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Original Article

Challenges in Evaluation and Management in Tumor-Induced Osteomalacia: A Retrospective Institutional and Literature-Based Scoping Review in Korean Patients

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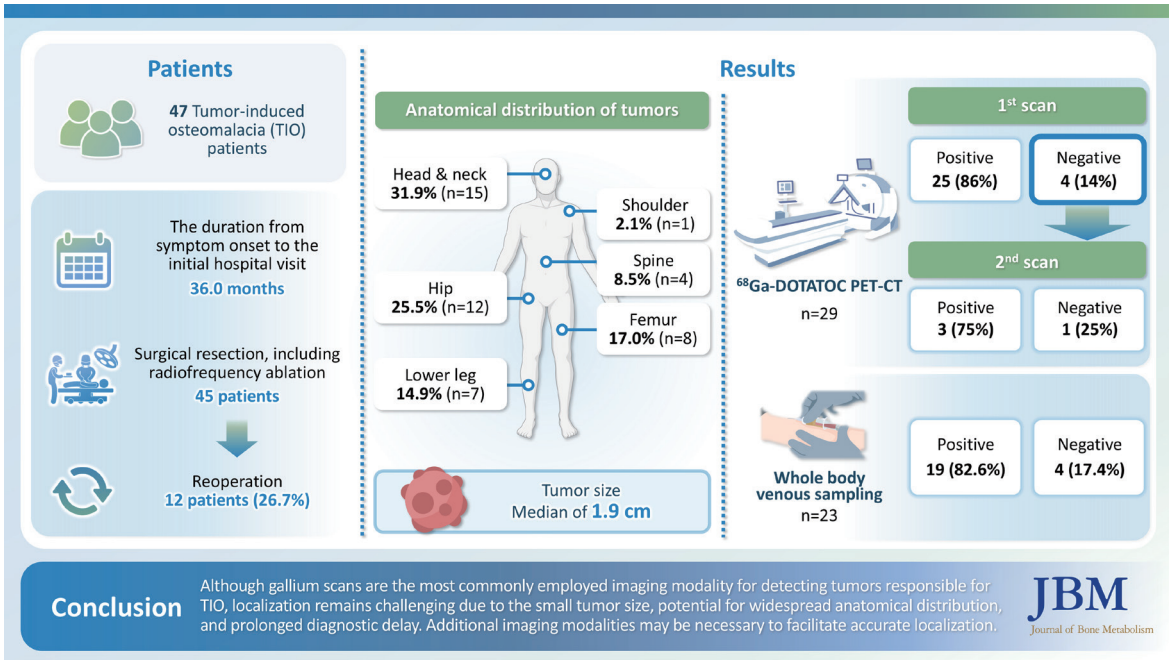
Background: Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by hypophosphatemia and osteomalacia, resulting from excessive production of fibroblast growth factor 23 by mesenchymal tumors. Although various imaging techniques are used to localize the tumor, the rarity of the disease poses significant challenges in tumor detection. **Methods:** After retrospectively analyzing 25 TIO patients who visited the Severance bone and mineral clinic between 2004 and 2024, we added all reported TIO cases in Korea by searching PubMed, Embase, and Web of Science. Using the PRISMA method, an additional 14 reports comprising 22 patients were included. **Results:** Among the 47 patients, 25 (53.2%) were male, with a median age of 52 years. Tumors were most commonly located in the lower extremities (57.5%), with a median size of 1.9 cm. Surgical resection, including radiofrequency ablation, was performed in 45 patients; reoperation was required in 26.7% (12/45) due to residual tumors. After gallium scans were covered by insurance, 83.3% (25/30) of patients underwent gallium-based imaging for tumor localization with 77.3% of tumors successfully localized in initial scan. Of the five patients with negative initial scans, four (80%) showed positive findings on a second scan conducted 1 to 2 years later. **Conclusions:** Although gallium scans are the most commonly employed imaging modality for detecting tumors responsible for TIO, localization remains challenging due to the small tumor size, potential for widespread anatomical distribution, and prolonged diagnostic delay. Repeating gallium imaging can yield positive results in previously negative cases, and additional imaging modalities may be necessary to facilitate accurate localization.

