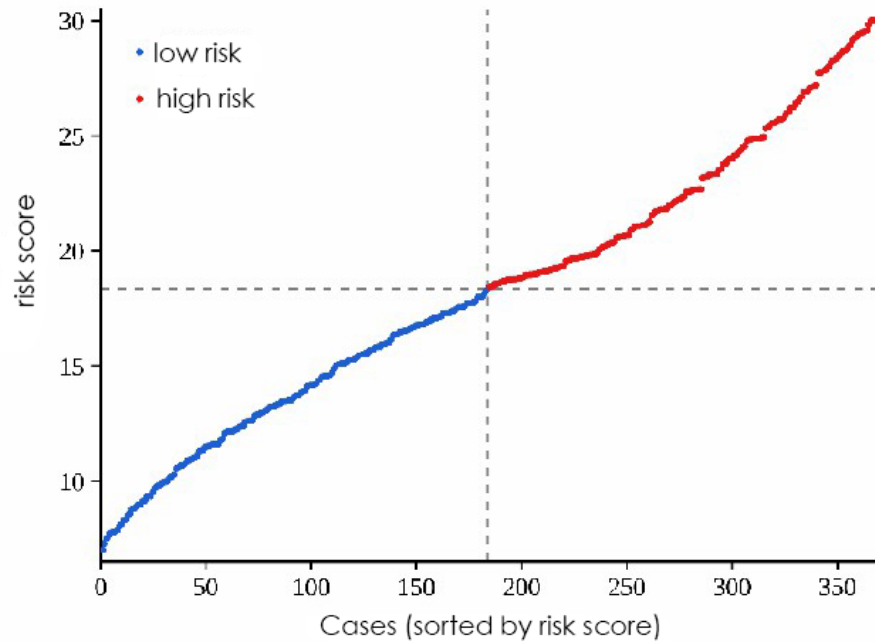


Figure 2. Distribution of patient risk scores.

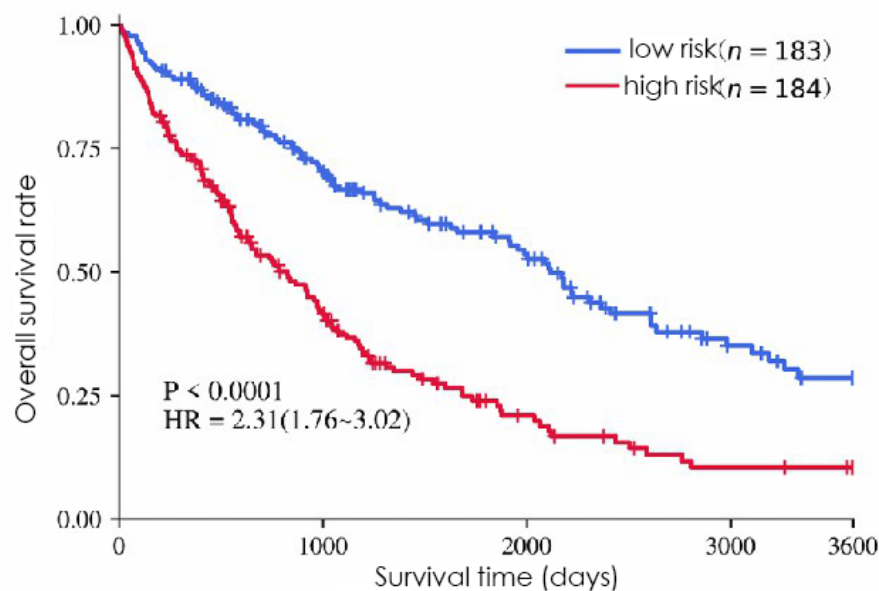
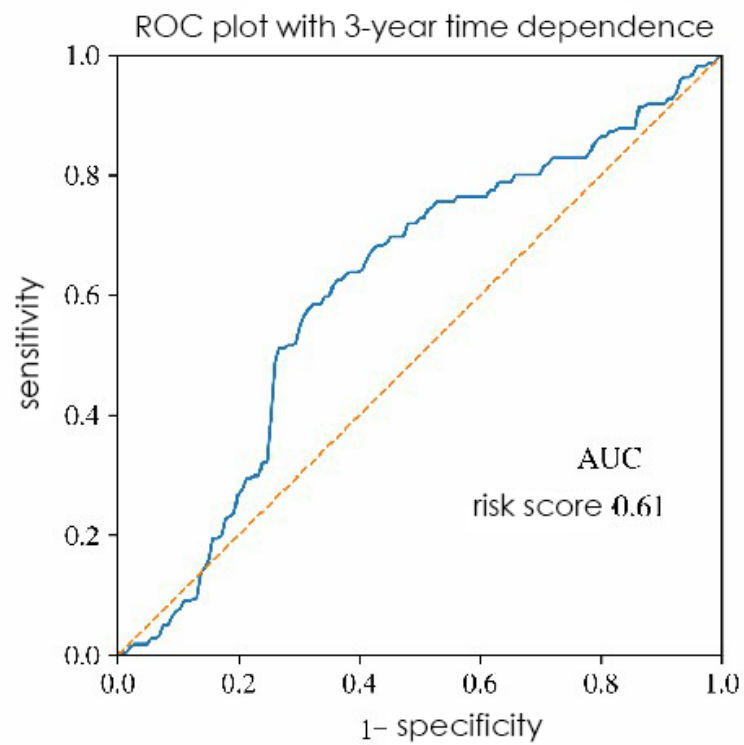
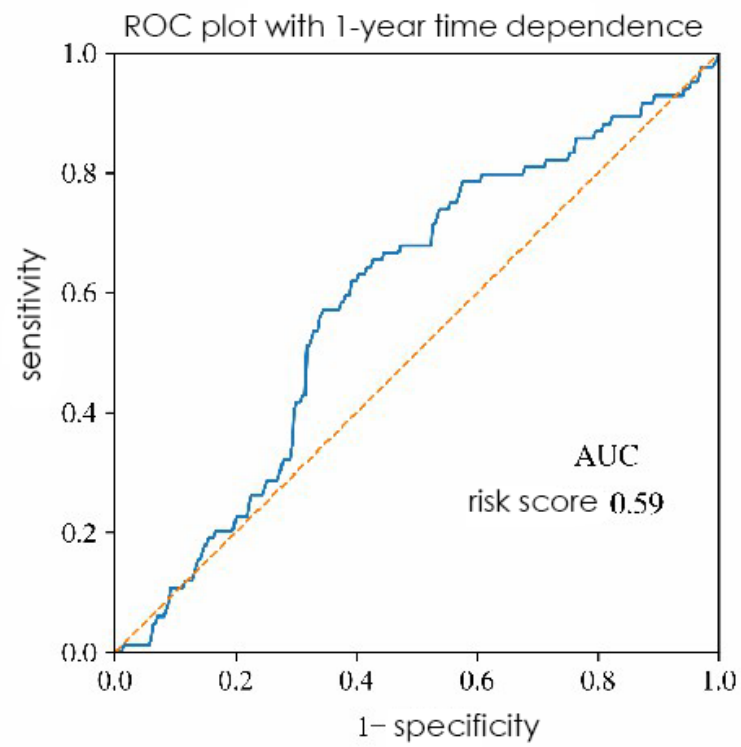


Figure 3. Kaplan Meier survival curve.



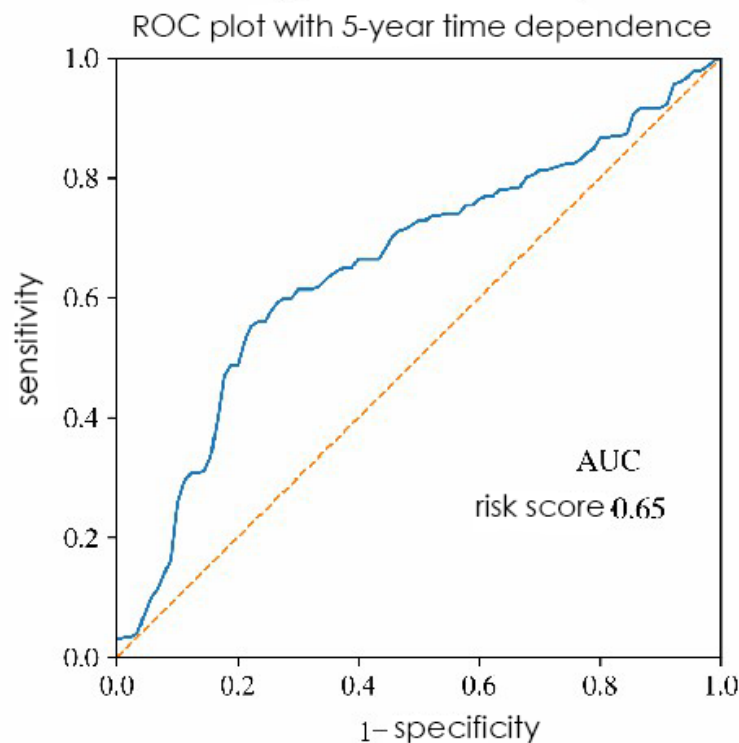


Figure 4. Evaluation of risk scores for 1, 3, and 5-year survival prediction ability.

3.3. Construction and validation of a prognostic column chart model for hepatocellular carcinoma based on hypoxia-related lncRNA

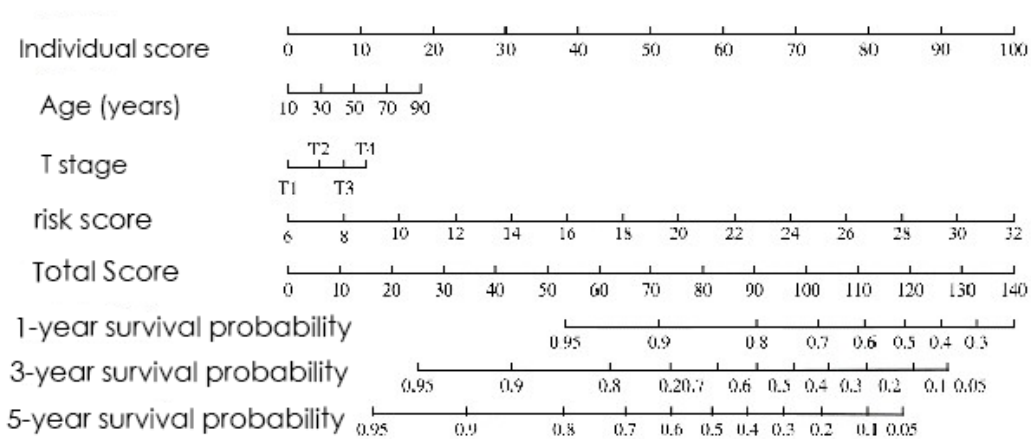
Using patient age, gender, T stage, M stage, N stage, and risk score as independent variables, with age assigned as < 60 years = 0 and ≥ 60 years = 1; Gender is female = 0, male = 1; T staging is as follows: Stage I = 1, Stage II = 2, Stage III = 3, Stage IV = 4; The value of M staging is M0 = 0 and M1 = 1; The value of N stages is set to N0 stage = 0 and N1 stage = 1; The risk score is assigned as < 18.28 points = 0, ≥ 18.28 points = 1. Using the patient's survival time and status as dependent variables, a univariate Cox proportional hazards regression model was employed to analyze the factors influencing the prognosis of hepatocellular carcinoma patients. The results showed that age, gender, T stage, M stage, N stage, and risk score were all correlated with the survival of hepatocellular carcinoma patients, and the differences were statistically significant (all $P < 0.05$), as shown in **Table 2**. Further incorporating the above six variables into a multivariate Cox proportional hazards regression model for analysis, the results showed that age, T stage, and risk score were still independently correlated with the survival of hepatocellular carcinoma patients, and the differences were statistically significant (all $P < 0.05$), as shown in **Table 3**. On this basis, age, T stage, and risk score were included in the column chart model to construct an individualized risk prediction model for predicting the 1, 3, and 5-year survival probabilities of hepatocellular carcinoma patients, as shown in **Figure 5**. The calibration curve results show that the model exhibits good calibration in predicting 1, 3, and 5-year survival rates. The predicted values are basically consistent with the actual observed values, and the curves at each time point are close to the reference line, as shown in **Figure 6**.

Table 2. Single factor Cox regression analysis of the impact on the survival of hepatocellular carcinoma patients

Variable	β value	SE value	Wald χ^2 value	HR value (95% CI)	P value
Age	0.039	0.006	40.449	1.040 (1.028, 1.053)	< 0.001
Gender	0.548	0.172	10.104	1.729 (1.234, 2.424)	0.001
T stage	0.466	0.074	39.180	1.593 (1.377, 1.843)	< 0.001
M stage	1.056	0.222	22.549	2.875 (1.859, 4.446)	< 0.001
N stage	0.428	0.093	21.354	1.534 (1.279, 1.839)	< 0.001
Risk score	0.220	0.071	9.450	1.246 (1.083, 1.433)	0.002

Table 3. Multivariate Cox regression analysis of factors affecting the survival of patients with hepatocellular carcinoma

Variable	β value	SE value	Wald χ^2 value	HR value (95% CI)	P value
Age	0.035	0.013	6.902	1.036 (1.009, 1.063)	0.009
Gender	0.201	0.128	2.447	1.221 (0.951, 1.569)	0.118
T stage	0.428	0.099	18.864	1.534 (1.265, 1.861)	< 0.001
M stage	0.152	0.122	1.507	1.162 (0.914, 1.476)	0.220
N stage	0.245	0.214	1.309	1.278 (0.840, 1.945)	0.253
Risk score	1.075	0.441	5.933	2.930 (1.234, 6.961)	< 0.001

**Figure 5.** Column chart constructed based on prognostic features of hypoxia related lncRNAs.

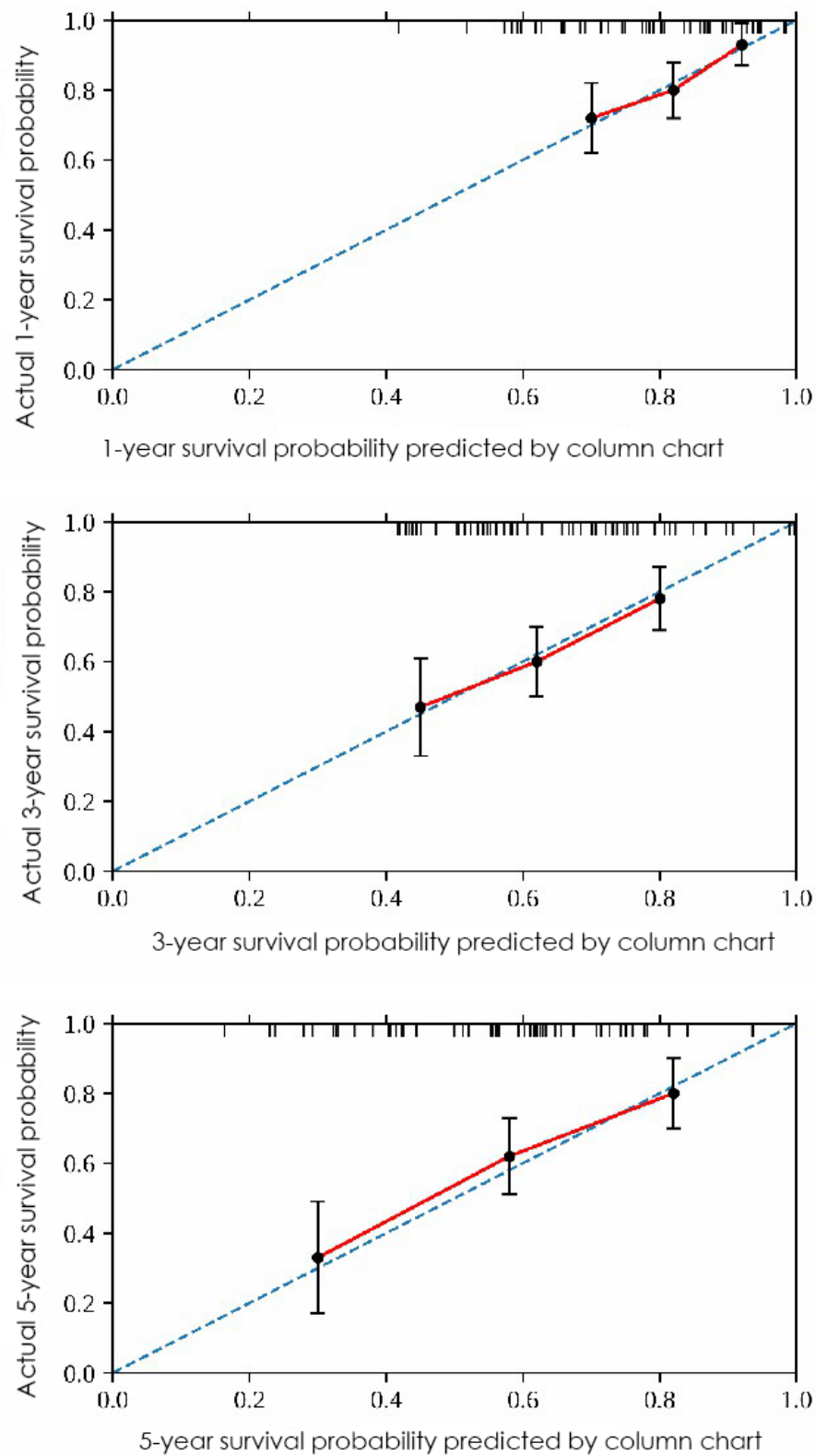


Figure 6. Validation of prognostic column chart based on hypoxia-related lncRNA.

