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Comparison of surgical treatments of tumor-induced osteomalacia in different locations in the lower limbs

A retrospective study

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Abstract

Tumor-induced osteomalacia (TIO) is a rare disease that behaves benignly. Very few reports about the features of the responsible tumors according to anatomical locations have been presented.

In this retrospective study of 53 patients with TIO-associated tumors in the foot/ankle, tibia and femur, we compared preoperative, postoperative, and follow-up courses, including alkaline phosphatase, phosphorus, and fibroblast growth factor 23, to compare the characteristics of TIO-associated tumors in these 3 locations (level of evidence: therapeutic level III).

Patients in the foot/ankle group had longer disease courses and therefore a significantly higher complication rate ($P < .001$). All TIO-associated tumors in the foot/ankle group involved soft tissue ($P = .021$), whereas most lesions in the tibia group involved bone, and therefore had much higher concentrations of alkaline phosphatase ($P = .020$). Additionally, serum phosphorus took much longer to normalize after surgery in the foot/ankle group than that in the other 2 groups ($P = .004$). Consequently, symptom remission was much better in the tibia and femur groups ($P = .008$). Moreover, the Ki 67 index in TIO-associated tumors was significantly higher in the foot/ankle group ($P < .001$) and the recurrence rate in this group was markedly higher ($P = .002$).

The TIO-associated tumors in the foot/ankle are characteristically of occult onset, more soft-tissue involvement, and more readily recurrence. More knowledge and examinations are necessary to enable early diagnosis, radical treatments, and minimize recurrence. New therapies are welcomed and needed.

Abbreviations: ALP = alkaline phosphatase, CD = cluster of differentiation, CT = computed tomography, FGF-23 = fibroblast growth factor 23, MRI = magnetic resonance imaging, P = phosphate, PET = ^{68}Ga positron emission tomography, TIO = tumor-induced osteomalacia, TMP/GFR = tubular maximum reabsorption of phosphorus/glomerular filtration rate.

Keywords: femur, foot/ankle, surgical treatment, tibia, tumor-induced osteomalacia

1. Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is an uncommon paraneoplastic syndrome that was 1st described by McCance in 1947.[1–3] It is as an acquired hypophosphatemic disorder caused by renal loss of phosphorus associated with overproduction of fibroblast growth factor 23 (FGF-23).[4] FGF-23 decreases renal phosphate reabsorption and inhibits production of 1, 25-$(OH)_2$D, which is necessary for optimal enteral calcium and phosphate (P) absorption.[5,6] As a result, bone demineralization occurs, potentially resulting in severe skeletal complications. The clinical manifestations of TIO may include extensive bone pain, musculoskeletal weakness, and pathologic fractures,[7] whereas the laboratory tests show low concentrations of serum P and 1, 25-$(OH)_2$D, and high concentrations of alkaline phosphatase (ALP) and FGF-23.[8]

Treating TIO with phosphates can only relieve symptoms to a certain extent, whereas complete surgical removal of the responsible tumor remains the gold standard for curative treatment.[9,10] However, the locations of the tumors and their characteristically small size, slow growth rate, and widely varying symptoms may make surgical management challenging. Because the foot/ankle is a very rare location for TIO, there are very few published studies about surgical treatments of such tumors in the ankle and foot or comparisons between the characteristics of these tumors in the foot and ankle with those in other locations. Thus, we performed the present study to compare traits of patients with TIO-associated tumors were in the foot/ankle, tibia, and femur, and provide more information about the features and treatments of such tumors.

2. Materials and methods

From January 2012 to June 2017, 56 patients with TIO-associated tumors in the foot/ankle, tibia, femur, and peripheral soft tissues were admitted to our hospital for treatments, 3 of whom were lost in follow-up. The inclusion criteria were: patients

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who had undergone surgical treatment in our hospital; availability of complete pre-, intra-, postoperative, and follow-up data; a solid tumor involving bone and/or soft tissue; and patients had provided written informed consent for the operative procedures. The exclusion criteria were: multiple TIO-associated tumors; questionable diagnosis of TIO; tumor not resected or otherwise removed completely; and prior surgical treatment of any TIO-associated tumors before the current hospital admission. This study was approved by the medical ethics committee of our hospital and was conducted in compliance with the ethics committee requirements.