Key Words: Gallium radioisotopes · Hypophosphatemia · Korea · Osteomalacia · Paraneoplastic syndromes

INTRODUCTION

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by hypophosphatemia and osteomalacia caused by excess production fibroblast growth factor 23 (FGF-23). FGF-23 is a biochemical factor secreted by bone in healthy individuals that regulates phosphate metabolism. It promotes the deg-

Graphical Abstract



radation of 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) in the kidneys, leading to decreased phosphate absorption in the intestines and renal proximal tubules.[1-3] FGF-23 also acts in the renal proximal tubules by inhibiting Na-Pi2a cotransporters, thereby increasing urinary phosphate excretion.[1-4]

Overproduction of FGF-23 results in hypophosphatemia, increased renal phosphate excretion, and elevated alkaline phosphatase (ALP) levels, with typically normal calcium, decreased 1,25(OH)$_2$D, and elevated parathyroid hormone levels. Most FGF-23–producing tumors are small, benign phosphaturic mesenchymal tumors (PMTs).[1-7]

Patients with TIO exhibit a wide range of musculoskeletal symptoms, including progressive pain, muscle weakness, multiple fractures, gait disturbances, fatigue, and even a decrease in height.[1,8,9]

Complete surgical resection of the causative tumor is considered the definitive treatment for TIO, resolving both clinical symptoms and biochemical abnormalities, including a significant increase in bone mineral density.[1,10] In cases where surgical excision is not feasible, radiofrequency ablation (RFA) or medical therapies—including conventional treatment with oral phosphate and calcitriol, and the newly approved burosumab—are considered alternatives.[2,4,11,12]

Therefore, accurate localization of the tumor is a crucial initial step in the diagnosis and management of TIO.[13] Among the various imaging modalities, ^{68}Ga-DOTATOC positron emission tomography/computed tomography (PET-CT) has emerged as one of the most promising techniques for tumor localization in TIO.[14]

It is known that somatostatin receptors (SSTRs) are overexpressed in mesenchymal tumors, which has led to the use of ^{111}Indium-based octreotide scans and ^{68}Ga-DOTATOC PET-CT scans—originally developed for targeting SSTRs in neuroendocrine tumors—for tumor detection in TIO.[4,6,14,15] Several studies have compared these techniques and have demonstrated that ^{68}Ga-DOTATOC PET-CT scans are superior in terms of shorter investigation time, reduced radiation exposure, greater availability, and cost-effectiveness.[16,17] Additionally, ^{68}Ga-DOTA-peptides show a higher affinity for SSTR2 than ^{111}In-DTPA-octreotide, offering improved sensitivity in detecting small neuroendocrine tumors.[12] After functional imaging is completed, anatomical imaging techniques such as magnetic resonance imaging (MRI) are used to correlate findings and confirm tumor localization.[7] If the tumor is not identifiable through imaging, whole-body venous sampling

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(WBVS) may be considered.[2,4,18] Although no standardized cutoff for the FGF-23 gradient has been established, a more than 1.5–2.0-fold increase in FGF-23 levels across sampled sites is clinically considered significant.[18,19]

Despite advances in diagnostic modalities, there is a lack of long-term, comprehensive research on TIO in Korea that includes biochemical trends and disease characteristics before and after tumor resection. In this study, we reviewed all papers published between 1994 and 2024 and included patients diagnosed with TIO at Severance Hospital between 2004 and 2024.

METHODS

1. Study subjects

We retrospectively analyzed 25 patients who were diagnosed with TIO and visited Severance Hospital between 2004 and 2024. We then expanded our research to include all reported TIO cases in Korea by searching PubMed, Embase, and Web of Science. The search strategy is detailed in Supplementary Table 1.