4. Discussions

The results of this study show that the risk score constructed based on hypoxia-related lncRNAs can effectively distinguish different prognostic populations. The overall survival outcome of the high-risk group is poor, and the risk score still maintains independent predictive value in multivariate analysis. This suggests that hypoxia-related lncRNAs are not just accompanying molecular changes, but are more likely to be important molecular phenotypes reflecting the malignant biological behavior of HCC. Previous studies have constructed hypoxia-related lncRNA prognostic models based on the TCGA cohort, all of which have shown that they can effectively distinguish between high-risk and low-risk patients, and exhibit certain stability in time-dependent ROC, column chart, and clinical stratification analysis^[10–12]. This study supports the feasibility of using the hypoxia lncRNA axis as a starting point for HCC prognosis assessment. Compared with traditional clinical pathological indicators, lncRNA features can capture deep molecular information, such as tumor microenvironment remodeling, metabolic adaptation, and epigenetic regulation to a certain extent, which is expected to improve the refinement level of risk stratification.

From a mechanistic perspective, hypoxia-related lncRNAs may promote HCC progression through multiple pathways. Firstly, under hypoxic conditions, HIF-1 α can directly regulate the transcription of various lncRNAs, which in turn can enhance the HIF signal in reverse, forming a positive feedback loop and continuously amplifying the tumor's adaptability to hypoxic environments^[13,14]. KDM4A-AS1 has been reported as a hypoxia-responsive lncRNA activated by HIF-1 α , which can promote proliferation, migration, and invasion through miRNA/AKT signaling, and form a positive feedback loop of KDM4A-AS1/KPNA2/HIF-1 α ^[15]. LINC00674 can be induced by hypoxia in HCC and serves as a HIF-1 target gene, activating signals such as NOX1/mTOR to promote HCC progression; It is suggested that it can serve as both a marker of hypoxia status and a functional driving factor^[16]. HCG15 has been reported as a hypoxia-responsive lncRNA, and its expression can be upregulated by hypoxia and HIF-1 α , which is associated with poor prognosis in TCGA data; Mechanistically, it can enhance the transcription factor axis to promote tumor cell invasion and proliferation^[17]. NEAT1, as an important representative of HIF-related non-coding transcriptional response, can be activated by HIF transcription and promotes tumor cell survival under hypoxia; Studies have also shown that knocking down HIF-1 α inhibits NEAT1 and reduces tumor progression in HCC, consistent with its role in hypoxia adaptation and poor prognosis^[18,19]. BSG-AS1 has been reported to promote HCC proliferation and migration in hypoxic environments and is associated with poor prognosis; HMMR-AS1 can mediate immune cell polarization (such as macrophage M2) through exosomes in hypoxic environments, thereby affecting HCC progression^[20,21]. CPS1-IT1 has been reported to have anti-cancer effects in HCC, low expression is associated with poor survival, and can inhibit metastasis by suppressing HIF-1 α activity and EMT^[22]. The above research suggests that hypoxia-related lncRNAs are not only effector molecules of hypoxia-related proteins, but may also be important nodes in regulating metabolic reprogramming and invasion and metastasis.

Evidences suggest that hypoxia-related lncRNAs are closely related to tumor immune microenvironment remodeling. Hypoxia can promote upregulation of immune checkpoint molecule expression, induce immune cell dysfunction, and enhance tumor immune escape ability^[23,24]. Recent studies have shown that MIR155HG can enhance the stability of HIF-1 α mRNA under hypoxic conditions, thereby upregulating PD-L1 expression and promoting HCC immune escape^[25]. Previous studies on hypoxia-related lncRNA risk models have also found that high-risk groups are often accompanied by activation of immune-related pathways,

differential expression of immune checkpoint molecules, and changes in immune cell infiltration profiles [26-28]. The value of hypoxia-related lncRNA models may not be limited to “predicting survival”, but may also extend to “suggesting biological behavior” and “assisting treatment decisions”.

Of course, this study still has certain limitations. Firstly, if the model is mainly established based on public databases, such as TCGA, there may be selection bias in sample sources, etiology composition, treatment strategies, and follow-up completeness, which affects the extrapolation of the model. Secondly, the key lncRNAs obtained through bioinformatics co-expression or regression screening cannot completely replace the verification of their functions and regulatory mechanisms in cell and animal experiments. Again, HCC has significant etiology and spatiotemporal heterogeneity, and hypoxia status, immune infiltration, and lncRNA expression profiles may not be consistent under different etiological backgrounds. Therefore, the applicability of the model in HBV-related, HCV-related, or metabolism-related HCC still needs further comparison. Prospective validation should be conducted in multi-center, independent external cohorts in the future, and combined with single-cell sequencing, spatial transcriptomics, and in vitro and in vivo functional experiments, to further elucidate the role of key hypoxia-related lncRNAs in HCC progression and their clinical translation prospects.

5. Conclusion

In summary, the hypoxia-related lncRNA prognostic model constructed in this study can effectively evaluate the survival risk of HCC patients. This model provides new research ideas for individualized risk stratification and potential targeted interventions for HCC. However, its clinical promotion still depends on further validation at larger sample sizes, multi-center, and mechanistic levels.

Disclosure statement

The author declares no conflict of interest.

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Cancer Pain in Adults: Contemporary Approaches to Assessment, Phenotyping, and Multimodal Management

Liying Yang¹, Mengnan Du^{2,3}, Huiling Liu^{2,3}, Yunchao Zhang^{2,3,4}, Wentao Li^{2,3,4}, Dan Yi^{2,3,4*}

¹Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China

²First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300000, China

³National Clinical Research Center for Chinese Medicine, Tianjin 300000, China

⁴Tianjin Cancer Institute of Traditional Chinese Medicine, Tianjin 300000, China

*Corresponding author: Dan Yi, 834871221@qq.com

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Abstract: As one of the most prevalent and burdensome symptoms across the cancer continuum, cancer pain affects patients with active disease, those approaching the end of life, and a growing population of long-term survivors. Despite advances in supportive oncology, clinically meaningful gaps in pain control persist. These gaps increasingly reflect limitations in implementation, inequitable access to care, delayed recognition of structural pain generators, and inconsistent integration of interdisciplinary services rather than a simple lack of therapeutic options. This narrative review provides a clinically oriented synthesis of contemporary guidelines and selected high-impact evidence on adult cancer pain management. We review the pathophysiology of cancer pain, multidimensional assessment, phenotype-informed pharmacologic strategies, disease-directed interventions, and nonpharmacologic supportive approaches. We also examine the tension between rational opioid stewardship and the risk of undertreatment in the context of the opioid crisis. Contemporary cancer pain management requires individualized, mechanism-informed care that extends beyond linear analgesic escalation. Three practical themes emerge from current evidence and guideline synthesis: first, routine multidimensional assessment is needed to distinguish nociceptive, neuropathic, mixed, and temporal pain phenotypes; second, disease-directed interventions such as palliative radiotherapy should be considered early when they address the underlying pain generator; and third, proactive multidisciplinary collaboration is essential to address functional impairment, psychosocial distress, and barriers to equitable care delivery.

Keywords: Cancer pain; Palliative care; Opioid analgesics; Neuropathic pain; Breakthrough cancer pain; Survivorship

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1. Introduction

Cancer pain remains a major source of suffering despite substantial advances in oncology and supportive

care. It is strongly associated with impaired physical function, sleep disturbance, psychological distress, and reduced quality of life ^[1,2]. Although pain is often most prominent in advanced disease, it is also highly prevalent during active anticancer treatment and among long-term survivors ^[1,3,4].

Importantly, cancer pain is not a single entity but a heterogeneous clinical syndrome arising from tumor invasion, treatment-related injury, inflammation, nerve damage, and structural instability ^[5–7]. Nociceptive and neuropathic mechanisms frequently coexist, while temporal features such as incident pain, end-of-dose failure, and breakthrough exacerbations further shape the clinical picture. As a result, pain intensity scores alone are insufficient to define the underlying biology or guide optimal treatment ^[8,9].

Historically, cancer pain management has been framed by the World Health Organization analgesic ladder. While that model remains influential, contemporary practice increasingly emphasizes repeated multidimensional assessment, recognition of pain phenotypes, early treatment of reversible structural causes, and timely integration of palliative and supportive care services ^[8,10–12]. A particularly important component of this shift is the accurate recognition and management of breakthrough cancer pain (BTcP), which remains common, disabling, and frequently misclassified ^[13,14].

Despite the availability of established guidelines, meaningful gaps persist between evidence-based recommendations and routine practice ^[15–17]. In many settings, these gaps reflect implementation failures, inequities in access, delayed referral, and the unintended consequences of restrictive opioid policies rather than a simple lack of analgesic options. This narrative review provides an interpretive clinical synthesis of contemporary guidelines and selected high-impact literature on adult cancer pain, with a focus on pathophysiology, multidimensional assessment, phenotype-guided treatment, and major barriers to effective implementation. To provide a practical overview of the clinical framework discussed throughout this review, a proposed algorithm for adult cancer pain assessment and management is presented in **Figure 1**.

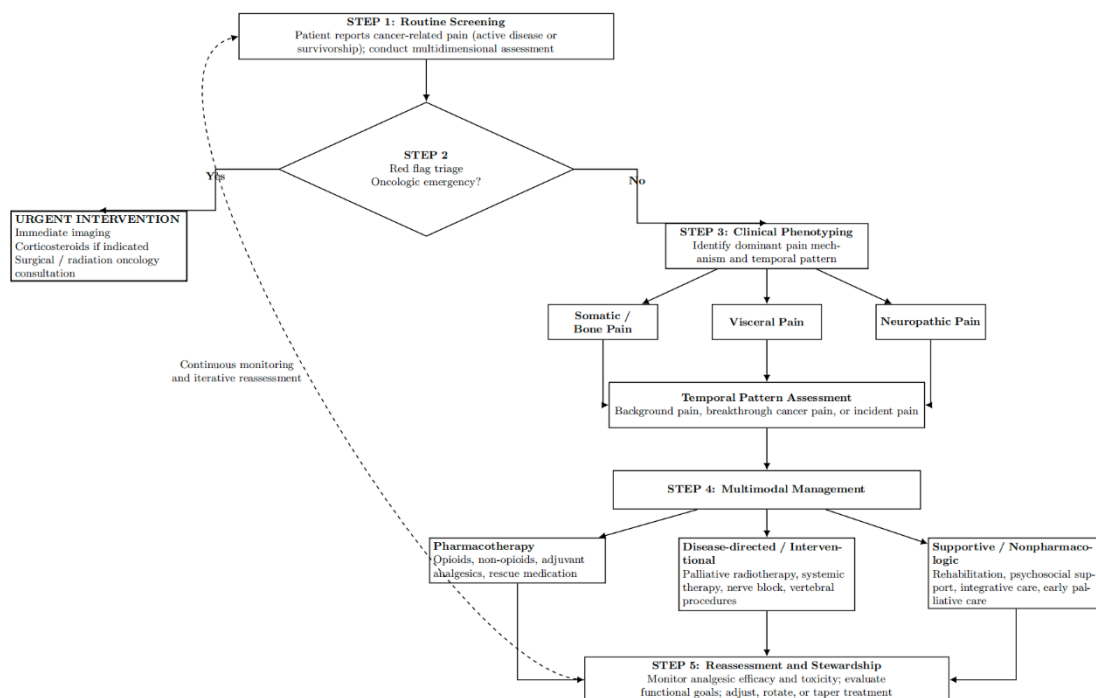


Figure 1. Proposed clinical algorithm for adult cancer pain assessment and management.

Patients with cancer-related pain should first undergo routine screening and multidimensional assessment. Red flag findings suggestive of oncologic emergencies warrant urgent evaluation and disease-directed intervention. In the absence of emergencies, pain should be phenotyped according to dominant mechanism and temporal pattern, followed by multimodal management incorporating pharmacologic, disease-directed/interventional, and supportive strategies. Continuous monitoring and iterative reassessment are required to optimize analgesia, reduce toxicity, and guide treatment adjustment.

2. Narrative review methodology

2.1. Rationale and review design

Given the breadth of adult cancer pain management—encompassing epidemiology, pathophysiology, assessment, pharmacologic treatment, interventional approaches, rehabilitation, and survivorship—a systematic review format was not considered the most appropriate design for the present article. Instead, we conducted an interpretive narrative review intended to provide a clinically focused synthesis of major contemporary guidelines and selected high-impact literature. The aim was to integrate evidence across domains and organize it into a practical framework for oncologists, palliative care clinicians, pain specialists, and supportive care teams.

2.2. Eligibility criteria

To structure the review, literature selection was guided by predefined eligibility criteria informed by the Population, Intervention, Comparison, Outcomes, and Study type [PICOS] framework. The population of interest included adults (≥ 18 years) with cancer-related pain across electronic patient-reported outcomes (ePROs), the disease continuum, including active disease and survivorship; pediatric populations were excluded. Interventions of interest included pharmacologic analgesics, adjuvant agents, palliative radiotherapy, interventional pain procedures, rehabilitation, and psychosocial or integrative supportive strategies. Outcomes of interest included pain intensity, functional interference, quality of life, and treatment-related adverse effects. Priority was given to clinical practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinically influential landmark studies. Basic science studies without direct clinical translation, non-indexed case reports, and pediatric-only literature were excluded.

The primary search focused on English-language publications from January 2010 through January 2025. Older landmark studies were retained selectively when they established widely used assessment instruments or foundational diagnostic criteria.

2.3. Search strategy and methodological limitations

A structured search of PubMed/MEDLINE was conducted in January 2025 using combinations of the following terms: “cancer pain,” “adult cancer pain,” “breakthrough cancer pain,” “neuropathic cancer pain,” “bone metastases pain,” “palliative radiotherapy,” “cancer survivorship pain,” “chemotherapy-induced peripheral neuropathy,” “opioid stewardship,” and “palliative care integration.” Additional targeted searches were performed on the official websites of major professional organizations, including American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and American Society for Radiation Oncology (ASTRO), to identify the most

recent clinical practice guidelines and related guidance documents ^[3,8,9,11,12,18]. Reference lists of included reviews and guideline documents were also screened selectively to identify major landmark studies.

As a narrative review, this article has important methodological limitations. The search relied primarily on a single bibliographic database and did not include a formal multi-database systematic screening process. Study selection was interpretive rather than protocol-driven, and no quantitative meta-analysis or formal risk-of-bias assessment was performed. Accordingly, this review should be interpreted as a clinically informed synthesis of contemporary guidelines and major studies rather than as an exhaustive systematic evidence review or a formal evidence-graded guideline.