Three experienced surgeons were involved in this study, who contributed to management of patients recruited in this study. Preoperative examinations, including measurement of alanine transaminase, ALP, calcium, P, parathyroid hormone, serum beta-CrossLaps, 25OHD, 1, 25-$(OH)_2$D, 24 hours urine calcium, 24 hours urine P, urine amino acid, FGF-23 concentrations, and tubular maximum reabsorption of phosphorus/glomerular filtration rate (TMP/GFR),[2,11–14] as well as estimation of bone mineral density, plain radiography, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), ^{68}Ga positron emission tomography (PET)/CT, and $^{99}Tc^{m}$-octreotide, were routinely performed on all patients suspected of TIO. All images and other data about the locations of TIO-associated tumors were collected. The routine biochemical variables were measured in our hospital's clinical laboratory, whereas serum full-length FGF-23 was measured by 2-site enzyme-linked immunosorbent assay with kit (Kainos Laboratories, Tokyo, Japan).[15–17]

Serum P concentrations on different postoperative days were measured and analyzed carefully, to determine the effect of surgical treatments of TIO. Once P concentrations had normalized, serum calcium and ALP concentrations were routinely measured. Pathologic indexes, including the following immunohistochemistry parameters: Ki 67, podoplanin, cluster of differentiation (CD) 34, CD99, CD68, CD56/neurokinin-1, vimentin, B-cell lymphoma-2, smooth muscle actin, and somatostatin, were also obtained. All follow-up information, including the laboratory findings of the patients in our study, was updated in January 2018. One-way analysis of variance, the Chi-squared and the *t* tests were used in statistical analysis, software programs used being SPSS 22.0 (IBM Corp, Armonk, NY) and Prism 5 (GraphPad Software, La Jolla, CA). A *P*-value of $<.05$ indicated a statistically significant difference.

3. Results

3.1. Diagnosis and surgical treatments of TIO-associated tumors

All studied patients were referred to our hospital because of progressive bone pain. Hypophosphatemia and osteomalacia were diagnosed on the basis of the relevant routine lab tests. TIO and Fanconi syndrome were often considered as possible diagnoses. To clarify the diagnosis, adjuvant examinations, including plain radiography, ultrasound, CT, MRI, PET-CT, and $^{99}Tc^{m}$-octreotide, were performed (Fig. 1). Once a clear abnormal mass had been identified, a diagnosis of TIO was suspected, and surgical treatment would be considered.

Preoperative biopsies were not routinely performed because TIO-associated tumors are usually small and benign. Complete resection of tumors involving only soft tissue, including the integrated capsule, was preferred. If the tumor was close to the bone margin and possibly involving bone, part of the bone cortex was also removed. For tumors located only in bone tissue, curettage with a minimum of 5 millimeters margin and subsequent bone allograft was usually considered as the 1st option. Tumors infiltrating both soft tissue and bone were managed by curettage or extensive tumor resection according to their anatomic location. The residual cavity after curettage was treated with phenol, high-temperature electric coagulation, or warm distilled water in turn before bone allografting.[18–20] After segmental resection, an allogeneic bone segment was used to fulfill the residual defect and reconstruct the local anatomic structure. If histopathologic examination revealed any malignancy, tumor resection with a wider margin was recommended.

Pathologic examination is an important means of making a definitive diagnosis. Phosphaturic mesenchymal tumor was the nature of a TIO-associated tumor (Fig. 1). It is benign and slow-growing, with various characteristic immunohistochemistry features. Details of pathology findings are described in Section 3.2.2, where the influence of different locations on the features of TIO-associated tumors is discussed.

Additionally, because TIO is tumor-induced, resolution after resection of the responsible tumor is crucial to make the diagnosis: the associated hypophosphatemia, osteomalacia, and related symptoms, should resolve completely. If so, the final diagnosis of TIO was confirmed, and those cases were included in our study.

3.2. Characteristics of TIO-associated tumors according to locations

3.2.1. Patients' clinical characteristics. The basic characteristics of the 53 patients in the foot/ankle, tibia, and femur groups are summarized in Table 1. Overall, 13 patients had TIO-associated tumors in the foot/ankle (6 males, 7 females, average age 45.23 years, age range 33–62 years), 9 patients had TIO-associated tumors in the tibia (5 males, 4 females, average age 38.33 years, age range 13–63 years), and 31 patients had TIO-associated tumors in the femur (17 males, 14 females, average age 40.87 years, age range 17–62 years). None of these characteristics differed significantly between the 3 groups (Table 1).

