J BONE ONCOL 45 (2024) 100600

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review

Preoperative evaluation and orthopedic surgical strategies for tumor-induced osteomalacia

Shuzhong Liu [a], Xi Zhou [a], Yong Liu [a,*], Jianguo Zhang [a], Weibo Xia [b,*]

[a] Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China
[b] Department of Endocrinology, National Health Commission Key Laboratory of Endocrinology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

HIGHLIGHTS

- Tumor-induced osteomalacia caused by culprit tumors in different parts of the body is a rare entity, resulting in great challenges to orthopedists.
- Qualitative and localized diagnosis led by Multi-Disciplinary Team (MDT) is a prerequisite for subsequent surgical intervention.
- Surgical treatment is the best treatment option for this disease, however, it may be quite difficult to remove the culprit tumor directly and surgical resection may bring huge damage.
- Exploring the orthopedic surgical strategy for TIO is beneficial and critical for improving the treatment effects of orthopedic surgery and improve the prognosis of TIO patients.

ARTICLE INFO

Keywords:
Tumor-induced osteomalacia
Culprit tumor
Phosphaturic mesenchymal tumor
Orthopedic surgery
Treatment effect

ABSTRACT

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is very rare, with about 1000 reported cases globally. Removing most TIO culprit tumors requires the evaluation and intervention of orthopedic doctors. However, orthopedic doctors often have a poor understanding of the optical treatment of TIO due to its rarity. In addition, most TIO patients lack specific clinical manifestations. Also, the clinical localization and qualitative diagnosis of TIO are difficult and thus can easily be misdiagnosed and mistreated. Furthermore, the true incidence rate of TIO may be underestimated. Although many breakthroughs have been made in exploring the pathogenesis, clinical diagnosis, and treatment of TIO, rational and standardized orthopedic surgical treatment experience summary and sorting for TIO patients are lacking. In this article, the recent experience and progress in the field of orthopedic surgical treatment for TIO globally have been summarized, providing a theoretical basis and new clinical practice guidance for the rational treatment of TIO patients.

1. Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome that was first reported by McCance in 1947 [1]. The key clinical manifestations of TIO include progressive bone pain, limb fatigue, limited mobility, shortened height, and pathological fractures, which seriously affect the quality of life of patients [2]. Misdiagnosis, especially in the early course of the disease, often leads to delayed diagnosis and unreasonable treatment [2,3]. Nevertheless, hypophosphatemia can be effectively corrected, and patient symptoms can gradually improve if precise diagnosis and total surgical removal of TIO causative tumors are achieved.

Although the culprit tumor of TIO is most common in limb bones and soft tissues, it is widely distributed in other parts, including subcutaneous tissue, joints, spine, palms, toes, and other places [2–4]. A large-scale analysis of TIO reported that causative tumors of about 74.3 % of TIO patients are located in the trunk, pelvis, and limbs, indicating that the surgical removal of most TIO causative tumors requires a thorough

* Corresponding authors at: Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 1 Shuaifuyuan Wangfujing, Beijing 100730, China (Y. Liu); Department of Endocrinology, National Health Commission Key Laboratory of Endocrinology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China (WB. Xia).
E-mail addresses: liuyong_pumch@163.com (Y. Liu), xiaweibo8301@163.com (W. Xia).

https://doi.org/10.1016/j.jbo.2024.100600
Received 12 January 2024; Received in revised form 24 March 2024; Accepted 27 March 2024
Available online 28 March 2024

preoperative evaluation by an orthopedic physician [5]. The establishment of orthopedic surgical treatment strategies may provide a basis for the realization of rational clinical TIO treatment. In this article, the surgical treatment strategies for patients with causative tumors related to orthopedics have been summarized to improve the understanding and clinical diagnosis and treatment of TIO.

2. Pathophysiology and pathogenesis

Calcium and phosphorus metabolism plays a key physiological role in the development and formation of human bones [6,7]. Therefore, maintaining normal phosphorus homeostasis is crucial for bone mineralization in the body. Bone matrix cannot complete normal mineralization when the blood phosphorus decreases, leading to osteomalacia. Parathyroid hormone (PTH), calcitonin, and vitamin D3 can regulate blood phosphorus levels in humans. However, vitamin D3 indirectly acts under the catalysis of liver 25-hydroxylase and kidney 1α-hydroxylase, generating 1,25- $(OH)_2$D3. The 1,25- $(OH)_2$D3 promotes the absorption of blood phosphorus and bone remodeling by acting on the intestine and bones, thereby increasing blood phosphorus levels [6,7].

The onset and progression of TIO are closely related to the autonomous secretion of phosphorus regulatory factor, fibroblast growth factor 23 (FGF-23), in culprit tumors [8,9]. FGF-23 is mainly secreted by osteocytes and osteoblasts. FGF-23 regulates phosphorus metabolism *in vivo* through the following mechanisms: (1) Na/Pi IIa and Na/Pi IIc are key carriers of reabsorbed phosphorus in the kidney. FGF23 inhibits the activities of sodium/phosphorus cotransporter IIa (Na/Pi IIa) and IIc (Na/Pi IIc) in the kidney, thus decreasing phosphorus reabsorption in the kidney and increasing phosphorus excretion, resulting in a decrease in blood phosphorus levels. (2) FGF23 inhibits kidney 1α-hydroxylase activity and promotes the activity of 24 hydroxylase, thus decreasing the synthesis of 1,25- $(OH)_2$D3 and active vitamin D. This reduces intestinal phosphorus absorption and blood phosphorus levels [6,7,10]. Besides FGF-23, various phosphorus-regulating factors related to phosphorus metabolism, including extracellular matrix phosphoglycoprotein (MEPE), fibroblast growth factor 7 (FGF-7), and secretory frizzled-related protein 4 (sFRP4) have been identified [6,7,11–15]. However, the detailed mechanism of action and interaction characteristics of MEPE, FGF-7, and sFRP4 require further clarification [6,7,15].

Studies have suggested that *FN1-FGFR1* and *FN1-FGF1* fusion genes are found in about half of the pathogenic tumors of TIO paraneoplastic syndrome [16]. In addition, Klotho and HIF-1α overexpression may be involved in the TIO pathogenesis [17,18]. As a result, genomics, metabolomics, and other related studies on the causative tumors of TIO have been conducted, providing a theoretical basis for elucidating the pathogenesis and treatment methods of TIO [19–21].

3. Diagnosis

3.1. Clinical manifestations

Although there is no significant gender difference in TIO patients [22], Rendina et al. (2022) found that adult males are more likely to develop TIO with more severe symptoms than females [23]. Most TIO patients experience bone pain at the hip joint and lumbar spine accompanied by fatigue and mobility disorders. However, other symptoms, such as skeletal deformities, short stature, pseudofracture, and pathological fractures, may occur if the disease is not timely diagnosed and treated, thus seriously affecting the quality of life. Jiang et al. (2012) analyzed the clinical data of 39 TIO patients and found that all patients (100 %) had muscle weakness/fatigue, bone pain, and walking difficulties, while 25 patients (64.1 %) had shorter height [3]. Moreover, 33 patients (84.6 %) had pathological fractures, mainly in the ribs, vertebrae, and neck of femur. Feng et al. (2017) reviewed and analyzed the clinical data of 144 TIO patients from a single center and found that bone pain (143/144, 99.3 %), walking difficulty (134/144, 93.1 %), pathological fractures (115/144, 79.9 %), height shortening (99/144, 68.8 %), and muscle weakness (94/144, 65.3 %) were the most common symptoms [2]. The misdiagnosis rate for TIO patients is 95.1 %, of which intervertebral disc herniation, ankylosing spondylitis, and osteoporosis are the top three misdiagnosed disorders [2]. These findings indicate that the clinical manifestations of TIO patients are not specific, leading to delayed diagnosis and treatment [2,24–26].

Crotti et al. [25] evaluated 17 patients [10 (58.8 %) females] and showed that the average age at TIO diagnosis was 55.3 ± 13.9 years (mean ± standard deviation). Besides, the diagnosis delay from symptom onset to detection of the culprit tumor was 6.6 ± 6.25 years. Bosman et al. [5] conducted searches on Pubmed, Embase, and Web of Science databases, selected case reports and series diagnosed with TIO, and summarized information, including tumor localization and treatment (as of April 2020). A total of 468 articles with 895 TIO cases were included in that study, making it one of the clinical retrospective studies with the highest number of patients [5]. Bosman et al. [5] found that the median age of TIO patients was 46 years (from 9 months to 90 years old), with most (58.3 %) patients being males. The median size of the tumor was 2.7 cm (from 0.5 to 25.0 cm) [5]. Furthermore, serum FGF23 was significantly correlated with tumor size ($r = 0.344$, $P < 0.001$) [5]. In addition, 62 % of cases (n = 61/99) had a T- score of lumbar spine ≤ -2.5 based on bone density data, and at least 39 % of cases had fractures (n = 346/895) [5]. Also, over 80 % of cases had a diagnosis delay of more than two years [5].

3.2. Laboratory examination of TIO

Tumors secrete phosphorus-regulating factors, thus increasing renal phosphorus excretion and decreasing intestinal phosphorus absorption. Therefore, laboratory tests have shown that TIO is associated with decreased blood phosphorus levels, increased FGF-23 levels, and increased 24-hour urine phosphorus excretion [2,27]. The amount of phosphate lost in the kidney can be evaluated by calculating the percentage of tubular reabsorption of phosphate (% TRP) and the maximum tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) [26]. The level of 1, 25-dihydroxyvitamin D decreases or remains normal in TIO patients [5]. In addition, laboratory tests have shown that blood calcium is normal or slightly reduced in TIO patients, while PTH is mostly normal, with some cases elevated due to FGF23 excess in TIO patients or hyperparathyroidism [28,29]. The levels of alkaline phosphatase (ALP) and procollagen type 1 N-peptide (P 1NP), osteoblast activity indicators, increase in TIO patients [2,3].

3.3. Qualitative diagnosis and localization diagnosis of TIO

Accurate qualitative and localized diagnosis of TIO is crucial for orthopedic surgical treatment. Tumors can be successfully located after several years, making the accurate determination and localization of tumor properties the most difficult step in the diagnostic process [30]. Multiple clinical studies have been made on the diagnosis and treatment of TIO in recent years [2,3,5,25]. Besides, the clinical methods for locating tumors and determining tumor properties, including functional imaging evaluation methods [positron emission tomography/computed tomography (PET/CT), octreotide with single photon emission computed tomography (octreo-SPECT) or octreotide SPECT/CT] and anatomic imaging evaluation methods (ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and segmented venous blood sampling to measure FGF-23 concentration) have been identified. For patients initially suspected to have TIO based on qualitative diagnosis, commonly employed localization methods include ultrasound, CT scans, and MRI imaging. In cases where suspected culprit tumors are located in the skin or superficial subcutaneous soft tissue, it is advisable to conduct preoperative ultrasound evaluations and perform localization markers. This step is crucial for assessing the tumor's blood supply, facilitating intraoperative exploration, guiding tumor resection, and

reducing the risk of complications. In instances where tumors are situated in deep soft tissue, preoperative MRI scans are preferred, provided there are no contraindications. MRI imaging aids in elucidating the tumor's growth pattern and its relationship with adjacent structures. For TIO patients with suspected causative tumors involving bone, preoperative CT scans of the surgical area are recommended as the primary imaging modality. CT imaging offers valuable insights into bone structure erosion and destruction, evaluates local bone stability, and assists in formulating preoperative surgical plans. In addition, when localizing and qualitatively diagnosing orthopedic-related TIO patients, suspected causative tumors often present challenges such as concealed locations, small volumes, and difficulty in visual identification during surgery. Therefore, intraoperative ultrasound is also of great value for the smooth surgical removal of the culprit tumors.

PET/CT is the commonly used examination method for tumor localization and determining the presence of distant metastasis. ^{18}F-fluorodeoxyglucose (FDG) is the commonly used imaging agent [31]. Tumor cells with high glucose metabolism can aggregate ^{18}F-FDG. Most culprit tumors are with high expression of somatostatin receptors on the surface of tumor cells. These somatostatin receptors can specifically bind to somatostatin to locate the tumor. ^{68}Ga-DOTATATE, a ^{68}Ga-labeled somatostatin analogue, is the most common imaging agent used to locate TIO lesions [32]. Preoperative ^{18}F-FDG PET/CT positivity can indicate an increased likelihood of TIO recurrence after surgical resection [33]. However, the chance of recurrence is extremely low when FDG PET/CT activity is not increased in the pathogenic tumor detected by ^{68}Ga-DOTATATE PET/CT [33]. Hou et al. [34] found that ^{68}Ga-DOTA-JR11 PET/CT can more sensitively detect TIO pathogenic tumors than other methods, thus improving the identification of multiple suspected pathogenic tumors displayed in ^{68}Ga-DOTATATE PET/CT. A *meta*-analysis showed that somatostatin receptor imaging mode can more accurately detect TIO than F-FDG PET/CT. Also, ^{68}Ga-DOTATATE PET/CT slightly outperforms octreotide scanning SPECT/CT in detecting TIO [35]. CT or MRI can be used for accurate diagnosis and differential diagnosis of TIO tumors since most TIO tumors are located in bones and soft tissues. In addition, CT or MRI can also be used to visually identify the anatomical lesions in TIO, such as subchondral fractures of the femoral head. Sekine et al. [36] conducted a prospective research and found that PET/MRI performs better than PET/CT in detecting occult tumors. The ^{68}Ga or ^{64}Cu PET/CT should be used as the first-line functional imaging method for TIO patients based on the global guidelines for the diagnosis and treatment of TIO published in 2022. However, octreotide scanning (^{99}mTc - or ^{111}In octreotide scanning) or FDG PET/CT can be used when the above examinations are not available. Notably, the specific optimal method should be selected based on different tumor sites [28].