3. Epidemiology and clinical burden

Cancer pain affects a substantial proportion of patients across the disease trajectory. Systematic review data indicate a high prevalence in advanced or terminal disease, substantial symptom burden during active anticancer treatment, and a persistent burden of post-treatment pain among survivors ^[1,3,4]. As cancer survivorship expands, chronic cancer-related and treatment-related pain is becoming an increasingly important component of long-term supportive care.

The burden of cancer pain extends well beyond sensory discomfort. Pain commonly interferes with mobility, sleep, mood, work, social participation, and adherence to cancer treatment, thereby contributing to overall loss of function and diminished quality of life ^[2,19,20]. These broader impacts underscore the need for multidimensional assessment rather than reliance on unidimensional intensity scores alone.

Despite the availability of effective pharmacologic and nonpharmacologic therapies, undertreatment remains common. Contributing factors include inadequate assessment, delayed recognition of structural or neuropathic drivers of pain, fragmented referral pathways, inequitable access to palliative and supportive care services, and clinician hesitation related to opioid prescribing ^[8,9,17,21].

4. Pathophysiology and clinical phenotyping

Effective management of cancer pain depends not only on symptom intensity, but also on identifying the dominant pain mechanism, associated structural drivers, and temporal pattern. In practice, this requires translating pathophysiology into clinically recognizable phenotypes that can inform targeted multimodal treatment. Rather than treating all pain exacerbations as a signal for linear opioid escalation, clinicians should evaluate whether the presentation is primarily nociceptive, neuropathic, mixed, structurally unstable, or temporally episodic ^[5-8].

4.1. Nociceptive syndromes

Nociceptive pain arises from activation of peripheral nociceptors by tissue injury, inflammation, or mechanical distortion. In cancer, this often reflects tumor infiltration, capsular stretch, visceral obstruction, or osseous destruction.

Somatic pain is typically well localized and described as aching, throbbing, or pressure-like. Bone pain is the most prominent somatic phenotype in oncology. Its pathogenesis is multifactorial, involving inflammatory mediators, osteoclast activation, microfracture, structural instability, and mechanical stress ^[6,22,23]. This complexity helps explain why systemic analgesics alone may be insufficient and why disease-

directed therapies, particularly radiotherapy or stabilization procedures, are often necessary components of pain control^[8,12].

Visceral pain is more often diffuse, cramping, squeezing, or poorly localized. It may arise from capsular distension, hollow-organ obstruction, ischemia, or mucosal infiltration^[6,23]. In selected settings, symptom relief depends not only on analgesics but also on treatment of the underlying driver, such as decompression, corticosteroids, or bowel-directed supportive measures.

4.2. Neuropathic syndromes

Neuropathic cancer pain results from injury to the somatosensory nervous system. Common causes include direct tumor invasion of nerves or plexuses, spinal cord or nerve root compression, surgery, radiotherapy, and neurotoxic chemotherapy^[5,6,18,24]. Patients often describe burning, shooting, stabbing, tingling, or electric shock-like pain, sometimes accompanied by numbness, sensory loss, or allodynia^[5,25].

Neuropathic features are clinically important because they are associated with greater functional impairment and may respond incompletely to opioid monotherapy^[5,8]. Their recognition should prompt consideration of adjuvant analgesics and, when clinically indicated, urgent evaluation for reversible structural causes such as nerve root compression or epidural disease^[8,9,26].

4.3. Sensitization and neuroimmune amplification

Persistent nociceptive and neuropathic signaling can drive both peripheral and central sensitization. Tumor cells, immune cells, and injured nerves release cytokines, growth factors, and excitatory neurotransmitters that amplify nociceptive transmission^[6,7,27]. Clinically, this neuroimmune crosstalk may contribute to disproportionate pain severity, widening pain distribution, allodynia, hyperalgesia, and reduced responsiveness to standard analgesic strategies. Recognition of these processes is relevant because it helps explain why some patients with mixed or longstanding pain do poorly with opioid escalation alone and may require a broader multimodal approach.

4.4. Temporal phenotypes: Background vs. breakthrough pain

Temporal pattern is a central component of cancer pain phenotyping. Patients may present with relatively stable background pain, movement-related incident pain, end-of-dose failure, or breakthrough cancer pain (BTcP)^[9,13,14]. These temporal patterns are not interchangeable and distinguishing them is essential for selecting appropriate rescue medication, adjusting baseline regimens, and identifying when disease progression or structural instability should be suspected. End-of-dose failure should not be misclassified as BTcP, because it generally indicates the need to reassess the maintenance opioid regimen rather than simply increase rescue dosing^[9,13].

5. Clinical assessment framework

Comprehensive assessment is the foundation of mechanism-informed cancer pain management. Numerical intensity scores are useful but insufficient in isolation. Evaluation should include pain location, radiation, quality, temporal pattern, precipitating factors, likely mechanism, impact on function, previous analgesic response, and associated psychosocial distress^[8,9,19,20]. A clinically useful assessment also distinguishes pain at rest from pain on movement, as incident pain often reflects structural pathology or instability that may

require more than medication adjustment.

Validated instruments can improve assessment consistency. The Brief Pain Inventory (BPI) captures both pain severity and functional interference ^[19]. The Edmonton Symptom Assessment System (ESAS) situates pain within the broader symptom context, including fatigue, nausea, anxiety, and depression ^[20]. The DN4 questionnaire may assist in identifying neuropathic features, although it should complement rather than replace clinical judgment ^[25].

A critical component of assessment is the identification of oncologic emergencies and other reversible causes of severe pain. New or rapidly worsening back pain, focal neurologic deficits, bladder or bowel dysfunction, or pain associated with suspected mechanical instability should prompt urgent evaluation for malignant spinal cord compression, epidural disease, or pathologic fracture ^[8,26,28,29]. More broadly, clinicians should routinely reassess whether apparent analgesic failure reflects undertreated baseline pain, a new neuropathic or structural pain generator, toxicity from prior treatment, or progressive disease.

6. Comparison of major guideline recommendations

Major professional organizations, including ESMO, NCCN, and ASCO, have issued influential guidance relevant to adult cancer pain management ^[3,8,9,11,18]. These documents share core principles, comprehensive assessment, individualized multimodal treatment, appropriate opioid use, and interdisciplinary care, but differ in emphasis according to target population and intended scope. NCCN provides highly operational clinical algorithms for active cancer pain, ESMO offers a broad pharmacologic and palliative framework, and ASCO has contributed particularly important guidance in survivorship, chemotherapy-induced peripheral neuropathy, and early palliative care integration ^[3,11,18]. **Table 1** summarizes selected cross-guideline themes.

Because these guidelines differ in methodology, update cycle, and clinical scope, they should be interpreted as complementary rather than directly interchangeable documents.

Table 1. Comparison of core cancer pain recommendations from major guidelines

Domain	ESMO (2018) ^[8]	NCCN (Version 2.2024) ^[9]	ASCO (2016, 2020) ^[3,18]
Assessment	Emphasizes detailed history, physical examination, and routine use of validated scales	Highly operational algorithms for comprehensive and urgent assessment	Focuses on survivorship assessment, functional interference, and CIPN
Opioid strategy	Morphine, oxycodone, hydromorphone as first-line for moderate/severe pain; detailed titration rules	Stepwise algorithms for opioid-naïve vs. opioid-tolerant patients	Recommends cautious long-term opioid prescribing for survivors; emphasizes risk assessment
Neuropathic pain	Recommends TCAs and gabapentinoids as adjuvants	Integrates adjuvants early; specific pathways for nerve compression	Strong recommendation for duloxetine in CIPN
Breakthrough pain	Advocates rapid onset transmucosal fentanyl for selected patients	Defines BTcP and end-of-dose failure; guides rescue dosing	Addressed within broader symptom management contexts
Interdisciplinary/ interventional care	Highlights palliative radiotherapy and early referral to pain specialists	Integrates interventional blocks, pumps, and neurosurgical consultation in refractory pathways	Landmark guidance on early integration of palliative care and rehabilitative strategies

Abbreviations: ASCO, American Society of Clinical Oncology; BTcP, breakthrough cancer pain; CIPN, chemotherapy-induced peripheral neuropathy; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; TCA, tricyclic antidepressant.

7. Pharmacologic management

Pharmacologic treatment should be tailored to the pain mechanism, temporal profile, comorbidity burden, organ function, and goals of care. In contemporary practice, analgesic selection is not simply a matter of escalating drug potency; rather, it involves matching the regimen to the dominant pain phenotype while also considering whether disease-directed or interventional treatment is needed to address the underlying pain generator. The quality of evidence varies substantially across analgesic classes and clinical phenotypes, making regular reassessment essential.

7.1. Nonopioid analgesics

Nonopioid agents remain important components of multimodal analgesia. Acetaminophen may provide modest benefit in selected mixed-mechanism syndromes, although its independent analgesic effect in severe cancer pain is weak^[8,30]. NSAIDs are particularly useful in inflammatory and bone-related pain phenotypes, where they may reduce opioid requirements and improve pain on movement. However, gastrointestinal, renal, and cardiovascular toxicities necessitate careful patient selection, especially in older adults and those with frailty, dehydration, thrombocytopenia, or baseline renal dysfunction^[8,30].

Corticosteroids may be helpful in selected situations, including pain related to raised intracranial pressure, nerve compression, capsular distension, or malignant bowel obstruction^[9,31–33]. Their use is generally best viewed as indication-specific and time-limited, given the risks of hyperglycemia, proximal myopathy, delirium, immunosuppression, and mood disturbance.

7.2. Opioids: Balancing access and the opioid crisis

Opioids remain the cornerstone of treatment for moderate to severe cancer pain, particularly when pain is clearly nociceptive or mixed and is causing substantial functional suffering^[8,9,34]. Agent selection, route of administration, and formulation should be individualized according to prior opioid exposure, pain severity, swallowing ability, renal and hepatic function, and the need for rapid titration.

At the same time, contemporary oncology practice must navigate the tension between appropriate opioid stewardship and the risk of undertreatment. Policies developed in response to the broader opioid crisis have, in some settings, created unintended barriers for patients with cancer, including delayed dispensing, prior authorization hurdles, pharmacy denials, and dose-limit restrictions that do not adequately account for cancer-related suffering^[15,17,21]. Clinicians should therefore practice rational opioid stewardship, using risk assessment, prescription monitoring, patient education, and careful follow-up, without allowing regulatory anxiety to normalize undertreatment of severe cancer pain^[8,17,21,34]. Opioid restrictions developed for chronic non-cancer pain should not be indiscriminately applied to patients with active cancer, as undertreatment of severe pain poses a greater immediate clinical risk.

Equally important, opioid dose escalation should not substitute for mechanistic reassessment. Escalating doses in the setting of neuropathic pain, spinal instability, incident bone pain, or opioid-related neurotoxicity may worsen outcomes if the underlying structural or pharmacologic problem is not recognized^[5,12,26,35,36].

7.3. Adjuvant analgesics

Adjuvant analgesics are particularly relevant for neuropathic and mixed-mechanism pain. Among these agents, duloxetine has the strongest direct evidence for painful chemotherapy-induced peripheral neuropathy (CIPN) and is specifically supported by ASCO guidance in that context^[18,37].

By contrast, the evidence base for gabapentinoids in cancer-related neuropathic pain is more limited and heterogeneous than their widespread clinical use might suggest ^[38–40]. Gabapentin and pregabalin may still be reasonable in selected patients, particularly when neuropathic features are prominent, but clinicians should monitor carefully for sedation, dizziness, gait instability, and additive central nervous system toxicity, especially in frail or older adults ^[41]. Tricyclic antidepressants and other adjuvants are also used in practice, although tolerability often limits their role in medically complex oncology populations ^[8,24,40].

For refractory pain, particularly when systemic toxicity limits further escalation, referral for specialist pain or palliative care assessment is appropriate. In carefully selected patients, neuraxial techniques or intrathecal drug delivery may reduce systemic opioid burden and improve analgesia ^[8,24,43].

7.4. Safety monitoring and adverse-effect management

Analgesic therapy should be accompanied by proactive monitoring and prevention of predictable toxicities. Opioid-induced constipation is common and should generally be managed prophylactically with bowel regimens unless contraindicated ^[8,9,34]. Sedation, delirium, cognitive slowing, and impaired balance warrant close surveillance, particularly in older adults, patients with pre-existing cognitive vulnerability, and those receiving concomitant sedatives ^[35,36,41].

Opioid-induced neurotoxicity may present with myoclonus, hallucinations, agitation, or paradoxical hyperalgesia and is often precipitated by dehydration, infection, or accumulation of renally cleared metabolites ^[35,36]. Respiratory depression is rare with appropriate opioid titration for cancer pain, but risk increases with concurrent sedative use, renal impairment, advanced frailty, or rapid dose escalation. Regular reassessment of analgesic benefit relative to toxicity should therefore accompany all opioid prescribing ^[34–36].

Key pharmacologic options for adult cancer pain management, together with representative indications, limitations, and major safety considerations, are summarized in **Table 2**.

Table 2. Representative pharmacologic approaches to adult cancer pain management

Class / Intervention	Representative agents	Typical clinical role	Key cautions/limitations
Nonopioid analgesics	Acetaminophen	Adjunct for mild to moderate mixed-mechanism pain; may modestly support opioid-sparing	Limited independent efficacy in severe cancer pain; dose caution in hepatic impairment
Nonopioid analgesics	NSAIDs	Particularly useful in inflammatory and bone-related pain; may improve pain on movement	Renal, gastrointestinal, cardiovascular, and bleeding risks; caution in frailty, thrombocytopenia, dehydration
Corticosteroids	Dexamethasone, prednisone	Indication-specific use in nerve compression, capsular distension, raised intracranial pressure, malignant bowel obstruction	Hyperglycemia, delirium, proximal myopathy, mood effects, immunosuppression; generally time-limited use
Strong opioids	Morphine, oxycodone, hydromorphone	Mainstay for moderate to severe nociceptive or mixed cancer pain	Sedation, constipation, delirium, respiratory risk, dose escalation without reassessment; metabolite accumulation in renal dysfunction for some agents
Rapid-onset rescue opioids	Transmucosal fentanyl formulations	Selected opioid-tolerant patients with true BTcP characterized by rapid onset and short duration	Requires careful patient selection and education; not appropriate for opioid-naïve patients

Class / Intervention	Representative agents	Typical clinical role	Key cautions/limitations
Short-acting rescue opioids	Immediate-release morphine, oxycodone, hydromorphone	Rescue dosing for episodic pain after optimization of background regimen	Overuse may signal uncontrolled baseline pain, end-of-dose failure, or a new structural pain generator
Adjuvant analgesics for neuropathic pain	Duloxetine	Best-supported option for painful CIPN; may help selected neuropathic phenotypes	Nausea, fatigue, drug interactions; not universally effective for all neuropathic cancer pain
Adjuvant analgesics for neuropathic pain	Gabapentin, pregabalin	Commonly used for neuropathic features or mixed pain	Sedation, dizziness, gait instability, cognitive adverse effects; renal dose adjustment often required
Adjuvant analgesics for neuropathic pain	TCAs	Occasionally used in selected neuropathic syndromes	Anticholinergic effects, orthostasis, arrhythmia risk; often poorly tolerated in older or frail patients
Specialist analgesic strategies	Neuraxial analgesia, intrathecal drug delivery	Refractory pain or systemic toxicity limiting conventional escalation	Requires specialist expertise, careful selection, and procedural resources

Abbreviations: BTcP, breakthrough cancer pain; CIPN, chemotherapy-induced peripheral neuropathy; NSAIDs, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressant.

8. Breakthrough Cancer Pain (BTcP) management

BTcP is typically defined as a transient exacerbation of severe pain occurring despite relatively controlled background pain ^[13,14]. Episodes may be spontaneous or precipitated by predictable triggers such as movement, swallowing, coughing, or procedures. They are often rapid in onset and short in duration, although substantial interpatient variability exists ^[13,14].