2. Selection criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We included reports involving Korean patients with TIO that provided initial laboratory findings, tumor size, treatment methods, and postoperative laboratory results. Reports were excluded if they did not involve Korean patients, lacked patient-specific data, had unavailable full texts, or focused on other hypophosphatemic conditions such as X-linked hypophosphatemia. A total of 169 studies were initially identified from the databases. After removing duplicates, titles and abstracts were screened based on the exclusion criteria. Subsequently, full texts were reviewed for eligibility (Fig. 1). This process yielded 14 reports covering 22 patients. After adding the 25 patients from Severance Hospital, our final study population included 47 patients.

3. Statistical methods

Data for this study were extracted from multiple sources, including the original electronic medical records at Severance Hospital. These data were reanalyzed and combined. Due to the small sample size, a quantitative summary was

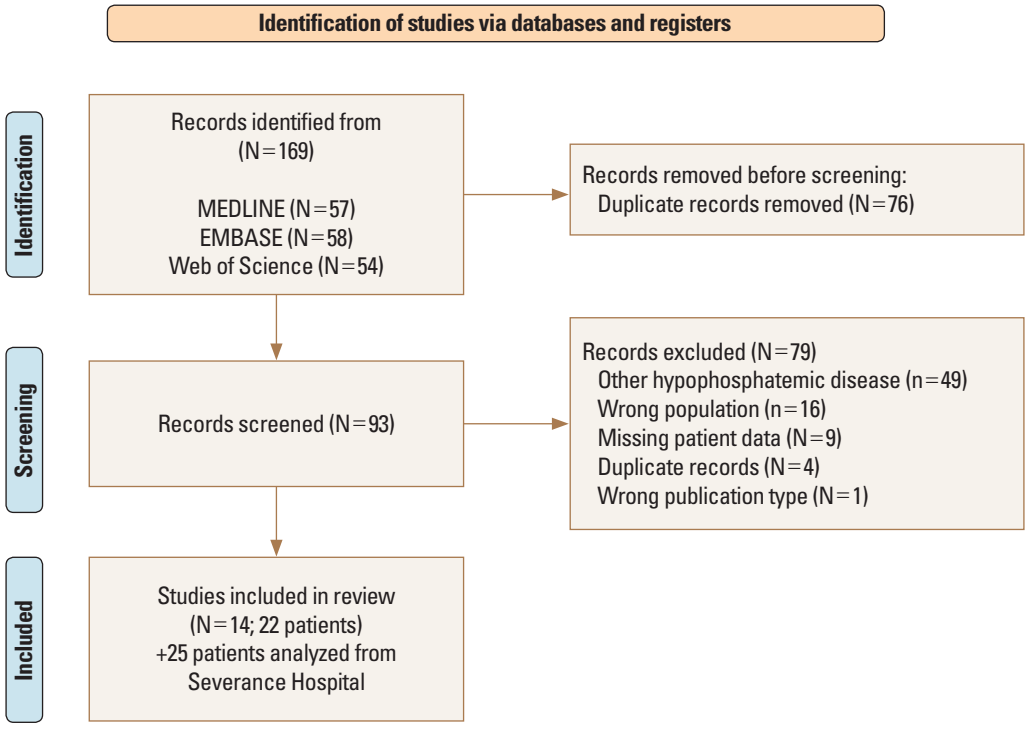

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection based on the PRISMA guidelines.

conducted using medians and interquartile ranges (IQRs).

RESULTS

Among the 47 patients, 25 (53.2%) were male, with a median age of 52 years (IQR, 34–60). The duration from symptom onset to the initial hospital visit was 36.0 months (IQR, 17.3–91.2). Tumors were predominantly small and benign, with a median longest axis of 1.9 cm (IQR, 1.5–2.8); only 2 patients (4.4%) had malignant tumors. Laboratory values at the initial visit indicated hypophosphatemia (1.7 mg/dL), elevated intact FGF-23 (261.8 pg/mL), and elevated (ALP, 339.0 IU/L), while calcium (8.9 mg/dL) and parathyroid hormone (54.0 pg/mL) levels were within normal ranges (Table 1).