The disease course tended to be longer for patients in the foot/ankle group than those in the other 2 groups; however, this difference was not statistically significant (Table 1). As for the preoperative symptoms, all the patients had bone pain and over 50% suffered from weakness and fracture, regardless of locations. However, the incidence of malformation, such as decrease in height, kyphosis, and claudication, was significantly higher in the foot/ankle group, consistent with their long clinical courses ($P<.001$; Table 1).

Preoperative laboratory findings, including concentrations of alanine transaminase, calcium, P, parathyroid hormone, serum beta-CrossLaps, 25OHD, 1, 25-$(OH)_2$D, 24 hours urine calcium, and 24 hours urine P, urine amino acid, FGF-23, and TMP/GFR, did not differ significantly between the 3 groups. The exception was ALP, which was a biomarker of bone metabolism, and was significantly higher in the tibia group than in the other 2 groups, indicating more severe bone destruction ($P=.020$; Table 1). There were no significant differences between the 3 groups in average bone mineral density, or mean tumor diameter measured by adjuvant examinations. Additionally, the detection rate of the various imaging examination methods utilized did not differ significantly between the 3 groups (Table 1).

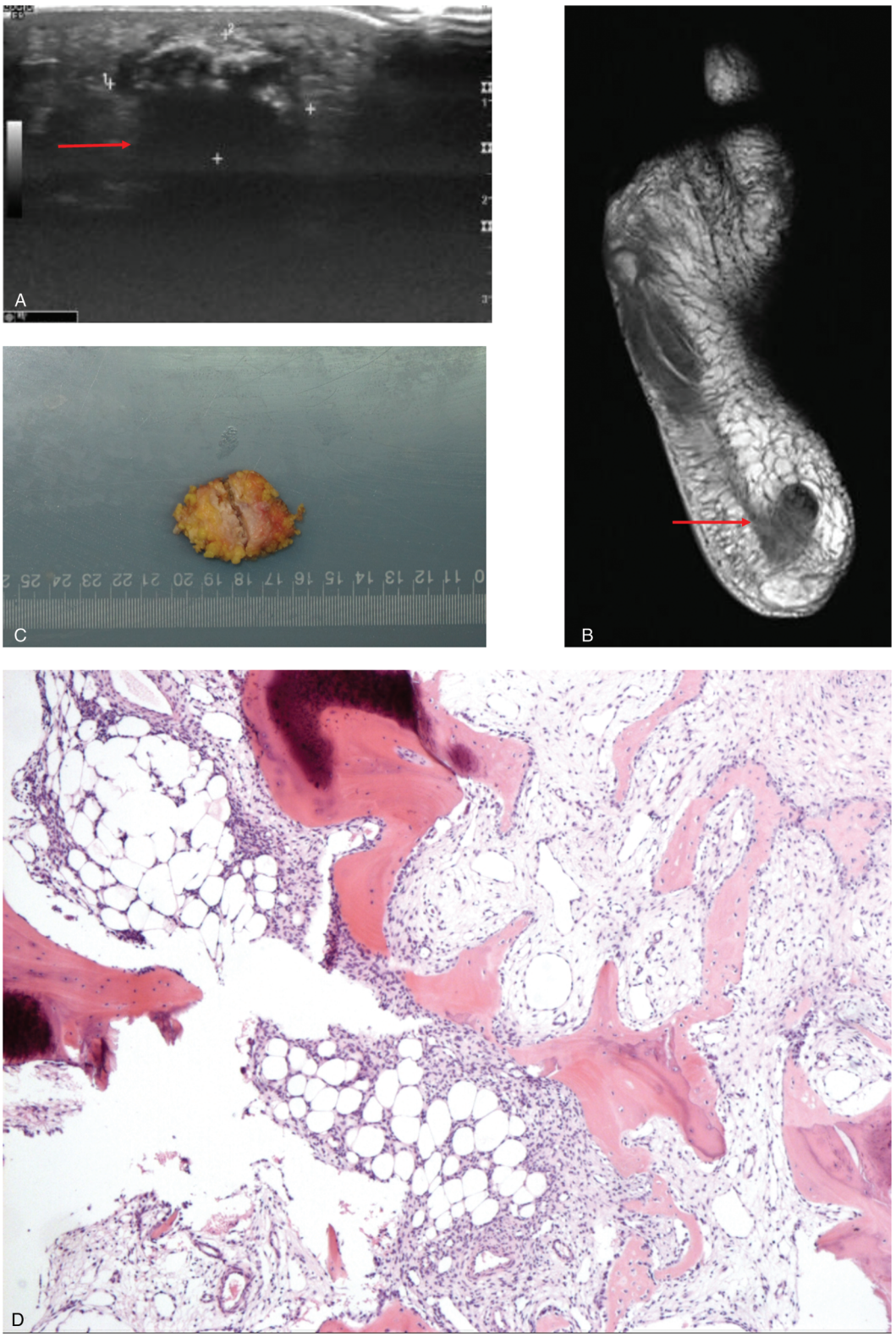

Figure 1. The images data of tumor-induced osteomalacia (TIO). (A) The ultrasound image of a TIO lesion in foot. (B) The magnetic resonance imaging image of the TIO lesion in foot. (C) A specimen of TIO lesion. (D) The pathologic analysis of TIO: phosphaturic mesenchymal tumor.

Table 1

Demographic and clinical characteristics of 53 patients.

Tumor location	Foot/ankle	Tibia	Femur	*P*
No. patients	13	9	31	
Age, mean ± SEM, yrs	45.23 ± 2.72	38.33 ± 5.69	40.87 ± 2.39	.452
Sex (male/female)	6/7	5/4	17/14	.864