Accurate characterization is essential because not all pain flares represent BTcP. Clinicians should distinguish true BTcP from end-of-dose failure, uncontrolled baseline pain, and pain caused by new structural progression ^[9,13]. Apparent “breakthrough” episodes that occur predictably before the next scheduled opioid dose usually indicate inadequate baseline coverage rather than a separate rescue-only phenomenon. Similarly, recurrent movement-evoked flares may signal unstable bone metastases or other treatable mechanical causes.

Once background pain is reasonably optimized, rescue treatment may include short-acting oral opioids or, in appropriately selected opioid-tolerant patients, rapid-onset transmucosal fentanyl formulations ^[9,34]. Choice of rescue agent should be guided by the onset, predictability, and duration of episodes, along with patient-specific factors such as route tolerance, prior opioid exposure, and safety risk.

9. Disease-directed and interventional strategies

Analgesia should not distract from the need to treat the underlying pain generator whenever feasible. In many patients, effective pain control depends on combining pharmacologic treatment with disease-directed or structurally targeted interventions.

Palliative radiotherapy is a key example and should be considered early for painful bone metastases, particularly when pain is localized and attributable to a radiographically defined lesion ^[12,42]. Single-fraction regimens provide meaningful relief for many patients and offer practical advantages in convenience and treatment burden ^[12,42]. Radiotherapy is therefore best understood not as a late salvage option, but as an important analgesic modality in its own right.

Mechanical instability requires urgent recognition. New back pain in the setting of spinal metastases

should prompt assessment for epidural extension, vertebral collapse, or neoplastic instability, with tools such as the Spinal Instability Neoplastic Score helping to structure decision-making ^[26,28]. Depending on neurologic status and structural findings, patients may require urgent imaging, corticosteroids, surgical consultation, decompression, or stabilization ^[26,28,29].

Selected interventional procedures can also provide meaningful opioid-sparing benefits. For example, celiac plexus neurolysis may reduce pain burden in pancreatic cancer, while neuraxial or intrathecal approaches may be appropriate in refractory cases managed by experienced teams ^[24,43,44].

10. Nonpharmacologic and supportive interventions

Nonpharmacologic approaches should be viewed as integral components of comprehensive cancer pain care rather than optional adjuncts reserved for refractory cases. Their greatest value often lies in reducing pain interference, improving coping, restoring function, and addressing the psychological and behavioral dimensions of suffering.

10.1. Rehabilitation and physical therapy

Rehabilitation remains underused in cancer pain management. Physical therapy, graded activity, gait training, mobility aids, and targeted exercise can reduce pain interference and improve function, particularly in patients with deconditioning, altered biomechanics after surgery, lymphedema, postural instability, or chronic post-treatment pain syndromes ^[3,4]. In survivorship settings, rehabilitation is especially important because the therapeutic goal often shifts from short-term symptom suppression to long-term functional restoration.

10.2. Psychological interventions

Pain and psychological distress are bidirectionally reinforcing. Cognitive behavioral therapy, coping-skills training, relaxation techniques, and other psychologically informed interventions may help reduce distress, catastrophizing, sleep disruption, and pain-related interference ^[2,4]. These approaches are best understood as adjunctive rather than substitutive therapies: they do not replace pharmacologic treatment for severe nociceptive pain, but they can substantially improve the overall experience and manageability of cancer-related suffering.

10.3. Integrative therapies

Selected integrative therapies may serve as safe adjuncts within an evidence-based supportive care framework. Acupuncture, for example, has shown potential benefit for some cancer-related pain symptoms and treatment-related arthralgias, although effect sizes and study quality remain variable across populations and indications ^[45]. Such interventions may be most useful when integrated into a broader multimodal plan rather than presented as stand-alone alternatives to established analgesic care.

10.4. Early palliative care integration

Early integration of palliative care improves symptom control, communication, care planning, and quality of life ^[10,11]. In the context of cancer pain, palliative care can facilitate opioid titration, management of complex adverse effects, clarification of goals of care, and coordination with radiation oncology, pain medicine, rehabilitation, and psychosocial services. Importantly, palliative care should be delivered alongside active

oncologic treatment when needed and should not be reserved for the final stages of life ^[10,11].

Major nonpharmacologic, supportive, and interdisciplinary strategies that complement pharmacologic treatment are summarized in **Table 3**.

Table 3. Nonpharmacologic, supportive, and interdisciplinary strategies in adult cancer pain management

Strategy	Representative components	Main clinical objectives	Typical settings/comments
Rehabilitation and physical therapy	Graded activity, strength and balance training, gait training, mobility aids, posture optimization	Reduce pain interference, improve mobility and function, decrease fall risk, support survivorship recovery	Especially useful in deconditioning, altered biomechanics, chronic post-treatment pain, and lymphedema-associated functional limitation
Psychological interventions	Cognitive behavioral therapy, coping-skills training, relaxation, sleep-focused support	Reduce distress, catastrophizing, insomnia, and pain-related disability; improve coping and self-efficacy	Best used as adjuncts within multimodal care rather than substitutes for analgesia in severe nociceptive pain
Integrative therapies	Acupuncture, mind-body interventions, selected supportive complementary therapies	Adjunctive symptom relief, improved coping, reduction in pain-related burden	Evidence varies by indication; best integrated into evidence-based supportive oncology programs
Early palliative care integration	Symptom management, goals-of-care discussions, care coordination, caregiver support	Improve symptom control, communication, treatment alignment, and quality of life	Should occur alongside active oncologic care when indicated, not only at end of life
Palliative radiotherapy	Single-fraction or multifraction radiotherapy for painful lesions	Treat underlying pain generator, especially bone metastasis-related pain; reduce analgesic burden	Should be considered early when pain is localized to a treatable lesion
Interventional pain procedures	Celiac plexus neurolysis, nerve blocks, neuraxial techniques, intrathecal systems	Opioid-sparing analgesia, refractory pain control, targeted treatment of specific syndromes	Requires expertise and careful patient selection
Multidisciplinary supportive care	Coordination among oncology, palliative care, pain medicine, rehabilitation, nursing, and psychosocial teams	Improve comprehensive assessment, streamline referral, and address complex physical and psychosocial contributors	Particularly important in refractory pain, frailty, survivorship, and high symptom burden

11. Special populations

11.1. Older adults

Pain management in older adults with cancer is particularly complex because frailty, polypharmacy, renal decline, sensory impairment, cognitive vulnerability, and fall risk amplify the harms of standard analgesic regimens ^[30,35,41]. At the same time, undertreated pain contributes to immobility, delirium, sleep disruption, and loss of independence. Management requires cautious titration, close monitoring for adverse effects, frequent medication review, and active involvement of caregivers when appropriate ^[41]. A “start low, go slow” approach is often prudent, but should not be misapplied as a rationale for persistent undertreatment.

11.2. Cancer survivors

Long-term survivors represent a distinct cancer pain population with needs that differ from those of patients with advanced progressive disease. Common syndromes include chemotherapy-induced peripheral neuropathy, persistent postsurgical pain, musculoskeletal dysfunction, and radiation-related fibrosis ^[3,4,7,18].

These pain states often persist long after curative-intent treatment has ended and may be associated with substantial functional limitation.

Management in survivorship should prioritize functional restoration, rehabilitation, psychosocial support, and mechanism-based nonopioid or adjuvant therapy^[3,4]. Although opioids may still be appropriate in selected cases, long-term opioid therapy warrants particular caution in this population because the balance of benefit, tolerance, dependence risk, and functional goals differs from that in advanced cancer care^[3,21,17]. When opioids are used, treatment plans should include clear functional targets, review intervals, and consideration of tapering or exit strategies.

Persistent pain in cancer survivors is increasingly recognized as a longterm functional issue rather than a transient symptom. These chronic syndromes often require prolonged rehabilitation, mechanismbased nonopioid analgesia, and adjuvant therapy rather than repeated opioid escalation. Prioritizing functional recovery, mobility, and longterm tolerability helps align pain management with the unique needs of survivorship, balancing effective relief with safety and quality of life.

11.3. Patients with renal dysfunction and clinical frailty

Renal dysfunction and frailty substantially complicate analgesic prescribing. Accumulation of active opioid metabolites may increase the risk of sedation, delirium, myoclonus, and neurotoxicity, particularly in dehydrated or cachectic patients^[35,36]. NSAID use may also be limited by renal vulnerability, gastrointestinal risk, or thrombocytopenia. In such settings, analgesic choice should be individualized, doses adjusted conservatively, and reassessment performed frequently, especially during acute illness or rapid clinical decline.

12. Implementation barriers and global equity

Global inequities further compound these implementation challenges across resourcelimited and resourceabundant settings alike. Persistent failures in cancer pain control are increasingly systemic rather than purely pharmacologic. Common barriers include fragmented care pathways, inconsistent pain assessment in routine oncology visits, delayed referral to palliative care or pain specialists, limited access to rehabilitation and psychosocial services, and insufficient recognition of oncologic emergencies or treatable structural pain syndromes^[8,11,15-17]. In some settings, payer restrictions and pharmacy-level barriers further delay timely access to appropriate opioid therapy or adjuvant medications^[21,17].

At a global level, disparities are even more profound. In many low- and middle-income countries, patients still lack reliable access to oral morphine, palliative radiotherapy, trained clinicians, and basic supportive infrastructure^[12,15]. These gaps are not merely technical shortcomings; they represent major inequities in health systems and in the distribution of relief from suffering. Addressing them will require policy reform, opioid availability safeguards, workforce training, radiotherapy capacity, and incorporation of symptom relief into universal health coverage agendas^[15].

13. Future directions

Future progress in cancer pain care will depend not only on new analgesics but also on better translation of mechanism-based science into clinically useful treatment pathways. Phenotype-enriched trials are needed

to determine which patients benefit most from specific adjuvant agents, early radiotherapy, interventional procedures, or combination strategies^[5-7,23,27]. In parallel, pragmatic studies should evaluate whether earlier multidisciplinary intervention improves outcomes compared with conventional stepwise analgesic escalation.

Digital symptom monitoring and electronic patient-reported outcomes (ePROs) also offer important opportunities to detect pain deterioration earlier, identify rescue-medication overuse, and trigger timely evaluation for structural emergencies or uncontrolled symptoms between clinic visits^[16]. Finally, implementation science will be essential: advances in evidence generation will have limited impact unless health systems can reliably deliver guideline-concordant, equitable, and timely pain care^[15-17].

14. Conclusions

Cancer pain is a heterogeneous clinical syndrome that cannot be managed adequately through intensity-based analgesic escalation alone. Contemporary care requires multidimensional assessment, recognition of pain mechanisms and temporal phenotypes, timely identification of structural emergencies, and integration of pharmacologic, disease-directed, interventional, rehabilitative, and psychosocial strategies. Opioids remain essential for many patients, but their use should be embedded within a broader framework of mechanism-informed, reassessed, and function-conscious care. The major challenge in modern cancer pain management is increasingly one of implementation: translating existing evidence and guideline principles into timely, equitable, and multidisciplinary clinical practice across the cancer continuum.

15. Clinical practice points

- (1) Use routine multidimensional assessment rather than pain intensity scores alone; include functional interference, temporal pattern, analgesic response, and psychosocial distress.
- (2) Differentiate nociceptive, neuropathic, mixed, and temporal pain phenotypes, as this distinction often determines whether opioid escalation, adjuvant therapy, imaging, radiotherapy, or procedural referral is most appropriate.
- (3) Consider disease-directed interventions early, especially for painful bone metastases, mechanical instability, nerve compression, or other identifiable structural pain generators.
- (4) Distinguish true breakthrough cancer pain from end-of-dose failure and uncontrolled background pain before intensifying rescue opioid prescribing.
- (5) Practice opioid stewardship without normalizing undertreatment; cancer-specific clinical context should remain central when balancing access, safety, and regulatory requirements.
- (6) In survivorship, emphasize functional restoration, rehabilitation, and mechanism-based long-term management rather than default continuation of opioid escalation strategies used in advanced disease.
- (7) Monitor proactively for constipation, sedation, delirium, neurotoxicity, gait instability, and respiratory risk, particularly in older adults and patients with renal dysfunction or frailty.

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A Review of Research Progress and Challenges in Deep Learning for Magnetic Resonance Imaging in the Diagnosis and Treatment of Prostate Cancer

Xiao Yuan*

School of Gongli Hospital Medical Technology, University of Shanghai for Science and Technology, Shanghai 200093, China

*Corresponding author: Xiao Yuan, 18909192891@163.com

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Abstract: Prostate cancer is a highly prevalent malignant tumor among men worldwide, and its precise diagnosis and treatment are crucial for improving patient prognosis. Multiparametric magnetic resonance imaging, as a core imaging modality, is widely used in clinical practice. In recent years, breakthroughs in deep learning technology have provided powerful tools for the intelligent analysis of MRI images, promoting the development of automated and precise diagnosis and treatment for prostate cancer. This article aims to systematically review the current applications of deep learning in the field of prostate cancer MRI, covering key directions such as lesion detection and segmentation, diagnosis and grading, prognosis prediction, and imaging genomics correlation. The article provides an in-depth analysis of current mainstream models, the challenges related to data and validation, and offers insights into future trends, with the goal of providing references for related research and clinical practice.

Keywords: Prostate cancer; Magnetic resonance imaging; Deep learning; Computer-aided diagnosis

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1. Introduction

Prostate cancer (PCa) is a malignant tumor with a high incidence among men globally, and its precise diagnosis and treatment heavily rely on imaging evaluation. Multiparametric magnetic resonance imaging (mpMRI), with its excellent soft tissue resolution and ability to fuse multi-sequence information, has become a core tool for the detection, localization, and risk stratification of prostate cancer. It can effectively identify clinically significant cancer foci (csPCa) and help many patients avoid unnecessary biopsy^[1]. However, the traditional interpretation of prostate mpMRI faces significant challenges. Its assessment is highly dependent

on the subjective experience of radiologists, leading to substantial inter-observer and intra-observer variability in interpretation. Moreover, analyzing vast amounts of imaging data is time-consuming and labor-intensive, increasing the clinical workload. Additionally, although mpMRI has a high negative predictive value, it still has a false-negative rate of approximately 15–20%, potentially missing some aggressive tumors. These limitations have driven the clinical search for more objective, efficient, and reproducible analysis methods ^[2].

Artificial intelligence (AI), particularly its important branch, deep learning (DL), provides a new tool for prostate cancer MRI analysis. Deep learning models can automatically learn complex feature patterns from large-scale, high-quality annotated medical imaging data that are difficult for the human eye to recognize. Compared to traditional machine learning methods, deep learning does not require manual feature design; instead, it extracts abstract representations directly from raw pixel data through multi-layer neural network architectures, demonstrating superior performance in image segmentation, classification, and prediction tasks ^[3]. Specifically in the field of prostate cancer, deep learning technology has been widely applied to several key aspects. In image segmentation, models based on U-Net and its variants can achieve automatic or semi-automatic delineation of the prostate gland, zones (such as the peripheral zone and transition zone), and suspicious lesions, laying the foundation for subsequent quantitative analysis ^[4]. One study used the SegNet model, combined with T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) maps, to achieve automatic segmentation of prostate zones and cancerous areas. In lesion detection and qualitative diagnosis, deep learning architectures such as convolutional neural networks (CNN) can distinguish between benign and cancerous tissues and further differentiate between clinically insignificant and significant prostate cancer ^[5]. Their diagnostic performance has shown potential comparable to or even superior to that of experienced genitourinary radiologists in multiple studies. One study developed the FocalNet algorithm, which showed no statistically significant difference in sensitivity compared to a group of genitourinary radiologists in detecting clinically significant index lesions ^[6]. Furthermore, some studies have indicated that deep learning models based on biparametric MRI (bpMRI) can achieve diagnostic accuracy comparable to standard mpMRI, providing greater assistance to less experienced physicians ^[7]. In the field of prognosis assessment, deep learning models, by integrating MRI imaging features with clinical data (such as PSA, age), have demonstrated potential in predicting biochemical recurrence, pathological stage, and even the risk of progression to castration-resistant prostate cancer (CRPC). ^[8] These applications suggest that deep learning not only holds promise for improving the objectivity and efficiency of diagnosis, reducing human variability, but may also advance prostate cancer diagnosis and treatment toward a more precise, individualized model ^[9]. This review will systematically outline the full landscape of deep learning applications in prostate cancer MRI, delving into specific application scenarios, current challenges, and future development directions, aiming to provide references for research and clinical practice in this field.