Tumor cells can autonomously secrete FGF-23 based on the perspective of TIO pathogenesis, necessitating the use of segmented venous blood sampling to measure the concentration level of FGF-23 and locate the tumor in TIO patients, especially when there are two or more suspicious lesions in functional imaging [28,37]. The concentration of FGF-23 is higher in the proximal vein of the tumor than in the distal vein of the tumor, indicating that FGF-23 can be used to determine the exact location of the pathogenic TIO tumor [28,38–40].

4. Principles and methods of orthopedic surgical treatment

Surgical treatment involving complete removal of the pathogenic tumor while avoiding residual culprit tumors as much as possible is the first-line treatment for TIO [5,28,41–43]. Surgical treatment can correct biochemical abnormalities and accelerate the process of bone mineral remineralization in most TIO cases. Notably, clinical manifestations and biochemical abnormalities may persist and recur when a small amount of tumor tissue remains. Studies conducted in Italy showed that patients who underwent lesion biopsy before surgery might suffer from tumor recurrence [23,28]. For phosphaturic mesenchymal tumor (PMT) that has been clinically considered for TIO diagnosis, puncture biopsy is not recommended since it may lead to tumor dissemination or persistent presence of the tumor [25]. Patients with local recurrence require a second or even multiple surgeries to remove the entire tumor or replace damaged tissue (implant placement).

Precise intraoperative localization of the causative tumor is crucial for the success of surgery. Causative tumors in TIO are small and hidden, making it more difficult for intraoperative exploration. Inaccurately identification of tumor location during surgery results in incomplete resection or residual tumor, leading to other symptoms or recurrence. Therefore, intraoperative ultrasound localization can facilitate the identification and surgical removal of occult culprit tumors [44]. Combined with the results of preoperative ultrasound, surgeons can identify and remove small and hidden causative tumors. Besides intraoperative ultrasound, Harbeck et al. reported that the culprit tumor causing TIO can be identified using a handheld gamma probe after intraoperative administration of ^{111} In pentetreotide to achieve satisfactory treatment results [45].

Moreover, the specific surgical plan should be based on the anatomical location of the pathogenic tumor, the feature of lesion, and the extent of involvement. The major surgical plans include complete tumor resection, tumor curettage, and bone cement injection for tumor inactivation [41–43]. However, orthopedic surgical treatment of PMT lacks international consensus. Liu et al. [22] conducted a retrospective analysis of 12 TIO patients and showed that accurate diagnosis and standardized surgical treatment are crucial for the clinical treatment of PMT. Radical resection and microwave ablation-assisted local expansion curettage can treat PMT [22]. Notably, the vast majority of TIO patients with causative tumors located within the skeleton and soft tissue should undergo total tumor resection [2,28,46]. Nevertheless, it is difficult to remove the causative tumor in the bone where some parts of tumor are hidden since this can seriously damage bone stability and function. Tumor curettage or bone cement injection tumor inactivation surgery should be performed in such cases. Moreover, artificial joint prostheses and allogeneic bone can be used to reconstruct and stabilize the anatomical structure and biomechanical stability for residual bone defects after segmental resection. Intraosseous injection of bone cement for tumor inactivation can also be used to treat TIO. Intraosseous injection of bone cement is also suitable in special situations, such as where there are complex local anatomical structures, significant damage during open surgery, and intolerance of open surgery. However, this treatment is limited to case reports, and its specific efficacy and long-term follow-up results require further follow-up [43,47].

Notably, differences in anatomical positions can affect the tumor characteristics of TIO. Li et al. [48] conducted a retrospective study containing 53 TIO patients with culprit tumors in the foot/ankle joint, tibia, and femur, and found that the foot/ankle group had a longer course of the disease and a significantly higher incidence of complications than patients with tumors in other parts ($P < 0.001$). Furthermore, the culprit tumors in the foot/ankle group involved soft tissue ($P = 0.021$), while most lesions in the tibia group involved bone, resulting in a significant increase in alkaline phosphatase concentration ($P = 0.020$) [48]. In addition, the normalization time of serum phosphorus after surgery was longer in the foot/ankle joint group than in the other two groups ($P = 0.004$) [48]. In addition, Ki-67 index and recurrence rate were significantly higher in the foot/ankle joint group ($P < 0.001$) than in the other two groups ($P = 0.002$) [48]. Various culprit tumors can affect different anatomical sites and manifest as soft tissue tumors, bone involvement accompanied by soft tissue tumors, and bone tumors. Compared with culprit tumors in soft tissue, causative tumors involving bones are complex and cannot be completely removed, and thus involve more complex and challenging surgeries [43,48,49]. Surgeons from different countries may have different treatment methods since tumors can be located in any part of the body. Nonetheless, the tumors should be removed with appropriately wide margins (R0 resection) to avoid residual tumors. In a retrospective study with 230 TIO patients, 83 % of

patients recovered after the initial surgery, 11 % of patients had persistent conditions, and 7 % had tumor recurrence (median recurrence time; 33 months) [49]. Woman gender, spinal tumors, bone tissue-related tumors, malignant tumors, and low preoperative serum phosphate levels are considered risk factors for refractory TIO [49]. Therefore, it is important to explore the effectiveness of orthopedic surgical treatment for culprit tumors at different anatomical sites to improve the understanding of the disease and surgical treatment (Fig. 1), especially for TIO's culprit tumors with complex anatomical structures.

4.1. Culprit tumors within soft tissue

Most culprit tumors are located within soft tissue without bone involvement. The first treatment step for such patients involves determination of the location and adjacent structure of the suspected pathogenic tumor [50]. Besides, the surgeon should pay special attention to the identification and protection of key anatomical structures, such as local nerves, blood vessels, muscles, fascia, and ligaments, during the surgical operation to avoid unnecessary injuries. Li et al. [48] conducted a retrospective study containing 53 TIO cases of culprit tumors located at the ankle, tibia, and femur and showed that the culprit tumors in the ankle were located in soft tissue, while most lesions in the tibia were located in the bone. Furthermore, the time required for postoperative blood phosphorus to return to normal was significantly increased in the ankle group compared with the other two groups ($P = 0.004$). Sun et al. [42] also showed that surgical resection can treat TIO patients with pathogenic tumors located in the limbs. Limb soft tissue PMT has a better surgical effect than intraosseous PMT [42]. For soft tissue causative tumors located in special anatomical locations, it is necessary to fully consider the specificity of the lesion location and develop reasonable surgical plans. In this review, we have compiled literature reports on TIO patients with culprit tumors located in the inguinal region (Table 1) [51–56].

4.2. Culprit tumors located in limb bones

Although complete tumor resection can lead to a good prognosis for TIO patients, the causative tumor is hidden in some patients (such as tumors located in the femoral head or tibial plateau), thus greatly increasing the complexity of surgical treatment. Complete removal of tumors near the joint usually leads to surface destruction of the joint, and thus can easily affect joint function. Therefore, lesion curettage or radiofrequency ablation is more suitable in such cases. Moreover, joint replacement surgery is suitable for patients whose tumor cannot be completely removed since it may result in persistent symptoms [57]. Zhu et al. [57] conducted a retrospective study with 16 TIO patients to evaluate the surgical treatment effect of joint replacement and tumor resection on PMTs and found that causative tumors were located on the

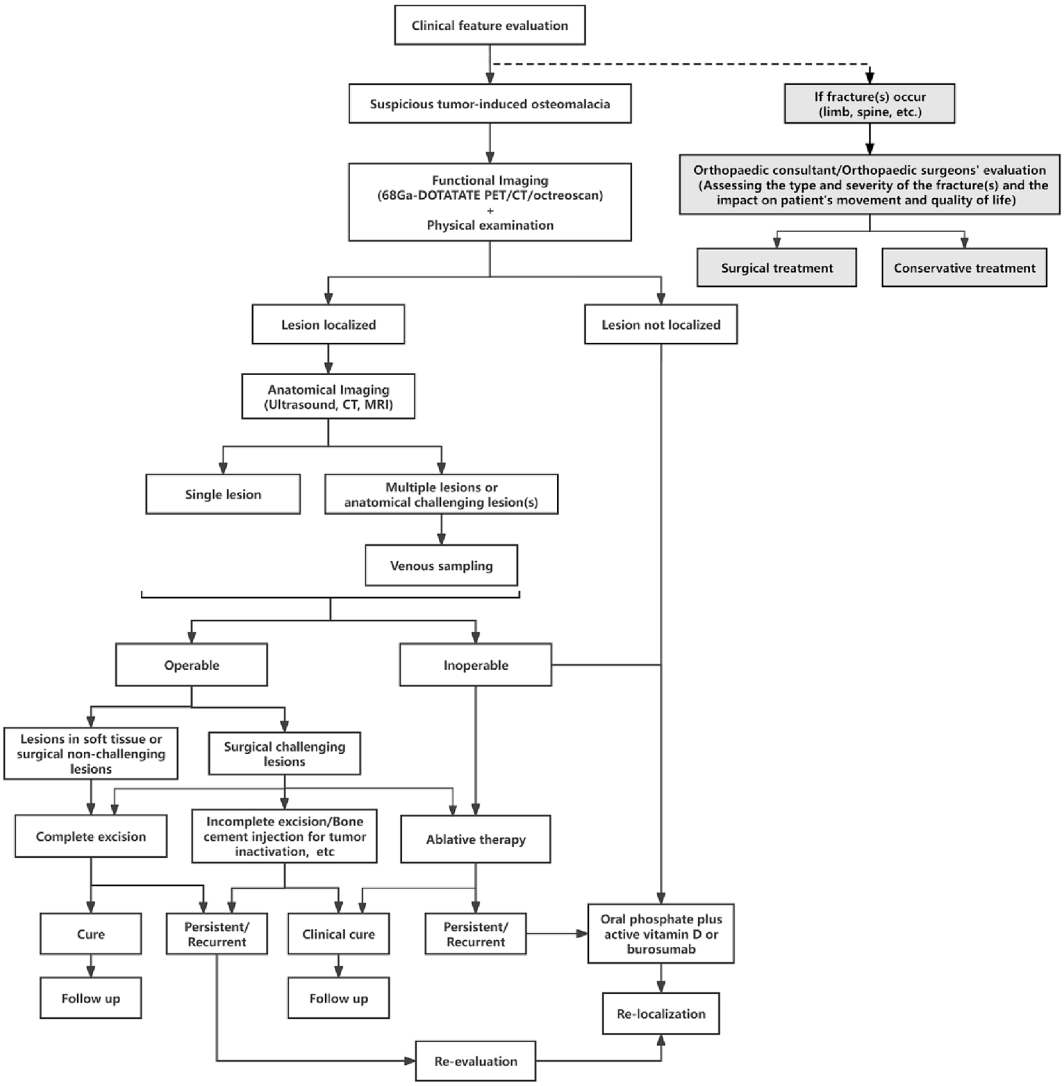

Fig. 1. Flow chart of orthopedic surgery treatment strategy for TIO.

Table 1
Clinical review of six previously published cases with culprit tumors in the inguinal region.

Authors	Year	Age (y), sex	Symptoms and course of disease	Serum phosphorus concentration	Localization methods	Localization	Tumor size	Treatment	Outcome	Follow up (month)	Histological diagnosis
Ha S[51]	2018	52, M	Pain in his neck, back, waist, left hip, right arm, chest	A low serum phosphorus concentration (1.3 mg/dL; normal range 2.5–4.5 mg/dL)	^{18}F-FDG PET/CT, ^{99}mTc whole body bone scans, CT	Right inguinal region	1.0-cm-sized round	The right inguinal nodule was surgically removed	Complete remission after operation	1	PMT
Tonello L [52]	2017	40, M	Several structural deformities for over three years	Inorganic phosphorus (serum)1.7 mg/dL (normal range 3.4–4.5 mg/dL)	MRI, PET/CT, bone scintigraphy with technetium	Left inguinoscrotal area	3.5 × 3.0 × 2.0 cm	Surgical resection with free margins	Complete remission after operation	3	PMT
Kobayashi H[53]	2017	37, M	Hip pain for 3 years	NA	MRI	Groin	NA	The lesion was excised	Complete remission after operation	170	NA
Zuo QY[54]	2017	F	2 years	0.36 mmol/L	OCT ^{99}mTc-octreotide; MRI; ultrasonography	In the mons pubis	/	/	/	/	PMT
Chouhan V [55]	2015	32, M	Pain in his right foot, both lower limbs for 18 months	The serum phosphate level was low (0.226 mmol/L)	MRI, PET/CT	In the right thigh	2.5 × 1.9 cm	The lesion was excised	Complete remission after operation	6	Benign fibrous histiocytoma; benign mesenchymal soft-tissue neoplasm
Takeuchi Y [56]	2004	37, M	Chronic pain of the spine, ribs, femurs, hip joints, and progressive muscle weakness for 2 years	A low serum phosphorus concentration (1.5 mg/dL; normal range 2.5–4.5 mg/dL)	MRI	In the right inguinal region	3.0 × 3.0 × 2.5 cm	Removal of the tumor	Complete remission after operation	NA	Hemangiopericytoma

Note: M: male; F: female; PMT: phosphaturic mesenchymal tumor; NA: none; CT:computed tomography; MRI: magnetic resonance imaging; OCT: Octreotide; PET/CT: Positron emission tomography/computed tomography.

metaphyseal joint surface after a one-year postoperative follow-up of bone metabolism index, hip/knee joint function, joint replacement complications, and symptoms. Thirteen cases were undergoing hip joint replacement, and three cases were undergoing knee joint replacement [57]. Further results showed that joint replacement and tumor resection can significantly and quickly improve bone metabolism indicators in TIO patients, without tumor recurrence during short-term follow-up [57]. Also, the postoperative joint function score of the patients was significantly improved [57]. The major postoperative complications in these patients mainly included postoperative pain, joint clicking, and secondary hyperparathyroidism [57].

