

# Hip metastasis presenting as anterior knee pain from nasopharyngeal carcinoma: A case report

JUAN LANG<sup>1</sup> and ZHONGKUI XIONG<sup>2,3</sup>

<sup>1</sup>Department of Pathology, Shaoxing People's Hospital, Shaoxing, Zhejiang 312000, P.R. China;

<sup>2</sup>Department of Radiation Oncology, Shaoxing Second Hospital, Shaoxing, Zhejiang 312000, P.R. China;

<sup>3</sup>Department of Medical Imaging, School of Medicine, Shaoxing University, Shaoxing, Zhejiang 312000, P.R. China

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**Abstract.** Nasopharyngeal carcinoma (NPC) in young patients aged  $\leq 30$  years often presents as advanced disease, yet these patients generally have an improved prognosis compared with patients aged  $>30$  years old. The incidence of bone metastasis in NPC ranges from 64-67%, with bone being the most common site of metastases. Referred pain, which is the perception of pain distant from the stimulus site, is a phenomenon of which the mechanism remains poorly understood. The present study describes a rare case of a 25-year-old woman with a past medical history of NPC. The initial symptom was right anterior knee pain (AKP), persisting for 4 months. Magnetic resonance imaging revealed abnormal signals in the right acetabulum and surrounding soft tissue mass, as well as minor abnormal signals in the right femoral head. Following these findings, the patient was diagnosed with NPC with bone metastasis. The patient received palliative radiotherapy and concurrent chemotherapy for one cycle, followed by adjuvant chemotherapy for 3 cycles. The AKP gradually subsided during the course of treatment.

## Introduction

Nasopharyngeal carcinoma (NPC) is a unique head and neck cancer with a marked uneven geographic global distribution, representing a notable public health burden in East and Southeast Asia (1). NPC exhibits two incidence peaks: One occurring in adolescents and the other in individuals aged

55-59 years (2). In southern China, the incidence rate is  $\sim 20$  cases per 100,000 individuals. In contrast, the incidence rate in Europe and the United States (US) is less than 1 case per 100,000 individuals. The 5-year overall survival (OS) rate is approximately 85%. However, around 20-30% of patients may experience locoregional recurrence and/or distant metastasis following treatment. Patients with NPC aged  $\leq 30$  years usually present at an advanced stage, but have an improved overall prognosis compared with patients aged  $>30$  years (3).

NPC is one of the most common Epstein-Barr virus (EBV)-associated epithelial cancers (4). EBV is a widely prevalent  $\gamma$ -herpesvirus and classified as a class 1 carcinogen (5). Pre-EBV DNA levels may serve as a notable predictor for optimizing the selection of cycles of induction chemotherapy for patients with NPC at lymph node stage (N) 3 (6). EBV DNA serves as a biomarker for biological relapse, facilitating the early detection of clinical recurrence in EBV-related NPC (7). Persistent or recurrent plasma EBV load, accompanied by elevated levels of interleukin-6 and vascular endothelial growth factor (VEGF), may serve as potential predictors of disease progression (8).

EBV-induced VEGF and granulocyte-macrophage colony stimulating factor promote metastasis of NPC through the recruitment and activation of macrophages (9). Patients with NPC with bone metastases exhibit a relatively lower risk of skeletal-related events than individuals with non-NPC head and neck cancers (10). Metastatic NPC with bone involvement is common, accounting for  $>50\%$  of metastatic cases (11). Bone is the most frequent site of metastasis for common cancers (including breast and prostate cancer) (12) and the incidence of bone metastasis has been steadily increasing over the years, primarily due to the higher life expectancy in patients with cancer (12). Bone metastases are common complications of numerous cancers, leading to bone-related issues that adversely affect the quality of life of the patient (12). Moreover, cancer-induced bone pain is common in patients with advanced cancers as these tumors have a notable affinity to metastasize to bone (13). Bone-directed therapy has the potential to enhance survival, particularly when administered in conjunction with radiotherapy (RT) targeting bone lesions (10).