2. Research progress in deep learning for prostate cancer detection, segmentation, and localization

2.1. Automatic segmentation of the prostate gland and zones

Accurate segmentation of the entire prostate gland is the foundation for subsequent analysis, and deep learning models (especially the U-Net series) have achieved near-expert-level accuracy in this task. Studies

have shown that models based on the U-Net architecture can efficiently segment the glandular region from prostate magnetic resonance imaging (MRI), with performance metrics such as the Dice similarity coefficient (DSC) generally showing excellent results. One study developed a model based on an attention-guided U-Net for prostate region segmentation in biparametric MRI (bpMRI) images, achieving a DSC of 0.82^[10]. Another study focusing on diffusion-weighted imaging (DWI) apparent diffusion coefficient (ADC) maps also confirmed that the U-Net model has high accuracy in prostate cancer lesion segmentation, with internal and external validation Dice scores reaching 0.822 and 0.7776, respectively^[11]. These achievements provide a reliable anatomical basis for subsequent lesion detection and risk stratification.

2.2. Detection and segmentation of clinically significant prostate cancer lesions

Distinguishing between “clinically significant” and “insignificant” cancer is a core clinical need. Deep learning models, through end-to-end training, can directly detect and delineate suspected lesions from MRI, and their performance is relatively good for lesions with a PI-RADS score ≥ 3 . Multiple studies have confirmed the potential of deep learning in this task. For example, a cascaded deep learning algorithm based on biparametric MRI (bpMRI) demonstrated performance comparable to that of experienced radiologists in detecting suspicious cancerous lesions and could reliably predict biopsy-confirmed clinically significant prostate cancer (csPCa). Another study developed a diagnostic support system based on a 3D deep convolutional neural network (3DCNN) for identifying high-grade prostate cancer, achieving a sensitivity and area under the curve (AUC) of 85% and 0.82, respectively^[12]. By learning complex patterns in images, these models can effectively distinguish significant cancer foci requiring clinical intervention from indolent lesions.

Recent advances include the development of weakly supervised or semi-supervised learning models to reduce reliance on pixel-level fine annotations, and the development of uncertainty estimation modules to provide confidence levels for model predictions, assisting physicians in decision-making. Acquiring large amounts of pixel-level annotated medical images is time-consuming and expensive, making weakly supervised or semi-supervised learning a research hotspot. One study proposed a dual-modal model that combines imaging data and clinical data (such as PSA level, prostate volume, and age). This model not only improved diagnostic performance (AUC reaching 0.82) but also introduced uncertainty analysis, enabling the identification of high-confidence predictions, thereby enhancing the reliability of automated medical decisions^[13]. Furthermore, the development of explainable artificial intelligence (XAI) models is crucial. They can provide visual and textual explanations for classification decisions using PI-RADS features, improving model transparency and clinical doctors’ trust, especially aiding non-expert doctors in assessing PI-RADS category 3 lesions^[14].

Although deep learning models excel in detecting typical peripheral zone lesions, their sensitivity still needs improvement for some challenging cases. Multifocal cancer foci may be missed due to small size or atypical signal, and cancer foci located in the anterior fibromuscular stroma or transition zone are more difficult to detect due to their special anatomical location and potential signal overlap with benign hyperplastic tissue. To address these challenges, future research trends involve developing multimodal fusion models that not only integrate multi-sequence MRI information (such as T2WI, DWI, and dynamic contrast-enhanced) but also incorporate clinical parameters (such as PSA density), pathological information, and even genomic data into the analysis framework to build more comprehensive and precise personalized diagnostic

and risk assessment systems.

3. Application of deep learning in prostate cancer diagnosis, grading, and risk stratification

3.1. Cancer vs. non-cancer classification and Gleason score prediction based on MRI

Deep learning models can directly perform automatic classification on multiparametric magnetic resonance imaging (mpMRI) images or segmented lesion regions to predict their probability of malignancy. Studies have shown that deep learning algorithms such as convolutional neural networks (CNNs) demonstrate significant advantages in distinguishing between benign and malignant prostate lesions. A systematic review noted that the median area under the receiver operating characteristic curve (AUC) for machine learning or deep learning models used to distinguish significant from insignificant prostate cancer could reach 0.79 (interquartile range: 0.77-0.87) ^[15]. Another study, an interpretable machine learning model based on multiparametric MRI radiomics (with the random forest model performing the best), was developed and externally validated. This model can effectively distinguish between benign and malignant prostate masses preoperatively, and its clinical interpretability was enhanced through the SHAP method ^[16].

3.2. Prognosis prediction and biochemical recurrence risk assessment

Imaging features extracted by deep learning are not only useful for diagnosis but also show value in predicting disease progression and recurrence risk in prostate cancer. These features can be used to predict the risk of disease progression during active surveillance, the risk of biochemical recurrence after radical treatment (such as radical prostatectomy), and the probability of distant metastasis ^[17]. One study applied deep learning algorithms such as CNN-BiLSTM to establish a biochemical recurrence prediction model based on various clinical information from patients after radical prostatectomy, achieving an accuracy of 76.7%. By integrating pre-treatment MRI image features and clinical information, the model can output individualized risk scores, thereby assisting clinicians in formulating more precise treatment strategies. Survival analysis models have also been used to establish associations between imaging features and patient recurrence-free survival. One study utilized deep learning algorithms for multimodal fusion analysis of clinical and imaging data from prostate cancer patients to promote precise prognosis assessment ^[18]. However, the results of these prediction models still require rigorous validation in prospective, large-scale clinical cohorts to confirm their general applicability and clinical utility. Furthermore, fusion models combining clinical information, radiomics features, and deep learning features have been shown to further improve predictive performance. One study constructed a clinical-radiomics-deep learning joint model for diagnosing clinically significant prostate cancer, achieving an AUC of 0.91, which outperformed single models or PI-RADS scores from senior physicians ^[19]. In predicting bone metastasis, a joint model constructed based on clinical, MRI radiomics, and deep learning also demonstrated excellent predictive ability ^[17].

4. Challenges and limitations analysis

High-quality, large-scale, multi-center annotated datasets are a key bottleneck for the development of deep learning models in prostate cancer diagnosis and treatment. The training and validation of models heavily depend on precise annotations using pathological results as the gold standard. However, obtaining such

annotations faces multiple challenges. Additionally, medical data privacy protection regulations are extremely strict, greatly limiting the centralized sharing and integration of data between different institutions, making it difficult to build large-scale, diverse datasets ^[20].

The inherent “black box” nature of deep learning models is a major obstacle to their widespread clinical acceptance ^[21]. To enhance model interpretability, current research is focusing on developing and applying various visualization techniques, such as class activation maps (CAM) and gradient-weighted class activation mapping (Grad-CAM). These techniques can intuitively display the image regions that the model focuses on for decision-making, thereby linking the model’s “attention” to the visual assessment of radiologists ^[22]. However, merely improving diagnostic metrics (such as sensitivity and specificity) is insufficient to prove the clinical value of a model. Models must undergo rigorous external validation and prospective clinical trials to demonstrate that they can genuinely improve clinical endpoints. Only when the interpretability of models is enhanced and their clinical utility is confirmed by high-level evidence, can deep learning truly integrate into and revolutionize the prostate cancer diagnosis and treatment workflow.

5. Future directions: Multimodal fusion and clinical translation prospects

5.1. Deep learning multimodal integration

Deeply integrating deep learning with radiomics and genomics is an important future direction to build more powerful predictive models and achieve non-invasive molecular subtyping. “Deep radiomics” represents this trend, combining deep features automatically extracted by deep learning with traditional handcrafted radiomics features to more comprehensively assess tumor heterogeneity and aggressiveness. In imaging genomics, deep learning holds promise for bridging the gap between MRI manifestations and key genomic features. Although current literature has limited studies directly linking MRI to specific gene states, some research has indirectly explored the connection between imaging and tumor biological behavior by analyzing the correlation between MRI features and tumor aggressiveness ^[23]. In the future, using deep learning to mine deep features from multiparametric MRI and correlating them with genomic data will provide a powerful tool for achieving non-invasive molecular subtyping and individualized treatment of prostate cancer.

5.2. Clinical decision support systems

The future success of deep learning models lies in their integration with existing clinical workflows and the development of decision support capabilities. An ideal clinical support system should automatically analyze images after scanning and present the analysis results to radiologists in real-time in the form of standardized reports or intuitive heatmap overlays, assisting in diagnosis. One study has already developed a deep learning-based multiparametric MRI artificial intelligence analysis system that can quickly provide diagnostic results. When combined with PET imaging, it can significantly improve the sensitivity and accuracy of prostate cancer diagnosis. This indicates that AI-assisted systems have the potential to enhance clinical diagnostic efficiency. On the other hand, developing AI navigation systems for ultrasound-MRI fusion targeted biopsy is another key direction. Such systems use deep learning algorithms to achieve real-time, precise registration of MRI and ultrasound images, thereby guiding the biopsy needle accurately to suspicious lesions identified on MRI, significantly improving biopsy precision and positive rate ^[24]. Research has confirmed that combining PSMA PET/CT with multiparametric MRI image fusion technology can more

precisely locate tumors and guide biopsy, thereby improving diagnostic accuracy. In the future, such real-time navigation systems will make targeted biopsy for small or difficult lesions more reliable, reduce unnecessary repeat biopsies, and optimize clinical decision-making pathways.

6. Conclusion

The application of deep learning in the field of prostate cancer MRI analysis marks a new era in imaging diagnosis, driven by data and intelligence. From automatic segmentation to prognosis prediction, existing technologies have demonstrated their potential to assist, and in some specific tasks, even match expert interpretation. Current research trends clearly point towards two directions of deep integration: first, model architectures themselves are evolving from performing isolated single tasks to integrated multi-task, end-to-end comprehensive systems that combine segmentation, detection, diagnosis, and prediction, aiming to simulate the comprehensive decision-making process of clinicians; second, integration with multi-omics data such as radiomics and genomics, which goes beyond merely improving diagnostic accuracy and strives to uncover the deep biological characteristics reflected by imaging features, such as the tumor microenvironment and gene expression profiles, laying the foundation for achieving true precision medicine.

However, transitioning from excellent research results to widespread clinical routine application involves challenges that must be carefully addressed. Data heterogeneity and annotation bottlenecks are fundamental obstacles limiting model generalization. Differences in data generated by different centers, scanning equipment, and protocols, as well as the significant reliance on expert time and effort for high-quality annotation, all test the robustness of models. More critically, many high-performance deep learning models are considered “black boxes,” lacking intuitive explanations for their decision logic, which is a major concern in clinical practice that emphasizes diagnostic reasoning and doctor-patient communication. Furthermore, the vast majority of current evidence comes from retrospective studies, lacking prospective, multi-center randomized controlled trials to confirm whether these tools can genuinely improve key clinical endpoints for patients (such as survival rate, quality of life), which is the final pass for clinical translation.

Looking ahead, the healthy development of this field requires a balance between technological innovation and clinical validation. Building large-scale, standardized, high-quality multi-center collaborative datasets is the cornerstone, requiring industry consensus, standardized acquisition protocols, and potentially new paradigms like weak supervision or self-supervised learning to break through annotation bottlenecks. Moreover, algorithm development must balance performance with interpretability. Integrating attention mechanisms and explainable artificial intelligence (XAI) techniques into model design, making the AI decision-making process transparent and traceable for doctors, is essential to establishing solid clinical trust. Additionally, all technological pathways must be validated through rigorous clinical trials, using evidence-based medicine to assess their clinical utility, cost-effectiveness, and impact on existing workflows.

In summary, deep learning is not intended to replace radiologists but to evolve into a powerful intelligent assistant. By integrating multi-source information, quantifying imaging features, reducing inter-observer variability, and providing objective decision support, it holds the potential to free doctors from heavy repetitive tasks, allowing them to focus more on complex decision-making, patient communication, and the formulation of personalized treatment plans. The future prostate cancer diagnosis and treatment system will be a synergistic system deeply integrating physician experience with artificial intelligence computational

capabilities, jointly advancing the goal of more precise, efficient, and personalized disease management.

Disclosure statement

The author declares no conflict of interest.

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Transcriptional Repression of SP1 by FOXA3 Suppresses Pancreatic Cancer Cell Proliferation and Migration

Bingjie Xu*

School of Gongli Hospital Medical Technology, University of Shanghai for Science and Technology, Shanghai 200093, China

**Author to whom correspondence should be addressed.*

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Abstract: *Objectives:* Transcriptional Repression of SP1 by FOXA3 Suppresses Pancreatic Cancer Cell Proliferation and Migration. *Methods:* Using overexpression and RNAi (RNAi) techniques, the expression levels of SP1 and FOXA3 in pancreatic cancer cells were adjusted, respectively. Cell proliferation and migration abilities were assessed by CCK - 8 proliferation assay and wound healing assay. The regulatory relationship between SP1 and FOXA3 expression was confirmed by Western blot analysis. *Results:* Functional assays showed that knockdown of SP1 significantly suppressed the proliferation and migration abilities of pancreatic cancer cells, indicating an oncogenic role of SP1 in pancreatic cancer. Mechanistic studies further demonstrated that overexpression of FOXA3 markedly downregulated the protein expression level of SP1. *Conclusion:* By transcriptionally suppressing SP1 expression, FOXA3 prevents the malignant progression of pancreatic cancer and attenuates SP1- mediated promotion of tumor cell proliferation and migration. Targeting the FOXA3/SP1 regulatory axis may offer a novel therapeutic approach for pancreatic cancer treatment.

Keywords: SP1; FOXA3; Proliferation; Migration

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1. Introduction

Pancreatic cancer is one of the most deadly cancers of the digestive system, with a steadily increasing incidence worldwide ^[1]. Due to its insidious early symptoms and lack of specific biomarkers, the majority of patients are diagnosed at locally advanced stages or with distant metastases, missing the opportunity for curative surgical resection ^[2]. Although some progress has been made in recent years in chemotherapy (e.g., agents targeting KRAS G12C, NTRK, MSI-H), Pancreatic cancer typically presents primary or acquired resistance to existing treatment modalities ^[3-5]. The 5-year survival rate remains stagnant at approximately 10%, indicating a very poor prognosis ^[6]. The high invasiveness of pancreatic cancer, Various desmoplastic

stromal reactions. Additionally, the uniquely immunosuppressive tumor microenvironment represents critical pathological features contributing to its aggressive progression and therapeutic resistance ^[7]. Therefore, in-depth explanation of important molecular events during pancreatic carcinogenesis and progression, and clarification of the transcriptional regulatory networks underlying proliferation, migration, and drug resistance, holds important theoretical, clinical and hypothetical value for finding new diagnostic biomarkers and efficient therapeutic targets.

SP1 (Specificity Protein 1), as a crucial transcription factor, plays a multifaceted regulatory role in the occurrence, progression, metastasis, metabolic reprogramming, and therapeutic resistance of various cancers. In terms of boosting tumor proliferation and progression, in hepatocellular carcinoma (HCC), SP1 mediates the regulation of LOXL2 by ZRANB1. Overexpression of SP1 reverses the suppression of growth and metastasis caused by ZRANB1 knockdown. Mechanistically, ZRANB1 directly binds to SP1 and stabilizes its protein level through deubiquitination ^[8]. In cisplatin-resistant colon adenocarcinoma cells, SP1 and GOLPH3 are co-overexpressed; knockdown of SP1 upregulates NDRG1, inhibits cell proliferation, promotes apoptosis, and improves chemosensitivity ^[9]. In regulating epithelial - mesenchymal transition (EMT) and metastasis, pan - cancer analysis confirms SP1 as a major driver of metastasis, promoting cancer cell survival, invasive growth, and metastatic colonization in multiple cancer types ^[10]. In prostate cancer, SP1 has been identified as a key regulator of EMT: its overexpression promotes EMT in vitro and boosts the invasive capacity of PC3 cells ^[11], but in vivo studies demonstrate that it inhibits lung metastasis, suggesting a microenvironment - dependent role. In lung cancer, SP1 functions as a downstream target of the Hippo - TEAD1 pathway and directly binds to the EHD1 promoter to promote its expression ^[12]. Clinical samples demonstrate significantly higher EHD1 expression in tissues from patients with metastatic lung adenocarcinoma. However, the mechanistic role of SP1 in pancreatic cancer remains unclear.