Disease course, mean ± SEM, yrs	7.81 ± 2.11	5.86 ± 1.13	4.27 ± 0.51	.068
Symptoms, n (%)				
Osteodynia	13 (100)	9 (100)	31 (100)	>.99
Weakness	9 (69.23)	5 (55.56)	27 (87.10)	.103
Cataclasis	12 (92.31)	5 (55.56)	20 (64.52)	.114
Malformation	8 (61.54)	5 (55.56)	3 (9.68)	<.001
Preoperative lab tests				
Alanine transaminase, U/L	31.46 ± 12.68	17.88 ± 4.57	20.34 ± 2.06	.354
ALP, U/L	235.3 ± 40.8	547.1 ± 215	266.3 ± 21.4	.020
Calcium, mmol/L	2.23 ± 0.04	2.32 ± 0.03	2.21 ± 0.03	.210
P, mmol/L	0.49 ± 0.03	0.47 ± 0.03	0.51 ± 0.02	.764
Parathyroid hormone, pg/mL	99.92 ± 22.00	98.44 ± 23.49	75.80 ± 12.67	.517
Serum beta-CrossLaps, ng/mL	0.65 ± 0.09	0.86 ± 0.24	0.69 ± 0.09	.580
25OHD, ng/mL	22.38 ± 5.05	14.41 ± 4.02	15.64 ± 1.13	.169
1–25OHD, pg/mL	16.11 ± 5.11	6.13 ± 1.78	12.85 ± 2.67	.400
24 h urine calcium, mmol	2.88 ± 0.49	2.41 ± 1.01	2.14 ± 0.28	.465
24 h urine P, mmol	27.16 ± 4.44	23.12 ± 4.23	22.01 ± 2.80	.579
Positive urine amino acid, n (%)	5 (38.46)	2 (22.22)	11 (35.48)	.716
TMP/GFR, mmol/L	0.47 ± 0.12	0.39 ± 0.04	0.44 ± 0.04	.770
FGF-23, pg/mL	2000 ± 1509	1728 ± 1095	1234 ± 950	.890
Preoperative adjuvant examinations				
Tumor diameter, cm	3.20 ± 0.35	2.70 ± 0.40	3.43 ± 0.41	.551
	Sensitivity			
Visible in X-ray, n (%)	9 (69.23)	3 (33.33)	23 (74.19)	.073
Visible in ultrasound, n (%)	13 (100)	7 (77.78)	23 (74.19)	.136
Visible in CT, n (%)	10 (76.92)	5 (55.56)	28 (90.32)	.058
Visible in MRI, n (%)	13 (100)	9 (100)	30 (96.77)	.709
Visible in ^{68}Ga PET/CT, n (%)	10 (76.92)	7 (77.78)	27 (87.10)	.657
Visible in $^{99}Tc^{m}$-octreotide, n (%)	11 (84.62)	8 (88.89)	25 (80.65)	.840

Reference ranges: alanine transaminase, 5–40 U/L; ALP, 30–120 U/L; calcium, 2.13–2.70 mmol/L; P, 0.81–1.45 mmol/L; parathyroid hormone, 12.0–65.0 pg/mL; serum beta-CrossLaps, 0.260–0.512 ng/mL; 25OHD, 8–50 ng/mL; 1, 25-$(OH)_2$D, 19.6–54.3 pg/mL; TMP/GFR, 0.7–1.4 mmol/L; and FGF-23, 10–50 pg/mL.

