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# Orthopedic surgical treatment of osteomalacia induced by culprit soft tissue tumor in the hip region: a single-center retrospective study

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## Abstract

**Background** Due to its occult position, complex anatomical structure, and spatial relationships, the causative tumor of Tumor-Induced Osteomalacia (TIO) in the hip region is quite difficult to detect and qualitatively diagnose in clinical practice. In this regard, clinicians often lack sufficient knowledge about such tumors, leading to frequent missed diagnoses, misdiagnoses, and unreasonable treatment.

**Objective** This study aimed to investigate the clinical characteristics of TIO patients with culprit soft tissue tumors in the hip region and evaluate the effect of surgical treatment on these individuals to improve clinicians' understanding of the rare phenomenon.

**Methods** The clinical data of all patients, from January 2013 to January 2023, who underwent surgical treatment for hip located culprit soft tissue tumors by the subspecialty group on bone and soft tissue tumors at our institution, were retrospectively analysed. Specifically, the clinical characteristics and therapeutic effects were examined and the patients' clinical experience was summarized.

**Results** Twenty-two patients, who met the inclusion criteria, were included. All patients experienced varying degrees of bone pain, commonly accompanied by weakness (16/22) and limited mobility (21/22), and 10 patients (45.5%) experienced a significant reduction in body height during the course of the disease. All patients underwent orthopedic surgery in the hip region, as hypophosphatemia occurred in all of them. Pathological diagnosis was confirmed to be consistent with causative tumors of TIO. All patients experienced a gradual increase in serum phosphorus postoperatively during short-term follow-up. The follow-up period was between 1 and 10 years, and the postoperative serum phosphorus levels were monitored at our hospital or other facilities close to the patients.

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**Conclusions** Oncogenic soft tissue tumors for TIO in the hip region are occult, making clinical misdiagnoses or missed diagnoses highly likely. Therefore, enhancing the clinician's understanding of this rare condition is imperative. Notably, for TIO patient whose culprit tumor can be located, complete surgical resection of the causative tumor is the best treatment option. Furthermore, close postoperative monitoring of serum phosphorus is necessary, and patients should be subjected to long-term follow-up for prompt detection of recurrent conditions.

## Highlights

- Tumor-induced osteomalacia caused by causative soft tissue tumor in the hip region is a rare entity, resulting in great challenges to orthopedists.
- Qualitative and localized diagnosis led by multi-disciplinary team is a prerequisite for subsequent surgical intervention.
- For the inguinally located culprit tumors, it may be quite effective after remove the culprit tumor directly and surgical resection may bring huge benefit.
- Exploring the site of onset of the causative tumor is beneficial for improving the treatment strategy of orthopedic surgery and understanding the prognostic characteristics of TIO patients.

**Keywords** Tumor-Induced osteomalacia, Hypophosphatemia, Phosphaturic mesenchymal tumor, Hip region, Diagnosis, Surgical treatment

## Introduction

Tumor-Induced Osteomalacia (TIO) is a relatively uncommon acquired Metabolic Bone Disorder (MBD) caused primarily by the causative tumor-secreted Fibroblast Growth Factor-23 (FGF-23), resulting in a significant rise in renal phosphorus excretion, leading to reduced serum phosphorus and bone mineralization [1–3]. The clinical manifestations of TIO are fatigue and progressive bone pain caused by persistent hypophosphatemia. In severe cases, fracture, bone deformity, and limited activity could also occur, negatively impacting patients' Quality of Life (QoL) and emotional state [1–6]. Laboratory examinations often reveal decreased serum phosphorus and elevated urine phosphorus and Alkaline Phosphatase (ALP) levels in TIO patients. Furthermore, the blood 1,25-$(OH)_2$-D3 level could be relatively low, and the Parathyroid Hormone (PTH) may be upregulated in some patients [4–6]. On the other hand, imaging manifestations include osteomalacia and reduced Bone Mineral Density (BMD).

McCance first reported TIO in 1947 [1]. Nearly 1000 TIO cases have been reported worldwide thus far, highlighting TIO as an extremely rare occurrence in clinical practice [7, 8]. As a result, clinicians commonly lack an understanding of TIO. Furthermore, missed diagnoses or misdiagnoses are highly likely because TIO's onset is slow, oncogenic tumor volume is often small with an occult location, clinical manifestations lack specificity, and localization diagnosis is quite difficult [2–5]. Different surgical treatment strategies are related to the overall treatment effect for TIO patients with culprit tumors located in various parts. Based on previous literature and accumulating single-center experience, conducting an in-depth analysis of surgical treatment strategies for TIO patients with causative tumors in different locations is critical. Specifically, the surgical treatment experience of TIO patients with pathogenic tumors in the hip region requires an in-depth exploration. Herein, the clinical data of all TIO patients with culprit tumors located in the hip region, who were treated in our institution were analyzed retrospectively. The purpose of this article is to investigate the clinical characteristics of TIO patients with culprit soft tissue tumors in the hip region and evaluate the effect of surgical treatment on these individuals. This study contributes to improve clinicians' understanding of clinical characteristics and surgical treatment for TIO patients whose causative tumors are located in the soft tissue around the hip region.

## Materials and methods

A retrospective analysis of clinical data was done, of patients who underwent surgery at our institution under the subspecialty of bone and soft tissue tumors, between January 2013 and January 2023, for tumor-induced osteomalacia due to soft tissue tumors around the hip region. The clinical characteristics of the patients were summarized and analyzed, and then the surgical team conducted telephone or outpatient follow-up for all patients. The study design was reviewed and approved by our hospital's Ethics Committee (No. SK-1658).

### Clinical data

The inclusion criteria were as follows: (1) Patients with clinical manifestations including progressively aggravated bone pain which mostly began at the weight-bearing joints (such as ankles, hips, knees, chest, back, sacrococcygeal region, etc.); (2) Patients with sustainable hypophosphatemia as revealed by laboratory examinations; (3) Patients whose treatment was supplemented with large doses of neutral phosphorus solution and active vitamin

**Table 1** General data and clinical manifestations of patients with TIO caused by causative soft tissue tumors in the hip region

| Cases | Age (y) | Sex | Symptoms | Time to diagnosis (y) | Bone pain sites | Difficulty in sitting up and walking | Fatigue | Limited mobility | Short stature | Osteoporosis | Pathological fractures/pseudofractures | History of orthopedic surgery unrelated to the causative tumor |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50 | F | Fatigue, bone pain, difficulty sitting up and walking | 4 | Systemic body pain, right ankle joint | Yes | Yes | Yes | None | None | Yes | None |
| 2 | 42 | F | Progressive bone pain, difficulty sitting and walking | 3 | Ribs, lower back, lower limbs | Yes | Yes | Yes | Yes, 3 cm | Yes | Yes | None |
| 3 | 62 | F | Pain in both feet, shoulder, back, and waist, difficulty sitting up and walking | 1 | Both feet, shoulders, back, waist, and knees | Yes | Yes | Yes | / | Yes | None | None |
| 4 | 47 | F | Pain in both lower limbs and limited limb movement | 3 | Double lower limbs, right back of foot, right lower leg, inner back of thigh, waist, ribs | Yes | Yes | Yes | / | Yes | None | None |
| 5 | 38 | M | Multiple bone pain, difficulty sitting and walking, and reduced height | 2 | Right palm, right heel, bilateral ribs, lower back, knees, and hips | Yes | Yes | Yes | Yes | Yes | Yes | None |
| 6 | 65 | M | Lower limb pain and weakness, difficulty sitting and walking, shortened height, and scoliosis deformity | 9 | Lower limbs, waist and back, bilateral knee joints, elbow joints, shoulder | Yes | Yes | Yes | Yes, 170→153 cm | Yes | Yes | Yes |