SP1 is aberrantly expressed in pancreatic cancer, according to our research. Additionally, we discovered a new mechanism controlling SP1, which was validated by preliminary validation of the upstream regulators of SP1 and the effects of knockdown of SP1 on tumor function in vitro.

2. Materials and methods

2.1. Cell lines

The Chinese Academy of Sciences' Shanghai Cell Bank provided the human pancreatic cancer cell lines HPNE, MIA PaCa - 2, and PANC - 1. These cells were kept in DMEM medium (Shanghai Yuanpei Biotechnology Co., Ltd.) supplemented with 10% fetal bovine serum (Wuhan Servicebio Technology Co., Ltd.), LTD (Ltd), and 5%100 penicillin (streptomycin), amphotericin B (Wuhan Servicebio Technology Co.), and 5%100 penicillin. In an incubator with 5% CO₂, MIA PaCa - 2 and PANC - 1 cells were cultivated at 37 °C and kept as monolayer cultures. Cells were subjected to experiments at roughly 70–80% of the influence.

2.2. Cellular RNA extraction

2.2.1. Lysis of adherent cells

- (1) Aspirate the culture medium from the dish and wash the cells once with 1× PBS buffer.
- (2) Remove the PBS buffer, then add 500 μL of Buffer QLS lysis solution to no more than 1.0×10⁷ cultured cells. Gently shake the culture dish to ensure the lysis solution is evenly distributed across the cell surface.

- (3) Repeatedly pipette to separate the cells, then transfer the complete cell lysate to a centrifuge tube.
- (4) Vortex vigorously or pipette repeatedly for 30 seconds to 2 minutes, until the lysate becomes clear and non-viscous. (Note: Generally, for complete lysis, vigorous vortexing or repeated pipetting for 30 seconds to 2 minutes is sufficient. If the sample stays viscous, the lysis time can be suitably increased.)
- (5) Let the lysate stand at room temperature for 2 minutes.

2.2.2. Purification steps

- (1) Add a 100% ethanol to the lysate mentioned above and mix it by pipetting. If the precipitate or viscous material is visible, the pipette will be repeated several times to break up the precipitate. (Note: The Quick RNA Mini Columns may be clogged by the inability to break up the precipitate, which could impact yield and purity.)
- (2) Immediately transfer the entire mixture to a Quick RNA Mini Column. Centrifuge at 12,000 rpm for 2 minutes at room temperature, then discard the flow-through.
- (3) Add 700 μ L of Buffer QWB to the Quick RNA Mini Column. Centrifuge at 12,000 rpm for 1 minute at room temperature, and discard the flow-through. (Note: Ensure that 100% ethanol has been added to Buffer QWB in the specified volume.)
- (4) Place the Quick RNA Mini Column into a new 2.0 ml Collection Tube and centrifuge at 12,000 rpm for 2 minutes at room temperature.
- (5) Transfer the Quick RNA Mini Column to a new RNase-Free Tube. Add 30 μ L to 200 μ L of RNase-Free Water to the center of the column membrane. Allow it to stand at room temperature for 3 minutes, then centrifuge at 12,000 rpm for 2 minutes at room temperature to elute the RNA. Store the eluted RNA at -80°C.

2.3. Reverse Transcription PCR

The extracted RNA was removed from the -80°C freezer. After thawing, 1 μ L of RNA was placed in a spectrophotometer to measure its concentration. Based on the concentration, the necessary volume was determined. For each sample, 3000 ng of RNA was taken, mixed with 2 μ g of random primers, and DEPC-treated water was added to a final volume of 35 μ L. A standard PCR device was used to heat the mixture for five minutes at 70 degrees Celsius. During this period, a 15 μ L reaction mixture was made, containing 10 μ L M - MLV buffer, 2 μ L 4 dNTPs, 2 μ L M - MLV reverse transcriptase, and 1 μ L RNase inhibitor per sample, for a total volume of 15 μ L. After the heating step, the 15 μ L mixture was added to each sample, followed by incubation at 37 C for 60 minutes and then at 70°C for 10 minutes. Following reverse transcription, the resulting cDNA was stored in a -20°C freezer.

2.4. Real-time quantitative PCR (qPCR)

- (1) Preparation of the qPCR reaction mixture: For each sample, take 1 μ L of cDNA, then add 5 μ L of SYBR Green, 3 μ L of double-distilled water, and 1 μ L of primers. After mixing, centrifuge the mixture in a balanced centrifuge at 1000 rpm for 1 minute.
- (2) qPCR program: 10 minutes of dehydration at 95°C, followed by 40 amplification cycles: 15 seconds at 95°C, 30 seconds at 60°C, and 35 seconds at 72°C. A final extension step is performed at 72°C for 10 minutes.

(3) Three replicate wells were set up for each group, and the CT value difference within each group did not exceed 1. If the difference exceeded 1, the experiment was repeated.

(4) Calculation:

$\Delta\text{CT} = \text{CT value of target gene} - \text{CT value of internal control}$

$\Delta\Delta\text{CT} = \Delta\text{CT value of experimental group} - \Delta\text{CT value of control group}$

Finally, $2^{-\Delta\Delta\text{CT}}$ is obtained.

(5) Interpretation:

If $2^{-\Delta\Delta\text{CT}}$ is greater than 1, it indicates that the expression level of the target gene in the experimental group is increased compared with the control group.

If $2^{-\Delta\Delta\text{CT}}$ is less than 1, it indicates that the expression level of the target gene in the experimental group is decreased compared with the control group.

2.5. Plasmid transfection

For plasmid transfection, small interfering RNA (siRNA) targeting Sp1 and overexpression RNA (oe-RNA) targeting FOXA3 were obtained from Shanghai Genechem Co., Ltd. (Shanghai, China). Cells were seeded in appropriate culture plates and allowed to reach the optimal confluence for transfection according to the manufacturer's recommendations. Transfection was performed using the siRNA transfection reagent jetPRIME (Polyplus Transfection, France) following the supplier's protocol. Briefly, the siRNA or oeRNA was mixed with the jetPRIME reagent and added dropwise to the cells. The transfected cells were then incubated under standard culture conditions for 24 hours before subsequent experiments.

2.6. Western blot

2.6.1. Sample preparation

Total protein was extracted from cells using IP lysis buffer (QIAGEN) supplemented with a protease inhibitor (Shanghai Beyotime Biotechnology Co., Ltd.) at a ratio of 100:1. Protein concentrations were measured using the BCA protein assay kit (Thermo Fisher Scientific). The protein samples were then mixed with loading buffer (Thermo Fisher Scientific) and boiled to achieve denaturation.

2.6.2. SDS-PAGE electrophoresis

Equal volumes of protein were loaded into the gel's wells, and electrophoresis was carried out at a constant voltage of 80 V until the molecules were fully separated.

2.6.3. Transfer

Using a "sandwich" structure (sponge-filter paper - gel - membrane - filter paper - sponge) and an electric field, the proteins on the gel were transferred onto a nitrocellulose (NC) membrane.

2.6.4. Blocking

For two hours, the membrane was blocked with 20% non-fat milk.

2.6.5. Antibody incubation

After blocking and washing, the membrane was incubated with a specific primary antibody against the target protein at 4°C for 12 hours to allow specific binding. All primary antibodies used in this experiment were

purchased from Wuhan Proteintech Biotechnology Co., Ltd. Following primary antibody incubation, the membrane was washed thoroughly and then incubated with the corresponding horseradish peroxidase (HRP)-conjugated secondary antibody for 1 hour at room temperature.

2.6.6. Signal detection and imaging

A chemiluminescent substrate was added to react with the HRP label on the secondary antibody, producing luminescence. Images of the resulting black bands were captured using a gel imaging system.

2.7. CCK-8 Cell Proliferation Assay

Cells were digested and counted. A total of 8×10^3 cells per well were seeded into 96-well plates, with 6 rows and 5 columns for each cell type. After 24 hours, the culture medium in each well was adjusted to 200 μ L, and the absorbance at 450 nm (OD450) was measured on the first day. The CCK-8 working solution was prepared by mixing 1 mL of CCK-8 stock solution (Beyotime Biotechnology Research Institute) with 9 mL of serum-free culture medium. All operations were performed under dark conditions. The culture medium in the wells to be measured was discarded, and 100 μ L of the CCK-8 working solution was added to each well. The plate was then incubated in a 37°C cell incubator in the dark for 1 hour. After incubation, the absorbance at 450 nm was measured for each well using a multimode microplate reader. This measurement was repeated every 24 hours for a total of five time points. The OD450 value of blank wells was subtracted from that of the experimental wells. After measurement and calculation, cell growth curves were plotted using Prism software.

2.8. Wound healing assay

Cells were digested and counted. A total of 8×10^5 cells per well were seeded into 6-well plates, with three wells for each cell type. After 24 hours, when the cells had formed a confluent monolayer covering the entire bottom of the wells, the culture medium was replaced with serum-free medium, and the cells were starved for 2 hours. Subsequently, a straight line was quickly and uniformly scratched in the center of each well using a 200 μ L pipette tip held vertically. The wells were gently washed twice with PBS (Wuhan Servicebio Technology Co., Ltd.), and then 2 mL of serum-free medium was added. The 6-well plate was placed under an inverted microscope, and images of the same position in each well were captured at 24 hours and 48 hours using a low-power lens (4 $\times$). ImageJ software was used to quantify the remaining wound area at 24 hours and 48 hours relative to the initial area at 0 hours. After measurement and calculation, cell migration rate graphs were plotted using Prism software.

2.9. Data Analysis

IBM SPSS 21 software was used for statistical analysis of all data. For data that exhibited homogeneity of variance and normal distribution, a *t*-test was applied. For data that did not meet these assumptions, a nonparametric test was used. **P* < 0.05; ***P* < 0.01; ****P* < 0.001. A *P*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. SP1 is a possible pro-inflammatory gene in pancreatic cancer

The expression of SP1 in pancreatic cancer was discovered from a website for online bioinformatics analysis,

Gene Expression Profiling Interactive Analysis (GEPIA, <http://gepia.cancer-pku.cn/>), based on data from The Cancer Genome Atlas (TCGA). The results showed that SP1 expression was low in normal pancreatic tissues but relatively high in pancreatic cancer tissues (**Figure 1A**). KaplanMeier (KM) survival analysis indicated that patients with high SP1 expression tended to have shorter overall survival and recurrencefree survival compared with those with low SP1 expression (**Figure 1B & 1C**). To further validate SP1 expression levels in tumor and normal pancreatic tissues, RTqPCR and Western blot assays were performed (**Figure 1D & 1E**). The results consistently showed that SP1 was upregulated in tumor specimens. Taken together, these findings suggest that SP1 may serve as a potential protumorigenic gene in pancreatic cancer.

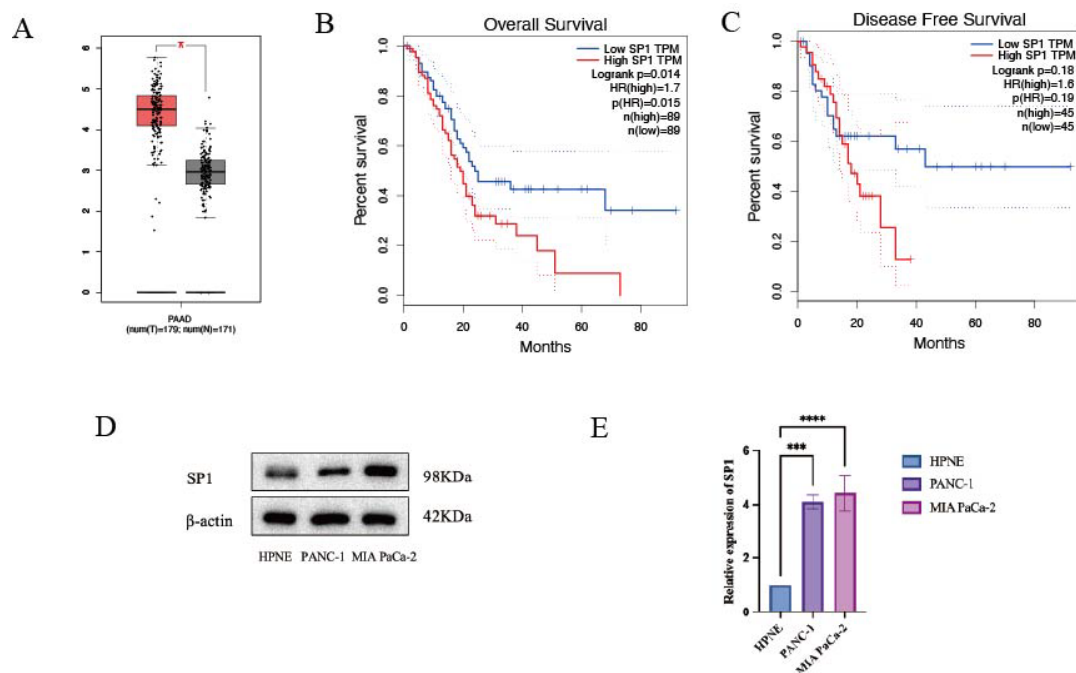


Figure 1. SP1 is highly expressed in pancreatic cancer and acts as a possible pro-tumorigenic gene. (A) SP1 is highly expressed in pancreatic cancer (GEPIA). (B) Pancreatic cancer patients with low SP1 expression have longer overall survival (GEPIA). (C) Pancreatic cancer patients with low SP1 expression have longer disease-free survival (GEPIA). (D) Western blot analysis of SP1 expression in normal pancreatic tissues and pancreatic cancer tissues. (E) RT-qPCR analysis of SP1 expression in normal pancreatic tissues and pancreatic cancer tissues. The above data are presented as mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$

To further study the function of SP1 in pancreatic cancer, we transfected SP1 siRNA into MIA PaCa - 2 and PANC - 1 cell lines.

3.2. Knockdown of SP1 suppresses the proliferation and migration of pancreatic cancer cells

As a transcription factor, SP1 has been reported to play a significant role in the occurrence and development of various tumors. To explore the potential function of SP1 in pancreatic cancer, CCK-8 and wound healing assays were performed to evaluate the effects of SP1 knockdown on the proliferation and migration of pancreatic cancer cells. Following SP1 knockdown, the proliferative capacity of pancreatic cancer cells was reduced, according to the CCK-8 assay results (**Figure 2A**). The wound healing assay results indicated that the migratory capacity of pancreatic cancer cells was also decreased after SP1 knockdown (**Figure 2B**), and

subsequent quantitative analysis further supported that cell migration was reduced (**Figure 2C**). According to these findings, SP1 might be a tumor suppressor gene in pancreatic cancer.