Tumors were most commonly located in the lower ex-

Table 1. Baseline characteristics of patients with tumor-induced osteomalacia

Variables	Reference range	Total (N=47)
Sex		
Male		25 (53.2)
Female		22 (46.8)
Age (yr)		52.0 (33.5–60.0)
Time from symptom onset to first visit (mon)[a]		36.0 (17.3–91.2)
Time to lesion localization (mon)[b]		2.0 (1.0–12.0)
Tumor size (cm)[c]		1.9 (1.5–2.8)
Serum intact FGF-23 (pg/mL)[d]	<40	261.8 (180.6–388.8)
Serum phosphate (mg/dL)[d]	2.5–4.2	1.7 (1.4–2.0)
Serum ALP (IU/L)[d]	50–151	339.0 (190.0–423.5)
Serum calcium (mg/dL)[d]	8.5–10.5	8.9 (8.5–9.2)
Serum PTH (pg/mL)[d]	17.3–74.1	54.0 (43.0–95.4)
TRP		73.0 (57.0–81.3)

The data is presented as median (interquartile range) or N (%).
[a]Time from the onset of symptoms to the initial hospital visit.
[b]Time from the initial hospital visit to localization of the tumor.
[c]Tumor size measured by the longest axis in the pathological report. For fragmented tumors, imaging findings were used.
[d]Biochemical parameters measured at the time of the patient's initial hospital visit. Twenty-four patients were available for fibroblast growth factor 23 (FGF-23) measurements.
ALP, alkaline phosphatase; PTH, parathyroid hormone; TRP, tubular reabsorption of phosphate.

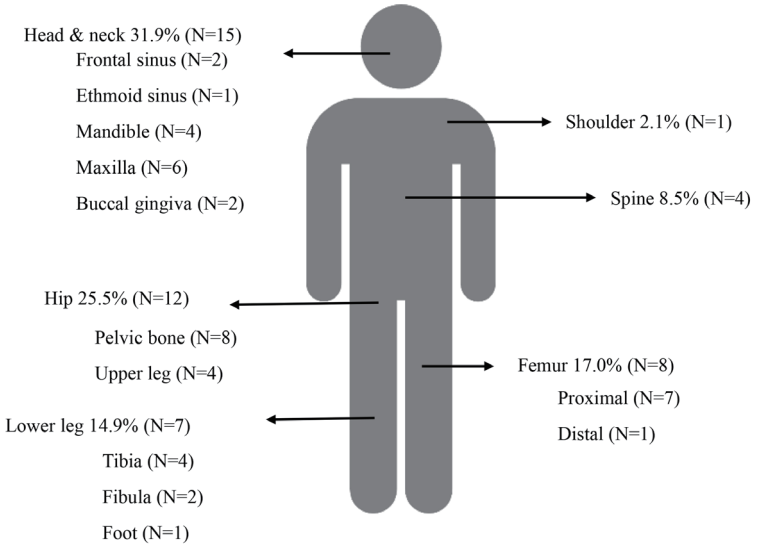

Fig. 2. Anatomical distribution of tumors in patients with tumor-induced osteomalacia (N=47).

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tremities (57.5%), particularly around the hip area (25.5%). This was followed by the head and neck region (31.9%), spine (8.5%), and upper extremities (2.1%). Among the 42 localized tumors, confirmed by pathology, 29 (69.0%) were located in bone and 13 (31.0%) in soft tissue. Soft tissue tumors were predominantly found in the head and neck region (53.8%, 7/13) and the lower extremities (46.2%, 6/13). All tumors (100%, N=44) were classified as PMTs based on surgical pathology, with clinical symptoms and laboratory values improving after resection (Fig. 2).

The median time from the initial hospital visit to tumor localization was 2.0 months (IQR, 1.0–12.0). The methods used for localization changed after 2016, when ^{68}Ga-DOTATOC PET-CT scans began to be covered by insurance in Korea.[20] Before 2016, MRI (23.5%) was the most commonly used imaging modality, followed by CT (17.6%), plain radiography (17.6%), and fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET-CT (11.8%). One case utilized ^{111}In-octreotide scintigraphy, which targets SSTRs in tumors. In eight cases, masses were initially identified through physical examination or visual inspection, with subsequent confirmation using CT prior to treatment. After 2016, among 30 cases, 25 (83.3%) tumors were localized using ^{68}Ga-DOTATOC PET-CT scans, followed by ^{18}F-FDG PET-CT (6.7%) and WBVS (6.7%) (Supplementary Table 2).