Referred pain is pain perception distant from the site of the stimulus, the mechanism of which is poorly understood (14). Anterior knee pain (AKP) represents one of the most common

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*Correspondence to:* Miss Juan Lang, Department of Pathology, Shaoxing People's Hospital, 568 North Zhongxing Road, Shaoxing, Zhejiang 312000, P.R. China  
E-mail: langjuancn@yeah.net

Dr Zhongkui Xiong, Department of Radiation Oncology, Shaoxing Second Hospital, 123 Yan'an Road, Shaoxing, Zhejiang 312000, P.R. China  
E-mail: xiongzk@yeah.net

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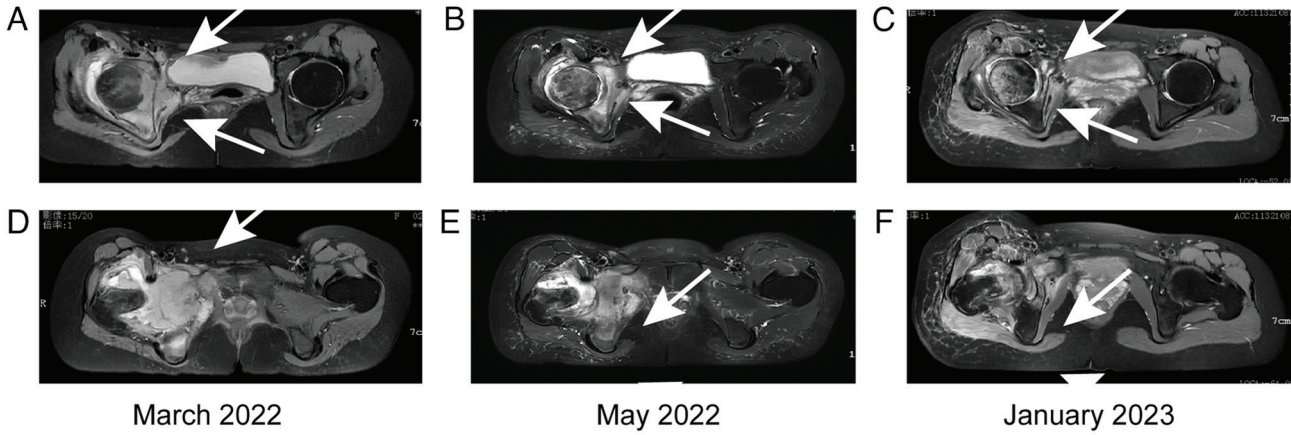


Figure 1. Magnetic resonance imaging images from March 2022 to January 2023. (A) Bone destruction in the right acetabulum (white arrows); (B) Bone destruction in the right acetabulum was gradually repaired (white arrows); (C) No obvious signs of bone destruction were observed in the right acetabulum (white arrows); (D) The tumor mass around the right hip joint (white arrow); (E) The tumor mass around the right hip joint decreased (white arrow); (F) No signs of tumor mass were observed around the right hip joint (white arrow).

reasons to consult with a clinician who specializes in the knee (15). The estimated prevalence of AKP among females aged 18-35 in the sample is between 12 and 13% (16). Despite the high incidence of the disorder, its etiology remains controversial (17). Knee pain may be referred from the hip (18). Hip pain that extends below the knee is commonly associated with a degenerate hip joint and follows the distribution of the saphenous nerve, branching from the femoral nerve (19). The knee joint is innervated anteriorly by branches of the femoral and sciatic nerves, and posteriorly by branches of the sciatic, obturator and saphenous nerves (14). Osteoarthritis of the hip and knee are prevalent in the general community and frequently prompt primary care consultations, where individuals present with regional pain or disability (20). In patients with malignancy, pain, particularly cancer-induced bone pain, is the most prevalent symptom, severely impacting quality of life. RT represents the standard of care for patients with symptomatic bone metastases, offering sustained pain relief with minimal toxicity and favorable cost-effectiveness (21).

In the present report, a rare case of metastasis of NPC to the hip joint presenting as AKP observed in Shaoxing Second Hospital (Shaoxing, China) is described.

### Case report

In March 2022, a 25-year-old female patient was admitted to Shaoxing Second Hospital with right AKP. The first symptom was right AKP for 4 months and the patient experienced systemic lupus erythematosus (SLE) 6 years prior. Before this medical consultation, the patient had been diagnosed with nasopharyngeal carcinoma in May 2020. The clinical staging at the primary diagnosis was tumor stage (T) 4, N3 with metastasis (M) not assessed (cT4N3Mx). The patient underwent albumin-binding paclitaxel [100 mg on the first day (d1), 200 mg d8] combined with nedaplatin (30 mg d8-10) during the first chemotherapy cycle (3 weeks per cycle, q3w) and albumin-binding paclitaxel (100 mg d1, 200 mg d8) with nedaplatin (30 mg d1-3) in the second and third chemotherapy cycles (q3w). The patient then received radical radiation therapy (RT), 95% primary gross tumor volume total dose (DT)=6,974

centigray (cGy)/32 fractions (Fx)/49 d, 95% planning target volume (PTV) 1 DT=6,016 cGy/32 Fx/49 d, 95% PTV2 DT=5,264 cGy/28 Fx/45 d. Subsequently, they underwent adjuvant chemotherapy, using gemcitabine (1.4 g d1, 8) combined with nedaplatin (30 mg d1-3) for 2 cycles (q3w) and paclitaxel (150 mg d1) with nedaplatin (30 mg d1-3) for 1 cycle (q3w). Maintenance therapy with capecitabine (1.25 g bid d1-14, q3w) was administered for 8 cycles after adjuvant chemotherapy.