ALP = alkaline phosphatase, CT = computed tomography, FGF-23 = fibroblast growth factor 23, h = hour, MRI = magnetic resonance imaging, P = phosphorus, PET/CT = positron emission tomography/computed tomography, SEM = standard error of the mean, TMP/GFR = tubular maximum reabsorption of phosphorus/glomerular filtration rate.

3.2.2. Perioperative and postoperative findings. No operative or hospital deaths or postoperative complications (Clavien grade ≥ 3[21]) occurred in any patient. All TIO-associated tumors in the foot/ankle group involved soft tissue, whereas bone tissue was more likely to be involved in the tibia group (Table 2).

Alanine transaminase, calcium, and P concentrations did not differ significantly between the groups postoperatively; however, serum P concentration took significantly longer to return to normal in the foot/ankle group ($P = .004$; Table 2). Conformably, this postoperative symptomatic improvement was slower in the foot/ankle group than in the other 2 groups ($P = .008$; Table 2). The significantly higher ALP concentrations in the tibia group was possibly attributable to the more frequent involvement of bone tissue ($P = .003$; Table 2).

All TIO-associated tumors were reported after pathologic examination as phosphaturic mesenchymal tumors. Interestingly, immunohistochemistry examination showed that Ki 67 was much more abundant in the foot/ankle group, reflecting the great proliferation of tumor cells in this group ($P < .001$; Table 2). Other indexes, such as podoplanin, CD56/neurokinin-1, neuron-specific enolase, vimentin, B-cell lymphoma-2, CD34, CD99, CD68, smooth muscle actin, and somatostatin receptor, showed no significant differences between the 3 groups.

3.2.3. Long-term follow-up. The patients were followed up for a median of 36 months. No distant metastasis or death occurred. The local recurrence rate was much higher in the foot/ankle group than in the other 2 groups ($P = .002$; Table 3).

Laboratory indexes showed no significant differences between the groups during follow-up. ALP concentrations in the tibia group were similar to those in the other 2 groups, which is consistent with the low recurrence rate (Table 3). The much lower levels of P, 25OHD, and 1, 25-$(OH)_2$D, and the much higher levels of parathyroid hormone and 24 hours urine P in the foot/ankle group were consistent with its highest recurrence rate (Table 3).

Besides, we reorganized the 53 patients into a recurrence group (11 patients) and nonrecurrence group (42 patients). The duration of follow-up was not significantly different; however, the amount of Ki 67 was significantly ($P = .013$; Table 4), indicating the importance of Ki 67 in predicting postoperative recurrence. Again, patients with TIO-associated tumors in the foot or ankle were found to have a higher local recurrence rate than those in the tibia group (both $P < .001$; Table 4). Serum P concentration was much lower, and urine calcium and P concentrations was much higher in the recurrence than the nonrecurrence group, whereas the much higher concentration of parathyroid hormone in the recurrence group indicated secondary hyperparathyroidism (Table 4). Patients with foot/ankle

Table 2

Peri- and postoperative status of patients.