**Table 1** (continued)

| Cases | Age (y) | Sex | Symptoms | Time to diagnosis (y) | Bone pain sites | Difficulty in sitting up and walking | Fatigue | Limited mobility | Short stature | Osteoporosis | Pathological fractures/pseudofractures | History of orthopedic surgery unrelated to the causative tumor |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | 47 | M | Low back discomfort, bone pain, difficulty sitting up and walking | 1 | Waist, lower limbs, chest | Yes | Yes | Yes | Yes, 176→164 cm | Yes | Yes | None |
| 8 | 45 | M | Whole body bone pain accompanied by fatigue, difficulty in sitting and walking, and shortened height | 1 | Right back of foot, left back of foot, ankle joint, knee muscle attachment points, and ribs | Yes | Yes | Yes | None | Osteopenia | Yes | None |
| 9 | 45 | M | Bone pain, fatigue, difficulty sitting and walking | 2 | Right ankle, right lower limb, right buttock area, left buttock, left lower limb, chest, lower back, both hands | Yes | Yes | Yes | Yes | Osteopenia | Yes | None |
| 10 | 47 | M | Pain in the left and right lower limbs and chest wall, difficulty in sitting and walking, and reduced height | 5 | Left heel, left lower limb, right lower limb and chest wall, low back pain, anterior chest wall | Yes | Yes | Yes | Yes, 160→158 cm | None | Yes | None |
| 11 | 44 | M | Bone pain | 1 | Bilateral chest ribs, low back pain, bilateral heels and knee joints | Yes | Yes | Yes | None | Yes | Yes | None |

**Table 1** (continued)

| Cases | Age (y) | Sex | Symptoms | Time to diagnosis (y) | Bone pain sites | Difficulty in sitting up and walking | Fatigue | Limited mobility | Short stature | Osteoporosis | Pathological fractures/pseudofractures | History of orthopedic surgery unrelated to the causative tumor |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | 26 | M | Multiple bone pain, difficulty sitting and walking | 5 | Left tibia, lumbosacral region, bilateral ribs | Yes | Yes | Yes | Yes | None | Yes | Yes |
| 13 | 52 | M | Multiple bone pain | 1.5 | Left knee joint, lower back, bilateral ribs, right knee | Yes | Yes | Yes | Yes, 161→158 cm | Yes | Yes | None |
| 14 | 59 | F | Persistent dull pain in the left chest, and the pain gradually affected the bilateral groin, lumbar back and shoulder | 7 | Left chest, bilateral groin, lumbar back and shoulder | Yes | / | Yes | None | Osteopenia | Yes | None |
| 15 | 28 | M | Bone pain | 2 | Outer side of right front foot, right foot, left knee joint, low back pain, bilateral ribs, left iliac joint | Yes | / | Yes | Yes, 2 cm | Osteopenia | Yes | None |
| 16 | 47 | F | Low back pain with difficulty moving | 2 | Low back pain, bilateral knee joint, bilateral heel pain, bilateral shoulder joint pain, rib, sternum, back pain, hip pain | Yes | Yes | Yes | None | Osteopenia | Yes | None |
| 17 | 49 | M | Progressive bone pain | 2 | Chest, waist, back, bilateral ribs, below knees, both hips | Yes | Yes | Yes | Yes, 172→167 cm | Yes | Yes | Yes |

**Table 1** (continued)

| Cases | Age (y) | Sex | Symptoms | Time to diagnosis (y) | Bone pain sites | Difficulty in sitting up and walking | Fatigue | Limited mobility | Short stature | Osteoporosis | Pathological fractures/pseudofractures | History of orthopedic surgery unrelated to the causative tumor |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | 49 | M | Bone pain, fatigue | 2 | Bilateral ankle joints, bilateral hip joints, lumbosacral region | Yes | Yes | Yes | None | Yes | Yes | Yes |
| 19 | 45 | F | Progressive bone pain | 2 | Low back pain, left hip, bilateral anterior chest wall, clavicle, shoulder joint, gums | Yes | / | Yes | None | Yes | Yes | Yes |
| 20 | 50 | M | Bone pain | 4 | Ribs, ankles, heels, and hips | Yes | / | Yes | None | Yes | Yes | Yes |
| 21 | 43 | F | Pain | 1 | Throughout the body | None | None | None | None | None | None | None |
| 22 | 24 | M | Fatigue, fracture | 2 | Waist, back, right lower limb | Yes | None | Yes | None | Yes | Yes | Yes |

Note: y: Year; F: Female; M: Male; cm: Centimeter

D to improve the symptoms of bone pain and maintain the serum phosphorus level; (4) Patients who underwent imaging examination (systemic examination and local imaging detection) which revealed the location of the causative soft tissue tumor; (5) Patients who experienced gradually improving bone pain symptoms and rapid rise in serum phosphorus after complete tumor excision for culprit lesions in the hip region; and (6) Patients who underwent pathological examination which revealed results consistent with a TIO's causative tumor.

The exclusion criteria were as follows: (1) Patients whose serum phosphorus did not rise to the normal range or were unable to maintain within the normal range during the postoperative follow-up visits; (2) Patients with incomplete clinical data; (3) The pathogenic tumors were not located in the hip region; (4) The pathogenic tumors with skeletal involvement; (5) Patients with osteomalacia caused by other factors apart from TIO.

#### Laboratory and imaging examinations

Laboratory examinations: Patients' clinical data were collected and organized during hospitalization to detect the levels of serum phosphorus and calcium, ALP, urine phosphorus and calcium, 24-hour urine phosphorus and calcium, PTH, blood 25-(OH)D3 and 1,25-$(OH)_2$-D3, and beta-carboxy-terminal cross-linking telopeptide of type I collagen (beta-CTX).

Imaging examinations: X-ray, MRI, octreotide imaging ($^{99}Tc^m$-octreo-SPECT), and $^{68}$Ga-DOTATATE PET/CT were performed. The examinations were conducted in combination with ultrasonography or CT of corresponding parts for qualitative and localization diagnoses if necessary.