Upon admission, the patient consented to the recommendation of the orthopedic surgeon for a magnetic resonance imaging examination. The findings revealed abnormal signals in the right acetabulum and surrounding soft tissue mass, slight abnormal signals in the right femoral head and normal hip joint space. These results suggested bone destruction in the right acetabulum (Fig. 1D) and a metastatic tumor around the same area (Fig. 1A) in March 2022. Single-photon emission tomography/CT imaging indicated elevated bone metabolism levels in the right acetabulum, ischium and upper segment of the femur, pointing to bone metastasis (Fig. 2E). The principal laboratory results are presented in Table I. The patient was administered 4 mg zoledronic acid (ZA) to reduce the damage caused by bone metastases every 4 weeks for 6 months starting March 2022. For 16 days, from March to April 2022, the patient received 10 mg morphine hydrochloride sustained-release tablets to relieve pains every 12 h and a 2.0 g moxalactam sodium injection for anti-infection twice daily for 3 days in April 2022. To alleviate pain and reduce the incidence of other bone-related events, the patient underwent palliative RT for the right acetabulum, ischium and upper thighbone with 95% PTV DT=3,900cGy/13Fx for 17 days from March to April 2022, alongside one cycle of concurrent chemotherapy and three cycles of adjuvant chemotherapy. The chemotherapy regimen included docetaxel (100 mg, d1, ivgtt, q3w) and capecitabine (1.25 g, po, bid, d1-14, q3w). Efficacy was assessed as partial remission (Fig. 1B and E in May 2022 and in Fig. 2A in July 2022, in Fig. 2B in July 2023). Efficacy was assessed as partial remission (Fig. 1C, and F) in January 2023. The AKP gradually subsided during the course of treatment. A right femoral neck fracture was evident 16 weeks post-palliative RT (Fig. 2C and D). Efficacy was assessed as disease progression.