However, clinical diagnosis and treatment of complex TIO tumors involving joints are complicated. Sun et al. [58] reported a 30-year-old woman with a history of gradual enlargement of the left knee surrounding mass within 11 years and worsening bone pain within two years. The patient first underwent bone cement prosthesis reconstruction after a thorough evaluation [58]. Pathology confirmed PMT when the blood phosphorus level rose to the normal range [58]. As a result, a subsequent tumor-type knee joint prosthesis replacement was performed to maximize joint mobility [58]. The blood phosphorus concentration remained within the normal range after one and a half years of surgery, and the symptoms of systemic bone pain significantly improved [58]. The prosthesis remained in good position, and there was no local recurrence [58].

Wang et al. [41] retrospectively analyzed 17 TIO patients with pathological tumors located in the long bone and compared the surgical treatment effects of lesion curettage and segmental resection of long bone lesions and showed that the complete resection rate was not significantly different between curettage surgery (67 %) and segmental resection surgery (80 %). However, the recurrence rate was significantly higher after curettage surgery (50 %) than after segmental resection (0 %) [41]. Besides, the complete resection rate was not significantly different between secondary segmental resection (75 %) and primary segmental resection (83 %) [41]. Therefore, curettage surgery should be performed first to maintain joint function and stability [41]. However, segmental resection surgery is recommended if the patient experiences recurrence during follow-up and imaging examination indicates residual or local tumor recurrence to achieve a better disease prognosis [41]. Pathology is the gold standard for diagnosis of suspected cases of TIO, indicating that PMT that has not been confirmed by pathology after undergoing highly traumatic open surgery can significantly affect the patients. Zhou et al. [43] reported bone cement injection tumor destruction technology that can treat TIO cases with pathogenic tumors involving limb bones and achieved satisfactory treatment and follow-up results. Bone cement can also facilitate intraoperative localization of the culprit tumor if tumor recurrence occurs during follow-up.

This review summarizes the literature on the diagnosis and treatment of TIO cases with culprit tumors located in the pelvic region (excluding the sacral region) and within the femoral head, and is summarized in Table 2 and Table 3 respectively. Orthopaedic surgical intervention in TIO cases is significantly limited when the causative tumor involves special bone structures, such as the femoral neck, femoral condyle, femoral head, tibial plateau, and pelvis because: (1) excessive pursuit of complete removal of the causative tumor body may lead to serious degradation or even loss of local bone and joint functions, and even lead to a series of important skeletal-related events, such as bone non-union, bone healing difficulties, bone defects, and fractures; (2) it may lead to disease recurrence or persistence if the complete resection of the causative tumor is not achieved. As a result, patients usually undergo further surgical intervention. Therefore, further studies should assess how to achieve clinical cure of TIO while ensuring local motor function.

4.3. Culprit tumors located in spinal region

It is difficult to completely remove causative tumors for TIO in the spinal region due to the complexity of the spinal anatomical structure [77–88]. The removal of causative tumor in the spinal region is one of the high-risk factors for poor prognosis after surgical intervention [49], indicating that partial or subtotal resection may also lead to sustained biochemical abnormalities or tumor recurrence in this region. Therefore, rigid internal fixation and effective support should be ensured in such cases to prevent osteomalacia-induced reduced bone density and the risk of bone non-union or fracture. Sciubba et al. [85] were the first to treat spinal PMT using En bloc resection surgery, and obtained a good therapeutic effect on patients with TIO where the causative tumor is located in the spinal region. Meng et al. [81] also showed that En bloc surgery can remove PMT in the thoracic vertebral region with satisfactory short-term follow-up effect. Although the scope of surgical resection is related to overall survival benefits, complete resection can also easily lead to various complications, such as spinal instability, decreased spinal mobility, neurological symptoms, dural rupture, and nerve damage [81–88]. PMT-induced osteomalacia limits clinical diagnosis and treatment of TIO. Besides, local recurrence can occur even if the patients undergo thorough surgical resection due to the complex nature of anatomical structure of the spinal region [82]. Liu et al. [82] indicated that TIO patients can benefit from multidisciplinary cooperation model of endocrinology, orthopaedics, otorhinolaryngology, nuclear medicine, radiology, pathology, and medical oncology experts. Liu et al. [47] also suggested that open surgery for spinal region PMT can completely remove the causative tumor. However, bone cement injection for tumor damage may also be a reasonable surgical treatment option for PMT patients who cannot undergo appropriate surgery or refuse open surgery. Nonetheless, the long-term follow-up efficacy of this treatment needs further study [47,82]. Bone cement can also serve as an indicator for tumor localization during preoperative reevaluation and reoperation for anatomically challenging TIO cases if the treatment effect of bone cement injection technique for tumor damage is not satisfactory or if pathology confirms that the excised tumor is not a causative tumor. However, the potential risks of bone cement application should be analyzed using studies with larger samples and longer follow-up times. Incomplete local tumor resection and leakage of bone cement into the spinal canal, and compression of the spinal cord are the most common postoperative complications. Therefore, the surgical scope, amount of bone cement injection, and postoperative complications should be further assessed [43]. In order to present the diagnosis and treatment experience of causative tumors for TIO in the spinal region more clearly, we have organized and drawn Table 4 based on the literature review.

4.4. Pathological characteristics of culprit tumors in TIO

Most tumors causing TIO are benign tumors [5]. Tumors often originate from mesenchymal tissue and have various pathological types, including vascular epithelial tumors (most common), hemangiomas, sarcomas, fibromas, and giant cell tumors [106,107]. Although there are many pathological tumor types, they are essentially homologous and can be collectively referred to as phosphaturia mesenchymal tissue tumors, including mixed connective tissue subtypes (PMTMCT), osteoblast-like subtypes, non-ossifying fibroadenoma-like subtypes, and ossifying fibroadenoma-like subtypes [54]. The concepts of PMT and PMTMCT were first proposed by Weidner in 1987 [108]. Weidner found that 10 of 17 PMT cases were mixed connective tissue tumors, while 4, 2, and 1 were osteoblastoma-like tumors, non-ossifying fibromatous tumors, and ossifying fibromatous tumor, respectively [108]. Folpe et al. [100] further analyzed 32 cases of TIO in 2004 to confirm that PMTMCT is a unique clinical pathological type and corrected the diagnosis of some pathological types. The typical pathological manifestations of PMTMCT include spindle-shaped and stellate cells with uniform color, small nuclei, and unclear nucleoli, rich blood vessels, thick-walled deformities. Visible pathological manifestations include calcification and metaplasia [100]. Immunohistochemistry can detect epithelial and mesenchymal components that exhibit fibroblast growth factor-23, somatostatin receptor 2A, and NSE immune responses [109].

Table 2
Clinical review of previously published causative tumors for TIO in the pelvic region (excluding the sacral region).

Authors	Year	Age (y), sex	Symptoms and course of disease	Laboratory findings	Localization methods	Localization	Tumor size	Treatment	Outcome	Follow up	Histological diagnosis
Horng JC [59]	2021	61, M	Bilateral tibial stress fractures 12 years previously. Several stress fractures in his feet 2 years prior to initial evaluation	Hypophosphatemia	^{68}Ga-DOTATATE PET/CT	Left ischial lesion	2.9 × 3.4 × 1.5 cm	Surgical excision; image-guided ablation	Despite surgical excision, the hypophosphatemia persisted	158 days	PMT; recurrent PMT
Turin CG [60]	2021	43, M	Progressive fatigue, weakness, muscle and joint pain in setting of recurrent fractures	Low phosphorus at 1.5 mg/dL	^{68}Ga-DOTATATE PET/CT	The left acetabular	1.4 cm	Biopsy; radical resection of the tumor of the posterior left acetabulum with reconstruction of the posterior wall and posterior column of the acetabulum through a Kocher-Langenbach approach	Complete resolution	6 months	PMT
Mishra SK [61]	2019	43, M	Five-year history of diffuse bony pains, pain in ribs, and proximal muscle weakness	Hypophosphatemia	^{68}Ga-DOTATATE PET/CT	The roof of right acetabulum	About 1.1 × 0.9 × 1.4 cm	A single session of RFA; biopsy of the lesion was performed before ablation	Complete resolution	24 months	Scanty tissue
Nakamura K[62]	2018	68, F	Progressive bone pain of the rib cage, and polyarthralgia and back pain for 3 years	Hypophosphatemia (1.7 mg/dL)	Bone scintigraphy, MRI, CT	The right acetabulum	NA	Open biopsy of the bone tumor; curettage of the tumor and the defects were filled with bone allografts; total hip arthroplasty. For the acetabular component, a Müller acetabular support ring was used. A press-fit type cementless femoral component was used	No remission; The patient started taking phosphate supplementation and alphacalcidol. Although a CT scan did not show findings of recurrence (data not shown), the patient is being kept under careful observation	12 months	PMT
Zuo QY [54]	2017	F	/	Hypophosphatemia (0.69 mmol/L)	MRI, CT	Right ilium	/	/	/	/	PMT
Morimoto T[63]	2014	35,F	Lower back pain	Severe hypophosphatemia (1.4 mg/ml)	^{18}F-fluorodeoxyglucose (FDG)PET/CT	In the right acetabulum	/	An open biopsy; transcatheter arterial embolization (TAE) of the feeding artery of the pelvic tumor	Regrowth of the pelvic tumor and multiple metastases in the lung and bones were observed 32 months after the second TAE	32 months	Malignant PMT
		31, M	Worsening bilateral thigh pain and gait disturbance for 21 years	Severe hypophosphatemia (1.3 mg/ml)	Bone scan; X-ray; CT; MRI	In the right ischium	/	An open biopsy; the patient underwent two courses of TAE of the feeding artery of the pelvic tumor, with only limited response, and therefore subsequently underwent tumor excision	Local recurrence in the pelvis, multiple coin lesions in the lung and a subcutaneous mass in the left elbow. Metastases of the PMT were diagnosed and the patient underwent chemotherapy. Succumbed to respiratory failure due to relapsing lung metastases and disseminated intravascular coagulation	/	PMTMCT; metastases from the PMT with malignant transformation
Radaideh AR[64]	2009	39, M	Low back pain for 3 years. A few months later, he developed limping on the left leg	Persistent hypophosphatemia 0.6 mmol/L (normal range: 0.81–1.6 mmol/L)	A three-phase ^{99}Tc bone scan	Medially to the left psoas muscle	5 × 1.2 × 1 cm	The tumor was resected	Complete resolution	3 years	PMTMCT

(*continued on next page*)

Table 2 (*continued*)

Authors	Year	Age (y), sex	Symptoms and course of disease	Laboratory findings	Localization methods	Localization	Tumor size	Treatment	Outcome	Follow up	Histological diagnosis
Nelson AE [65]	2003	52, M	Fracture of the right third metatarsal and multiple rib fractures after gym exercise	Hypophosphatemia	Whole body bone scintigraphy; Plain radiography; Whole body scintigraphy with octreotide	In the right superior pubic ramus	2.7 × 2.7 × 4 cm	Excision biopsy; removal of the angiolipoma; surgically removed en bloc	Complete resolution	12 months	A benign angiolipoma
François S [66]	1997	10, M	Diffuse bone and muscle weakness for two years	Phosphorus was very low (0.43 mmol/l)	Radiograph	In the left superior pubic ramus	NA	Complete tumor resection and the space was filled with bone graft	Complete resolution	NA	Benign mesenchymal tumor

Note: M: male; F: female; PMT: phosphaturic mesenchymal tumor; PMTMCT: phosphaturic mesenchymal tumor, mixed connective tissue variant; NA: none; CT:computed tomography; MRI: magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography.

Mesenchymal components can also show diffuse positive staining for CD68 and variable focal staining for SMA and CD34 [109]. In a retrospective review, most culprit tumors were classified as PMT (65.4 %), followed by hemangiopericytoma and giant cell tumors [5]. Bosman et al. [5] found that PMT accounted for 75.5 % of all cases based on cases published by Folpe et al. in 2004 [100].

4.5. Perioperative management, postoperative recovery and standardized follow-up

For patients with TIO, surgical treatment is the first-line treatment. Successful removal of the causative tumor can lead to the reversal of biochemical abnormalities and the alleviation of clinical symptoms. However, due to the rarity of TIO and its specific diagnostic criteria, special attention must be paid to the perioperative management of these patients to ensure optimal outcomes. Phosphate supplementation has been shown to contribute to the occurrence of hyperparathyroidism (HPT) in patients with TIO, including secondary HPT (SHPT) and tertiary HPT (THPT) [110]. Ni et al. [110] found that HPT is common in patients with TIO, and therefore such patients should not be administered with high doses of phosphate before surgery. Following surgery, it is essential to monitor the patient's blood phosphorus levels in a standardized manner to track the trend of changes. Typically, blood phosphorus levels can gradually normalize within a few days or weeks after surgery. Concurrently, the circulating levels of FGF23 rapidly decline, leading to an improvement in the patient's clinical symptoms. Furthermore, post-surgery, bone density in various parts of the patient's body increases, aiding in the gradual recovery of symptoms associated with osteoporosis. Therefore, monitoring these parameters in a standardized manner is critical in post-surgery care to ensure optimal recovery [1–3,111]. However, bone mass recovery requires a clinical process, and patients may experience Hunger Bone Syndrome (HBS) as bones remineralize, characterized by secondary hyperparathyroidism with or without hypocalcemia, hypophosphatemia, and/or hypomagnesemia [35,112–114]. Therefore, perioperative management of TIO patients is of significance and longer follow-up time is required to observe the changes in bone microstructures after tumor resection. Clinicians should pay special attention to monitoring and nursing of postoperative biochemical indicators, bone density, and clinical symptoms in the short term after surgery [111,115,116].