#### Preoperative treatment and assessment

Following admission to the orthopedic ward, all clinically suspected TIO patients stopped using neutral phosphorus and active vitamin D reagents before orthopedic surgery. Following that, baseline serum phosphorus levels were retested. Simultaneously, relevant preoperative examinations were intensively performed to rule out surgical contraindications, and orthopedic surgery plans were finally formulated. All patients underwent orthopedic surgery to remove culprit soft tissue tumors in the hip region.

#### Surgical treatment

All patients were evaluated in detail and final diagnoses were established through inpatient assessments or consultations with the Endocrinology, Orthopaedics, Nuclear medicine, Radiology, and Pathology departments, along with inferences drawn from clinical data and literature reports. Regarding treatment, all patients underwent surgery in the hip region. Complete resection (including tumor body and surrounding tissue) was performed during surgery, as all oncogenic tumors comprised soft tissues.

#### Pathological examination

Pathological diagnosis: Following surgery, tumor tissue specimens were obtained and sent for hematoxylin and eosin (H&E) and immunohistochemical staining. At least one senior pathologist (above associate professor of pathology) in PUMCH analyzed the tumor's nature and pathological characteristics, and then the pathological data were summarized.

#### Follow up

The endocrinology and orthopedics departments closely followed up on all patients after surgery. Furthermore, the patients' serum phosphorus levels were retested almost daily postoperatively, compared with the preoperative baseline levels, and then analyzed. Additionally, the patients' postoperative serum phosphorus levels, symptom changes, degree of relief, and prevalence of local recurrence and postoperative complications were regularly monitored.

#### Statistics

The results were presented as means, standard deviations, and proportions. The cure rate was ultimately determined. Data processing and statistical analyses were performed using the MedCalc Statistical Software version 15.2.2 (MedCalc Software, Ostend, Belgium).

## Results

#### Basic clinical information of patients

Between January 2013 and January 2023, the bone and soft tissue tumor sub-professional group of the orthopedics department in Peking Union Medical College Hospital completed the surgical treatment of 22 patients (14 males and 8 females, age range = 24–65 years, average age during disease diagnosis = 45.6 ± 10.2 years) with oncogenic tumors located in the hip region (See Table 1 for data details of the cases). All TIO cases included in the final analysis were confirmed through clinical, imaging, and pathological diagnoses. The time to diagnosis of all 22 patients ranged from 1 to 9 years, with an average time interval of 2.8 ± 2.1 years from the initial onset of symptoms to a definite diagnosis (Fig. 1). All patients experienced varying degrees of bone pain in different parts, including joints, mainly in the lower limbs, back, waist and other weight-bearing body parts. Significant height reduction was observed in 10 patients, and most cases were complicated with overt muscle weakness (16/22) and limited mobility (21/22). Difficulty in sitting up and walking was found in 21 patients. All patients showed no significant fever or other peculiar manifestations.

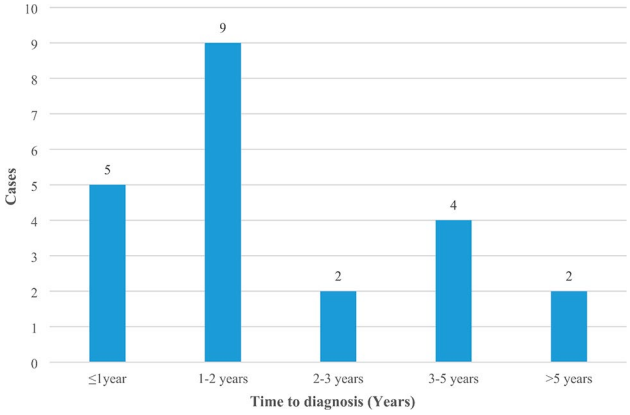


**Fig. 1** Diagram of time to diagnosis distribution for all patients included in this study

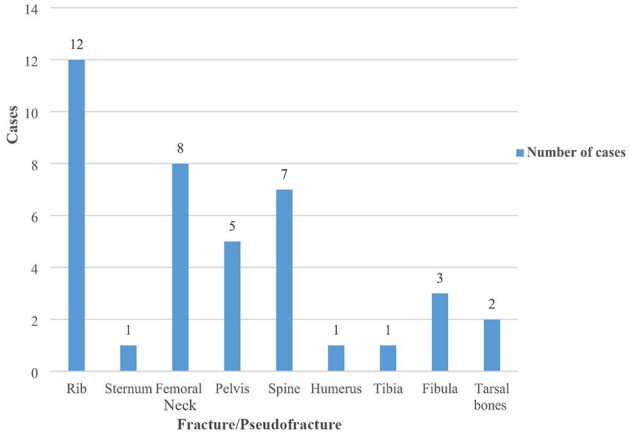


**Fig. 2** Distribution map of fracture sites in 19 patients with fractures/pseudofractures

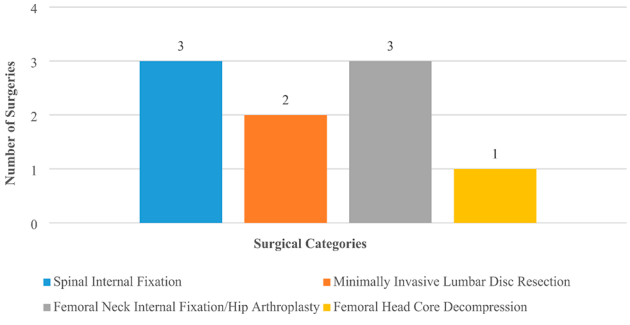


**Fig. 3** Classification of surgical types unrelated to the causative tumor for TIO during the course of the disease

Nineteen patients experienced fractures or pseudofractures in different parts during the course of the disease (Fig. 2). Seven patients underwent non-pathogenic tumor-related orthopedic surgery after symptoms manifested (Fig. 3).

## Laboratory and imaging examinations

### *Laboratory examination results*

Routine examination results other than bone metabolism indicators of all 22 TIO patients were almost at a normal range, and the autoantibody series and tumor indexes were almost negative. The pre-surgery serum phosphorus and calcium, ALP, urine phosphorus and calcium, 24-hour urine phosphorus and calcium, PTH, blood 25-(OH)D3 and 1,25-$(OH)_2$-D3, and beta-CTX levels were reviewed. Before surgery, the average serum phosphorus of all involved patients was $0.5 \pm 0.1$ mmol/L (Normal range: 0.81–1.45 mmol/L).

### *Imaging examination results*

All patients were examined by X-ray, MRI and whole-body bone scan. The X-ray revealed irregular bone density, as well as bone destruction and abnormality. The patients were also examined using $^{99}Tc^{m}$-octreo-SPECT and $^{68}$Ga-DOTATATE PET/CT, along with ultrasonography or CT of corresponding parts for qualitative and localization analysis. Table 2 shows the anatomical distribution of the culprit soft tissue tumors in the hip region.