^{68}Ga-DOTATOC PET-CT demonstrated high sensitivity, with 25 of 29 patients (86.2%) showing positive results on the first scan. Four patients with initially negative results underwent a second scan 1 to 2 years later while receiving medical supplementation. Of these, three were successfully localized; only one case remained undetected by ^{68}Ga-DOTATOC PET-CT and was subsequently identified using WBVS. Overall, the detection rate of ^{68}Ga-DOTATOC PET-CT scans was 96.6%.

Among the 23 patients who underwent WBVS, 19 (82.6%) showed positive results, with the highest tumor-to-peripheral FGF-23 gradient correlating with the tumor location. The median ratio was 1.3 (IQR, 1.2–1.5), which was lower than previously reported values (Table 2).

Surgical resection was performed in 44 patients (91.5%), followed by RFA in 2 patients (4.3%) and medical treatment in 2 patients (4.3%). RFA was selected for tumors located in the humeral head and acetabulum to avoid functional impairment associated with surgery. Patients who declined surgical intervention received medical supplementation instead. One patient with malignant TIO and lung and pancreatic metastases underwent surgery but did not show improvement, although serum phosphate levels were maintained under chemotherapy. In patients who underwent complete tumor removal, serum FGF-23, phosphate, and ALP levels returned to normal. However, the time required for normalization varied by parameter: serum phosphate typically normalized within one month, while ALP required a longer duration (Table 3, Fig. 3).

Reoperation was required in 26.7% of cases due to residual tumors, with a median time to reoperation of 62.5 weeks (IQR, 42.0–84.0).

Table 2. Detection rate of ^{68}Ga-DOTATOC positron emission tomography-computed tomography and whole-body venous sampling

Variables	Total
^{68}Ga-DOTATOC scan (N=29)	
1st scan (N=29)	
Positive	25 (86.2)
Negative	4 (13.8)
2nd scan (N=4)	
Positive	3 (75.0)
Negative	1 (25.0)
Whole-body venous sampling (N=23)	
Positive	19 (82.6)
Negative	4 (17.4)

The data is presented as N (%).

DISCUSSION

^{68}Ga-DOTATOC PET-CT scans are now the most common-

Table 3. Postoperative laboratory characteristics of patients with tumor-induced osteomalacia

Variable	Numerical value	Total number
Malignancy	2 (4.3)	47
Before surgery[a]		47
Serum FGF-23 (pg/dL)	261.8 (180.6–388.8)	
Serum phosphate (mg/dL)	2.1 (1.9–2.7)	
Serum ALP (IU/L)	183.0 (128.5–349.0)	
After surgery		
Serum FGF-23 (pg/dL)	26.9 (12.4–39.7)	18
Serum phosphate (mg/dL)	2.5 (2.2–3.2)	37
Serum ALP (IU/L)	145.0 (108.0–262.3)	33

The data is presented as median (interquartile range) or N (%).
[a]Fibroblast growth factor 23 (FGF-23) levels are from the initial evaluation; serum phosphate and alkaline phosphatase (ALP) levels are from the most recent preoperative measurements.