Extensive tumor resection does not completely eliminate the possibility of metastasis or recurrence. Therefore, patients who are subjected to surgical resection of the responsible tumor have to undergo long-term and standardized follow-up [2,28,117]. In a retrospective study of 230 TIO patients, the majority of cases remained in remission after the initial surgery, symptoms persisted in 11 % of cases while recurrence occurred in 7 % of cases (with a median recurrence time of 33 months) [49]. If the tumor cannot be completely removed, treatment can be performed by supplementing drugs such as phosphate and calcitriol as well as radiofrequency ablation among others. Serum phosphorus and clinical symptoms can be improved to a certain extent, however, it is difficult to maintain blood phosphorus levels at normal levels for a long time. Global guidelines for clinical management of TIO patients recommend that [28]: i. For cases that can be surgically removed, complete surgical resection should be performed to achieve complete removal of pathogenic tumors; ii. For TIO patients diagnosed with unresectable or unidentifiable pathogenic tumors, treatment with oral phosphate plus active vitamin D or burosumab is necessary, and effectiveness, clinical reactions, and adverse events of the treatment should be regularly evaluated; iii. Every 3–4 months, TIO patients who cannot be resected or for whom the causative tumor cannot be identified but are given a stable dose of oral phosphate plus active vitamin D or burosumab should be followed up to monitor serum and urine calcium, phosphate, creatinine, PTH, total or bone specific ALP and renal ultrasound. Frequent monitoring is required after starting treatment and dose adjustment; iv. Functional imaging follow-up is conducted every 1–2 years for TIO

Table 3
Clinical review of previously published TIO patients with causative tumors in the femoral head.

Authors	Year	Case	Age (y), sex	Symptoms	Preoperative blood phosphorus	Localization methods	Localization	Treatment	Outcome	Follow up	Histological diagnosis
Zhang Z [67]	2023	Case 1	36,F	Low back pain with mild motor dysfunction for 2 years	0.50 mmol/L	SPECT Whole Body Bone Scanning; ^{68}Ga-DOTATATE PET/CT	A single lesion in the right femoral head (a size of about 20 mm × 10 mm × 10 mm)	CT guided right femoral tumorectomy and bone grafting	Improvement	6 months	PMT with positive staining of CD56, SATB2 and FLI-1
Zhang Y [68]	2023	Case 1	27, M	Bone pain	0.3–0.4 mmol/L	^{68}Ga-DOTATATE PET/CT	In the right femoral head	Right hip arthroplasty	Improvement after the first operation; 8 years later with lung nodule as culprit lesion causing recurrent TIO	8 years	PMT
Hervier E [69]	2023	Case 1	31,F	Progressive bone pain and muscle weakness, painful nonunion traumatic rib fractures, chronic lower back pain, left hip pain, and muscle weakness	0.59 mmol/L	^{68}Ga-DOTATATE PET/CT	In a lucent lesion of the left femoral head	A bone biopsy; CT-guided radiofrequency ablation	Improvement	3 years	Bland stellate to short spindle cells, filling the medullary spaces, set in a background of myxoid to hyalinized matrix. The histologic features could reasonably exclude the diagnosis of osteoid osteoma
Arita S [70]	2022	Case 1	57, M	Lower back pain and gait disturbance. Six years earlier, the symptoms of right lower limb pain, chest pain, lower back pain, fatigue, weakness of the trunk and muscle weakness had gradually appeared	1.5 mg/dL	Somatostatin receptor scintigraphy	In the right femoral head (approximately 18 × 13 mm)	Cemented hemiarthroplasty	Improvement	9 months	PMT
Ni HJ[71]	2021	Case 1	48, M	An acute exacerbation of chronic lower back pain and severe bilateral leg weakness, present for at least 6 years. Pain severely restricted his mobility confining him to life in his apartment. Short stature	0.21–0.76 mmol/L	A whole-body bone scan; ^{68}Ga-DOTATATE PET/CT	In the left femoral head (measuring 27 mm)	CT guided steroid injections; bilateral total hip replacement	Improvement	10 months	PMT
Yang M [72]	2019	Case 1	37, M	Debilitating bone pain and progressive generalized weakness needing assistance of a rolling walker for ambulation over the past several years	Severe hypophosphatemia	Whole-body bone scintigraphy; ^{68}Ga-DOTATATE PET/CT	Near the right femoral neck	Right total hip replacement	His FGF23 dropped to 161 RU/ml at day 1 postsurgery	/	Benign PMT
Colangelo L[73]	2018	Case 1	33, M	Five years' history of lumbar and pelvis pain together with multiple vertebral fractures	0.41 mmol/L	A full-body CT scan; the Octreoscan; ^{99}m-Technetium (^{99}mTc)-HYNIC-TOC (hydrazinonicotinyl-Tyr3-octreotide)	In the right femoral head	Excision of the femoral head; The patient underwent an operation with the plan being to first remove the femoral head lesion while performing an	Improvement	4 months	Mesenchymal highly vascular tumor

(*continued on next page*)

Table 3 (*continued*)

Authors	Year	Case	Age (y), sex	Symptoms	Preoperative blood phosphorus	Localization methods	Localization	Treatment	Outcome	Follow up	Histological diagnosis
								intraoperative FGF23 assay to confirm tumor resection			
Jadhav S [74]	2014	Case 1	38, M	Low backache, diffuse bony pains, proximal muscle weakness	Hypophosphatemia	^{99}mTc-HYNIC-TOC SPECT CT scan	In the head of right femur	A single session of RA	Three months after RFA, ^{99}mTc SPECT/CT showing the absence of uptake in the same area	3 months	Only scanty fibrocartilaginous tissue, insufficient for opinion
Hesse E [75]	2007	Case 1	60,F	Severe pain in her back and chest wall, muscle weakness, and reduced physical activity	Hypophosphatemia	^{111}In-octreotide scintigraphy, and ^{68}Ga PET/CT	In the right femoral head	A standard total right hip arthroplasty was performed to remove the entire tumor	Improvement	7 months	A cell-rich hemangiopericytoma-like mesenchymal tumor
Hesse E [76]	2007	Case 1	40,F	Acquired hypophosphatemic, vitamin D–resistant osteomalacia	0.45 mmol/L	PET/CT	In the right femoral head	Multiple tissue samples were obtained with the use of needle biopsy guided by CT; CT-guided RA; Complete tumor ablation was achieved 6 days later, after a second round of RA	Improvement	1 years	A benign mesenchymal tumor

Note: M: male; F: female; PMT: phosphaturic mesenchymal tumor; NA: none; CT:computed tomography; MRI: magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography; RA: radiofrequency ablation; FGF23: fibroblast growth factor 23.

patients who cannot identify the causative tumor, and anatomical imaging follow-up is conducted for patients with unresectable tumors.

4.6. Refractory and recurrent TIO

In the latest systematic review, it was observed that 5.5 % (57 out of 1070) of patients diagnosed with TIO were deemed unsuitable for surgical treatment due to impracticality or ineffectiveness of surgical intervention [23]. In a recent cohort study conducted by Crotti et al., which spanned from September 2000 to May 2020 and included 17 patients, approximately 18 % (3 out of 17) were found ineligible for surgical treatment due to the localization of tumors (second sacrum, skull, left femoral Scarpa triangle) [25]. These three patients (18 %) were only administered supportive drug treatment owing to the unsuitability of tumor localization for surgical eradication [25]. Malignant TIO refers to tumors with the potential for metastasis or local recurrence. Within the study cohort, a total of 67 patients with malignant TIO were identified, comprising 35 males (52.2 %) and 32 females (47.8 %). This constituted approximately 3.9 % (67 out of 1725) of the total patients included in the study [23].

About 20 % of TIO patients experience recurrence or inability to recover after surgery [20]. Clinical diagnosis and treatment of refractory/recurrent TIO is very challenging [20,49,118]. Li et al. [49] retrospectively analyzed 230 TIO patients who underwent surgical treatment at Peking Union Medical College Hospital. After initial surgery, 26 cases (11.3 %) persisted while 16 cases (7.0 %) recurred. The overall ineffective rate of treatment was 18.3 %, with a median recurrence time of 33 months. Compared with the recovery group, patients in the refractory group were more likely to be female (59.5 % vs 41.0 %, $p = 0.029$), and had lower preoperative serum phosphorus levels (0.44 ± 0.13 vs 0.50 ± 0.11 mmol/L, $p = 0.002$). The refractory rate of head/neck tumors was the lowest (7.5 %), while that of spinal tumors was the highest (77.8 %). The refractory rate for bone tumors was higher than that of soft tissue tumors (32.7 % vs 7.0 %, $p < 0.01$). The prognosis of malignant tumors was worse than that of benign tumors ($p < 0.01$). In multivariate regression analysis, women, spinal tumors, bone tissue involvement tumors, malignant tumors, and preoperative low serum phosphorus levels were identified as risk factors for refractory outcomes. In clinical practice, for cases where rigid internal fixation materials have been used for the first surgery (such as spinal screw rod systems, artificial joints, etc.), orthopedic physicians should overcome difficulties such as artifact interference caused by internal fixation materials in imaging examination, tumor dissemination, or multi-focal distribution in re-evaluation of refractory cases. Accurate determination of the location and extent of the causative tumor using clinical data and auxiliary examination will inform on further assessment and development of intervention plans.

4.7. Management of fractures caused by severe osteomalacia in TIO

In TIO, high secretion of FGF-23 leads to increased renal phosphorus excretion and reduced intestinal phosphorus absorption, resulting in reduced bone resorption of calcium and phosphorus and inhibited bone mineralization in osteoblasts. For TIO patients with longer or more severe disease course, a severe decrease in bone density often leads to occurrence of multiple fractures throughout the body. Bone microstructure dysplasia in TIO patients can be accompanied by severe skeletal malformations, such as spine, limbs, etc., which can lead to bone pain and seriously affect the quality of life (QoL) for patients [119]. Therefore, apart from resection surgery for TIO causative tumors, occurrence of fractures during the disease course is a key and challenging factor in orthopedic surgical management [53,120,121].

Kobayashi et al. [53] found that hip fractures and subchondral insufficiency fractures of the femoral head are very common in TIO patients. Hip fractures in TIO patients can be improved after surgery and medication, and conservative treatment can be performed. However,

Table 4
Clinical review of previously published TIO patients with causative tumors in the spinal region.

Authors	Year	Case	Age (y), sex	Symptoms	Preoperative blood phosphorus	Localization methods	Localization	Treatment	Outcome	Follow up (M)	Histological diagnosis
Chen D[88]	2024	Case 1	47, male	Joint stiffness, pain in his bilateral foot, weakness	Hypophosphatemia	Octreotide; ^{68}Ga-DOTATATE PET/CT scan	Extradural tumor in the intraspinal canal from T11 to L5	Resection of the tumor at the lower segment of the right femur, and postoperative pathology showed malignant phosphaturic mesenchymal tumor tumors; A gross total resection was performed without intraoperative complications	Improvement	3	Malignant PMT
Pannu CD [89]	2023	Case 1	61, male	Generalised myopathy, bone and joint pain and malaise	Hypophosphatemia	^{68}Ga-DOTATATE PET/CT	In the left pedicle of T9	Excision biopsy was performed in an elective setting after stabilizing the spine with a unilateral single-level screw rod construct following the excision of the left T9 pedicle	Improvement	12	PMT
		Case 2	40, female	Severe thoracic back pain after falling on her mid-thoracic back	Hypophosphatemia	MRI	Between the right T5/6 costovertebral regions	The needle biopsy; excision biopsy	Improvement	72	PMT
		Case 3	71, male	A sudden, spontaneous fracture of the right neck of femur. Unable to walk on his feet	Hypophosphatemia	^{68}Ga-DOTATATE PET/CT	In the left lamina of T5 (measuring approximately 18 × 19 mm)	An en-bloc resection of T5 lamina and spinous process	Improvement	6	PMT
Agarwal A [90]	2023	Case 1	65, female	/	Low serum phosphate level	PET/CT	/	/	/	/	PMT
Mancini AJ [77]	2022	Case 1	60, female	Multiple fractures, pain	1.5–2.4 mg/dL (reference: 2.5–4.9 mg/dL)	^{68}Ga-DOTATATE, MRI	Posterior right T12 vertebral body	Thoracic hemilaminectomy with en bloc spondylectomy of the T12 tumor with T10–L2 posterior instrumented fusion	Improvement	26	PMT
Filipová L [91]	2022	Case 1	53, female	Bone pain, muscle weakness and multiple bone fractures	Hypophosphatemia due to renal phosphate wasting and elevated plasma fibroblast growth factor 23	^{68}Ga-DOTATOC PET/CT, CT scan, MRI	In the vertebral body of L2	Surgical resection of the tumor	Improvement	NA	PMT (benign variant)
Sistani G[80]	2022	Case 1	70, female	Unsteady and shuffling gait and generalized body pain	A low phosphate level of 0.48 mmol/l (normal range: 0.8–1.45 mmol/l)	CT,MRI,bone scintigraphy	Sacral spinal canal and extending through the anterior sacral foramina	Incomplete resection, the patient underwent radiation and was placed on phosphorus and calcitriol	Improvement	NA	PMT
Garg B[78]	2020	Case 1	55, male	Bone pain at multiple sites and difficulty in standing up	Serum phosphate (1.4 mg/dL, normal range 2.5–4.5 mg/dL)	^{68}Ga-DOTANOC PET/CT, CT, MRI	Posterior arch and transverse process of the T2 vertebra	Complete tumour excision (laminectomy + costotransversectomy + pediculotomy + hemicorpectomy) + instrumented fusion)	Improvement	36	PMT
Liu S[82]	2020	Case 1	52, male	Back pain, systemic bone pain	Hypophosphatemia (0.53 mmol/L; normal: 0.81–1.45 mmol/L)	MRI of spine and PET/CT	L5 (in the left posterior part of the spinal canal at the level of L5)	Posterior L5 tumor resection, bone cement reconstruction, L4-S1 spinal canal decompression, and L3-S2 internal fIxation	Improvement	36	PMT