### *Pathological results*

The pathological results of all 22 cases confirmed Phosphaturic Mesenchymal Tumors (PMTs). Finally, all patients were conclusively diagnosed with TIO by combining clinical manifestations, laboratory examination, radiological characteristics and pathological results (Table 2). According to the pathological specimen examination results completed by pathology experts, all surgical specimens of 22 patients had negative margins.

## Surgical treatment, and follow-up

After surgery, the average recovery time for serum phosphorus in all patients was $4.7 \pm 1.5$ days. Following surgery, bone pain and weakness symptoms were gradually improved, and serum phosphorus levels were significantly increased in all patients (Table 3). The trend chart of blood phosphorus changes before and after surgery (removal of culprit tumor) for all patients can be clearly seen from Fig. 4. The serum phosphorus levels in 21 cases remained in the normal range at 1–10 years of follow-up visits. During follow-up, local recurrence was observed in only a single patient (Table 4). Due to postoperative recurrence, the patient underwent reevaluation, however, no significant culprit tumor was found. The patient is still under close follow-up observation due to the small size of the causative tumor and the inability of imaging examination to accurately locate the lesion. Among all the patients included in the study, the clinical data of three patients are shown in Fig. 5, 6 and 7. Hitherto, TIO patients who have been treated by our team have been followed up on regularly in the orthopedic and

**Table 2** Locations and sizes of causative soft tissue tumors in the hip region

| Cases | Age (y) | Sex | Preoperative serum phosphorus (mmol/L) | Localization | Tumor size (cm) | Operation | Complication | Histological diagnosis |
|---|---|---|---|---|---|---|---|---|
| 1 | 50 | F | 0.73 | Deep surface of the origin of the gracilis muscle at the root of the left thigh | 1.0×1.0×1.0 | Complete tumor resection | None | PMT |
| 2 | 42 | F | 0.53 | Below the left inguinal ligament | 4.0×3.0×2.0 | Complete tumor resection | None | PMT |
| 3 | 62 | F | 0.54 | In the superficial fascia layer behind the root of the right thigh | 3.0×2.0×2.0 | Complete tumor resection | None | PMT |
| 4 | 47 | F | 0.54 | Right inguinal region | 1.0×1.0×0.3 | Complete tumor resection | None | PMT |
| 5 | 38 | M | 0.55 | Root of right thigh | 2.0×2.0×1.5 | Complete tumor resection | None | PMT |
| 6 | 65 | M | 0.36 | Surface of femoral vein in the right inguinal region | 2.0×2.0×1.0 | Complete tumor resection | None | PMT |
| 7 | 47 | M | 0.43 | Deep surface of sartorius muscle below left inguinal ligament | 3.0×2.0×2.0 | Complete tumor resection | None | PMT |
| 8 | 45 | M | 0.63 | Deep posterior surface of femoral vein in right groin area | 1.0×1.0×0.5 | Complete tumor resection | None | PMT |
| 9 | 45 | M | 0.33 | Deep layer of superficial fascia on the anterior side of the root of the right thigh | 2.0×2.0×1.0 | Complete tumor resection | None | PMT |
| 10 | 47 | M | 0.66 | Around the right femoral neck | 3.0×2.0×1.0 | Complete tumor resection | None | PMT |
| 11 | 44 | M | 0.55 | Below the left inguinal ligament | 5.0×4.0×3.0 | Complete tumor resection | None | PMT |
| 12 | 26 | M | 0.53 | Between the medial semitendinosus and adductor magnus of the left thigh root | 1.5×1.0×0.5 | Complete tumor resection | None | PMT |
| 13 | 52 | M | 0.41 | Right inguinal region | 1.0×1.0×1.0 | Complete tumor resection | None | PMT |
| 14 | 59 | F | 0.3 | Behind the left femoral neck | 1.0×1.0×0.8 | Complete tumor resection | None | PMT |
| 15 | 28 | M | 0.42 | Left anterior femoral neck muscle space | 1.5×1.0×1.0 | Complete tumor resection | None | PMT |
| 16 | 47 | F | 0.7 | Right inguinal region | 5.0×4.0×3.0 | Complete tumor resection | None | PMT |
| 17 | 49 | M | 0.38 | Dorsal side of right inguinal canal area | 3.0×2.5×2.0 | Complete tumor resection | None | PMT |
| 18 | 49 | M | 0.44 | Left inguinal region | 3.0×2.0×2.0 | Complete tumor resection | None | PMT |
| 19 | 45 | F | 0.74 | Left inguinal region | 1.0×1.0×1.0 | Complete tumor resection | None | PMT |
| 20 | 50 | M | 0.67 | Left inguinal region | - | Complete tumor resection | None | PMT |
| 21 | 43 | F | 0.59 | Left inguinal region | 4.0×3.0×2.0 | Complete tumor resection | None | PMT |
| 22 | 24 | M | 0.4 | Right inguinal region | 3.0×3.0×2.0 | Complete tumor resection | None | PMT |

Note: Normal range of serum phosphorus: 0.81–1.45 mmol/L; y: Year; F: Female; M: Male; cm: Centimeter; PMT: Phosphaturic Mesenchymal Tumor

endocrinology clinics, and their condition has remained relatively stable.

## Discussion

Tumor-induced osteomalacia (TIO) is a rare acquired hypophosphatemic osteomalacia characterized by decreased renal tubular phosphorus reabsorption and increased renal phosphorus excretion caused by the tumor secretion of phosphorus regulating factors [1, 2, 9–11]. The culprit tumors of TIO are mostly benign tumors originating from mesenchymal tissue, often found in bone or soft tissue [2–4, 12]. This type of tumor is difficult to detect through routine physical examination as it grows slowly and often has an occult location and small volume. According to literature reports, TIO tumors are mostly found in the lower limbs (56%), head (31%), upper limbs (5%), and hip (3%) [2, 3, 13–15]. The culprit tumors can occur both in soft tissues (67%) and in skeletal sites (33%) [2, 3]. After suspecting TIO in clinical diagnosis, it is still necessary to localize the causative tumor through imaging. Most causative tumors of TIO can be located through CT, MRI, $^{99}Tc^{m}$-octreo-SPECT, and $^{68}Ga$ DOTATATE PET/CT [16–22]. Histologically, causative tumors are mainly characterized by spindle or star-shaped tumor cells, small nuclei, unclear nucleoli, and low mitosis activity [23]. Furthermore, cells are often embedded in mucinous or mucinous cartilage-like matrices accompanied by chondroid or osteoid calcifications, and blood vessel abundance is always seen in tumor tissue [23–25]. Herein, the pathological examination results of all patients confirmed PMTs; hence, a TIO diagnosis was conclusively reached. Table 5 summarizes previously