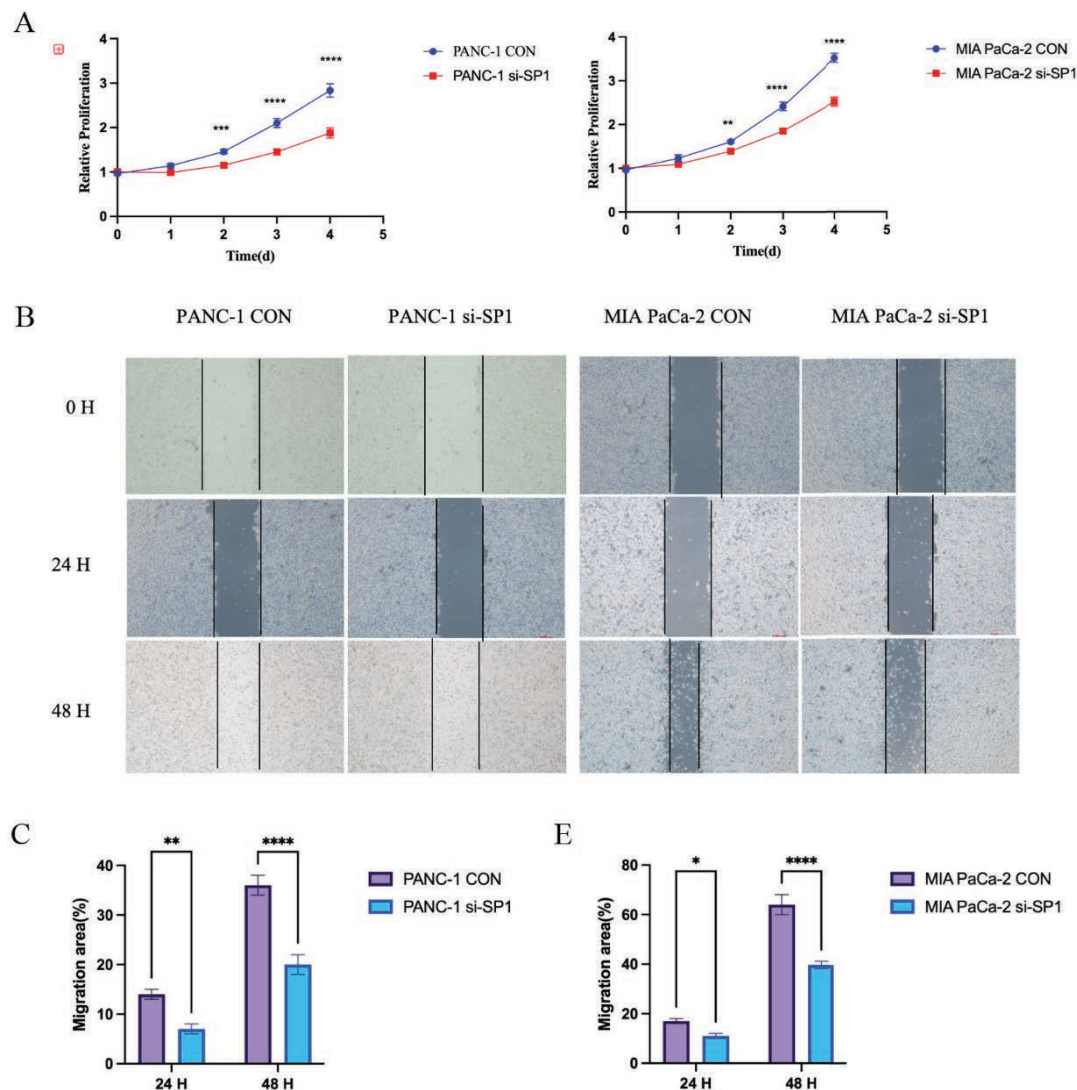


Figure 2. SP1 knockdown prevents pancreatic cancer cells from proliferating and migrating. (A) CCK-8 assay analysis of the proliferative capacity of pancreatic cancer cells in the SP1 knockdown group and the control group. (B) Wound healing assay analysis of the migratory capacity of pancreatic cancer cells in the SP1 knockdown group and the control group. (C) Statistical analysis of the wound healing assay results. (For data with homogeneity of variance and normal distribution, a *t*-test was employed; for data that did not match these requirements, a nonparametric test was applied. **P* < 0.05; ***P* < 0.01; ****P* < 0.001. A *P*-value < 0.05 was considered statistically significant.)

To further study the mechanism of SP1 in pancreatic cancer, we predicted its potential transcription factors using the JASPAR website and found that FOXA3 may be a transcription factor of SP1. The study transfected FOXA3 oe - RNA into MIA PaCa - 2 and PANC - 1 cell lines.

3.3. Overexpression of FOXA3 inhibits SP1 expression

To study the regulatory effect of FOXA3 on SP1, we performed Western blot analysis on MIA PaCa - 2 and

PANC - 1 cells overexpressing FOXA3. The results showed that SP1 expression was lowered following FOXA3 overexpression (**Figure 3**), showing that FOXA3 negatively regulates SP1 production and may be a negative regulator of SP1. Western blot examination of SP1 expression following overexpression of FOXA3.

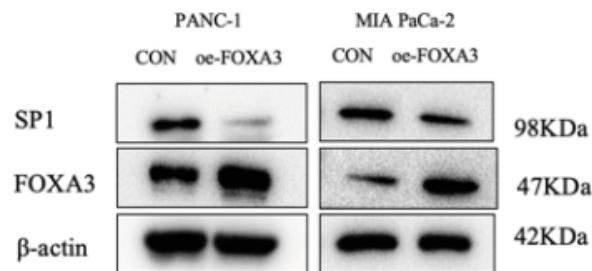


Figure 3. FOXA3 inhibits the expression of SP1.

4. Conclusion

This study shows that SP1 promotes proliferation and migration in pancreatic cancer and, for the first time, reveals that FOXA3 negatively regulates SP1 expression, thereby expanding the transcriptional regulatory network in pancreatic cancer. This axis is useful as a potential therapeutic target and as a biomarker. Compared with previous studies, this work supports the prevailing view of SP1 as a pro-tumorigenic factor and complements the upstream regulatory mechanism, yet lacks molecular evidence of direct binding of FOXA3 to the SP1 promoter as well as in vivo validation. Future research should enhance the chain of evidence through ChIP assays, animal models, and clinical cohorts, as well as investigate combination therapeutic techniques targeting this axis.

Disclosure statement

The author declares no conflict of interest.

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The Anti-aging Mechanisms of Plant Polyphenols and Challenges to Their Bioavailability: A Systematic Literature Review

Rong Liu*, Wenying Yang, Xiang Wang, Muyang Li, Yuxuan He

School of Biological Sciences and Technology, Hunan Agricultural University, Changsha 410000, Hunan, China

*Corresponding author: Rong Liu, 2084901277@qq.com

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Abstract: As natural bioactive compounds obtained from the daily diet, plant polyphenols have shown potential in anti-aging research to exert their effects through multi-target regulatory networks, such as the AMPK/SIRT1 axis and inflammatory and oxidative stress pathways. However, their oral bioavailability is quite low, which has become a major obstacle limiting their progression towards clinical application. This review provides a systematic overview of progress in this field and further explores the potential applications of plant polyphenols in supportive cancer therapy through their intervention in the aging process. It notes that although current research is becoming increasingly detailed in its exploration of mechanisms, there remain widespread shortcomings, such as insufficient physiological relevance and relatively weak clinical evidence. Future work should focus more on validating mechanisms in physiologically relevant models and promoting the design of more rigorous clinical trials; only then can plant polyphenols truly be transformed from laboratory potential into tangible clinical benefits.

Keywords: Plant polyphenols, Anti-aging, Bioavailability, Nanodelivery systems, Clinical translation

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1. Introduction

With the global population aging at an ever-increasing rate, aging and the associated chronic diseases have become central challenges for public health.^[1] Phytochemicals derived from the daily diet, particularly plant polyphenols, have taken a prominent position in the field of anti-aging research due to their wide range of food sources, diverse biological activities and relatively high safety profile^[2]. Phytopolyphenols constitute a large class of secondary metabolites widely distributed in plant-based foods such as fruits, vegetables, tea and spices^[3].

Numerous preclinical studies have indicated that phytopolyphenols not only scavenge free radicals through direct antioxidant action, but also exert anti-aging effects at multiple levels—including energy

metabolism, inflammation and autophagy—by modulating complex cellular signaling pathways ^[4]. However, a significant gap exists between their exceptional in vitro activity and their unclear in vivo efficacy, primarily attributable to the inherent challenge of low bioavailability ^[5]; this contradiction constitutes the core tension in research within this field.

This review aims to systematically collate and evaluate recent research progress regarding the anti-aging effects of plant polyphenols and the challenges associated with their bioavailability. The primary objectives of this paper are to summarise the key molecular mechanisms and core targets underlying the anti-aging effects of plant polyphenols, analyze cutting-edge technical strategies for enhancing their bioavailability, assess the limitations and controversies of current research, and identify knowledge gaps, whilst providing directional recommendations for future basic research and clinical translation.

2. Mechanisms of anti-aging: From antioxidant effects to multi-target network regulation

Early research into plant polyphenols focused primarily on their direct antioxidant effects; however, in recent years, studies have clearly demonstrated that plant polyphenols function as part of a complex network regulating biological responses, achieving their effects by modulating several evolutionarily conserved longevity pathways and cellular homeostasis maintenance systems ^[6].

Key pathways and major findings: The AMPK/SIRT1 energy metabolism axis is regarded as a central hub ^[7]. Xu and his collaborators noted that many types of polyphenols act as natural activators of AMPK; by modulating cellular energy status, they induce autophagy and improve mitochondrial function ^[7]. This pathway is closely linked to SIRT1. Yang and Sauve ^[8] provided a systematic account of the central role of NAD⁺ metabolism, noting that polyphenols or NAD⁺ precursors indirectly activate SIRT1 by elevating NAD⁺ levels, thereby forming the metabolic basis of anti-aging. The suppression of chronic low-grade inflammation is another key mechanism; researchers such as Xiang Lu et al. ^[9] summarised that quercetin can combat atherosclerosis by inhibiting common inflammatory pathways such as NF-κB and the NLRP3 inflammasome. More in-depth studies, such as that by López-Sánchez et al. ^[10], found that kaempferol can specifically inhibit complement C3 activation and the generation of pro-inflammatory type A1 astrocytes. Finally, there is the regulation of cell fate; plant polyphenols not only protect normal cells but also induce the death of abnormal cells. For instance, Deng et al. ^[11] found that okra flavonoids can induce apoptosis, senescence, and autophagy in colorectal cancer cells, whilst Park et al. ^[4] noted that quercetin induces cell cycle arrest in endometriosis cells by regulating Cyclin D1 and related miRNAs.

Trend Analysis: Research trends in this field have shifted from describing individual antioxidant phenomena to analyzing the regulation of complex signaling networks by polyphenols ^[7]. An emerging frontier focuses on the interactions between polyphenols and the gut microbiota ^[12]. Yang Wenhan ^[13] noted that the anti-aging activity of ferulic acid metabolites produced by the gut microbiota is superior to that of the parent compound. Dong et al. ^[14] further proposed that anthocyanins eliminate senescent endothelial cells via the ‘gut microbiota + metabolites + vasculature’ axis. This suggests a profound shift in research perspective from a ‘single compound–single target’ model to a systemic interaction model involving ‘dietary components–microbiome–host’ ^[13-14].

3. Bioavailability challenges and innovations in delivery technologies

Although research into the mechanisms of action is progressing rapidly, the extremely low oral bioavailability commonly encountered with plant polyphenols has become a fundamental bottleneck limiting their translation into clinical applications ^[5].

Regarding key research findings and methodological evaluations, the pharmacokinetic study by Zabela et al. ^[15] provides precise quantitative evidence. They observed that following oral administration of kaempferol to rats, the plasma concentration of the parent compound was extremely low, whilst after intravenous administration, its plasma half-life was approximately only 3 minutes, indicating rapid clearance. To overcome this bottleneck, formulation innovation has become a new research focus, with nanotechnology representing the most promising solution ^[16]. In their review, Mundekkad and Cho ^[16] noted that formulating curcumin into nanoliposomes, polymeric nanoparticles or micelles can significantly improve its water solubility, stability, targeting ability and bioavailability.

Regarding research trends and innovation, current delivery strategies are evolving from simple solubilization towards intelligent and functionalized approaches ^[16]. Furthermore, the use of prodrug strategies and the activation of gut microbiota metabolism have emerged as novel concepts for enhancing bioavailability ^[13].

4. Controversies and the challenges of clinical translation

Although preclinical data are abundant, there remain significant controversies and unresolved discrepancies in the field of plant polyphenol research.

On the one hand, the main point of contention concerns the directness and specificity of the mechanism of action, as exemplified by the relationship between resveratrol and SIRT1. In their review, Rogina and Tissenbaum ^[17] noted that there is still debate as to whether resveratrol can directly activate SIRT1. This indirectly highlights a common issue in polyphenol research: due to their multi-target nature, it is extremely difficult to identify their most critical and direct targets ^[17].

Next are the consequences of this double-edged sword and the potential pitfalls in clinical applications. Fernando and his team, in their paper ^[18], offer a particularly cautionary perspective. They noted that the dual nature of phytochemicals—acting as antioxidants or, conversely, as pro-oxidants—may lead to opposite outcomes when used in conjunction with cancer radiotherapy and chemotherapy. This inconsistency highlights the gap in understanding and the latent dangers involved in transitioning from dietary supplementation to adjuvant therapy ^[18]. It is worth noting that recent research has increasingly turned its attention to the other side of this ‘double-edged sword’—namely, the potential of plant polyphenols to eliminate age-related cells caused by treatment and mitigate the toxicity associated with radiotherapy and chemotherapy, thereby offering potential as an adjunctive therapy ^[19-20]. This demonstrates that the role of plant polyphenols in cancer treatment is not simply one of ‘interference’ or ‘assistance’, but is closely linked to dosage, timing of administration, and the specific type of polyphenol involved; more detailed research designs are required to clarify the boundaries of their use.

Setting aside the effects and risks, the lack of clinical evidence and the contradictions within it have become the most fundamental challenges in this field. Benameur and his collaborators state directly in their paper ^[5] that the primary reason for the inconsistent results of clinical trials using curcumin to treat

neurological disorders is its extremely low bioavailability. Braidy and Liu ^[21], in their analysis of the risks and benefits of NAD⁺ precursor therapy, also noted that high-quality, long-term human trials remain scarce to date. This translational gap between animal and human studies underscores the significant challenges posed by species differences ^[5, 21].

Methodological differences also play a role, but these controversies stem in part from variations in research methodologies. For instance, in vitro studies frequently employ polyphenol concentrations far exceeding physiologically achievable levels, whilst clinical trials lack standardized references regarding subject selection, the form of the intervention, dosage, duration of treatment and endpoints ^[15, 22].

5. Outlook: From anti-aging to supportive cancer care

The mechanisms by which plant polyphenols delay the aging process—such as modulating the AMPK/SIRT1 pathway, suppressing inflammatory responses and oxidative stress, and eliminating senescent cells—are intrinsically linked to some key clinical challenges in cancer treatment. When chemotherapy and radiotherapy kill tumor cells, they often induce a state of ‘treatment-induced senescence’ in normal cells. This not only leads to delayed adverse effects such as cardiac damage, impaired neurological function and suppressed bone marrow function, but also promotes tumor recurrence and metastasis via the senescence-associated secretory phenotype (SASP) ^[19-20].

In recent years, due to their favorable safety profile and multifaceted effects, plant polyphenols have begun to be explored as adjunctive therapies in cancer supportive care. Studies have indicated that quercetin can reduce cisplatin-induced lymphocyte DNA damage and oxidative stress ^[23], resveratrol and curcumin significantly increased the survival rate of cardiomyocytes following doxorubicin treatment in vitro ^[24], whilst rosmarinic acid has been reported to possess dual effects of reducing chemotherapy toxicity and reversing drug resistance ^[25]. These findings suggest that plant polyphenols, by targeting ageing-related pathways, hold promise in reducing treatment-related toxicity, improving patient tolerance and enhancing quality of life.

It should be noted that the use of plant polyphenols in cancer treatment is still in a relatively preliminary exploratory phase. The ‘antioxidant-prooxidant duality’ concept proposed by Fernando et al. ^[18] highlights that the efficacy of polyphenols when used in combination with radiotherapy and chemotherapy depends largely on dosage, timing of administration, and the specific type of polyphenol. Future research must further clarify: the optimal dosage and time window for combining plant polyphenols with chemotherapy or radiotherapy to avoid interfering with antitumour efficacy; the use of biomarkers based on ageing phenotypes to identify patient groups most likely to benefit; high-quality clinical trials to validate their clinical efficacy and safety; and the integration of ageing intervention strategies into the comprehensive management of cancer treatment, which may well become a new pathway for improving patient outcomes.

6. Methodological assessment and general limitations

A critical review and examination of the existing literature at the methodological level facilitates a more objective assessment of the strength of evidence in this field. The strengths of the research as a whole lie in: 1) in-depth exploration of mechanisms ^[7,10]; 2) innovative integration of technologies ^[13,26]; and 3) the diversity of research models ^[11,27]. However, the widespread limitations are more pronounced, as shown in **Table 1** below.