(*continued on next page*)

Table 4 (*continued*)

Authors	Year	Case	Age (y), sex	Symptoms	Preoperative blood phosphorus	Localization methods	Localization	Treatment	Outcome	Follow up (M)	Histological diagnosis
Wang X[83]	2019	Case 1	34, female	Bone pain, unable to walk	Hypophosphatemia	PET/CT	L1	Complete resection	Improvement	60	PMT
Yang M[72]	2019	Case 1	70, male	Persistent muscle aches, joint aches, and weakness	Hypophosphatemia and elevated FGF23 at 930 RU/ml	Whole-body bone scintigraphy, MRI, In-^{111} pentetreotide scintigraphy (Octreoscan), Ga^{68}-DOTATATE PET/CT	At the anterior portion of the T11 vertebral body	Partial corpectomy of T11	His FGF23 level dropped to 78 RU/ml immediately after surgery	NA	Benign PMT
Agarwal N [79]	2019	Case 1	71, male	NA	NA	NA	Right C2 lamina	C2 hemilaminectomy	Improvement	NA	PMTMCT
Yamada Y [92]	2018	Case 1	68, male	NA	NA	NA	L	Biopsy	NA	NA	PMTMCT
		Case 2	54, male	NA	NA	NA	L5	Resection	No recurrence	NA	PMTMCT
Kobayashi H [93]	2017	Case 1	62, male	NA	Elevated FGF-23	NA	L1	Incomplete resection	Recurrence	99	NA
Zuo QY[54]	2017	Case 1	Female	Bone pain, muscle weakness, general debility, unable to walk	Hypophosphatemia, elevated ALP and PTH	OCT, PET/CT, MRI	L1	Tumor resection	Recurrence	34	PMT
		Case 2	Female	Bone pain, muscle weakness, general debility, unable to walk	Hypophosphatemia, elevated ALP,	OCT, PET/CT, MRI	L1	Tumor resection	Improvement	22	PMT
		Case 3	Female	Bone pain, muscle weakness,	Hypophosphatemia, elevated ALP and PTH	OCT, PET/CT, MRI	S1	Tumor resection	Improvement	22	PMT
Maehara J [94]	2016	Case 1	54, male	Chronic pain in his chest, back and both legs	Low serum phosphorus (2.0 mg/dl)	^{68}Ga-DOTATOC PET/CT, CT, MRI	L5	Total excision	Improvement	NA	PMT
Meng T[81]	2015	Case 1	60, male	Bone pain, weakness, paresthesia	Hypophosphatemia, elevated PTH	MRI	T1	Complete resection, supplementation of calcitriol	Improvement	48	PMT
Nakamura T [84]	2015	Case 1	72, male	Weakness	Hypophosphatemia, elevated ALP and PTH	MRI, bone scan	C5	Complete resection, supplementation of phosphate and calcitriol	Improvement	60	PMTMCT
Puthenveetil PJ[87]	2013	Case 1	61, female	Musculoskeletal pain, weakness, fractures	Hypophosphatemia, increased ALP and FGF-23	PET/CT	T12	Complete resection, supplementation of calcium and phosphate	Persistent serum abnormalities	30	PMTMCT
Gandhi GY [95]	2012	Case 1	66, female	Bone pain, weakness	Hypophosphatemia, elevated ALP and PTH	MRI, bone scan	L4	Complete resection	Improvement	6	PMTMCT
Akhter M[96]	2011	Case 1	52, female	Fracture	Hypophosphatemia and elevated FGF-23	PET/CT, MRI	C5	Complete resection	Improvement	12	PMTMCT
Mavrogenis AF[97]	2010	Case 1	42, female	Bone pain, paresthesias	Elevated FGF-23	MRI	S1	Complete resection	Improvement	12	PMTMCT
Marshall AE [98]	2010	Case 1	55, female	Bone pain; fractures	Hypophosphatemia and elevated FGF-23	PET/CT	T12	Complete resection	Improvement	NA	PMTMCT
Pirola E[86]	2009	Case 1	57, male	Fractures, paresthesias	Hypophosphatemia, elevated ALP and PTH	CT, MRI	T4	Complete resection, supplementation of vitamin D and phosphate	Improvement	24	PMT
Sciubba DM [85]	2009	Case 1	56, female	Bone pain, weakness, fractures	Hypophosphatemia, low level of vitamin D3, elevated ALP and PTH	PET/CT	T8	Complete resection	Improvement	14	PMT

(*continued on next page*)

Table 4 (*continued*)

Authors	Year	Case	Age (y), sex	Symptoms	Preoperative blood phosphorus	Localization methods	Localization	Treatment	Outcome	Follow up (M)	Histological diagnosis
Chua SC[99]	2008	Case 1	34, female	Musculoskeletal pain, fatigue	Hypophosphatemia, elevated ALP and PTH	High-resolution CT and MRI, PET/CT	T3-4	Partial resection, supplementation of phosphate and calcitriol	Recurrence	60	Plasmacytoma
Folpe AL [100]	2004	Case 1	32, female	Normal	Normal	NA	C1	Partial resection, radiotherapy	Unresectable local recurrence, lung and bone metastases	48	Malignant PMTMCT
Dissanayake AM[101]	2003	Case 1	58, male	Musculoskeletal pain, fractures	Hypophosphatemia, elevated ALP	Bone scintigraphy and CT	L2	Complete resection	Normalization of lab findings;	6	Haemangiopericytoma
Terek RM [102]	2001	Case 1	14, male	Bone pain, skeletal abnormalities	Hypophosphatemia, elevated ALP	–	S1-2	Partial resection, chemotherapy (doxorubicin)	Persistent serum abnormalities	11	Osteosarcoma
Yu GH[103]	1995	Case 1	58, female	Musculoskeletal pain, weakness	Hypophosphatemia, elevated ALP and PTH	NA	C2	Partial resection	Persistent serum abnormalities	NA	PMT
Stone MD [104]	1992	Case 1	33, female	Bone pain, weakness, fractures	Hypophosphatemia	–	T3-4	Complete resection, supplementation of vitamin D, phosphate, and calcium	Normalization of lab findings	12	Neuroendocrine tumor
Boriani S [105]	1978	Case 1	18, male	Bone pain, weakness	Hypophosphatemia, elevated ALP	–	S1-3	Complete resection, radiotherapy	Normalization of lab findings	12	Osteosarcoma

Note: ALP: alkaline phosphatase; PTH: parathyroid hormone; PMT: phosphaturic mesenchymal tumor; PMTMCT: phosphaturic mesenchymal tumor, mixed connective tissue variant; M: month; C: cervical spine; T: thoracic spine; L: lumbar spine; S: sacral spine; NA: none; CT:computed tomography; MRI: magnetic resonance imaging; OCT: Octreotide; PET/CT: Positron emission tomography/computed tomography; FGF23: fibroblast growth factor 23.

subchondral insufficiency fractures of the femoral head can result in progressive collapse of the femoral head, which is the main reason why patients experience persistent pain after successful TIO treatment.

Reducing bone density in osteomalacia leads to fractures and increases the risk of bone non-union or delayed bone healing [122]. Inoue et al. [123] reported a 48-year-old male TIO case with left neck femur insufficiency fracture. The pathogenic tumor located in the patient's maxillary sinus could not be completely removed. Therefore, the patient's symptoms persisted, and without serious trauma, he experienced a left neck femur fracture [123]. Due to expected delayed fracture healing, the surgeon used implants and multiple screws for internal fixation to achieve better stability [123]. During the 30-month follow-up period after surgery, the patient showed no symptoms and was able to achieve independent walking [123]. The clinical course of TIO is gradual, therefore, early diagnosis is important for preventing bone-related events. However, when the fracture is inevitable, surgical treatment of osteomalacia patients with femoral neck fractures should consider a longer time for complete fracture healing, and the use of implants with sufficient stability should be paid attention to by orthopedic doctors.

5. Other management options

Compared with surgical treatment, ablation therapy is less invasive and has fewer side effects [7]. Ablation treatment involves the use of heating (microwave, ultrasound, laser or radio frequency), cooling (frozen ablation) or chemical agents (percutaneous ethanol infusion) to destroy histiocytes, interrupt blood supply, and induce apoptosis. Ablation therapy can be performed under the guidance of multimodal data signals such as ultrasound, CT, MRI, ^{18}F-FDG PET/CT, or ^{68}Ga-DOTATATE PET/CT [7]. For TIO patients, surgical resection of pathogenic tumors is the preferred treatment option. When tumor location is special and surgical resection is not feasible, image-guided ablation is an effective, minimally invasive, and safe alternative treatment option [59,61]. Xian et al. [124] reported that ultrasound-guided radiofrequency ablation is a safe and effective minimally invasive treatment option, and may be a valuable surgical alternative for TIO patients. Maybody et al. [125] performed biopsy and cryoablation under the guidance of ^{68}Ga DOTATOC PET/CT, while autoradiography was performed on the biopsy sample to show the *in situ* correlation between ^{68}Ga DOTATOC uptake and histopathology with millimeter resolution. On this basis, Cowan et al. [126] reported that CT-guided cryoablation expands the range of treatment options for TIO patients, especially for those who refuse surgery or have poor surgical conditions.

Global guidelines for TIO diagnosis and treatment proposed the use of oral phosphate combined with active vitamin D or Burosumab for TIO cases that cannot be resected or whose pathogenic tumors cannot be identified to maintain calcium and phosphorus metabolism, improve hypophosphatemia, and alleviate disease progression [28]. The specific recommended daily supplementation doses are: 20 to 40 mg/kg daily (1–3 g/d for adults) of elemental phosphorus and 20 to 30 ng/kg daily (0.5 to 1.5 ug/d for adults) of calcitriol. Phosphate supplements should be divided into 4 to 6 doses per day and increased to the target dose within a few days to weeks. Renal function, serum calcium, phosphate, alkaline phosphatase, PTH, and 24-hour urine calcium levels should be monitored every 3 to 6 months. The treatment dose should be adjusted as appropriate to prevent the occurrence of complications, including hypercalcemia, secondary hyperparathyroidism, renal stones and decreased renal functions, diarrhea, and gastrointestinal reactions [127].

For patients who cannot tolerate phosphorus solution or who suffer from secondary hyperparathyroidism, cinacalcet is a potential treatment option. Cinacalcet is a calcium sensitive receptor agonist that can act on surface calcium receptors of the parathyroid gland, inhibiting PTH secretion and reducing urinary phosphorus excretion. It is one of the auxiliary treatment options for TIO patients [128]. Bhadada et al. [129]

reported a TIO patient for whom the tumor lesion could not be located, therefore, the patient was subjected to total parathyroidectomy due to recurrent hypercalcemia hyperparathyroidism. The decrease in PTH level and improvement of hypophosphatemia postoperatively suggested that total parathyroidectomy might be a potential considerable therapy for TIO patients. However, the association between PTH and FGF-23 should be investigated further and treatment of TIO by suppressing PTH levels requires more evidence. The efficacy of octreotide in improving hypophosphatemia has not been fully established [130].

Research hotspots for TIO treatment include the anti FGF-23 monoclonal antibodies [37]. Burosumab, a full human monoclonal antibody of FGF23 [131], can combine with FGF23 and inhibit its biological activities as well as downstream signaling pathways, increase phosphorus reabsorption by the kidneys and serum vitamin D levels, thereby improving bone mineralization and alleviating the related bone diseases. In April 2018, burosumab was approved for use in X-linked dominant hypophosphatemic rickets (XLH) in adults and children over 1-year old [132]. A study on the efficacy and safety of burosumab for TIO treatment found that patient blood phosphorus levels increased after burosumab treatment. Nine cases (9/13, 62.9 %) had the average peak blood phosphorus levels at the 24th week, while six cases (6/13, 46.2 %) had the average low blood phosphorus level at the 48th week [133]. For TIO patients whose tumors cannot be removed, burosumab is a potential effective treatment method [133–137]. The recommended initial dose of burosumab for TIO treatment is 0.5 mg/kg, once every 4 weeks; the maximum dose is 2 mg/kg (not exceeding 180 mg) every 2 weeks. Dose adjustment should be based on serum phosphate levels, and serum phosphate levels should be assessed on an empty stomach monthly during the treatment process [127].

6. Future prospects

Most of the current studies on TIO pathogenesis are focused on FGF-23, however, its etiology and pathogenesis should be investigated further. The advances in genomics, transcriptome, metabolomics and other analytical assays will play an important role in clarification of its pathogenesis, which will be of significance in informing the clinical treatment of TIO.

As a rare entity, TIO is associated with a huge economic burden and life pressure to patients and their families. Its true incidence is likely to be underestimated because some doctors have insufficient knowledge of the disease. In recent years, international scholars have begun to pay attention to and study the disease burden as well as mental health issues of TIO cases [138,139]. In clinical practice, there is a need to popularize the clinical characteristics and diagnosis as well as treatment options for this disease. Allowing more clinical doctors to master the diagnosis and treatment of the disease as well as optimizing the diagnosis and treatment modes are prerequisites for avoiding delayed diagnosis and treatment. Early diagnosis and reasonable treatment will reduce the occurrence of complications and improve the quality of life of TIO patients. In TIO diagnosis, more diagnostic techniques are showing better sensitivity and specificity, however, large-scale and high-quality clinical studies should be performed to confirm their utility. With development of intraoperative localization technologies, tumor resection guided by 3D navigation technologies and exploration of various intraoperative tracking technologies will achieve more accurate intraoperative structural or functional localization, and contribute to complete intraoperative tumor resection [45,93].