**Table 3** Changes of serum phosphorus level in TIO patients with causative soft tissue tumors in the hip region

| Cases | Age (y) | Sex | PreoperativeP(mmol/L) | Postopera-tive day1(mmol/L) | Postop-erative day 2(mmol/L) | Postop-erative day 3(mmol/L) | Postop-erative day 4(mmol/L) | Postop-erative day 5(mmol/L) | Postop-erative day 6(mmol/L) | Postop-erative day 7(mmol/L) | Postop-erative day 8(mmol/L) | Postoper-ative day 9(mmol/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50 | F | 0.73 | 0.54 | / | 1.01 | / | 1.18 | / | / | / | / |
| 2 | 42 | F | 0.53 | 0.58 | 0.77 | 0.85 | 0.97 | / | 1.04 | / | / | / |
| 3 | 62 | F | 0.54 | 0.78 | / | 0.95 | 1.15 | / | / | / | / | / |
| 4 | 47 | F | 0.54 | 1.04 | 0.94 | 1.03 | / | / | / | / | / | / |
| 5 | 38 | M | 0.55 | 0.45 | 0.79 | 0.82 | 0.95 | / | / | / | / | / |
| 6 | 65 | M | 0.36 | 0.7 | 0.83 | 0.96 | / | / | / | / | / | / |
| 7 | 47 | M | 0.43 | 0.52 | 0.64 | 0.78 | 0.79 | / | 0.93 | / | / | / |
| 8 | 45 | M | 0.63 | 0.5 | 0.7 | / | / | / | 1.1 | / | / | / |
| 9 | 45 | M | 0.33 | 0.4 | 0.7 | / | / | / | / | / | / | / |
| 10 | 47 | M | 0.66 | 0.75 | 0.73 | / | / | / | 0.87 | / | / | / |
| 11 | 44 | M | 0.55 | 0.66 | 0.78 | 0.75 | / | / | / | / | / | / |
| 12 | 26 | M | 0.53 | 0.8 | / | 0.71 | / | 0.84 | / | / | / | / |
| 13 | 52 | M | 0.41 | 0.41 | 0.62 | 0.91 | 1.07 | 1.14 | 1.04 | 0.9 | 0.86 | / |
| 14 | 59 | F | 0.3 | 0.35 | 0.41 | 0.59 | 0.73 | 0.93 | 1.07 | / | / | / |
| 15 | 28 | M | 0.42 | 0.75 | 0.73 | / | / | / | 0.87 | / | / | / |
| 16 | 47 | F | 0.7 | 0.55 | 0.57 | 0.85 | 0.99 | 1.12 | / | / | / | / |
| 17 | 49 | M | 0.38 | 0.46 | 0.47 | 0.47 | 0.61 | 0.69 | 0.78 | 0.83 | / | / |
| 18 | 49 | M | 0.44 | 0.58 | 0.6 | 0.76 | 0.82 | 0.85 | / | / | / | / |
| 19 | 45 | F | 0.74 | 0.43 | 0.6 | 0.6 | / | / | 1.03 | / | / | / |
| 20 | 50 | M | 0.67 | 0.84 | 0.84 | 0.96 | / | / | 1.33 | / | / | / |
| 21 | 43 | F | 0.59 | 0.43 | / | 0.67 | / | / | 0.89 | / | / | 1.05 |
| 22 | 24 | M | 0.4 | 0.37 | 0.39 | 0.66 | / | / | 0.95 | / | / | / |

Note: Normal range of serum phosphorus: 0.81–1.45 mmol/L; y: Year; F: Female; M: Male; P: Phosphorus; The serum phosphorus levels of Case 9 and Case 11 recovered to normal range at one month after surgery

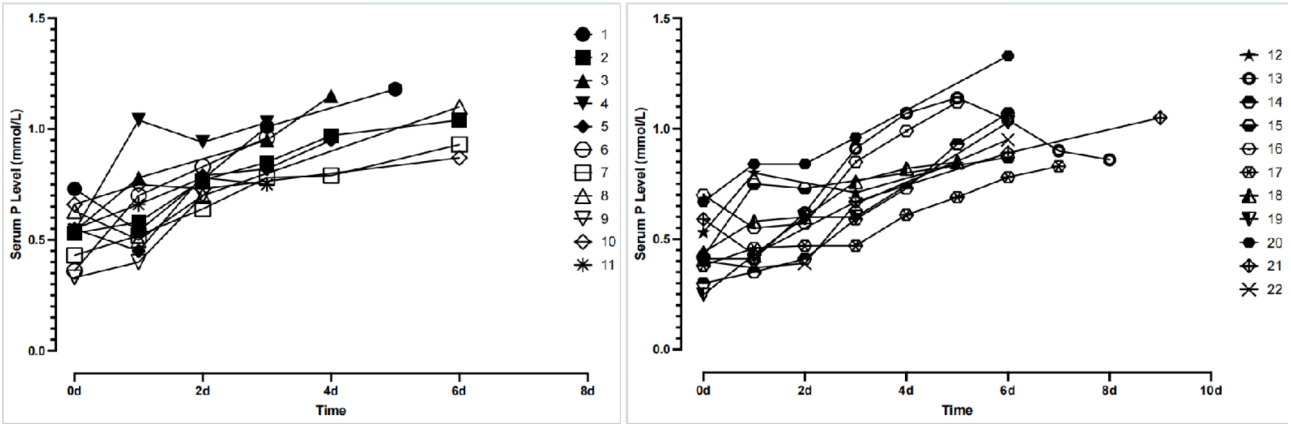


**Fig. 4** The chart illustration of post-surgery trends in the level of serum phosphorus in all patients involved in this study. Note: "0d" represents "Early morning on the day of surgery"; "1–22" represents Patient serial number; P: Phosphorus

**Table 4** Summary of laboratory test indicators for the recurrent case

| Case | Age (y) | Sex | Time | Blood calcium (mmol/L) | 1,25-(OH)2-D3 (pg/ml) | ALP (U/L) | PTH (pg/ml) | β-CTX (ng/ml) | Urinary phosphorus (mmol/L) | Urinary calcium (mmol/L) |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient 12 | 26 | M | Preoperative | 2.19 | 0.53 | 11.55 | 388 | 30.4 | 1.92 | 2.19 |
| | | | **Time** | **Preoperative P (mmol/L)** | **Postoperative day 1 (mmol/L)** | **Postoperative day 2 (mmol/L)** | **Postoperative day 3 (mmol/L)** | **Postoperative day 4 (mmol/L)** | **Postoperative day 5 (mmol/L)** | **Follow up at the 54$^{th}$month (mmol/L)** |
| | | | Postoperative | 0.53 | 0.8 | / | 0.71 | / | 0.84 | 0.3 |

Note: Normal range of serum phosphorus: 0.81–1.45 mmol/L; y: Year; M: Male; P: Phosphorus