Tumor location	Foot/ankle	Tibia	Femur	*P*
No. patients	13	9	31	
TIO involved area, n (%)				
Soft tissue	13 (100)	5 (55.56)	19 (61.29)	.021
Bone tissue	5 (38.46)	7 (77.78)	15 (48.39)	.183
Postoperative results, mean ± SEM				
Mortality, n (%)	0	0	0	>.99
Overall complications (≥Clavien grade 3)	0	0	0	>.99
Alanine transaminase, U/L	25.50 ± 6.03	14.83 ± 2.88	17.65 ± 1.61	.151
ALP, U/L	229.8 ± 26.4	674.7 ± 322	202.6 ± 21.1	.003
Calcium, mmol/L	2.18 ± 0.03	2.21 ± 0.05	2.16 ± 0.03	.668
P (POD 0), mmol/L	0.49 ± 0.03	0.57 ± 0.02	0.50 ± 0.03	.369
P (POD 1), mmol/L	0.50 ± 0.03	0.56 ± 0.04	0.49 ± 0.03	.462
P (POD 3), mmol/L	0.62 ± 0.07	0.73 ± 0.09	0.68 ± 0.04	.593
P (POD 5), mmol/L	0.84 ± 0.08	0.86 ± 0.05	0.86 ± 0.05	.970
P (POD 7), mmol/L	0.89 ± 0.09	0.91 ± 0.07	0.89 ± 0.05	.985
P (POD 10), mmol/L	0.86 ± 0.08	1.09 ± 0.13	0.92 ± 0.05	.197
P (POD 14), mmol/L	0.96 ± 0.12	1.18 ± 0.12	1.01 ± 0.04	.273
POD of serum P recovery, d	12.00 ± 3.63	3.71 ± 0.61	4.30 ± 0.47	.004
Postoperative hospital stay, d	9.46 ± 1.47	8.56 ± 1.31	9.39 ± 0.85	.113
Symptomatic remission, n (%)	8 (61.54)	7 (77.78)	30 (96.78)	.008
Immunohistochemistry, n (%)				
Ki 67, mean ± SEM, %	8.83 ± 0.83	4.14 ± 1.64	2.60 ± 0.50	<.001
Podoplanin+	10 (76.92)	4 (44.44)	19 (61.29)	.311
CD56/neurokinin-1+	10 (76.92)	9 (100)	24 (77.42)	.296
Neuron-specific enolase+	11 (84.62)	9 (100)	30 (96.77)	.212
Vimentin+	13 (100)	8 (88.89)	29 (93.55)	.533
B-cell lymphoma-2+	7 (53.85)	5 (55.56)	18 (58.06)	.967
CD34+	9 (69.23)	4 (44.44)	26 (83.87)	.057
CD99+	5 (38.46)	4 (44.44)	8 (25.81)	.504
CD68+	8 (61.54)	8 (88.89)	19 (61.29)	.295
Smooth muscle actin+	10 (76.92)	3 (33.33)	13 (41.94)	.063
Somatostatin+	6 (46.15)	5 (55.56)	8 (25.81)	.183

Reference ranges: alanine transaminase, 5–40 U/L; ALP, 30–120 U/L; calcium, 2.13–2.70 mmol/L; P, 0.81–1.45 mmol/L.

ALP = alkaline phosphatase, P = phosphorus, POD = postoperative days, SEM = standard error of the mean, TIO = tumor-induced osteomalacia.

Table 3

Long-term follow-up of patients.

Tumor location	Foot/ankle	Tibia	Femur	*P*
No. patients	13	9	31	
Length of follow-up, mo	30.0 ± 4.71	39.4 ± 7.73	33.7 ± 3.41	0.532
Recurrence, n (%)	7 (53.85)	0	4 (12.90)	0.002
Lab tests				
ALP, U/L	255.5 ± 98.8	200.6 ± 56.4	175.8 ± 31.1	0.618
Calcium, mmol/L	2.31 ± 0.03	2.32 ± 0.05	2.34 ± 0.04	0.934
P, mmol/L	0.66 ± 0.08	1.22 ± 0.15	2.16 ± 1.13	0.575
Parathyroid hormone, pg/mL	158.9 ± 106	89.64 ± 17.96	61.7 ± 8.88	0.106
Serum beta-CrossLaps, ng/mL	1.07 ± 0.55	1.08 ± 0.32	1.31 ± 0.30	0.875
25OHD, ng/mL	11.9 ± 2.7	15.88 ± 2.56	15.96 ± 2.37	0.759
1–25OHD, pg/mL	44.25 ± 15.6	120.0 ± 22.4	121.7 ± 37.5	0.464
24 h urine calcium, mmol	5.81 ± 1.63	3.63 ± 0.38	4.20 ± 1.29	0.699
24h urine P, mmol	46.33 ± 17.7	23.14 ± 4.31	26.69 ± 5.09	0.195

Reference ranges: ALP, 30–120 U/L; calcium, 2.13–2.70 mmol/L; P, 0.81–1.45 mmol/L; parathyroid hormone, 12.0–65.0 pg/ml; serum beta-CrossLaps, 0.260–0.512 ng/ml; 25OHD, 8–50 ng/ml; 1, 25-$(OH)_2$D, 19.6–54.3 pg/ml.