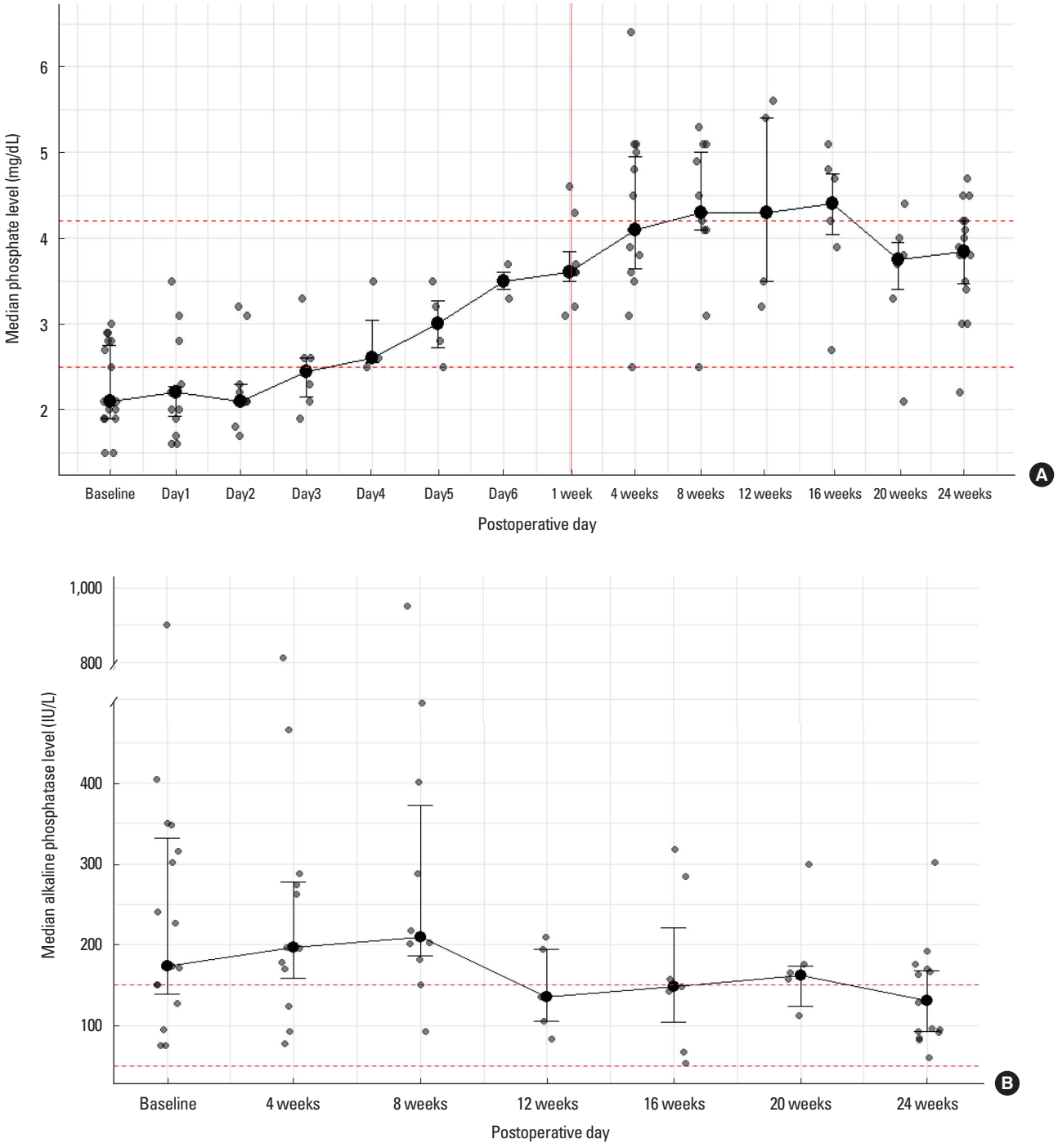

Fig. 3. Postoperative changes in serum biochemical parameters in patients who underwent successful tumor resection. (A) Changes in postoperative value of serum phosphate. (B) Changes in postoperative value of serum alkaline phosphatase.

ly used modality for localizing causative tumors in TIO, significantly reducing the time from diagnosis to localization from 50.0 months (IQR, 27.0–57.0) to 1.5 months (IQR, 1.0–2.0). This earlier localization facilitates prompt surgical resection, which leads to rapid normalization of serum phosphate and FGF-23 levels, along with improved clinical outcomes, including resolution of musculoskeletal symptoms. [1] However, even with the widespread adoption of gallium-based scans, the interval from symptom onset to successful tumor localization often still exceeds three years