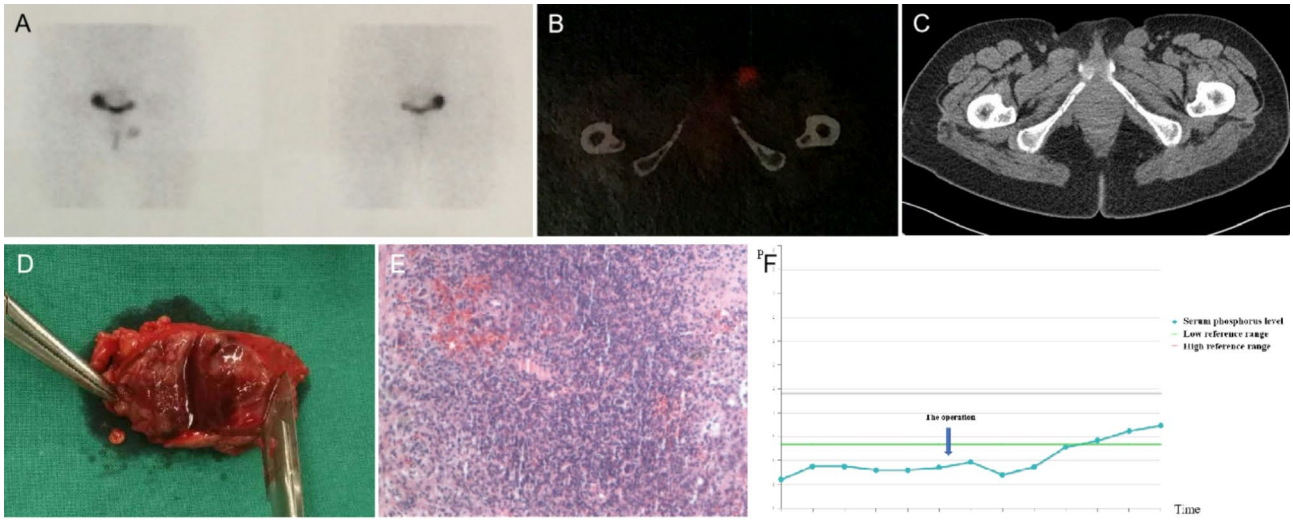


**Fig. 5** Case 1 (**A**) The $^{99}Tc^{m}$-octreo-SPECT showing local bone metabolism was active in left inguinal region. (**B**) PET/CT revealing the increased expression in the inguinal region. (**C**) CT revealing the mass, which was highly indicative of the culprit tumor. (**D**) The mass in the left inguinal region was completely excised. (**E**) Pathologic histology of tumor specimens was consistent with the diagnosis of phosphaturic mesenchymal tumor. (**F**) Serum phosphorus levels significantly elevated to the normal range after the operation

reported studies on TIO with culprit soft tissue tumors located in the hip region [26–30].

In this study, specific diagnostic criteria were consistent with the diagnostic process outlined in the International TIO Diagnosis and Treatment Guidelines [22, 31]. Regarding qualitative diagnosis, TIO should be considered when patients exhibit symptoms of osteomalacia induced by excessive renal phosphorus loss. Detection of gene mutations, including *FGF-23*, Matrix Extracellular Phosphoglycoprotein (*MEPE*), Secreted Frizzled-related

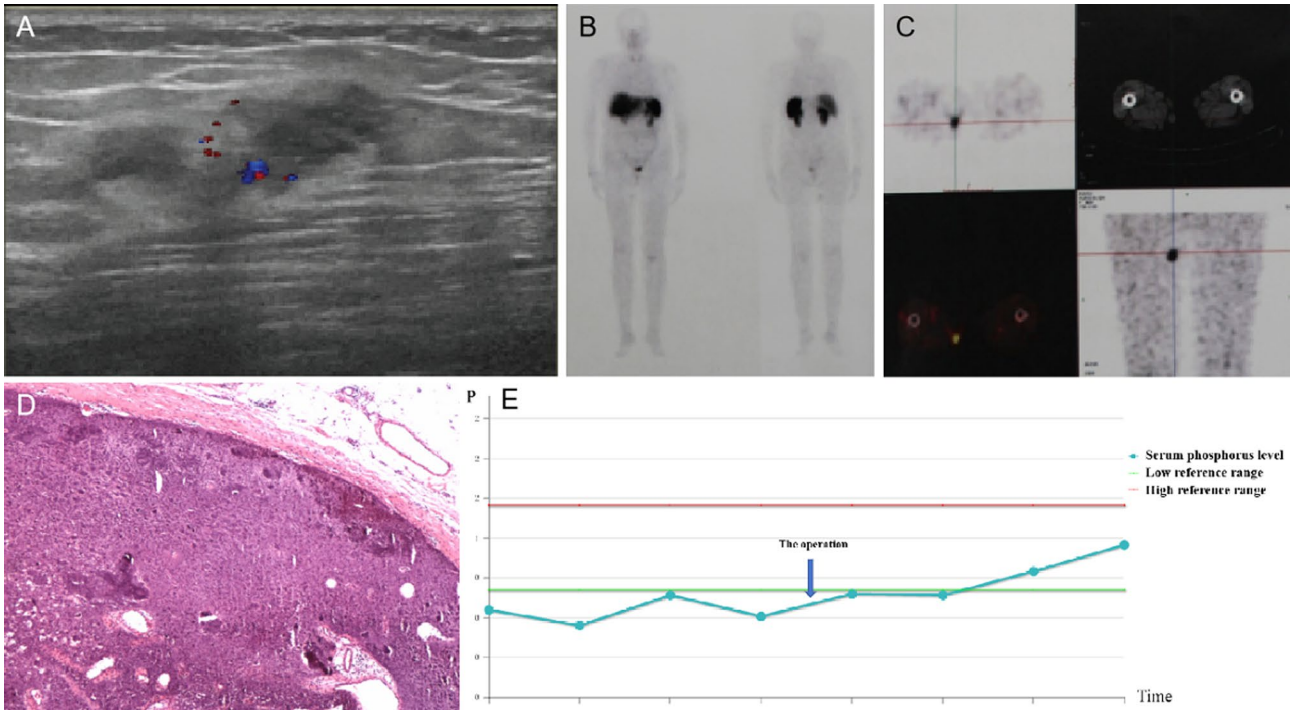


**Fig. 6** Case 2 (**A**) The Dopple ultrasonography showed the soft tissue tumor was in the right hip region. (**B**) The $^{99}Tc^{m}$-octreo-SPECT showing local metabolism was active in right hip region. (**C**) The first-line $^{68}Ga$ DOTATE PET/CT scan showed the lesion with high intake. (**D**) Pathologic histology of tumor specimens confirmed the diagnosis of phosphaturic mesenchymal tumor. (**E**) Serum phosphorus levels significantly elevated to the normal range after the operation