Table 1. Current limitations in polyphenol research and strategies for improvement

Limiting factors	Specific manifestations	Impact and recommendations for improvement
Neglect of bioavailability	A large number of mechanistic studies have conducted in vitro experiments using high concentrations without taking in vivo pharmacokinetics into account, raising doubts about their physiological relevance ^[15] .	Extreme caution should be exercised when extrapolating conclusions. There is a need to strengthen studies combining PK and PD, using concentrations that are more physiologically relevant ^[15] .
Fragmented research	Much of the research has focused on repeatedly validating the roles of a small number of key molecules in the same pathways, whilst there has been insufficient exploration of a broader range of plant resources and more novel mechanisms ^[22] .	This results in limited knowledge gains. Efforts to explore non-star polyphenols and new paradigms of action should be encouraged ^[22] .
Insufficient analysis of complex systems	Although studies on traditional Chinese medicine formulations ^[27] and crude plant extracts ^[6] have utilized network pharmacology for prediction, they have largely been limited to compound-target predictions, lacking rigorous experimental validation of synergistic or antagonistic interactions between multiple components ^[22] .	The explanation of the mechanism is superficial. It needs to be validated through quantitative analysis and orthogonal experiments ^[22] .
Weak foundations in clinical translation	There are differences between animal models and human diseases; clinical trials tend to be small in scale, short, and lack standardized endpoints, and there is a dearth of long-term safety data ^[21] .	This represents the greatest bottleneck in the field; there is a need to promote standardized, large-scale RCT studies and to systematically assess the risks and benefits ^[21] .
Individual differences and the lack of precision in application	Very few studies have examined the influence of an individual's genetic background, gut microbiota composition and baseline dietary patterns on the effects of polyphenols ^[13] .	This limits the precision of the application; future research will need to incorporate the principles of personalized nutrition and precision medicine ^[13] .

7. Conclusion

This review systematically summarises research progress on plant polyphenols in the field of anti-aging. Key findings indicate that plant polyphenols establish a complex anti-aging network through multiple mechanisms, including the regulation of the AMPK/SIRT1 energy metabolism axis, the suppression of inflammation and oxidative stress, the modulation of cell fate, and interactions with the gut microbiota ^[7, 9–11]. However, their extremely low bioavailability severely limits their efficacy in vivo ^[5, 15], and technological innovations such as nanodelivery have become key strategies for overcoming this bottleneck ^[16]. Furthermore, although preclinical evidence is abundant, the field still faces issues including direct disputes regarding core mechanisms ^[17], a severe lack of clinical evidence ^[5, 21], and a degree of fragmentation in research ^[22].

The identified research gaps primarily include: (1) the mechanisms of action of polyphenols at physiologically relevant concentrations ^[15]; (2) in-depth exploration of non-star polyphenols and polyphenol synergistic effects ^[22]; (3) personalised effects based on human gut microbiota characteristics ^[13]; and (4) a systematic assessment of the safety and potential risks of long-term high-dose polyphenol supplementation ^[21].

Recommendations for future research: Firstly, to advance ‘physiological relevance’ studies, encouraging research in models that more closely mimic the human internal environment, whilst strengthening integrated PK/PD analyses ^[15]. Secondly, to conduct rigorous clinical translation studies, prioritizing large-scale, long-term, double-blind, randomized controlled trials for specific polyphenol formulations that have undergone delivery technology optimization and demonstrate significantly improved bioavailability ^[21]. Finally, precision nutrition and integrated intervention strategies should be explored, investigating the contribution

of polyphenols within specific dietary patterns, examining synergistic effects with other interventions, and combining individual omics data to develop personalized polyphenol intervention protocols ^[13].

Implications for related fields: For nutrition and food science, attention should be paid to optimising the retention and bioavailability of polyphenols through food processing technologies and dietary combinations ^[2]; in the fields of pharmacy and pharmaceutical formulation, the development of highly efficient and safe delivery systems is a matter of urgency ^[16]; and in clinical medicine and public health, health claims regarding polyphenol supplements should be treated with caution until high-level clinical evidence is available, whilst the consumption of natural polyphenol sources through a varied diet should be actively promoted ^[18,21].

Disclosure statement

The authors declare no conflict of interest.

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Clinical Diagnosis, Treatment and Prevention Strategies of HIV/AIDS-related Tumors

Dong Guo¹, Yaxian Zhang^{2*}

¹Chifeng Cancer Hospital (Chifeng Second Affiliated Hospital), Chifeng 024000, Inner Mongolia Autonomous Region, China

²Chifeng Center for Disease Control and Prevention (Chifeng Health Inspection Institute), Chifeng 024000, Inner Mongolia Autonomous Region, China

**Author to whom correspondence should be addressed.*

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Abstract: HIV/AIDS-related tumors represent a significant challenge in the global public health arena. This article systematically elaborates on the clinical characteristics, diagnosis and treatment strategies, as well as prevention and control measures of HIV/AIDS-related tumors. The HIV virus causes immune deficiency by attacking CD4+ T lymphocytes, significantly increasing the risk of tumor development. Common types include Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer. Clinical diagnosis and treatment need to comprehensively consider the treatment of the tumor itself and immune reconstitution, adopting a combination of surgery, radiotherapy, chemotherapy, targeted therapy, and highly active antiretroviral therapy. In terms of prevention and control, the focus should be on primary prevention, including HIV screening, early diagnosis and treatment, and regular tumor screening, to reduce the disease burden and improve patient prognosis.

Keywords: HIV/AIDS; Related tumors; Clinical diagnosis and treatment; Prevention and control measures

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1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) is a severe immunodeficiency disease caused by infection with the Human Immunodeficiency Virus (HIV). Since its first discovery in 1981, HIV/AIDS has caused more than 40 million deaths worldwide, and there are still 38 million infected people currently ^[1]. With the widespread application of Highly Active Antiretroviral Therapy (HAART), the survival time of HIV-infected individuals has been significantly prolonged, but tumors have become one of the leading causes of death in this population ^[2].

HIV infection leads to a progressive decrease in CD4+ T lymphocytes, impairing the body's immune surveillance function, which significantly increases the risk of tumor development. Studies have shown

that HIV-infected individuals have a several-fold to several dozen-fold higher risk of developing certain specific cancers compared to the general population. For example, the risk of anal cancer is increased by approximately 19 times, the risk of Hodgkin's lymphoma is increased by 5–14 times, and the risk of lung cancer is increased by 2–5 times^[3]. HIV/AIDS-related tumors not only have a high incidence rate but also are characterized by insidious onset, rapid progression, and atypical clinical manifestations, posing great challenges to early diagnosis and treatment.

This article aims to systematically review the clinical characteristics, diagnosis and treatment strategies, as well as prevention and control measures of HIV/AIDS-related tumors, providing references for clinicians to improve the diagnosis and treatment level of HIV/AIDS-related tumors and improve patient prognosis.

2. Clinical characteristics of HIV/AIDS-related tumors

The occurrence of HIV/AIDS-related tumors is closely related to the immune deficiency caused by HIV infection. The HIV virus continuously attacks the body's CD4+ T lymphocytes, gradually destroying the body's immune surveillance function, allowing tumor cells to escape immune clearance, thereby increasing the risk of tumor development. Common HIV-related tumors include Kaposi's sarcoma, non-Hodgkin lymphoma, invasive cervical cancer, as well as non-AIDS-defining tumors such as lung cancer, liver cancer, and anal cancer^[4].

2.1. HIV-related tumors

2.1.1. Kaposi's sarcoma

It is the most common AIDS-defining tumor, induced by human herpesvirus type 8 infection. The incidence rate is significantly higher in HIV-infected individuals who have not received HAART treatment. The typical clinical manifestation is multiple nodules or plaques on the skin and mucous membranes, which can involve internal organs, and the prognosis is poor. With the popularization of HAART, the incidence rate of Kaposi's sarcoma has decreased significantly, but it is still one of the tumor types that requires the most vigilance in the HIV/AIDS population^[5].

2.1.2. Non-Hodgkin's lymphoma

It is the second most common AIDS-defining tumor in HIV-infected individuals, and most are associated with Epstein-Barr virus infection. Diffuse large B-cell lymphoma is the most common type. Patients often present with systemic symptoms such as fever, progressive lymph node enlargement, night sweats, and weight loss. The lesions often involve extranodal organs, and the clinical aggressiveness is stronger. The prognosis is worse than that of non-Hodgkin's lymphoma in the general population^[6].

2.1.3. Invasive cervical cancer

It is an AIDS-defining tumor, closely related to persistent infection with high-risk human papillomavirus (HPV). The incidence rate of cervical cancer in HIV-infected women is much higher than that in ordinary women, and it is more likely to progress to invasive lesions. Guidelines recommend that HIV-infected women should undergo cervical cancer screening every year for early intervention.

2.2. Non-AIDS-defining tumors

In recent years, the proportion has gradually increased, including lung cancer, liver cancer, anal cancer, etc. The occurrence of these tumors is not only related to the immune deficiency caused by HIV infection, but also related to other risk factors existing in patients themselves. For example, lung cancer is related to smoking exposure, liver cancer is related to hepatitis B and C virus infections, and anal cancer is related to high-risk HPV infection. In clinical diagnosis and treatment, it is necessary to take into account the management of underlying diseases and tumor treatment.

3. Clinical diagnosis and treatment of HIV/AIDS-related tumors

In clinical diagnosis and treatment, the treatment of HIV/AIDS-related tumors needs to comprehensively consider the treatment of the tumor itself and the patient's immune function status, and adopt a combination of surgery, radiotherapy, chemotherapy, targeted therapy, and highly active antiretroviral therapy to achieve the best therapeutic effect while reducing adverse drug reactions ^[7].

3.1. Treatment of the tumor itself

3.1.1. Surgical treatment

For early-stage, localized HIV/AIDS-related tumors, surgical treatment is an effective method. Surgery can remove tumor tissue, reduce tumor burden, and improve patient survival. However, strict indications for surgery should be mastered, and the patient's immune function status and surgical risks should be fully evaluated.

3.1.2. Radiotherapy

Radiotherapy is a treatment method that uses radiation to kill tumor cells. For HIV/AIDS-related tumors that cannot be surgically removed or recur after surgery, radiotherapy can be used as an effective palliative treatment method to relieve patient symptoms and improve quality of life.

3.1.3. Chemotherapy

Chemotherapy is a treatment method that uses chemical drugs to kill tumor cells. For advanced, metastatic HIV/AIDS-related tumors, chemotherapy is one of the main treatment methods. Commonly used chemotherapy drugs include vincristine, bleomycin, doxorubicin, paclitaxel, etc. However, chemotherapy drugs have certain toxic and side effects, and close monitoring of patient adverse reactions is required; the treatment plan should be adjusted in a timely manner ^[8].

3.1.4. Targeted therapy

Targeted therapy is a treatment method that targets specific targets of tumor cells. Compared with traditional chemotherapy drugs, targeted therapy has the advantages of high specificity and low toxicity and side effects. Currently, targeted therapy drugs for HIV/AIDS-related tumors are constantly being developed, such as vascular endothelial growth factor inhibitors for Kaposi's sarcoma and CD20 monoclonal antibodies for non-Hodgkin's lymphoma.

3.2. Immune reconstitution

Highly Active Antiretroviral Therapy (HAART) is the cornerstone of HIV/AIDS treatment. By inhibiting HIV replication, it reconstructs the patient's immune function and reduces the risk of opportunistic infections and tumor development. Studies have shown that HAART can significantly reduce the tumor incidence rate in HIV/AIDS patients and improve patient survival ^[9].

In the treatment of HIV/AIDS-related tumors, HAART should be initiated as early as possible and continued throughout the treatment process. At the same time, close monitoring of the patient's CD4+ T lymphocyte count and HIV viral load is required, and the treatment plan should be adjusted in a timely manner to ensure the therapeutic effect ^[10].

3.3. Selection of treatment plans

The treatment plan for HIV/AIDS-related tumors should be formulated based on the patient's specific conditions, including factors such as tumor type, stage, patient's immune function status, and physical condition. When selecting a treatment plan, the effectiveness and safety of the treatment should be fully considered, and the relationship between the therapeutic effect and adverse drug reactions should be balanced ^[11].

For early-stage, localized tumors, surgical treatment or radiotherapy should be prioritized, combined with HAART treatment. For advanced, metastatic tumors, a comprehensive treatment plan combining chemotherapy, targeted therapy, and HAART treatment should be adopted. For patients with severely impaired immune function, HAART treatment should be given first, and tumor treatment should be carried out after immune function is reconstructed ^[12].

4. Prevention and control measures of HIV/AIDS-related tumors

Primary prevention is the core of reducing the disease burden of HIV/AIDS-related tumors. Comprehensive prevention and control measures should be adopted, including HIV screening, early diagnosis and treatment, and regular tumor screening, to achieve early detection, early diagnosis, and early treatment of tumors, and ultimately improve the long-term survival prognosis of patients.

4.1. HIV screening, early diagnosis and treatment

HIV screening, early diagnosis, and treatment are key measures to prevent HIV/AIDS-related tumors. Through extensive HIV screening, HIV-infected individuals can be detected in a timely manner, and HAART treatment can be initiated as early as possible to inhibit HIV replication, reconstruct the patient's immune function, and reduce the risk of tumor development ^[13].

At the same time, follow-up management of HIV-infected individuals should be strengthened, and regular monitoring of CD4+ T lymphocyte counts and HIV viral loads should be conducted to ensure that patients take their medications regularly and maintain a state of viral suppression. Studies have shown that regular medication intake and maintenance of viral suppression in HIV-infected individuals can significantly reduce the risk of tumor development ^[14].

4.2. Regular tumor screening

Regular tumor screening is an important means for early detection of HIV/AIDS-related tumors. An individualized tumor screening plan should be formulated based on factors such as the patient's age,

gender, duration of HIV infection, and CD4+ T lymphocyte count. For HIV-infected individuals, regular cervical cancer screening (such as Pap smear test, HPV testing), anal cancer screening (such as digital rectal examination, anoscopy), and lymphoma screening (such as lymph node biopsy, bone marrow aspiration) should be conducted. Early detection, early diagnosis, and early treatment can significantly improve the treatment effect of HIV/AIDS-related tumors and improve patient prognosis.

5. Conclusion

HIV/AIDS-related tumors are an important challenge in the global public health field. They have a high incidence rate, rapid disease progression, and difficult treatment, posing a serious threat to the lives and health of patients. With the widespread application of HAART, the survival time of HIV-infected individuals has been significantly prolonged, but tumors have become one of the leading causes of death in this population. The clinical diagnosis and treatment of HIV/AIDS-related tumors need to comprehensively consider the treatment of the tumor itself and the patient's immune function status, and adopt a combination of surgery, radiotherapy, chemotherapy, targeted therapy, and HAART. At the same time, primary prevention should be strengthened, including HIV screening, early diagnosis and treatment, and regular tumor screening, to reduce the disease burden and improve patient prognosis.

In the future, further research on HIV/AIDS-related tumors is needed to deeply explore their pathogenesis, develop more effective treatment methods and prevention measures, improve the diagnosis and treatment level of HIV/AIDS-related tumors, and bring more hope to patients.

Disclosure statement

The authors declare no conflict of interest.

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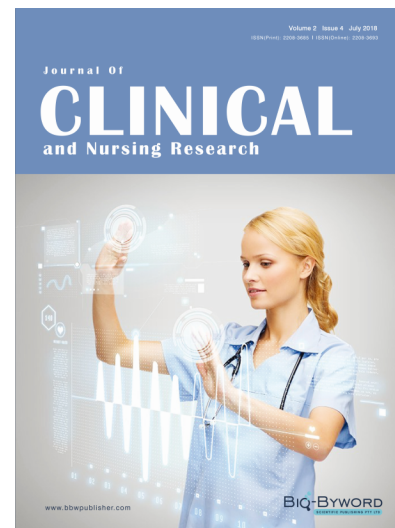
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