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from the onset of symptoms. This is primarily due to the small size of the tumors and their potential to occur anywhere in the body, which continues to pose a challenge for accurate localization. Tumors causing osteomalacia are frequently found in the lower extremities, particularly around the hip, inguinal region, and femur. Additionally, a substantial number of tumors are located in the head and neck region, underscoring the importance of whole-body imaging during the diagnostic process.[3]

We observed that the failure rate of initial ^{68}Ga-DOTATOC PET-CT scans was 14%, which is higher than previously reported in the literature. Feng et al. [3] reported the detection rate of 97.7%, corresponding to a failure rate of 2.3%. Notably, 4 out of 5 patients in our study who initially had negative scans showed positive findings on repeat imaging.[3] This highlights the importance of performing repeat ^{68}Ga-DOTATOC PET-CT scans in patients with initially unlocalized tumors. Moreover, in cases where ^{68}Ga-DOTATOC PET-CT was initially unsuccessful, conventional imaging techniques such as ^{18}F-FDG PET-CT, often in combination with functional imaging or WBVS, were able to localize the tumor—demonstrating the value of a multimodal imaging approach.

Complete surgical excision of the tumor led to immediate improvement in serum FGF-23 levels, followed by normalization of phosphate and ALP levels. Two patients with tumors located in the humeral head and acetabulum who underwent RFA demonstrated comparable biochemical responses, supporting the effectiveness of RFA in cases where surgery is contraindicated due to the risk of functional impairment.[3,8]

Reoperation due to residual tumors involved 11 benign tumors and 1 malignant tumor, highlighting the importance of wide-margin resection or extended curettage to prevent residual disease.[10,21] In 91.7% of reoperation cases, tumors were located in bone; only one case involved soft tissue. Tumor recurrence has been reported to be higher in the spine and lower in the head and neck regions.[21] In our study, no tumor recurrence was observed. The locations of residual tumors were as follows: 50% in the lower extremities, 33% in the head and neck region, and 17% in the spine.

Two malignant tumors were identified—one located in the soft tissue of the spine and the other in the maxillary bone. Only one patient exhibited lung metastasis. Neither serum FGF-23 levels nor tumor size showed significant differences between malignant and benign TIO tumors.[10] This study has some limitations. Although we attempted to include all reported TIO cases in Korea, the overall sample size remains modest. Additionally, the inclusion of cases from dental journals may have introduced selection bias, potentially overrepresenting tumors located in the head and neck region, as patients often consult dentists after a palpable mass develops, which may correspond to larger tumors. Furthermore, the retrospective nature of this study imposes inherent limitations, including incomplete follow-up data and potential information bias.

TIO is a rare but clinically significant condition that underscores the need for accurate diagnosis and localization of the causative tumor. The variability in tumor location highlights the importance of comprehensive imaging strategies. While ^{68}Ga-DOTATOC PET-CT remains a promising modality, it should be complemented by other imaging techniques to ensure accurate localization.

DECLARATIONS

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Ethics approval and consent to participate