Protein 4 (*sFRP4*), and Phosphate Regulating Endopeptidase Homolog X-linked (*PHEX*) has some reference value for the definite diagnosis of TIO [2–5,32–34]. According to past and latest international consensus on the diagnosis and treatment of TIO, preoperative FGF23 testing is helpful, however, not necessary for the final diagnosis of TIO cases [22, 31]. The guidelines indicate that if preoperative FGF23 testing is possible, it can be attempted, but not all patients must complete it to obtain a definitive diagnosis [22]. In addition, due to the potential for significant errors and heterogeneity in preoperative FGF23 detection under different centers and instrument conditions, the consensus of using this detection method needs to be further reached. Pathological examination is currently the 'gold standard' for establishing TIO diagnosis [7, 32–34]. On the other hand, localization diagnosis involves detecting the tumor characteristics, including its localization in some patients via ultrasound, CT, or MRI. However, given the occult nature and small size of the tumor body, $^{99}Tc^{m}$-octreo-SPECT and $^{68}Ga$ DOTATATE PET/CT are required for full localization [16–22]. The tumor tissue of patients with TIO's culprit tumor in the hip region is often soft and small in size. We employed $^{99}Tc^{m}$-octreo-SPECT and $^{68}Ga$ DOTATATE PET/CT during clinical diagnosis to facilitate precise diagnosis and accurate surgical resection [16–22]. According to literature, the $^{99}Tc^{m}$-octreo-SPECT whole-body scan and $^{68}Ga$ DOTATATE PET/CT are effective methods for locating TIO culprit soft tissue tumors [16–18, 21]. Some studies recently reported the increasing popularity of $^{68}Ga$ DOTATATE PET/CT as an ideal method for locating TIO culprit tumors, highlighting that it can even detect tumors not identified by $^{99}Tc^{m}$-octreo-SPECT [16–18, 21]. Therefore, to improve diagnostic accuracy and devise an effective follow-up treatment plan, a proper TIO diagnosis needs to fully integrate patients' clinical manifestations, laboratory tests, and various qualitative, and localization methods [31, 35, 36].

For patients with TIO, a detailed preoperative evaluation and qualitative diagnosis, as well as a clear localization diagnosis, were necessary. Regarding surgical treatment, the first step for TIO cases with causative tumors located in the hip region is to determine the affected site and structures adjacent to the tumor. Due to the complex anatomical structure of the hip region and the existence of local anatomical variations in some patients, special attention should be paid to identifying important anatomical structures, such as nerves (ilioinguinal nerve, genitofemoral nerve, and so on.), blood vessels (femoral artery, femoral vein, and so on.), muscles, ligaments, and spermatic cord, among others, to avoid unnecessary iatrogenic injuries. In our study, no patients experienced any iatrogenic intra-operative injuries to critical structures surrounding the tumors. Due to the

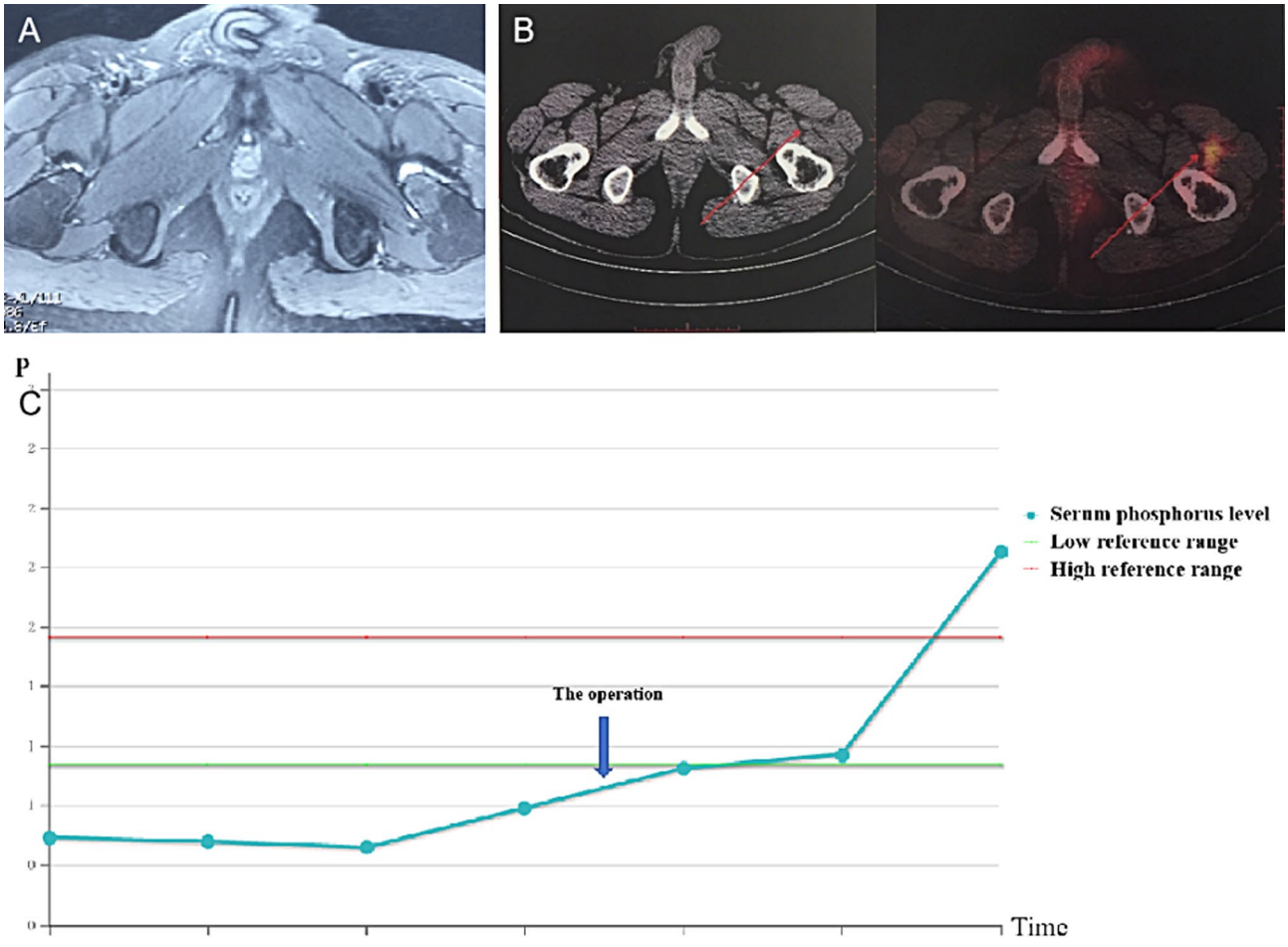


**Fig. 7** Case 3 (**A**) MRI of the pelvis revealing the pathogenic tumor. (**B**) The first-line $^{68}$Ga DOTATE PET/CT showed high intake in the left hip region. (**C**) Serum phosphorus levels significantly elevated to the normal range after the operation

unique anatomical location of the tumors, the surgical approach is often depending on the location of the suspected causative tumor. Among TIO patients, the local recurrence rate of those with soft tissue tumors is lower than that of those whose tumors involve bones. In this regard, only one patient had the recurrent situation in our analysis [35]. Herein, the causative tumors were all soft tissue tumors; hence, we performed complete resection (including the tumor body and surrounding tissue) during surgery. Our single team experience is that the resection range should be set to the surrounding tissue at 1.0 cm around the tumor to completely remove the culprit tumors and reduce the recurrence rate as much as possible. The incidence of intraoperative complications is determined by the stability of intraoperative procedures and sufficient mastery of local anatomical structures. Therefore, careful manipulation and identification of neural and vascular anatomy are crucial during surgery.