The anti FGF-23 monoclonal antibodies require more evidence to support their effectiveness and safety in TIO treatment. Surgery is the frontline method for TIO treatment [28,137,140]. Summarizing the experience of orthopedic surgical treatment for TIO with causative tumors located in different parts is of great clinical value, and is of crucial significance for improving the effectiveness of orthopedic surgical treatment. In orthopedic surgical treatment, selection of the resection range and surgical method for patients with tumors that involve bones that cannot be completely removed is a major challenge. The location and extent of involvement of the pathogenic tumors are important bases for formulating surgical plans, however, more clinical evidence is required to develop better treatment plans. Personalized surgical plans are of great significance. Different anatomical sites and tumor ranges restrict the selection of surgical plans, and different surgical strategies are associated with clinical cure or persistence of TIO cases. In persistent and/or recurrent, refractory TIO, diagnostic methods, including biochemical evaluation, functional, and anatomical imaging should be repeated to detect metastasis or multiple lesions and exclude other diseases. Studies should aim at developing better clinical treatment options for refractory, recurrent, and multifocal culprit tumors involved in TIO development [29,49,118].

7. Summary

Clinical diagnosis and treatment of tumor-induced osteomalacia have shown some progress in various aspects, however, a more standardized orthopedic surgical treatment system should be established. The long-term treatment effects of various treatment modes should be confirmed further. Surgery is among the first-line treatment options for TIO. Clinical treatment for most TIO patients should be performed by orthopedic specialists, and choosing the most appropriate and effective orthopedic surgical treatment strategies is crucial for TIO patients with pathogenic tumors located in different parts of the body. Surgical treatment plans, comprehensive treatment modes, and patient prognosis characteristics of orthopedic-related TIO should be investigated further. The orthopedic surgical treatment strategies summarized in this review will play a positive role in improving the clinical diagnosis and treatment of TIO patients.

CRediT authorship contribution statement

Shuzhong Liu: Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Xi Zhou:** Methodology, Conceptualization. **Yong Liu:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Jianguo Zhang:** Formal analysis, Resources, Writing – review & editing, Supervision. **Weibo Xia:** Conceptualization, Formal analysis, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank our colleagues at the Departments of Orthopaedic Surgery, Endocrinology, Anesthesiology, Pathology, Radiology, Nuclear Medicine in Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Authors' contributions

SZL, XZ, and YL wrote the paper. YL, WBX, and JGZ revised the manuscript for important intellectual content and technical details. All authors have read and approved the final manuscript. We confirm that all of us have met the criteria for authorship as established by the ICMJE.

Funding

This study was supported by The first batch of Young Scholars

Support Program of Peking Union Medical College (Project No. 2022002; Grant recipient: S.L.). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

The anonymized data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

[1] R.A. McCANCE, Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years, Q. J. Med. 16 (1) (1947) 33–46.

[2] J. Feng, Y. Jiang, O. Wang, et al., The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases, Endocr. J. 64 (7) (2017) 675–683.

[3] Y. Jiang, W.B. Xia, X.P. Xing, et al., Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: Report of 39 cases and review of the literature, J. Bone Miner. Res. 27 (9) (2012) 1967–1975.

[4] W.J. Yu, J.W. He, W.Z. Fu, et al., Reports of 17 Chinese patients with tumor-induced osteomalacia, J. Bone Miner. Metab. 35 (3) (2017) 298–307.

[5] A. Bosman, A. Palermo, J. Vanderhulst, et al., Tumor-induced osteomalacia: A systematic clinical review of 895 cases, Calcif. Tissue Int. 111 (4) (2022) 367–379.

[6] S. Minisola, M. Peacock, S. Fukumoto, et al., Tumor-induced osteomalacia, Nat. Rev. Dis. Primers 3 (2017) 17044.

[7] Z. Yin, J. Du, F. Yu, et al., Tumor-induced osteomalacia, Osteoporos. Sarcopenia 4 (4) (2018) 119–127.

[8] T. Shimada, S. Mizutani, T. Muto, et al., Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia, PNAS 98 (11) (2001) 6500–6505.

[9] T. Larsson, R. Marsell, E. Schipani, et al., Transgenic mice expressing fibroblast growth factor 23 under the control of the alpha1(I) collagen promoter exhibit growth retardation, osteomalacia, and disturbed phosphate homeostasis, Endocrinology 145 (7) (2004) 3087–3094.

[10] E.A. Imel, A. Biggin, A. Schindeler, et al., FGF23, Hypophosphatemia, and emerging treatments, JBMR Plus. 3 (8) (2019) e10190.

[11] P.S. Rowe, P.A. de Zoysa, R. Dong, et al., MEPE, a new gene expressed in bone marrow and tumors causing osteomalacia, Genomics 67 (1) (2000) 54–68.

[12] T.O. Carpenter, B.K. Ellis, K.L. Insogna, et al., Fibroblast growth factor 7: an inhibitor of phosphate transport derived from oncogenic osteomalacia-causing tumors, J. Clin. Endocrinol. Metab. 90 (2) (2005) 1012–1020.

[13] R. Nakanishi, M. Shimizu, M. Mori, et al., Secreted frizzled-related protein 4 is a negative regulator of peak BMD in SAMP6 mice, J. Bone Miner. Res. 21 (11) (2006) 1713–1721.

[14] T.J. Berndt, S. Schiavi, R. Kumar, "Phosphatonins" and the regulation of phosphorus homeostasis, Am. J. Physiol. Renal Physiol. 289 (6) (2005) F1170–F1182.

[15] S.C. Schiavi, R. Kumar, The phosphatonin pathway: new insights in phosphate homeostasis, Kidney Int. 65 (1) (2004) 1–14.

[16] S. Minisola, S. Fukumoto, W. Xia, et al., Tumor-induced Osteomalacia: A Comprehensive Review, Endocr. Rev. 44 (2) (2023) 323–353.

[17] Y. Kinoshita, Y. Takashi, N. Ito, et al., Ectopic expression of Klotho in fibroblast growth factor 23 (FGF23) -producing tumors that cause tumor-induced rickets /osteomalacia (TIO), Bone Rep. 10 (2019) 100192.

[18] Q. Zhang, M. Doucet, R.E. Tomlinson, et al., The hypoxia-inducible factor-1alpha activates ectopic production of fibroblast growth factor 23 in tumor-induced osteomalacia, Bone Res. 4 (2016) 16011.

[19] Y. Gong, X. Ni, C. Jin, et al., Serum metabolomics reveals dysregulation and diagnostic potential of oxylipins in tumor-induced osteomalacia, J. Clin. Endocrinol. Metab. 107 (5) (2022) 1383–1391.

[20] X. Li, Y. Gong, Q. Zhang, et al., UPLC-MS based serum metabolomics for early diagnosis of refractory tumor-induced osteomalacia: a case-control study, J. Clin. Endocrinol. Metab. (2023) dgad034.

[21] N. Wu, Z. Zhang, X. Zhou, et al., Mutational landscape and genetic signatures of cell-free DNA in tumour-induced osteomalacia, J. Cell Mol. Med. 24 (9) (2020) 4931–4943.

[22] Y. Liu, H. He, C. Zhang, et al., Phosphaturic mesenchymal tumors: rethinking the clinical diagnosis and surgical treatment, J. Clin. Med. 12 (1) (2022) 252.

[23] D. Rendina, V. Abate, G. Cacace, et al., Tumor-induced osteomalacia: a systematic review and individual patient's data analysis, J. Clin. Endocrinol. Metab. 107 (8) (2022) e3428–e3436.

[24] K. Dahir, M.B. Zanchetta, I. Stanciu, et al., Diagnosis and management of tumor-induced osteomalacia: perspectives from clinical experience, J. Endocr. Soc. 5 (9) (2021) bvab099.

[25] C. Crotti, F. Bartoli, L.A. Coletto, et al., Tumor induced osteomalacia: A single center experience on 17 patients, Bone 152 (2021) 116077.

[26] N. Hidaka, M. Koga, S. Kimura, et al., Clinical challenges in diagnosis, tumor localization and treatment of tumor-induced osteomalacia: outcome of a retrospective surveillance, J. Bone Miner. Res. 37 (8) (2022) 1479–1488.

[27] P. Florenzano, I.R. Hartley, M. Jimenez, et al., Tumor-induced osteomalacia, Calcif. Tissue Int. 108 (1) (2021) 128–142.

[28] S.M. Jan de Beur, S. Minisola, W.B. Xia, et al., Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia, J. Intern. Med. 293 (3) (2023) 309–328.

[29] M.L. Brandi, G.P.R. Clunie, P. Houillier, et al., Challenges in the management of tumor-induced osteomalacia (TIO), Bone 152 (2021) 116064.

[30] F.T. Beil, J. Stürznickel, T. Rolvien, et al., Tumorlokalisation und Therapie der onkogenen Osteomalazie [Tumor localization and treatment of tumor-induced osteomalacia], Z Rheumatol. 81 (3) (2022) 182–188. German.

[31] F. Lococo, A. Cesario, M. Paci, et al., PET/CT assessment of neuroendocrine tumors of the lung with special emphasis on bronchial carcinoids, Tumour Biol. 35 (9) (2014) 8369–8377.

[32] A. Kato, Y. Nakamoto, T. Ishimori, et al., Diagnostic performance of 68Ga-DOTATOC PET/CT in tumor-induced osteomalacia, Ann. Nucl. Med. 35 (3) (2021) 397–405.

[33] P. Wang, S. Zhang, L. Huo, et al., Prognostic value of positive presurgical FDG PET/CT in the evaluation of tumor-induced osteomalacia, Clin. Nucl. Med. 46 (3) (2021) 214–219.

[34] G. Hou, Y. Zhang, Y. Liu, et al., Head-to-head comparison of 68Ga-DOTA-TATE and 68Ga-DOTA-JR11 PET/CT in patients with tumor-induced osteomalacia: a prospective study, Front. Oncol. 24 (12) (2022) 811209.

[35] Y. Jiang, G. Hou, W. Cheng, Performance of 68Ga-DOTA-SST PET/CT, octreoscan SPECT/CT and 18F-FDG PET/CT in the detection of culprit tumors causing osteomalacia: a meta-analysis, Nucl. Med. Commun. 41 (4) (2020) 370–376.

[36] T. Sekine, F.G. Barbosa, B.R. Sah, et al., PET/MR outperforms PET/CT in suspected occult tumors, Clin. Nucl. Med. 42 (2) (2017) e88–e95.

[37] S. Fukumoto, FGF23-related hypophosphatemic rickets/osteomalacia: diagnosis and new treatment, J. Mol. Endocrinol. 66 (2) (2021) R57–R65.

[38] D. Ovejero, M.T. Collins, RAS in FGF23: another piece in the puzzle, J. Clin. Endocrinol. Metab. 99 (1) (2014) 63–66.

[39] W.H. Chong, P. Andreopoulou, C.C. Chen, et al., Tumor localization and biochemical response to cure in tumor-induced osteomalacia, J. Bone Miner. Res. 28 (6) (2013) 1386–1398.

[40] T. Nasu, S. Kurisu, S. Matsuno, et al., Tumor-induced hypophosphatemic osteomalacia diagnosed by the combinatory procedures of magnetic resonance imaging and venous sampling for FGF23, Intern. Med. 47 (10) (2008) 957–961.

[41] H. Wang, D. Zhong, Y. Liu, et al., Surgical treatments of tumor-induced osteomalacia lesions in long bones: seventeen cases with more than one year of follow-up, J. Bone Joint Surg. Am. 97 (13) (2015) 1084–1094.

[42] Z.J. Sun, J. Jin, G.X. Qiu, et al., Surgical treatment of tumor-induced osteomalacia: a retrospective review of 40 cases with extremity tumors, BMC Musculoskelet. Disord. 16 (2015) 43.

[43] X. Zhou, S. Liu, A. Song, et al., Successful and effective treatment of oncogenic osteomalacia with bone cement, Pol. Arch. Intern. Med. 130 (4) (2020) 332–334.

[44] J.P. Tiernan, A. Klucinski, N.F. Peel, et al., Ischiorectal fossa phosphaturic mesenchymal tumour excised using intra-operative endoanal ultrasonography, Colorectal Dis. 13 (8) (2011) e250–e251.

[45] B. Harbeck, H. Schöcklmann, A. Seekamp, et al., Tumor-induced osteomalacia: successful treatment by radio-guided tumor surgery, J. Clin. Rheumatol. 15 (1) (2009) 31–34.

[46] S.Z. Liu, X. Zhou, A. Song, et al., Tumor-induced osteomalacia caused by a phosphaturic mesenchymal tumor of the femur, Chin. Med. J. (Engl.) 132 (19) (2019) 2380–2381.

[47] S.Z. Liu, X. Zhou, A. Song, et al., Oncogenic osteomalacia, QJM 112 (11) (2019) 882–883.

[48] Y. Li, Y. Li, M. Hui, et al., Comparison of surgical treatments of tumor-induced osteomalacia in different locations in the lower limbs: A retrospective study, Medicine (Baltimore) 98 (11) (2019) e14846.

[49] X. Li, Y. Jiang, L. Huo, et al., Nonremission and recurrent tumor-induced osteomalacia: a retrospective study, J. Bone Miner. Res. 35 (3) (2020) 469–477.

[50] S. Liu, X. Zhou, A. Song, et al., Successful treatment of tumor-induced osteomalacia causing by phosphaturic mesenchymal tumor of the foot, Medicine (Baltimore) 98 (27) (2019) e16296.