ALP = alkaline phosphatase, h = hour, P = phosphorus.

Table 4

Long-term follow-up of patients.

	Recurrence	Nonrecurrence	*P*
No. patients	11	42	
Length of follow-up, months	46.8 ± 2.32	41.0 ± 3.10	.412
Ki 67, mean ± SEM, %	7.67 ± 1.45	3.00 ± 0.56	.013
Tumor location, n (%)			
Foot/ankle	7 (63.64)	6 (14.29)	<.001
Tibia	0	9 (21.43)	<.001
Femur	4 (36.36)	27 (64.29)	.098
Lab tests			
ALP, U/L	241.3 ± 104	185.9 ± 28.6	.491
Calcium, mmol/L	2.37 ± 0.15	2.33 ± 0.03	.627
P, mmol/L	0.612 ± 0.08	1.19 ± 0.08	.009
Parathyroid hormone, pg/mL	228.1 ± 141	68.8 ± 8.96	.002
Serum beta-CrossLaps, ng/mL	2.27 ± 0.65	1.12 ± 0.21	.121
25OHD, ng/mL	9.20 ± 0.06	15.9 ± 1.63	.120
1–25OHD, pg/mL	28.64 ± 0.006	115.0 ± 23.2	.074
24 h urine calcium, mmol	8.80 ± 0.06	4.07 ± 0.81	.035
24 h urine P, mmol	67.0 ± 0.58	25.8 ± 3.51	<.001

Reference ranges: ALP, 30–120 U/L; calcium, 2.13–2.70 mmol/L; P, 0.81–1.45 mmol/L; parathyroid hormone, 12.0–65.0 pg/ml; serum beta-CrossLaps, 0.260–0.512 ng/ml; 25OHD, 8–50 ng/ml; 1, 25-$(OH)_2$D, 19.6–54.3 pg/ml.

ALP = alkaline phosphatase, h = hour., P = phosphorus.

lesions warrant much closer follow-up than patients with lesions in other locations.

Few patients with recurrence (2 in the foot/ankle group and 1 in the femur group) came to our hospital for a 2nd surgical treatment because of economics problems, insurance limitations, or inconvenience. We therefore collected insufficient data to assess management of recurrence. In conclusion, whereas surgical treatment of TIO-associated tumors is important, close postoperative follow-up is even more important, especially for patients with foot or ankle lesions.

4. Discussion

The TIO is a rare disease that is well known to behave benignly. New bone matrix cannot mineralize properly because of secondary hypophosphatemia.[2–4] It may occur at any age, but is more common in adults aged 40 to 60 years old. Doctors in our hospital reported the 1st case of TIO in China in 1980. They subsequently found that TIO-associated tumors mostly locate in the femur, tibia, foot and ankle, all of which are weight-bearing. However, there have only been single case reports of TIO-associated tumors in the foot or ankle thus far.[2,22] To our knowledge, our study is the 1st to report a retrospective analysis of 13 patients with TIO-associated tumors in the foot or ankle, and an average follow-up of 30 months. Their clinical features, perioperative concerns, and prognosis are all summarized in this study. Furthermore, to our knowledge, the present study is the 1st to compare characteristics of TIO-associated tumors in the foot/ankle, tibia, and femur, thus providing more information about these tumors in the lower limbs, and guidance concerning treatments.

4.1. TIO-associated tumors in the foot/ankle cause more severe symptoms

Changes in serum P, 25OHD, 1, 25-$(OH)_2$D, and FGF-23 concentrations did not differ significantly between the foot/ankle group and the other 2 groups, nor did bone mineral density, tumor size, or rate of detection by various imaging modalities. However, the rate of malformation was significantly higher in the foot/ankle than in the other 2 groups, which is possibly attributable to the longer and more cryptic disease course (Table 1).

Clinicians may not identify that a TIO-associated tumor is responsible for extensive bone pain early in the course of the disease, especially when the lesion is in the foot or ankle, because the lesion characteristically grows very slowly.[9,12,23,24] Thus, delayed diagnosis is unavoidable. Consequently, malformation, such as a decrease in height, kyphosis, occult fractures, and joint laxity can develop, eventually resulting in the correct diagnosis. In the study cohort, TIO-associated tumors in the foot and ankle were more likely to involve soft tissue than bone tissue (Table 2), making it harder to distinguish the tumor from fibroma, osteochondroma, or giant cell tumor of bone. Additionally, ALP concentrations were lower in the foot/ankle group than the other 2 groups, which would have contributed to difficulties in diagnosis. Consequently, the symptoms of patients with TIO-associated tumors in the foot or ankle tended to be more severe.