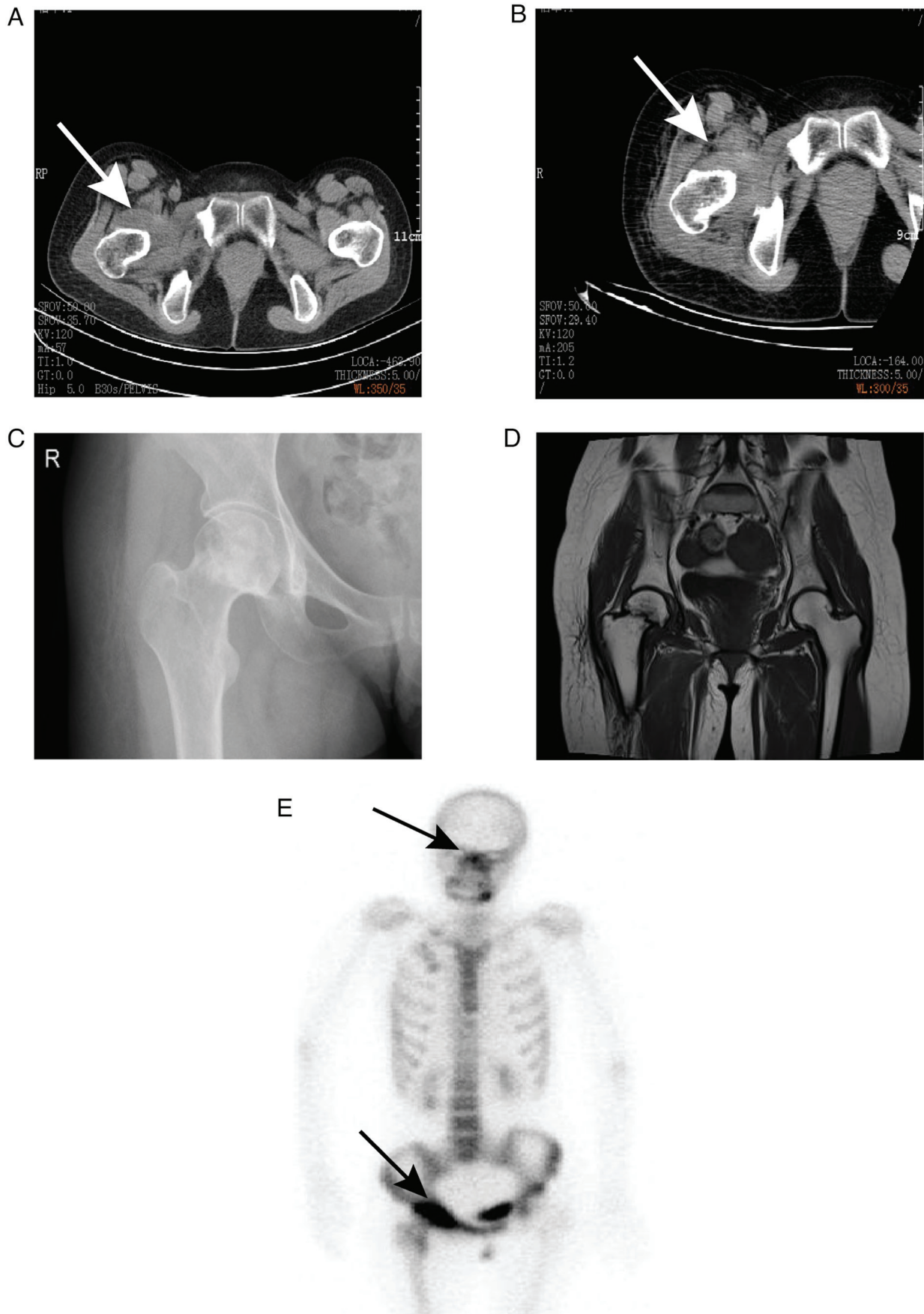


Figure 2. Radiological imaging. (A) Mass around the right hip joint observed in CT imaging (white arrow; July 2022). (B) A similar mass (white arrow) around the right hip joint in subsequent CT imaging (July 2023). (C) Increased density shadow (white arrow) observed in the right acetabulum and right femoral head and neck on X-ray imaging (May 2023). (D) Right femoral neck fracture (white arrow) identified in magnetic resonance imaging (August 2023). (E) Single-photon emission CT/CT imaging revealed heightened metabolic activity in the right acetabulum, ischium and upper thighbone, with increased radioactive uptake in the nasopharynx (black arrows; March 2022).



Table I. Results of laboratory tests during palliative radiotherapy.

Laboratory parameter	Reference range	Day before palliative RT (March 2022)	Day of the tenth palliative RT (April 2022)	2 weeks after palliative RT (May 2022)
White blood cell count, x10 <sup>9</sup> /l	3.5-5.5	12.6	5.3	4.1
Absolute neutrophil count, x10 <sup>9</sup> /l	1.8-6.3	11.1	4.3	3.1
Hemoglobin, g/l	115-150	96	89	115
Platelet, x10 <sup>9</sup> /l	125-350	523	481	375
Cholinesterase, U/l	5,300-11,300	3,703	2,737	4,827
Albumin, U/l	40.0-55.0	31.8	30.7	37.7
Urea, mmol/l	2.6-7.5	4.2	2.5	3.6
Creatinine, mmol/l	41-73	35	35	37
Hypersensitive C-reactive protein, mg/l	0.0-5.0	75.4	90.9	14.1
CYFRA 21-1, ng/ml	0.00-7.00	7.19	Not applicable	2.28

Immunological tests 3 months before AKP (September 2021; including anti-cardiolipin antibody (IgG), anti-proteinase-3 antibody, anti-myeloperoxidase antibody and anti-glomerular basement membrane antibody) were negative.

In the present study, the AKP was unlikely to be related to SLE, as the SLE was effectively managed before the onset of AKP. The patient was treated with 5 mg metacortandracin tablets and hydroxychloroquine tablets (0.1 g po bid), and she was regularly followed up in the outpatient of Departments of Rheumatology and Radiation Oncology, Shaoxing Second Hospital and received routine outpatient examinations and treatments.

## Discussion

A total of >90% of the global population is infected with EBV and is associated with several diseases (22). Reactivation of EBV is most commonly associated with pneumonia (16.80%), NPC (11.02%) and autoimmune disorders (7.04%) (23). NPC is the most frequent EBV-positive malignancy (24). Viruses contribute to the onset of SLE, with EBV being the most substantiated causative factor (25). The present case involved a young patient with NPC with a history of SLE. NPC in young patients is often advanced but has an improved prognosis compared with older adults (26). Regarding the definition of young patients, there is a lack of consistency in criteria across various clinical trials and clinical researches (16,27-29); most studies establish an upper age limit of < 30 years (16).