[51] S. Ha, S. Park, H. Kim, H. Go, S.H. Lee, J.Y. Choi, J.Y. Hong, J.S. Ryu, Successful localization using 68Ga-DOTATOC PET/CT of a phosphaturic mesenchymal tumor causing osteomalacia in a patient with concurrent follicular lymphoma, Nucl. Med. Mol. Imaging 52 (6) (2018) 462–467, https://doi.org/10.1007/s13139-018-0546-5. Epub 2018 Sep 12. PMID: 30538778; PMCID: PMC6261860.

[52] L. Tonello, A.P. Gatti, J.D. Neto, U.F. Teixeira, M. Bertozzi Goldoni, P.R.O. Fontes, J.A. Sampaio, L.M.P. Lima, F.L. Waechter, A case of oncogenic osteomalacia owing to inguinal tumor, Oxf. Med. Case Rep. 26 (10) (2017) omx045, 10.1093/omcr/omx045. PMID: 29744113; PMCID: PMC5934660.

[53] H. Kobayashi, N. Ito, T. Akiyama, T. Okuma, Y. Kinoshita, M. Ikegami, Y. Shinoda, S. Fukumoto, S. Tanaka, H. Kawano, Prevalence and clinical outcomes of hip fractures and subchondral insufficiency fractures of the femoral head in patients with tumour-induced osteomalacia, Int. Orthop. 41 (12) (2017) 2597–2603, https://doi.org/10.1007/s00264-017-3610-3. Epub 2017 Aug 23 PMID: 28836028.

[54] Q.Y. Zuo, H. Wang, W. Li, et al., Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients, BMC Musculoskelet. Disord. 18 (1) (2017) 403.

[55] V. Chouhan, K. Agrawal, T.K. Vinothkumar, A. Mathesul, Bilateral insufficiency fracture of the femoral head and neck in a case of oncogenic osteomalacia, J. Bone Joint Surg. Br. 92 (7) (2010) 1028–1031, https://doi.org/10.1302/0301-620X.92B7.24526. PMID: 20595128.

[56] Y. Takeuchi, H. Suzuki, S. Ogura, R. Imai, Y. Yamazaki, T. Yamashita, Y. Miyamoto, H. Okazaki, K. Nakamura, K. Nakahara, S. Fukumoto, T. Fujita, Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia, J. Clin. Endocrinol. Metab. 89 (8) (2004) 3979–3982, https://doi.org/10.1210/jc.2004-0406. PMID: 15292336.

[57] W. Zhu, Q. Ma, Y. Bian, et al., Total hip/knee arthroplasty in the treatment of tumor-induced osteomalacia patients: More than 1 year follow-up, PLoS One 12 (5) (2017) e0177835.

[58] J. Sun, X. Zhou, W. Xia, et al., Unusual Presentation and Surgical Treatment of a Phosphaturic Mesenchymal Tumor in a Knee, Front Surg. 25 (9) (2022) 746623.

[59] J.C. Horng, E. Van Eperen, S. Tutton, et al., Persistent phosphaturic mesenchymal tumor causing tumor-induced osteomalacia treated with image-guided ablation, Osteoporos Int. 32 (9) (2021) 1895–1898.

[60] C.G. Turin, R.J. Wilson, C. Mangone, K. Rosenspire, J. Berman, M. Walker, R. Amaravadi, M.M. Al, A case of tumor-induced osteomalacia: finding the culprit acetabular tumor and successful resection with a novel hip joint-preserving surgery, J. Orthop. Case Rep. 11 (3) (2021) 37–41, https://doi.org/10.13107/jocr.2021.v11.i03.2078. PMID: 34239825; PMCID: PMC8241250.

[61] S.K. Mishra, M.S. Kuchay, I.B. Sen, A. Garg, S.S. Baijal, A. Mithal, Successful management of tumor-induced osteomalacia with radiofrequency ablation: a case series, JBMR Plus. 3 (7) (2019) e10178.

[62] K. Nakamura, M. Ohishi, T. Matsunobu, Y. Nakashima, A. Sakamoto, A. Maekawa, Y. Oda, Y. Iwamoto, Tumor-induced osteomalacia caused by a massive phosphaturic mesenchymal tumor of the acetabulum: A case report, Mod. Rheumatol. 28 (5) (2018) 906–910, https://doi.org/10.3109/14397595.2016.1173322. Epub 2016 May 4 PMID: 27141918.

[63] T. Morimoto, S. Takenaka, N. Hashimoto, N. Araki, A. Myoui, H. Yoshikawa, Malignant phosphaturic mesenchymal tumor of the pelvis: A report of two cases, Oncol. Lett. 8 (1) (2014) 67–71, https://doi.org/10.3892/ol.2014.2081. Epub 2014 Apr 22. PMID: 24959220; PMCID: PMC4063565.

[64] A.R. Radaideh, D. Jaradat, M.M. Abu-Kalaf, M.K. Nusier, Resolution of severe oncogenic hypophosphatemic osteomalacia after resection of a deeply located soft-tissue tumour, Curr. Oncol. 16 (5) (2009) 87–90, https://doi.org/10.3747/co.v16i5.412. PMID: 19862367; PMCID: PMC2768508.

[65] A.E. Nelson, R.C. Bligh, M. Mirams, A. Gill, A. Au, A. Clarkson, H. Jüppner, S. Ruff, P. Stalley, R.A. Scolyer, B.G. Robinson, R.S. Mason, P.C. Bligh, Clinical case seminar: Fibroblast growth factor 23: a new clinical marker for oncogenic osteomalacia, J. Clin. Endocrinol. Metab. 88 (9) (2003) 4088–4094, https://doi.org/10.1210/jc.2002-021919. PMID: 12970268.

[66] S. François, G. Lefort, M.L. Poli-Merol, D. Gaillard, B. Roussel, V. Sulmont, S. Daoud, Rachitisme vitamino-résistant guéri par l'éxérèse d'une tumeur osseuse. Revue de la littérature [Vitamin-resistant rickets cured by removal of a bone tumor. Review of the literature], Rev Chir Orthop Reparatrice Appar Mot. 83 (4) (1997) 387–392. French. PMID: 9452815.

[67] Z. Zhang, J. Li, Z. Zhang, Z. Shao, Tumor-induced osteomalacia: a case report and etiological analysis with literature review, Orthop. Surg. 15 (12) (2023) 3342–3352, https://doi.org/10.1111/os.13901. Epub 2023 Nov 7. PMID: 37933469; PMCID: PMC10694022.

[68] Y. Zhang, P. Wang, H. Jing, Lung nodule as culprit lesion causing recurrent tumor-induced osteomalacia revealed by 68 Ga-DOTATATE PET/CT, Clin. Nucl. Med. 48 (9) (2023) 826–827, https://doi.org/10.1097/RLU.0000000000004771. Epub 2023 Jul 22 PMID: 37486706.

[69] E. Hervier, K. Gorican, S. Boudabbous, E. Biver, S. Ferrari, E. Saiji, V. Garibotto, I. Mainta, Unusual phosphaturic mesenchymal tumor mimicking osteoid osteoma, Radiol Case Rep. 18 (8) (2023) 2738–2743, https://doi.org/10.1016/j.radcr.2023.05.008. PMID: 37304318; PMCID: PMC10250829.

[70] S. Arita, T. Nsihino, Y. Mitani, K. Sakashita, S. Totsuka, R. Watanabe, H. Mishima, H. Kawai, D. Matsubara, Y. Oda, M. Yamazaki, Hemiarthroplasty for tumor-induced osteomalacia caused by tumor localized in femoral head: a case report, J. Surg. Case Rep. 10 (2022) rjac478, https://doi.org/10.1093/jscr/rjac478. Erratum in: J Surg Case Rep. 2022 Dec 27;2022(12):rjac613. PMID: 36285172; PMCID: PMC9581504.

[71] H.J. Ni, R. Clifton-Bligh, M.M. Brzozowska, Tumor-induced osteomalacia - a mystery illness beyond aches, pains, and depression, Endocr. Regul. 55 (3) (2021) 163–168, https://doi.org/10.2478/enr-2021-0017. PMID: 34523297.

[72] M. Yang, K.B. Doshi, M.C. Roarke, B.D. Nguyen, Molecular imaging in diagnosis of tumor-induced osteomalacia, Curr. Probl. Diagn. Radiol. 48 (4) (2019) 379–386, https://doi.org/10.1067/j.cpradiol.2018.06.005. Epub 2018 Jun 27. PMID: 30078476.

[73] L. Colangelo, C. Cipriani, J. Pepe, A. Corsi, C. Sonato, G. Follacchio, M. Cilli, W. Gianni, F. Ferrone, O. Moreschini, L.A. Fitzpatrick, S. Minisola, A challenging case of tumor-induced osteomalacia: pathophysiological and clinical implications, Calcif. Tissue Int. 103 (4) (2018) 465–468, https://doi.org/10.1007/s00223-018-0429-x. Epub 2018 May 7 PMID: 29736882.

[74] S. Jadhav, R. Kasaliwal, N.S. Shetty, S. Kulkarni, K. Rathod, B. Popat, H. Kakade, A. Bukan, S. Khare, S. Budyal, V.S. Jagtap, A.R. Lila, T. Bandgar, N.S. Shah, Radiofrequency ablation, an effective modality of treatment in tumor-induced osteomalacia: a case series of three patients, J. Clin. Endocrinol. Metab. 99 (9) (2014) 3049–3054, https://doi.org/10.1210/jc.2013-4515. Epub 2014 Jun 24 PMID: 24960541.

[75] E. Hesse, E. Moessinger, H. Rosenthal, F. Laenger, G. Brabant, T. Petrich, K. F. Gratz, L. Bastian, Oncogenic osteomalacia: exact tumor localization by co-registration of positron emission and computed tomography, J. Bone Miner. Res. 22 (1) (2007) 158–162, https://doi.org/10.1359/jbmr.060909. PMID: 17014386.

[76] E. Hesse, H. Rosenthal, L. Bastian, Radiofrequency ablation of a tumor causing oncogenic osteomalacia, N. Engl. J. Med. 357 (4) (2007) 422–424, https://doi.org/10.1056/NEJMc070347. PMID: 17652663.

[77] A.J. Mancini, A. Sabet, G.P. Nielsen, et al., Tumor-induced osteomalacia treated with T12 tumor resection, Endocrinol. Diabetes Metab. Case Rep. 1 (2022) (2022) 22–0344.

[78] B. Garg, N. Mehta, A. Goyal, et al., Oncogenic osteomalacia due to phosphaturic mesenchymal tumour in the upper thoracic spine, BMJ Case Rep. 13 (12) (2020) e238209.

[79] N. Agarwal, S.S. Kale, K. Kumari, Tumor-induced osteomalacia due to a phosphaturic mesenchymal tumor in the cervical spine: a case report and literature review, Neurol. India 67 (5) (2019) 1334–1340.

[80] G. Sistani, Y. Sallam, W.P. Ng, et al., Spinal intradural phosphaturic mesenchymal tumor, Can. J. Neurol. Sci. 49 (1) (2022) 120–122.

[81] T. Meng, W. Zhou, B. Li, et al., En bloc resection for treatment of tumor-induced osteomalacia: a case presentation and a systematic review, World J. Surg. Oncol. 13 (2015) 176.

[82] S. Liu, X. Zhou, A. Song, et al., Surgical treatment of recurrent spinal phosphaturic mesenchymal tumor-induced osteomalacia: A case report, Medicine (Baltimore) 99 (4) (2020) e18603.

[83] X. Wang, J. Gao, S. Han, et al., Spinal phosphaturic mesenchymal tumors: Case report and literature review, J. Clin. Neurosci. 63 (2019) 234–239.

[84] T. Nakamura, T. Aizawa, T. Hoshikawa, et al., Tumor-induced osteomalacia caused by phosphaturic mesenchymal tumor of the cervical spine, J. Orthop. Sci. 20 (4) (2015) 765–771.

[85] D.M. Sciubba, R.J. Petteys, S.F. Shakur, et al., En bloc spondylectomy for treatment of tumor-induced osteomalacia, J. Neurosurg. Spine 11 (5) (2009) 600–604.

[86] E. Pirola, F. Vergani, P. Casiraghi, et al., Oncogenic osteomalacia caused by a phosphaturic mesenchymal tumor of the thoracic spine, J. Neurosurg. Spine 10 (4) (2009) 329–333.

[87] P.J. Puthenveetil, E.M. Hattab, M. Peacock, et al., Thoracic phosphaturic mesenchymal tumors causing oncogenic osteomalacia, J. Clin. Neurosci. 20 (8) (2013) 1057–1061.

[88] D. Chen, L. Zhang, J. Zhang, M. Yin, X. Gao, Q. Huang, L. Li, X. Yang, Treatment and diagnose of spinal phosphaturic mesenchymal tumor: a case report and a systematic literature review, World Neurosurg. 184 (2024) 65–73, https://doi.org/10.1016/j.wneu.2024.01.032. Epub ahead of print. PMID: 38218444.

[89] C.D. Pannu, D. Baxter, H. Anwar, Spinal phosphaturic mesenchymal tumors: a rare etiology causing tumor-induced osteomalacia-a review of experience at a UK tertiary referral center and literature review, Eur. Spine J. (2023), https://doi.org/10.1007/s00586-023-08031-6. Epub ahead of print. PMID: 37964171.

[90] A. Agarwal, G. Bathla, V. Gupta, Tumor-induced osteomalacia secondary to phosphaturic mesenchymal tumor, Radiol Imaging Cancer. 5 (2) (2023) e220170.

[91] L. Filipová, V. Zikán, M. Krsek, D. Netuka, M. Michal, I. Lazúrová, Tumor induced osteomalacia - A long way toward correct diagnosis and management, Bone Rep. 8 (16) (2022) 101180, https://doi.org/10.1016/j.bonr.2022.101180. PMID: 35281212; PMCID: PMC8914328.