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Chong WH, Molinolo AA, Chen CC, et al. Tumor-induced osteomalacia. Endocr Relat Cancer 2011;18:R53-77. https://doi.org/10.1530/erc-11-0006.
2. Dahir K, Zanchetta MB, Stanciu I, et al. Diagnosis and management of tumor-induced osteomalacia: Perspectives from clinical experience. J Endocr Soc 2021;5:bvab099. https://doi.org/10.1210/jendso/bvab099.
3. Feng J, Jiang Y, Wang O, et al. The diagnostic dilemma of tumor induced osteomalacia: A retrospective analysis of 144 cases. Endocr J 2017;64:675-83. https://doi.org/10.1507/endocrj.EJ16-0587.
4. Yin Z, Du J, Yu F, et al. Tumor-induced osteomalacia. Osteoporos Sarcopenia 2018;4:119-27. https://doi.org/10.1016/j.afos.2018.12.001.
5. Rendina D, Abate V, Cacace G, et al. Tumor-induced osteomalacia: A systematic review and individual patient's data analysis. J Clin Endocrinol Metab 2022;107:e3428-e36. https://doi.org/10.1210/clinem/dgac253.
6. Jung J, Kim M, Kim SW, et al. Tumor-induced osteomalacia as a result of a phosphaturic mesenchymal tumor: Detecting rare origin. Appl Sci 2023;13:1081. https://doi.org/10.3390/app13021081.
7. Dadoniene J, Miglinas M, Miltiniene D, et al. Tumour-induced osteomalacia: A literature review and a case report. World J Surg Oncol 2016;14:4. https://doi.org/10.1186/s12957-015-0763-7.
8. Li X, Jiang Y, Huo L, et al. Nonremission and recurrent tumor-induced osteomalacia: A retrospective study. J Bone Miner Res 2020;35:469-77. https://doi.org/10.1002/jbmr.3903.
9. Aligail K, Dave JA, Ross IL. Tumor-induced osteomalacia: A case report. J Med Case Rep 2022;16:22. https://doi.org/10.1186/s13256-021-03220-7.
10. Okajima K, Kobayashi H, Ito N, et al. Extended curettage for tumour-induced osteomalacia in the bone. Jpn J Clin Oncol 2024;54:463-70. https://doi.org/10.1093/jjco/hyad180.
11. Sharma J, Kasliwal R, Jain T, et al. Emerging role of gallium-68 DOTANOC PET/CT guided radiofrequency ablation in the treatment of tumor-induced osteomalacia. JCEM Case Rep 2024;2:luae044. https://doi.org/10.1210/jcemcr/luae044.
12. Pauwels E, Cleeren F, Bormans G, et al. Somatostatin receptor PET ligands - the next generation for clinical practice. Am J Nucl Med Mol Imaging 2018;8:311-31.
13. Jan de Beur SM, Miller PD, Weber TJ, et al. Burosumab for the treatment of tumor-induced osteomalacia. J Bone Miner Res 2021;36:627-35. https://doi.org/10.1002/jbmr.4233.
14. Rikitake J, Ashida K, Nagayama A, et al. Successful superficial blood sampling to localize a fibroblast growth factor-23-producing tumor. Am J Case Rep 2024;25:e943152. https://doi.org/10.12659/ajcr.943152.
15. Dhammi IK, Jain AK, Singh AP, et al. Oncogenic osteomalacia: Problems in diagnosis and long-term management. Indian J Orthop 2010;44:453-7. https://doi.org/10.4103/0019-5413.69320.
16. Tolomeo A, Lopopolo G, Dimiccoli V, et al. Impact of 68Ga-DOTATOC PET/CT in comparison to 111In-Octreotide SPECT/CT in management of neuro-endocrine tumors: A case report. Medicine (Baltimore) 2020;99:e19162. https://doi.org/10.1097/md.0000000000019162.
17. Malan N, Vangu MD. Normal variants, pitfalls and artifacts in Ga-68 DOTATATE PET/CT imaging. Front Nucl Med 2022;2:825486. https://doi.org/10.3389/fnume.2022.825486.
18. Takeuchi Y, Suzuki H, Ogura S, et al. Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia. J Clin Endocrinol Metab 2004;89:3979-82. https://doi.org/10.1210/jc.2004-0406.
19. Hong CM, Jeong YJ, Kim HW, et al. KSNM60 in nuclear endocrinology: From the beginning to the future. Nucl Med Mol Imaging 2022;56:17-28. https://doi.org/10.1007/s13139-021-00728-0.
20. Álvarez-Rivas N, Lugo-Rodríguez G, Maneiro JR, et al. Tumor-induced osteomalacia: A systematic literature review. Bone Rep 2024;21:101772. https://doi.org/10.1016/j.bonr.2024.101772.
21. Hoong CWS, Sfeir J, Algeciras-Schimnich A, et al. A retrospective cohort of tumor-induced osteomalacia and case series of malignant disease. J Clin Endocrinol Metab 2025;110:e397-e411. https://doi.org/10.1210/clinem/dgae183.

https://doi.org/10.11005/jbm.25.901