4.2. TIO-associated tumors in the foot/ankle require comprehensive treatments

Surgical treatment is crucial to curing TIO, and the key element is accurate targeting of the TIO-associated tumor. We performed ^{68}Ga PET/CT and ^{99}Tc^{m}-octreotide scans preoperatively to help in ascertaining the nature of the responsible lesion, and plain radiography, ultrasound, CT, and MRI to help us in precisely locating it.[25–28] In our study, MRI had the highest rate of detection of TIO-associated tumors in various locations in lower limbs, suggesting its importance in the diagnosis of TIO-associated tumors. Since all of the TIO-associated tumors in the foot/ankle group involved soft tissue, ultrasound was also very effective.

Complete resection of a TIO-associated tumor is essential to achieving optimal therapeutic effects. We used phenol, high-temperature electrocautery, and warm distilled water to clean the surface of the residual cavity after resection of the tumor, to minimize the possibility of residual. Postoperatively, all study patients' P concentrations improved, and most symptoms resolved.

The complexity of anatomical structures in the foot and ankle makes it difficult to excise TIO-associated tumors in this location. Although postoperative pathologic examination of the resected tissue confirmed complete resection of TIO-associated tumor with clear margins, the invasive tumor cells were hard to remove thoroughly, largely because the complex anatomy and sophisticated function of the foot or ankle which means that extended resection was not feasible for patients with TIO-associated tumors in this region, unlike tibia or femur tumors. Consequently, the postoperative recovery of the patients in the foot/ankle group was less complete and slower, and their long-term local recurrence rate much higher (Tables 2–4).

Another interesting finding was the significant differences in the amounts of Ki 67 in the 3 groups. Ki 67, an immunohistochemistry marker of proliferation, is widely used.[29–31] The greater the amount of Ki 67, the more vigorously tumor cells grow.[32–34] In our study, Ki 67 was much more abundant in the foot/ankle group than in the other 2 groups (Table 2), indicating more vigorous proliferation of tumor cells in this group, and consequently a worse prognosis.

The higher concentration of parathyroid hormone in patients in the foot/ankle group during follow-up also points to a higher incidence of secondary hyperparathyroidism (Table 3). Therefore, a close follow-up of patients with TIO-associated tumors in the foot or ankle is strongly suggested, as is administrated of necessary symptomatic treatments for hyperparathyroidism and hypophosphatemia.

We recommend that patients with TIO-associated tumors in the foot or ankle should be treated comprehensively. For example, we suggest using CT-navigation to locate tumor intraoperatively.[35] Serum FGF-23 concentrations in blood samples collected from different sites can also contribute precisely to locating the tumor and determining its severance.[36] We also recommend anti-FGF-23 antibody, a new biologic product, postoperatively especially when the TIO-associated tumors were not resected completely.[2] Some research supports the use of radiotherapy and radiofrequency ablation but these modalities are still under study.[23,37]

The TIO is a rare disease, the features of which vary according to the location of the responsible tumors. The foot and ankle is a rare location for TIO-associated tumors and has therefore been poorly researched. Our study fills some of the gaps by summarizing the features of TIO-associated tumors in the foot and ankle, and comparing them with those in the tibia and femur, which are relatively common locations for such tumors, thus providing more information about the characteristics of TIO-associated tumors in the foot and ankle, and suggestions for their treatments. More cases and experience are needed. Our team will

continue to devote itself to treating more patients and investigating TIO-associated tumors further to gather more information about this rare disease.

Author contributions

Ye Li helped in surgical treatments of TIO and data collection; Yatong Li was in charge of clinical data collection, analysis, and language editing; and Min Hui was in charge of clinical data collection and non-surgical treatments of TIO. All these 3 authors contributed equally.

Xiaoting Liu was in charge of pathologic immunohistochemistry detection and analysis.

Yong Liu, Jin Jin, and Peng Gao were in charge of the surgical treatments. Jin and Gao were both correspondence authors in this article, who guided this research program.

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