[92] Y. Yamada, I. Kinoshita, K. Kenichi, H. Yamamoto, T. Iwasaki, H. Otsuka, M. Yoshimoto, S. Ishihara, Y. Toda, Y. Kuma, N. Setsu, Y. Koga, Y. Honda, T. Inoue, H. Yanai, K. Yamashita, I. Ito, M. Takahashi, S. Ohga, M. Furue, Y. Nakashima, Y. Oda, Histopathological and genetic review of phosphaturic mesenchymal tumours, mixed connective tissue variant, Histopathology 72 (3) (2018) 460–471, https://doi.org/10.1111/his.13377. Epub 2017 Nov 16 PMID: 28858396.

[93] H. Kobayashi, T. Akiyama, T. Okuma, Y. Shinoda, H. Oka, N. Ito, S. Fukumoto, S. Tanaka, H. Kawano, Three-dimensional fluoroscopic navigation-assisted surgery for tumors in patients with tumor-induced osteomalacia in the bones, Comput. Assist. Surg. (Abingdon). 22 (1) (2017) 14–19, https://doi.org/10.1080/24699322.2017.1282044. PMID: 28081649.

[94] J. Maehara, K. Yamashita, A. Hiwatashi, O. Togao, K. Kikuchi, Y. Matsumoto, K. Iura, Y. Oda, I. Ichino, Y. Nakamoto, H. Honda, Primary phosphaturic mesenchymal tumour of the lumbar spine: utility of 68Ga-DOTATOC PET/CT findings, BJR Case Rep. 2 (4) (2016) 20150497, https://doi.org/10.1259/bjrcr.20150497. PMID: 30460030; PMCID: PMC6243314.

[95] G.Y. Gandhi, A.A. Shah, K.J. Wu, V. Gupta, A.R. Shoraka, Tumor-induced osteomalacia caused by primary fibroblast growth factor 23 secreting neoplasm in axial skeleton: a case report, Case Rep Endocrinol. 2012 (2012) 185454, https://doi.org/10.1155/2012/185454. Epub 2012 Dec 17. PMID: 23346426; PMCID: PMC3533608.

[96] M. Akhter, P.A. Sugrue, R. Bains, Y.A. Khavkin, Oncogenic osteomalacia of the cervical spine: a rare case of curative resection and reconstruction, J. Neurosurg. Spine 14 (4) (2011) 453–456, https://doi.org/10.3171/2010.11.SPINE09750. Epub 2011 Jan 28 PMID: 21275557.

[97] A.F. Mavrogenis, V.I. Sakellariou, K. Soultanis, H. Mahera, D.S. Korres, P. J. Papagelopoulos, A nonphosphaturic mesenchymal tumor mixed connective tissue variant of the sacrum, Orthopedics 33 (11) (2010) 851, https://doi.org/10.3928/01477447-20100924-27. PMID: 21053876.

[98] A.E. Marshall, S.E. Martin, N.P. Agaram, J.H. Chen, E.M. Horn, A.C. Douglas-Akinwande, E.M. Hattab, A 61-year-old woman with osteomalacia and a thoracic spine lesion, Brain Pathol. 20 (2) (2010) 499–502, https://doi.org/10.1111/j.1750-3639.2009.00360.x. PMID: 20438469; PMCID: PMC8094844.

[99] S.C. Chua, S.R. O'Connor, W.L. Wong, R.H. Ganatra, Case report: Solitary plasmacytoma of bone with oncogenic osteomalacia: recurrence of tumour confirmed by PET/CT. A case report with a review of the radiological literature,

Br. J. Radiol. 81 (964) (2008) e110–e114, https://doi.org/10.1259/bjr/58168443. PMID: 18344267.
[100] A.L. Folpe, J.C. Fanburg-Smith, S.D. Billings, M. Bisceglia, F. Bertoni, J.Y. Cho, M. J. Econs, C.Y. Inwards, S.M. Jan de Beur, T. Mentzel, E. Montgomery, M. Michal, M. Miettinen, S.E. Mills, J.D. Reith, J.X. O'Connell, A.E. Rosenberg, B.P. Rubin, D. E. Sweet, T.N. Vinh, L.E. Wold, B.M. Wehrli, K.E. White, R.J. Zaino, S.W. Weiss, Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature, Am. J. Surg. Pathol. 28 (1) (2004) 1–30, https://doi.org/10.1097/00000478-200401000-00001. PMID: 14707860.
[101] A.M. Dissanayake, J.L. Wilson, I.M. Holdaway, I.R. Reid, Oncogenic osteomalacia: culprit tumour detection whole body magnetic resonance imaging, Intern. Med. J. 33 (12) (2003) 615–616, https://doi.org/10.1111/j.1445-5994.2003.00488.x. PMID: 14656239.
[102] R.M. Terek, G.P. Nielsen, Case 29–2001, N. Engl. J. Med. Overseas Ed 345 (2001) 903–908.
[103] G.H. Yu, R.L. Katz, A.K. Raymond, R.F. Gagel, A. Allison, I. McCutcheon, Oncogenous osteomalacia: fine needle aspiration of a neoplasm with a unique endocrinologic presentation, Acta Cytol. 39 (4) (1995) 831–832. PMID: 7631565.
[104] M.D. Stone, C. Quincey, D.J. Hosking, A neuroendocrine cause of oncogenic osteomalacia, J. Pathol. 167 (2) (1992) 181–185, https://doi.org/10.1002/path.1711670204. PMID: 1378890.
[105] S. Boriani, M. Campanacci, Osteoblastoma associated with osteomalacia (presentation of a case and review of the literature), Ital. J. Orthop. Traumatol. 4 (3) (1978) 379–382. PMID: 553864.
[106] M.A. Nuovo, H.D. Dorfman, C.C. Sun, et al., Tumor-induced osteomalacia and rickets, Am. J. Surg. Pathol. 13 (7) (1989) 588–599.
[107] W.H. Chong, A.A. Molinolo, C.C. Chen, et al., Tumor-induced osteomalacia, Endocr. Relat. Cancer 18 (3) (2011) R53–R77.
[108] N. Weidner, Cruz D. Santa, Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets, Cancer 59 (8) (1987) 1442–1454.
[109] H. Wu, M.M. Bui, L. Zhou, et al., Phosphaturic mesenchymal tumor with an admixture of epithelial and mesenchymal elements in the jaws: clinicopathological and immunohistochemical analysis of 22 cases with literature review, Mod. Pathol. 32 (2) (2019) 189–204.
[110] X. Ni, W. Liu, D. Zhang, et al., Hyperparathyroidism in a Large Cohort of Chinese Patients with Tumor-Induced Osteomalacia, J. Clin. Endocrinol. Metab. 5 (2022) dgac650.
[111] L. Colangelo, J. Pepe, L. Nieddu, et al., Long-term bone mineral density changes after surgical cure of patients with tumor-induced osteomalacia, Osteoporos Int. 31 (7) (2020) 1383–1387.
[112] S. Kumar, T. Diamond, Lessons learnt from delayed diagnosis of FGF-23-producing tumour-induced osteomalacia and post-operative hungry bone syndrome, Bone Rep. 12 (2020) 100276.
[113] D. Rendina, G. De Filippo, L. Tauchmanova, et al., Bone turnover and the osteoprotegerin-RANKL pathway in tumorinduced osteomalacia: a longitudinal study of five cases, Calcif. Tissue Int. 85 (2009) 293–300.
[114] M.T. Kilbane, R. Crowley, E. Heffernan, et al., High bone turnover and hyperparathyroidism after surgery for tumor-induced osteomalacia: A case series, Bone Rep. 15 (2021) 101142.
[115] A. Verma, S. Tewari, A. Kannaujia, Perioperative management of patients with severe hypophosphataemia secondary to oncogenic osteomalacia: Our experience and review of literature, Indian J Anaesth. 61 (7) (2017) 590–593.
[116] X. Ni, Y. Feng, W. Guan, et al., Bone impairment in a large cohort of chinese patients with tumor-induced osteomalacia assessed by HR-pQCT and TBS, J. Bone Miner. Res. 37 (3) (2022) 454–464.
[117] Z.Z. Zhu, W.B. Xia, F. Qi, et al., Clinical Characteristics and Surgical Outcomes of Sinonasal Lesions Associated With Tumor-Induced Osteomalacia, Otolaryngol Head Neck Surg. 165(1)(2021)223-231.
[118] L. Cianferotti, C. Delli Poggi, F. Bertoldo, et al., Persistence and recurrence in tumor-induced osteomalacia: A systematic review of the literature and results from a national survey/case series, Endocrine 76 (3) (2022) 709–721.
[119] X. Ni, W. Guan, Y. Jiang, et al., High prevalence of vertebral deformity in tumor-induced osteomalacia associated with impaired bone microstructure, J. Endocrinol. Invest. 46 (3) (2023) 487–500.
[120] S. Kaniuka-Jakubowska, W. Biernat, A. Lewczuk, et al., Oncogenic osteomalacia should be considered in hypophosphatemia, bone pain and pathological fractures, Endokrynol. Pol. 63 (3) (2012) 234–238.
[121] T. Niemeier, L. Leddy, M. Bolster, et al., Insufficiency fracture associated with oncogenic osteomalacia, J. Clin. Rheumatol. 19 (1) (2013) 38–42.
[122] E.M. Ryhänen, C. Schalin-Jäntti, N. Matikainen, Prolonged hypophosphatemia and intensive care after curative surgery of tumor induced osteomalacia: A case report, Front Endocrinol (Lausanne). 3 (12) (2021) 686135.
[123] Y. Inoue, T. Fukui, K. Oe, et al., A case of femoral neck insufficiency fracture due to tumor-induced osteomalacia, Case Rep. Orthop. 6 (2021) (2021) 6668006.
[124] M.F. Xian, K.M. Pan, J.C. Zhang, et al., Application of ultrasound-guided biopsy and percutaneous radiofrequency ablation in 2 cases with phosphaturic mesenchymal tumor and literature review, Clin. Hemorheol. Microcirc. 77 (1) (2021) 61–69.
[125] M. Maybody, R.K. Grewal, J.H. Healey, et al., Ga-68 DOTATOC PET/CT-Guided Biopsy and Cryoablation with Autoradiography of Biopsy Specimen for Treatment of Tumor-Induced Osteomalacia, Cardiovasc. Interv. Radiol. 39 (9) (2016) 1352–1357.
[126] S. Cowan, S.A. Lozano-Calderon, R.N. Uppot, et al., Successful CT guided cryoablation of phosphaturic mesenchymal tumor in the soft tissues causing tumor-induced osteomalacia: a case report, Skeletal Radiol. 46 (2) (2017) 273–277.
[127] Y. Jiang, X. Li, L. Huo, et al., Consensus on clinical management of tumor-induced osteomalacia, Chin. Med. J. (Engl) 134 (11) (2021) 1264–1266.
[128] J.L. Geller, A. Khosravi, M.H. Kelly, et al., Cinacalcet in the management of tumor-induced osteomalacia, J. Bone Miner. Res. 22 (6) (2007) 931–937.
[129] S.K. Bhadada, S. Palnitkar, S. Qiu, et al., Deliberate total parathyroidectomy: a potentially novel therapy for tumor-induced hypophosphatemic osteomalacia, J. Clin. Endocrinol. Metab. 98 (11) (2013) 4273–4278.
[130] D. Ovejero, D. El-Maouche, B.A. Brillante, et al., Octreotide is ineffective in treating tumor-induced osteomalacia: results of a short-term therapy, J. Bone Miner. Res. 32 (8) (2017) 1667–1671.
[131] C. Crotti, F. Zucchi, C. Alfieri, et al., Long-term use of burosumab for the treatment of tumor-induced osteomalacia, Osteoporos Int. 34 (1) (2023) 201–206.
[132] Y.N. Lamb, Burosumab: first global approval, Drugs 78 (6) (2018) 707–714.
[133] Y. Imanishi, N. Ito, Y. Rhee, et al., Interim analysis of a phase 2 open-label trial assessing burosumab efficacy and safety in patients with tumor-induced osteomalacia, J. Bone Miner. Res. 36 (2) (2021) 262–270.
[134] D. Miyaoka, Y. Imanishi, M. Yano, et al., Effects of burosumab on osteocalcin and bone mineral density in patient with 15-year history of nonremission tumor-induced osteomalacia initially treated with conventional therapy: Case report, Bone Rep. 13 (2020).
[135] L. Colangelo, C. Sonato, M. Riminucci, et al., Appropriate dosing of burosumab in tumor-induced osteomalacia, Osteoporos Int. 34 (2) (2023) 421.
[136] I.R. Hartley, M.T. Collins, Burosumab for tumor-induced osteomalacia: not enough of a good thing, J. Bone Miner. Res. 36 (12) (2021) 2453–2454.
[137] M.P. Whyte, Tumor-induced osteomalacia: treatment progress using burosumab, an anti-FGF23 monoclonal antibody, J. Bone Miner. Res. 36 (4) (2021) 625–626.
[138] F. Jerkovich, S. Nuñez, Y. Mocarbel, et al., Burden of disease in patients with tumor-induced osteomalacia, JBMR Plus. 5 (2) (2020) e10436.
[139] S. Minisola, A. Barlassina, S.A. Vincent, et al., A literature review to understand the burden of disease in people living with tumour-induced osteomalacia, Osteoporos Int. 33 (9) (2022) 1845–1857.
[140] A.L. Day, O.M. Gutiérrez, B.L. Guthrie, et al., Burosumab in tumor-induced osteomalacia: A case report, Joint Bone Spine 87 (1) (2020) 81–83.