Following the complete removal of the culprit tumor, the patient's serum phosphorus should be monitored closely until the serum phosphorus is restored to normal. In literature, the serum phosphate levels are normalized in about 5 days (2–10 days) after surgery [2]. For TIO patients with complete removal of the culprit tumors, the consensus recommends biochemical parameters (especially serum phosphate) should be measured initially every 6 months and then at yearly intervals with the dual-energy X-ray absorptiometry examination [31]. For patients with unidentifiable or unresectable tumors on stable doses of oral phosphate salts plus active vitamin D, or burosumab, the interval examinations for biochemical parameters should be shortened to every 3 to 4 months to adjust the drug doses and prevent the side effects during the long-term medical treatment [22]. More frequent monitoring may be required when initiating treatment or after dose adjustment [22]. In addition, for TIO patients with unidentifiable tumors and those with unresectable tumors, the functional imaging or anatomical imaging is suggested to be performed every 1–2 years, respectively [22]. Furthermore, apart from the examinations, postoperative symptom changes should also be monitored regularly by the endocrinology and orthopedic clinics during

**Table 5** Summary of five previously published studies with culprit soft tissue tumours in the hip region

| Authors | Year | Age (y), sex | Symptoms | Serum phosphorus concentration | Localization methods | Localization | Tumor size | Treatment | Outcome | Follow up (Month) | Histological diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ha S [26] | 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 [27] | 2017 | 40, M | Several structural deformities (fractures with poor bone healing, verte bral and limb shortening) 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 [29] | 2017 | 37, M | Hip pain for 3 years | NA | MRI | Groin | NA | The lesion was excised | Complete remission after operation | 170 | NA |
| Chouhan V [30] | 2015 | 32, M | 18 months prior to presentation, had initially experienced pain in his right foot, both lower limbs, predominantly involving the hips and lower back | 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 [28] | 2004 | 37, M | Chronic pain of the spine, ribs, femurs, and 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: Normal range of serum phosphorus: 0.81–1.45 mmol/L; y: Year; M: Male; P: Phosphorus; NA: None; cm: Centimeter; PMT: Phosphaturic Mesenchymal Tumor; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PET/CT: Positron Emission Tomography-Computed Tomography

follow-up [37–40]. Further qualitative and targeted diagnoses, as well as treatment, should be administered if the serum phosphorus continues to be lower than normal or fall back. Standardized regular follow-up is vital, and the recurrence after the operation is a critical clinical concern [22, 31, 41].

Ablation therapy is regarded as a less invasive method and reported to have fewer side effects [4]. If causative tumor is located at a site such that surgical intervention is not feasible, image-guided ablation is an effective, minimally invasive, and safe alternative option for TIO patients [42, 43]. Global guidelines for TIO have proposed the use of oral phosphate combined with active vitamin D in TIO patients for whom culprit tumors cannot be resected completely or whose culprit tumors cannot be identified [22]. The specific recommended daily supplementation doses and precautions are clearly stated in global guidelines [22, 31]. In recent years, research hotspots for TIO treatment include the anti-FGF-23 monoclonal antibodies [44]. However, the long-term treatment effect still needs further evidence. In literature, about 20% of TIO patients experience recurrence or inability to recover after surgery [45]. Clinical diagnosis and treatment for refractory/recurrent TIO is quite challenging [35, 45, 46]. In a multivariate regression analysis, Li et al. [35] reported female sex, spinal tumors, bone involvement by tumors, malignant tumors, and preoperative low serum phosphorus levels were identified as risk factors for refractory outcomes in patients with TIO.

To the best of our knowledge, this is currently the most comprehensive study on TIO cases with causative soft tissue tumors located in the hip region. However, it still has some inevitable shortcomings. First, the sample size was too small, complicating the comprehensive analysis of the clinical prognostic factors of this type of patients. Second, although we have comprehensively summarized data from our team and previous literature reports to improve the capabilities of orthopedic physicians to diagnose these tumors, this remains a single-center study. Third, the time span of this study is relatively long, and the display of preoperative FGF23 levels may cause confusion and misunderstanding among readers. Therefore, this study did not compare and analyze the correlation between FGF23 levels and surgery in patients with TIO. Finally, there may be some unavoidable bias in the research results as this was a retrospective study.

In conclusion, although osteomalacia induced by hip located culprit soft tissue tumors is extremely rare, its true incidence rate is likely to be underestimated and its occurrence and development can seriously affect patients' QoL. Therefore, enhanced clinicians' understanding of osteomalacia induced by culprit soft tissue tumors in the hip region could improve the disease's diagnostic accuracy and effectively inform the selection of an appropriate treatment option to improve surgical treatment effect of TIO patients with causative tumors located in hip parts. To bring more hope to patients with osteomalacia induced by culprit soft tissue tumors in the hip region, orthopedic surgical strategy should be explored and accumulated further.

#### Abbreviations

| | |
|---|---|
| TIO | Tumor-Induced Osteomalacia |
| MBD | Metabolic Bone Disorder |
| PMT | Phosphaturic Mesenchymal Tumor |
| FGF-23 | Fibroblast Growth Factor-23 |
| QoL | Quality of Life |
| ALP | Alkaline Phosphatase |
| PTH | Parathyroid Hormone |
| beta-CTX | beta-carboxy-terminal cross-linking telopeptide of type I collagen |
| CT | Computed Tomography |
| MRI | Magnetic Resonance Imaging |
| SPECT | Single Photon Emission Computed Tomography |
| PET/CT | Positron Emission Tomography-Computed Tomography |
| H&E | hematoxylin and eosin |
| MEPE | Matrix extracellular phosphoglycoprotein |
| sFRP4 | Secreted Frizzled-related Protein 4 |
| PHEX | Phosphate Regulating Endopeptidase Homolog X-linked |

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#### Author contributions

X. Z. and S. Z. L. wrote the paper. X. Z., S. Z. L., A. N. L., and J. Y. X. analyzed the collected data for the patients. X. Z. and Y. L. performed the operations. L. S. Z., X. Z., Y. L., and W. B. X. took care of the patients. Y. L. and W. B. X. revised the manuscript for important intellectual content and technical details. We confirm that all of us have met the criteria for authorship as established by the ICMJE.

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#### Data availability

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

### Declarations

#### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (approval number S-K1658). This study was conducted in accordance with the principles of the Declaration of Helsinki. All data were anonymized, and the requirement for informed consent was waived by the Institutional Review Board due to the retrospective nature of the study design.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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