Recent therapeutic advancements have notably enhanced the survival rates of patients with cancer with bone metastases (30). Bone metastasis is the most frequent site of metastasis in NPC cases, occurring in 64-67% of instances (31). Bone metastasis in NPC commonly occurs in the spine, pelvis, ribs, skull and long limb bones with spinal metastasis being the most frequent, followed by pelvic and rib metastases. Once tumors metastasize to bone, they become a major cause of morbidity and mortality due to notable complications (13). Skeletal scintigraphy is the primary imaging method for

detecting skeletal metastases (32). Positron emission tomography/CT surpasses traditional techniques in detecting distant metastasis in primary NPC (33). Patients with cancer with bone metastasis frequently face skeletal complications that affect their quality of life (30). Key skeletal complications from bone metastases encompass cancer-induced bone pain, hypercalcemia, pathological fractures, metastatic spinal cord compression and cancer cachexia (30).

Referred pain is perceived at a location distant from the actual site of the stimulus. AKP is a common knee issue among physically active individuals (34). The causes of AKP in patients with cancer differ from those in patients without cancer (35). In patients without cancer, AKP is often linked to persistent hip muscle weakness, pathological femoral anteversion or femoral malrotation (36,37). Knee pain can also be referred from the hip (38). Orthopedic consultation is crucial for managing bone metastases, especially in addressing potential pathological fractures or notable bone pain (39). The literature supports multidisciplinary approaches, including orthopedic surgery consultations, for optimal management of bone metastases (40). Such collaboration ensures comprehensive care that meets both oncologic and orthopedic needs, thereby improving patient outcomes. In the present study, a multidisciplinary team, comprising an orthopedic surgeon, a radiation oncologist, a medical oncologist, a radiology expert, a pathologist and an otolaryngologist, was involved in diagnosis and management.

RT is critical for the treatment of NPCs, which are typically radiosensitive tumors (26). The oligometastatic state is hypothesized to represent an intermediate stage of cancer between curable, localized and widespread metastatic disease (41). Oligometastatic patients can attain long-term survival through aggressive treatments such as chemotherapy, surgery or definitive RT targeting the metastases (42,43). External-beam RT remains the primary treatment for palliating pain from bone metastases (32) and is highly effective for bone pain (44). Patients with NPC with <3 bone metastatic sites who underwent ≥6 chemotherapy cycles demonstrated improved survival and prognosis (45). Patients with a solitary bone metastasis should be

considered for combined chemoradiotherapy (46). The median survival time for patients with NPC with bone metastasis was 14.0 months (47). Moreover, serum alkaline phosphatase (ALP) and plasma EBV DNA levels at initial diagnosis are prognostic indicators for bone-only metastasis in NPC. RT for bone metastasis enhances the prognosis of patients with high pretreatment serum ALP and plasma EBV DNA levels (48).

A previous study reported that patients who experienced pain relief following palliative radiation therapy benefited for 56.6% of their remaining lifespan (49). The addition of local therapy (LT) directed at metastasis demonstrated an improvement in OS compared with the non-LT group in a matched-pair study (50). Patient survival improved with selective RT following distant metastasis in NPC treated with dose-dense cisplatin and fluorouracil (51). In metastatic patients with NPC, overweight or obesity was associated with extended OS but did not affect progression-free survival compared with those with underweight or normal weight status (52). Response rates of ~85% were reported, with complete pain relief achieved in ~50% of the patients (44). Pain relief typically occurred rapidly, with >50% of responders showing an improvement within 1-2 weeks (44). The combination of ZA with palliative chemotherapy did not enhance OS in patients with NPC diagnosed with bone-only metastasis. However, ZA application effectively prevented skeletal-related events (38).

In conclusion, when severe knee pain presents in patients with malignant tumors, a thorough physical examination and comprehensive imaging studies of the knee and ipsilateral hip joint are essential to assess for potential metastasis. Combining LT with systemic therapy for symptomatic bone oligometastatic lesions is valuable for symptom relief, enhancing quality of life and improving survival outcomes.

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### Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

### Authors' contributions

ZX contributed to the concept and design of the present study. JL performed data collection and analysis and wrote the manuscript. ZX and JL confirm the authenticity of all raw data. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Written informed consent was obtained from the patient for the publication of potentially identifiable images or data contained in the present article.

### Competing interests

The authors declare that they have no competing interests.

### Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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